Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

PROGNOSTIC SIGNIFICANCE OF THE PROMINENT VEIN SIGN ON SUSCEPTIBILITY-WEIGHTED IMAGING FOR COLLATERAL CIRCULATION ASSESSMENT IN ACUTE LARGE VESSEL OCCLUSION STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Acute ischemic stroke (AIS) due to large vessel occlusion (LVO) presents significant challenges in clinical management, with collateral circulation playing a pivotal role in determining tissue viability and patient outcomes. Susceptibility-weighted imaging (SWI) has emerged as a valuable non-invasive modality for assessing cerebral hemodynamics by visualizing the prominent vein sign (PVS), which reflects increased deoxyhemoglobin concentration and oxygen extraction in hypoperfused brain regions. This synthesis examines the pathophysiological basis, prevalence, and imaging characteristics of PVS, highlighting its correlation with leptomeningeal collateralization and its prognostic significance in both short- and long-term functional outcomes. Comparative analyses with other imaging techniques, including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), magnetic resonance angiography (MRA), and computed tomography angiography (CTA), underscore the complementary role of SWI in collateral assessment. The integration of quantitative and qualitative PVS evaluation methods enhances the accuracy of collateral grading and supports individualized treatment planning, particularly in selecting candidates for recanalization therapies. Challenges related to technical variability, interpretative subjectivity, and confounding clinical factors are addressed, emphasizing the need for standardized imaging protocols and robust validation. Emerging technological innovations and advanced analytic approaches promise to refine collateral imaging further, facilitating personalized stroke therapy. Incorporating PVS assessment into routine clinical workflows offers a non-contrast, accessible tool to improve prognostication and optimize therapeutic strategies in acute LVO stroke management.

Keywords: Prognostic Significance, Prominent Vein Sign (PVS), Susceptibility-Weighted Imaging (SWI), Collateral Circulation, Acute Ischemic Stroke, Large Vessel Occlusion (LVO), Stroke Imaging Biomarkers, Cerebral Perfusion, Stroke Prognosis, Meta-Analysis, Systematic Review.

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INTRODUCTION

Acute ischemic stroke (AIS) remains a leading cause of morbidity and mortality worldwide, with large vessel occlusion (LVO) representing a particularly severe subtype due to the extensive territory at risk and the potential for rapid neurological deterioration (Jiang, Zhang, Pang, Shi, et al., 2021) (Xiang, Liang, et al., 2023). The clinical outcome in AIS is highly heterogeneous, even among patients with similar vascular occlusions, and this variability is largely attributed to differences in collateral circulation. Collateral vessels provide alternative pathways for cerebral blood flow when principal arteries are obstructed, thereby stabilizing cerebral perfusion and influencing the extent of the ischemic penumbra, infarct size, and the duration and severity of ischemia (Jiang, Zhang, Pang, Shi, et al., 2021) (Liebeskind, Jahan, et al., 2014). The evaluation of collateral status is therefore essential for clinical decision-making and prognostication in acute stroke. Recent advances in neuroimaging have enabled more refined assessment of cerebral hemodynamics and tissue viability. Among these, susceptibility-weighted imaging (SWI) has emerged as a sensitive magnetic resonance imaging (MRI) technique that exploits differences in magnetic susceptibility between tissues, particularly deoxygenated hemoglobin, to visualize venous structures and oxygen metabolism in the brain (Jiang, Zhang, Pang, Shi, et al., 2021). SWI is capable of detecting the prominent vein sign (PVS), which manifests as hypointense and enlarged veins in the affected hemisphere, reflecting increased oxygen extraction in hypoperfused regions (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shao, et al., 2021). This imaging marker has garnered significant attention as a potential surrogate for collateral flow and tissue viability in the context of AIS. The presence of PVS on SWI is thought to be closely related to the pathophysiology of acute cerebral ischemia. In the setting of LVO, impaired arterial inflow leads to increased oxygen extraction from the residual blood supply, resulting in elevated levels of deoxyhemoglobin in the draining veins. This physiological adaptation is visualized as PVS on SWI, providing an indirect measure of the metabolic state of the ischemic tissue (Xiang, Liang, et al., 2023). Notably, PVS is more frequently observed in patients with anterior circulation infarcts due to LVO, and its presence is almost ubiquitous in this subgroup (Jiang, Zhang, Pang, Shao, et al., 2021). The extent and distribution of PVS may therefore offer valuable insights into the adequacy of collateral circulation and the potential for tissue salvage. The prognostic significance of PVS has been investigated in several studies and meta-analyses. Xiang et al. identified key clinical factors associated with the presence of PVS, such as prior stroke or transient ischemic attack, atrial fibrillation, and severe intracranial large artery stenosis or occlusion. Their findings suggest that PVS is significantly related to the severity of arterial occlusion and is associated with unfavorable outcomes, particularly in patients undergoing recanalization therapies. However, the relationship between PVS and prognosis appears to be less pronounced in patients managed conservatively (Xiang, Liang, et al., 2023). Ping Lua et al. conducted a quantitative meta-analysis encompassing 16 cohort studies and found that the presence of PVS on SWI was linked to poor 90-day functional outcomes and a higher likelihood of early neurological deterioration in AIS. Nevertheless, some studies reported no significant association, highlighting the need for further research to clarify the prognostic value of PVS in different clinical contexts. The assessment of collateral circulation using imaging modalities remains a subject of ongoing investigation. While digital subtraction angiography is considered the gold standard, its invasiveness and limited availability restrict its routine use. Non-invasive techniques such as time-of-flight magnetic resonance angiography (TOF-MRA) and computed tomography angiography (CTA) are commonly employed, but their ability to accurately characterize collateral flow is variable (Lua et al., 2023). SWI offers a complementary approach by visualizing venous changes that reflect underlying hemodynamic and metabolic alterations.

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The integration of SWI-derived markers such as PVS into clinical workflows may enhance the precision of stroke assessment and guide therapeutic decision-making. It is important to recognize that the interpretation of PVS is subject to certain limitations. The identification of PVS is often based on qualitative or semi-quantitative assessment, introducing potential observer bias. Quantitative susceptibility mapping, an extension of SWI, has been proposed as a means to objectively measure venous oxygen saturation and provide more robust information about cerebral ischemia (Jiang, Zhang, Pang, Shao, et al., 2021). Furthermore, the relationship between PVS and collateral status is complex and may be influenced by additional factors such as ischemic tolerance, which refers to the brain's intrinsic ability to withstand hypoperfusion through adaptive mechanisms (Xu et al., 2019). This phenomenon may partially explain why some patients with poor collaterals still achieve favorable outcomes, underscoring the multifactorial nature of stroke prognosis. The clinical utility of PVS as a prognostic marker is further supported by its association with established imaging scores and clinical parameters. For instance, the Alberta Stroke Program Early CT Score (ASPECTS) has been linked to collateral grade, suggesting that rapid imaging algorithms can distinguish differences in collateral status and, by extension, the likelihood of favorable outcomes (Liebeskind, Jahan, et al., 2014). Moreover, the presence of PVS on SWI has been correlated with the severity of neurological deficits and the risk of early neurological deterioration, reinforcing its potential role in risk stratification (Lua et al., 2023) (Xiang, Liang, et al., 2023). In summary, the integration of SWI and the evaluation of PVS represent promising advances in the imaging assessment of AIS. By providing a non-invasive window into the metabolic and hemodynamic state of the brain, PVS may serve as a valuable marker for collateral circulation and prognosis in patients with acute LVO stroke (Jiang, Zhang, Pang, Shi, et al., 2021) (Xiang, Liang, et al., 2023)(Lua et al., 2023). The continued refinement of imaging techniques and the standardization of PVS assessment are essential for translating these insights into improved clinical outcomes.

Background and Rationale

Epidemiology and Impact of Acute Ischemic Stroke

Acute ischemic stroke (AIS) represents a major global health burden, characterized by the sudden loss of neurological function due to the occlusion or severe stenosis of cerebral arteries, most commonly the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA) (Lee et al., 2021)(Yuan et al., 2018). The epidemiological significance of AIS is underscored by its high incidence, morbidity, and mortality rates, as well as its profound socioeconomic impact. Patients affected by AIS often present within a narrow therapeutic window, typically within 8 hours of symptom onset, which is critical for the implementation of effective interventions and for minimizing irreversible brain injury. The clinical spectrum of AIS is highly heterogeneous, influenced by factors such as the location and extent of vascular occlusion, the presence of vascular risk factors, and the adequacy of collateral circulation (Lee et al., 2021). Collateral circulation, defined as the network of subsidiary vascular channels that compensate for impaired cerebral blood flow, plays a crucial role in determining the severity of ischemic injury, the size of the infarct core, and the extent of the ischemic penumbra. The variability in collateral flow is a key determinant of clinical outcomes, with robust collateral networks often associated with smaller infarct volumes and improved functional recovery (Jiang, Zhang, Pang, Shi, et al., 2021) (Liebeskind, Jahan, et al., 2014). AIS due to large vessel occlusion (LVO) is particularly devastating, as it frequently results in extensive brain tissue damage and severe neurological deficits (Yuan et al., 2018). The assessment of collateral status has therefore become an integral component of acute stroke management, informing both prognosis and therapeutic decision-

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making (Jiang, Zhang, Pang, Shi, et al., 2021) (Liebeskind, Jahan, et al., 2014). Imaging modalities such as susceptibility-weighted imaging (SWI) and diffusion-weighted imaging (DWI) have advanced the ability to visualize and quantify ischemic changes, with SWI providing unique insights into the oxygen extraction fraction and venous deoxygenation in affected brain regions (Jiang, Zhang, Pang, Shi, et al., 2021) (Lou et al., 2014). The impact of AIS extends beyond the acute phase, with many survivors experiencing long-term disability, reduced quality of life, and increased dependency (Elijovich et al., 2015). Functional outcomes are commonly measured using scales such as the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS), which capture the degree of neurological impairment and the level of independence in daily activities (Lee et al., 2021) (Yuan et al., 2018) (Elijovich et al., 2015). Early neurological deterioration (END) and hemorrhagic transformation (HT) are recognized complications that further worsen prognosis, particularly in patients with inadequate collateral flow or extensive ischemic injury (Xiang, Liang, et al., 2023). Epidemiological studies have highlighted the association between vascular risk factors, such as hypertension, atrial fibrillation, and prior transient ischemic attacks (TIA), and the incidence of AIS, as well as their influence on collateral sufficiency and clinical outcomes (Lee et al., 2021) (Xiang, Liang, et al., 2023) (Liebeskind, Jahan, et al., 2014). The presence of prominent vessel sign (PVS) on SWI, which reflects increased deoxyhemoglobin concentration due to elevated oxygen extraction in ischemic tissue, has emerged as a potential imaging biomarker for assessing collateral status and predicting prognosis (Jiang, Zhang, Pang, Shi, et al., 2021) (Jiang, Zhang, Pang, Shao, et al., 2021). However, the relationship between PVS and collateral circulation remains an area of ongoing investigation, with some studies reporting a correlation between extensive PVS and poor collateralization, while others suggest that more prominent hypointense vessels may indicate better collateral flow (Jiang, Zhang, Pang, Shi, et al., 2021) (Verma et al., 2014). The heterogeneity in the presentation and progression of AIS underscores the need for individualized assessment and management strategies. Advances in neuroimaging, particularly the integration of SWI and DWI, have enhanced the ability to stratify patients based on the extent of ischemic injury and collateral reserve, thereby optimizing treatment planning and improving outcomes (Lou et al., 2014) (Jiang, Zhang, Pang, Shao, et al., 2021). The epidemiological and clinical impact of AIS necessitates continued research into reliable imaging markers and therapeutic approaches to mitigate its burden on individuals and healthcare systems (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shao, et al., 2021).

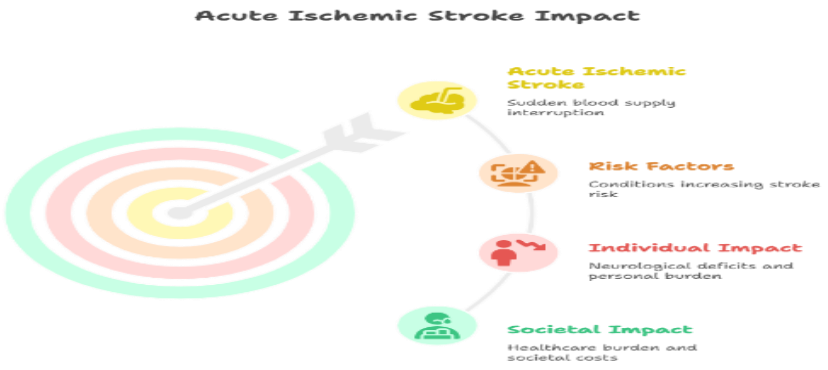

Figure 1: Overview of the Epidemiology and Impact of Acute Ischemic Stroke (Feigin et al., 2021)

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Explanation:

*The **"Overview of the Epidemiology and Impact of Acute Ischemic Stroke"** diagram summarizes the major elements that define the scope and consequences of AIS. It begins with the Global Incidence, emphasizing its prevalence worldwide, particularly among older populations. Age and Gender Distribution show that incidence increases with age and varies slightly by sex. Risk Factors such as hypertension and smoking contribute significantly to stroke risk. The Geographic and Socioeconomic Variation highlights disparities in access to care and outcomes. Clinical Outcomes include mortality, long-term disability, and the risk of recurrence. Finally, the Healthcare Burden reflects the immense strain AIS places on health systems, including hospitalization costs, rehabilitation demands, and long-term care.*

Pathophysiology of Large Vessel Occlusion

Large vessel occlusion (LVO) in the cerebral circulation is a critical event that disrupts the normal hemodynamics of the brain, leading to acute ischemic stroke. The pathophysiology of LVO is characterized by the sudden blockage of major cerebral arteries, such as the internal carotid artery or the proximal segments of the middle cerebral artery, resulting in a rapid reduction of cerebral blood flow (CBF) to the dependent brain tissue. This abrupt cessation of flow initiates a cascade of metabolic and cellular disturbances that ultimately determine the extent of tissue injury and clinical outcome (Jiang, Zhang, Pang, Shi, et al., 2021) (Xiang, Liang, et al., 2023). The cerebral collateral circulation plays a crucial role in modulating the effects of LVO. Collateral vessels, which include leptomeningeal anastomoses and other subsidiary vascular networks, provide alternative pathways for blood to reach ischemic regions when primary conduits are obstructed. The efficiency and robustness of these collateral channels are highly variable among individuals and are a major determinant of the heterogeneity observed in stroke severity, infarct size, and the evolution of the ischemic penumbra, the area of hypoperfused but potentially salvageable tissue surrounding the infarct core. The presence of effective collateral flow can stabilize CBF, prolong the survival of at-risk tissue, and extend the therapeutic window for reperfusion interventions. When a large cerebral artery is occluded, the immediate consequence is a steep drop in perfusion pressure distal to the blockage. This hypoperfusion leads to a mismatch between oxygen supply and metabolic demand in the affected brain regions. In response, the tissue increases its oxygen extraction fraction (OEF) in an attempt to compensate for the reduced delivery of oxygenated blood. This compensatory mechanism results in a higher concentration of deoxyhemoglobin within the venous drainage of the ischemic territory (Jiang, Zhang, Pang, Shi, et al., 2021). The elevated deoxyhemoglobin content can be visualized using susceptibility-weighted imaging (SWI), where it manifests as hypointense, enlarged veins, a phenomenon known as the prominent vessel sign (PVS) (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shi, et al., 2021). The extent and distribution of PVS on SWI are thought to reflect the underlying pathophysiological processes of LVO. Regions with prominent PVS indicate areas of increased OEF and ongoing metabolic stress, often corresponding to the ischemic penumbra. The presence of PVS has been associated with both the severity of hypoperfusion and the adequacy of collateral circulation, although the relationship is complex and may be influenced by factors such as the site of occlusion, the duration of ischemia, and individual vascular anatomy (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shi, et al., 2021). Some studies suggest that extensive PVS correlates with poor collateralization and worse outcomes, while others report that more pronounced PVS may be linked to better collateral flow and improved prognosis, highlighting the need for further research to clarify these associations (Xiang, Liang, et al., 2023). The dynamic interplay between arterial occlusion, collateral flow, and tissue oxygenation underpins the clinical

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and imaging manifestations of LVO. Advanced imaging modalities, including SWI and diffusion-weighted imaging (DWI), have enabled more precise characterization of these processes. For instance, the SWI-DWI mismatch ratio has emerged as a potential marker for assessing the extent of salvageable tissue and the effectiveness of collateral circulation, with larger mismatch ratios indicating better leptomeningeal collateralization and more favorable outcomes (Jiang, Zhang, Pang, Shi, et al., 2021). Quantitative susceptibility mapping further refines this assessment by allowing direct measurement of venous oxygen saturation and the volumetric extent of hypointense vessels, providing a more objective evaluation of ischemic burden and collateral status (Jiang, Zhang, Pang, Shao, et al., 2021) (Jiang, Zhang, Pang, Shi, et al., 2021). The heterogeneity in clinical presentation and prognosis among patients with LVO underscores the importance of individualized assessment of collateral circulation and tissue viability. Factors such as the location and etiology of the occlusion, the presence of cardioembolism, and the degree of pre-existing vascular disease all influence the development and efficacy of collateral pathways. Moreover, the subjective nature of some imaging markers, such as PVS, introduces variability in interpretation, emphasizing the need for standardized and quantitative approaches in both research and clinical practice (Jiang, Zhang, Pang, Shao, et al., 2021) (Mucke et al., 2015). Therapeutic strategies aimed at enhancing collateral flow or protecting the ischemic penumbra have been explored, including pharmacological agents that promote angiogenesis and vasculogenesis. However, large randomized trials have often yielded negative results, possibly due to suboptimal patient selection and insufficient assessment of collateral effects. Ongoing research is focused on refining imaging techniques and identifying reliable biomarkers, such as PVS on SWI, to guide treatment decisions and improve outcomes in acute LVO stroke (Bang et al., 2015). In summary, the pathophysiology of large vessel occlusion is defined by the interplay between abrupt arterial blockage, compensatory collateral circulation, and the metabolic adaptations of ischemic brain tissue. Imaging markers like PVS on SWI provide valuable insights into these processes and hold promise for enhancing prognostic accuracy and guiding therapeutic interventions in acute stroke management (Jiang, Zhang, Pang, Shi, et al., 2021) (Xiang, Liang, et al., 2023) (Bang et al., 2015).

Collateral Circulation in Cerebral Ischemia

Anatomy and Physiology of Cerebral Collaterals

The cerebral collateral circulation comprises a subsidiary network of vascular channels that play a crucial role in stabilizing cerebral blood flow (CBF) when primary arterial conduits are compromised, such as during acute large vessel occlusion stroke. These collateral pathways are responsible for the marked heterogeneity observed in stroke presentations, influencing the severity of the ischemic penumbra, the eventual infarct size, and the duration and intensity of cerebral ischemia (Jiang, Zhang, Pang, Shi, et al., 2021) (Xiang, Liang, et al., 2023). The anatomical basis of cerebral collaterals involves both pre-existing and dynamically recruited vessels, which can be broadly categorized into primary, secondary, and tertiary collaterals. Primary collaterals are represented by the circle of Willis, a ring-like arterial structure at the base of the brain that provides immediate compensatory flow between the anterior and posterior circulations, as well as between the left and right hemispheres. This structure allows for rapid redistribution of blood flow in the event of proximal arterial occlusion, although its effectiveness is highly variable among individuals due to anatomical variations. Secondary collaterals are formed by leptomeningeal anastomoses, which are small arterial connections between the distal branches of the major cerebral arteries, such as the anterior, middle, and posterior cerebral arteries.

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These vessels become especially important when primary collaterals are insufficient or absent, as they can redirect blood flow from non-affected territories to ischemic regions. Tertiary collaterals, including extracranial-intracranial anastomoses, may also contribute to cerebral perfusion under chronic or severe ischemic conditions, although their role is less prominent in the acute phase. Physiologically, the effectiveness of collateral circulation is determined by several factors, including the caliber and patency of the collateral vessels, the pressure gradients across the vascular territories, and the capacity for dynamic vasodilation in response to ischemia (Jiang, Zhang, Pang, Shi, et al., 2021). The presence of robust collateral flow can mitigate the extent of tissue injury by maintaining perfusion to the ischemic penumbra, thereby prolonging the therapeutic window for reperfusion therapies and reducing infarct growth (Liebeskind, Jahan, et al., 2014) (Xiang, Liang, et al., 2023). Conversely, poor collateral status is associated with rapid progression of infarction and worse clinical outcomes. The assessment of collateral circulation has become increasingly relevant in acute stroke management, as it provides critical information for prognosis and treatment planning. Imaging modalities such as digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have traditionally been used to visualize collateral vessels, but each has limitations in terms of invasiveness, spatial resolution, or sensitivity to slow flow (Jiang, Zhang, Pang, Shi, et al., 2021) (Bang et al., 2015). More recently, susceptibility-weighted imaging (SWI) has emerged as a non-invasive MRI technique that exploits differences in magnetic susceptibility between tissues to visualize venous structures and indirectly assess oxygen extraction and perfusion status (Jiang, Zhang, Pang, Shi, et al., 2021). The prominent vein sign (PVS) on SWI, characterized by hypointense and enlarged veins in the affected hemisphere, reflects increased oxygen extraction in response to hypoperfusion and has been linked to the presence and efficacy of collateral circulation (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shao, et al., 2021). Collateral circulation is not only anatomically determined but also influenced by physiological and pathological factors. Chronic conditions such as hypertension and a history of smoking have been associated with the development of more extensive collateral networks, potentially due to adaptive vascular remodeling in response to repeated ischemic insults (Liebeskind, Jahan, et al., 2014) (Lua et al., 2023). However, acute elevations in blood pressure and the absence of prior hypertension may paradoxically indicate poor collateral status, possibly reflecting a lack of preconditioning and vascular adaptation (Liebeskind, Jahan, et al., 2014). The dynamic interplay between these factors underscores the complexity of collateral physiology in the context of cerebral ischemia. In summary, the anatomy and physiology of cerebral collaterals are central to the brain's ability to withstand acute ischemic insults. The structural diversity and functional adaptability of these vessels determine the extent of tissue survival and recovery potential following large vessel occlusion. Advances in imaging, particularly SWI and the identification of PVS, have enhanced our ability to non-invasively evaluate collateral status, offering valuable insights for individualized stroke management (Jiang, Zhang, Pang, Shi, et al., 2021) (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shao, et al., 2021).

Table 1: Anatomy and Physiology of Cerebral Collaterals

Type of Collateral	Anatomical Location	Physiological Role	Clinical Significance
Primary Collaterals	Circle of Willis (anterior communicating artery, posterior communicating artery)	Provides immediate redistribution of blood during large vessel occlusion	Variability in completeness affects stroke outcomes and cerebral perfusion

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Secondary Collaterals	Leptomeningeal (pial) arteries on the cortical surface	Reactivate during reduced cerebral perfusion to maintain oxygen supply	Key determinant of infarct size and stroke progression
Tertiary Collaterals	Extracranial-intracranial anastomoses (e.g., ophthalmic artery, external carotid branches)	Engage over time when primary/secondary routes are insufficient	Often develop in chronic hypoperfusion states or progressive steno-occlusive diseases
Deep Collateral Pathways	Thalamoperforating arteries, anterior choroidal arteries	Maintain perfusion to deep brain structures during proximal occlusion	May reduce damage in basal ganglia and internal capsule areas during stroke
Microvascular Collaterals	Capillary-level anastomoses within ischemic penumbra	Maintain low-level perfusion in microcirculation	Target of neuroprotective therapies and vascular remodeling research

Role of Collaterals in Stroke Outcome

Collateral circulation plays a fundamental role in determining the outcome of patients experiencing acute ischemic stroke due to large vessel occlusion. The extent and efficiency of collateral blood flow can significantly influence the degree of tissue survival, infarct size, and ultimately, clinical recovery. Collaterals provide alternative pathways for blood to reach ischemic brain regions when primary arterial routes are obstructed, thereby sustaining penumbral tissue and delaying irreversible injury (Souza et al., 2012). The dynamic interplay between arterial inflow, microvascular perfusion, and venous outflow forms a comprehensive collateral cascade, which is crucial for maintaining cerebral viability during acute ischemia (Faizy & Heit, 2021). The assessment of collateral status has become increasingly important in acute stroke management, as robust collateral networks are associated with smaller infarct volumes and improved functional outcomes. For instance, studies have demonstrated that patients with more extensive collateral flow exhibit better clinical scores and reduced infarct expansion, as measured by imaging modalities such as diffusion-weighted imaging (DWI) and the National Institutes of Health Stroke Scale (NIHSS) (Souza et al., 2012). The relationship between collateral circulation and final infarct volume is further supported by statistical analyses, including generalized linear models and correlation coefficients, which consistently show that higher collateral scores predict more favorable outcomes (Kimmel et al., 2019). Imaging techniques have evolved to provide non-invasive and reliable markers of collateral status. Susceptibility-weighted imaging (SWI) has emerged as a valuable tool for visualizing prominent vessel signs (PVS), which reflect the presence of deoxygenated blood in veins draining ischemic tissue. The extent of PVS on SWI correlates with the adequacy of collateral flow, as more prominent vessels are indicative of increased oxygen extraction in regions with preserved, albeit reduced, perfusion (Lee et al., 2021) (Faizy & Heit, 2021). This imaging marker allows for collateral estimation without the need for contrast agents, making it particularly advantageous for patients with contraindications to contrast-based studies (Lee et al., 2021). The prognostic significance of collateral circulation is further highlighted by its association with clinical outcomes. Patients exhibiting robust collaterals, as inferred from imaging or clinical assessment, tend to have better modified Rankin Scale (mRS) scores at follow-up, reflecting greater functional independence (Jing et al., 2021) (Kimmel et al., 2019). Conversely, poor collateral status is linked to larger infarct volumes, higher NIHSS scores, and worse disability. The ability to predict these outcomes early in the course of stroke has direct implications for treatment planning, including the selection of candidates for reperfusion therapies

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and the anticipation of potential complications (Jing et al., 2021) (Souza et al., 2012). Moreover, the evaluation of collateral flow is not limited to arterial pathways. Recent evidence suggests that venous assessment, such as the cerebral venous outflow score (COVES), may provide additional prognostic information by capturing the downstream effects of collateral circulation on microvascular and venous compartments (Faizy & Heit, 2021). This holistic approach recognizes that effective collateralization is not solely an arterial phenomenon but involves the entire vascular network, including tissue-level and venous pathways. In summary, the role of collaterals in stroke outcome is multifaceted, encompassing the preservation of at-risk tissue, the limitation of infarct growth, and the prediction of clinical recovery. The integration of advanced imaging markers such as PVS on SWI and comprehensive collateral scoring systems enhances the ability to stratify patients and tailor therapeutic interventions. The growing body of evidence underscores the necessity of incorporating collateral assessment into routine stroke evaluation to optimize prognostication and guide management strategies (Souza et al., 2012) (Lee et al., 2021) (Faizy & Heit, 2021) (Kimmel et al., 2019).

Imaging Modalities for Collateral Assessment

Imaging modalities play a central role in the assessment of collateral circulation in patients with cerebral ischemia, particularly in the context of acute large vessel occlusion (LVO) stroke. The evaluation of collateral flow is essential for predicting tissue viability, guiding therapeutic decisions, and estimating prognosis. Several imaging techniques have been developed and refined for this purpose, each with distinct advantages and limitations. Magnetic resonance imaging (MRI) offers a suite of sequences that are highly informative for collateral assessment. Among these, susceptibility-weighted imaging (SWI) has gained attention due to its sensitivity to venous blood oxygenation changes, which indirectly reflect regional perfusion and collateral status. The prominent vein sign (PVS) on SWI is characterized by the visualization of dilated hypointense veins in the affected hemisphere, which are thought to arise from increased oxygen extraction in hypoperfused tissue. The presence and extent of PVS have been associated with the degree of collateral circulation, as regions with robust collateral flow tend to exhibit more pronounced venous changes on SWI (Lua et al., 2023) (Kim et al., 2014). This imaging marker provides a non-invasive means to infer the adequacy of collateral supply and has shown potential in predicting clinical outcomes in acute stroke patients (Lua et al., 2023). Diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) are also integral to the assessment of ischemic tissue and collateral status. DWI identifies regions of restricted diffusion, corresponding to infarcted or severely ischemic tissue, while PWI delineates areas of hypoperfusion. The mismatch between DWI and PWI can be used to estimate the ischemic penumbra, representing tissue at risk but potentially salvageable with timely reperfusion. The Alberta Stroke Program Early CT Score (ASPECTS) applied to DWI and SWI can further quantify the extent of ischemic damage and collateral involvement, with discrepancies between these modalities (such as the reverse mismatch pattern) providing additional insights into collateral dynamics (Dejobert et al., 2016). Time-of-flight magnetic resonance angiography (TOF-MRA) is frequently employed to visualize intracranial vessels and detect occlusions or stenoses. When combined with SWI and DWI, TOF-MRA enables comprehensive evaluation of both arterial patency and downstream venous changes, facilitating a more nuanced understanding of collateral pathways (Yuan et al., 2018). The integration of these modalities allows for the identification of occluded vessels, assessment of infarct core, and visualization of collateral-related venous alterations. Computed tomography (CT)-based techniques, particularly CT perfusion (CTP) and multiphase CT angiography (mCTA), are widely used in the acute setting due to their rapid acquisition and broad availability. CTP provides quantitative maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean

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Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

transit time (MTT), which are instrumental in delineating the ischemic core and penumbra. mCTA, on the other hand, enables dynamic assessment of collateral filling over multiple phases, offering a temporal perspective on collateral recruitment (Lenga et al., 2016). The correlation between SWI-based PVS and collateral scores derived from mCTA has been explored, with studies employing statistical analyses such as Spearman's correlation coefficient and logistic regression to evaluate predictive accuracy (Oh & Lee, 2022). These approaches underscore the complementary nature of MRI and CT modalities in collateral assessment. Digital subtraction angiography (DSA) remains the gold standard for direct visualization of collateral vessels, providing high spatial and temporal resolution. However, its invasive nature and limited availability in the hyperacute phase restrict its routine use for initial collateral evaluation (Jensen-Kondering & Böhm, 2013). Non-invasive modalities such as SWI, DWI, PWI, and mCTA are therefore preferred for rapid triage and treatment planning. The assessment of collateral circulation is further complicated by technical and patient-related factors. For example, SWI quality can be compromised by motion or dental artifacts, necessitating careful image acquisition and interpretation (Lou et al., 2014). Interrater reliability in evaluating collateral-related imaging markers, such as PVS on SWI or collateral scores on mCTA, is an important consideration, with studies employing kappa statistics to quantify agreement (Oh & Lee, 2022). Collateral grading systems, whether based on imaging or angiographic criteria, are essential for standardizing assessment and facilitating prognostic modeling. Logistic regression analyses have been widely used to determine the independent predictive value of collateral imaging markers for clinical outcomes, such as the modified Rankin Scale (mRS) or the occurrence of malignant cerebral edema (MCE) (Kehagias et al., 2005) (Lua et al., 2023). The integration of collateral assessment into outcome prediction models enhances the precision of prognostication and supports individualized treatment strategies. The relationship between collateral status and clinical outcomes is well established, with better collateral flow associated with smaller infarct volumes, reduced infarct expansion, and improved functional recovery (Miteff et al., 2009). Imaging modalities that reliably capture collateral dynamics, such as SWI with PVS assessment, thus hold significant promise for optimizing acute stroke management. The findings of Ping Lua et al. (Lua et al., 2023) highlight the utility of PVS-SWI as a marker for evaluating collateral circulation and predicting the risk of adverse outcomes such as MCE, reinforcing the value of advanced MRI techniques in this context. In summary, the multimodal imaging approach, encompassing SWI, DWI, PWI, TOF-MRA, CTP, mCTA, and, when feasible, DSA, provides a comprehensive framework for collateral assessment in cerebral ischemia. The integration of these modalities, coupled with robust statistical analysis and standardized grading systems, advances our ability to stratify risk, guide therapy, and improve outcomes in patients with acute LVO stroke (Lou et al., 2014) (Dejobert et al., 2016) (Yuan et al., 2018) (Jensen-Kondering & Böhm, 2013) (Oh & Lee, 2022) (Kehagias et al., 2005) (Lua et al., 2023) (Kim et al., 2014) (Lenga et al., 2016) (Miteff et al., 2009).

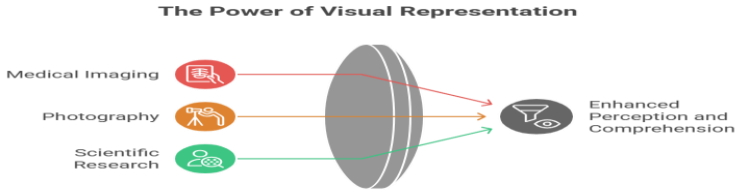

Figure 2: Key Imaging Modalities for Collateral Circulation Assessment in Acute Ischemic Stroke

Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

Explanation

The diagram titled ***"Key Imaging Modalities for Collateral Circulation Assessment in Acute Ischemic Stroke"*** *outlines three main imaging approaches:* ***CT-Based Imaging****, including single- and multiphase* ***CT Angiography (CTA)*** *and* ***CT Perfusion (CTP)****;* ***MR-Based Imaging****, such as* ***MR Angiography (MRA)****,* ***Perfusion-Weighted Imaging (PWI)****, and* ***Susceptibility-Weighted Imaging (SWI);*** *and the* ***invasive angiographic method, Digital Subtraction Angiography (DSA),*** *regarded as the gold standard for real-time visualization of cerebral collaterals. These modalities differ in their spatial and temporal resolution, accessibility, and diagnostic value in acute stroke management (Liebeskind, 2018).*

Imaging Techniques in Acute Ischemic Stroke

Overview of Neuroimaging Modalities

Neuroimaging plays a central role in the evaluation and management of acute ischemic stroke, providing critical information on vascular status, tissue viability, and collateral circulation. Several imaging modalities are routinely employed, each offering distinct advantages and limitations in the acute setting. Computed tomography (CT) and magnetic resonance imaging (MRI) are the primary modalities for initial assessment. Non-contrast CT is widely used for rapid exclusion of intracranial hemorrhage and for early detection of ischemic changes. The Alberta Stroke Program Early CT Score (ASPECTS) is a semiquantitative system applied to both CT and MRI to assess the extent of ischemic injury within the middle cerebral artery (MCA) territory, with higher scores indicating less extensive infarction and better prognosis (Chen et al., 2015) (Xiang, Wei, et al., 2023). This scoring system divides the MCA territory into ten regions, assigning one point for each region without evidence of infarction, thus facilitating standardized evaluation and prognostication. Diffusion-weighted imaging (DWI), a specialized MRI sequence, is highly sensitive for detecting acute infarction, often within minutes of symptom onset. DWI identifies areas of cytotoxic edema as regions of high signal intensity, while the apparent diffusion coefficient (ADC) map helps confirm true restricted diffusion by demonstrating corresponding hypointensity (Chen et al., 2015). DWI lesion volume has been shown to correlate with initial stroke severity and functional outcome, and is frequently used in conjunction with other imaging markers to guide therapeutic decisions (Souza et al., 2012). Susceptibility-weighted imaging (SWI) is an advanced MRI technique that exploits differences in magnetic susceptibility to enhance visualization of venous structures and blood products. SWI is particularly sensitive to deoxygenated blood, making it valuable for detecting the prominent vein sign (PVS), which reflects increased oxygen extraction in hypoperfused brain regions. The presence and extent of PVS on SWI have been associated with the status of collateral circulation and may serve as a surrogate marker for tissue at risk of infarction (Lee et al., 2021). SWI can also be used to assess the asymmetrical prominent veins sign (APVS), which, when combined with other imaging markers such as fluid-attenuated inversion recovery vascular hyperintensity (FVH), enhances the prediction of clinical outcomes (Xiang, Wei, et al., 2023). Collateral circulation assessment is crucial in acute large vessel occlusion (LVO) stroke, as robust collateral flow can sustain penumbral tissue and improve the likelihood of favorable outcomes. Several imaging-based collateral grading systems exist, including those based on multiphase MR angiography (MRA) and conventional angiography. The MR acute ischemic collateral (MAC) score, derived from dynamic contrast-enhanced MRA, enables semiquantitative evaluation of collateral flow, with higher scores indicating better collateralization (Lee et al., 2021). Angiographic collateral grading, such as the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) system, is performed during digital subtraction angiography

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Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

and provides a comprehensive assessment of collateral pathways (Bang et al., 2011). Studies have demonstrated that higher collateral grades are associated with increased rates of successful reperfusion and improved functional outcomes (Liebeskind, Tomsick, et al., 2014) (Bang et al., 2011). Advanced MRI techniques, including quantitative susceptibility mapping (QSM), further refine the assessment of venous oxygenation and tissue viability. QSM enables quantification of magnetic susceptibility differences between affected and unaffected hemispheres, providing insights into the oxygenation state of abnormal veins in stroke patients (Xia et al., 2014). This quantitative approach complements qualitative assessments from SWI and enhances the understanding of pathophysiological changes in acute ischemia. Statistical analyses in neuroimaging studies often involve a combination of parametric and non-parametric tests, depending on data distribution. For example, the Kolmogorov-Smirnov test is used to assess normality, while Student's t-test, Chi-square test, Mann-Whitney U-test, and Kruskal-Wallis test are applied to compare groups based on variable type and distribution. Correlation analyses, such as Pearson or Spearman methods, are employed to explore relationships between imaging findings and clinical variables, and logistic regression is used to identify independent predictors of outcome (Xu et al., 2021). Receiver operating characteristic (ROC) curve analysis is frequently utilized to evaluate the predictive value of imaging markers for clinical prognosis (Xiang, Wei, et al., 2023). The integration of multiple imaging modalities and advanced analytic techniques allows for a comprehensive evaluation of acute ischemic stroke. This multimodal approach supports individualized treatment planning, facilitates prognostication, and informs the selection of patients most likely to benefit from reperfusion therapies (Kimmel et al., 2019) (Lenga et al., 2016). The ongoing refinement of neuroimaging protocols and the development of novel imaging biomarkers, such as PVS on SWI, continue to enhance the precision and utility of imaging in acute stroke care.

Susceptibility-Weighted Imaging (SWI)

Principles of SWI Technology

Susceptibility-weighted imaging (SWI) is a magnetic resonance imaging (MRI) technique that exploits the magnetic susceptibility differences between tissues to generate enhanced contrast, particularly for venous structures and regions with altered blood oxygenation. The fundamental principle underlying SWI is the sensitivity of gradient-echo sequences to local magnetic field inhomogeneities, which arise from variations in tissue composition, such as the presence of deoxyhemoglobin, iron, or calcium. These susceptibility differences induce phase shifts in the MR signal, which can be accentuated by using long echo times and high spatial resolution (Wang et al., 2021). In SWI, both magnitude and phase images are acquired using a three-dimensional, fully flow-compensated, high-resolution gradient-echo sequence. The phase images are particularly sensitive to local susceptibility changes, as they reflect the cumulative effect of microscopic field gradients over the echo time. By combining the magnitude and filtered phase images, SWI produces images with enhanced visualization of venous vasculature and microbleeds, as well as other structures with distinct susceptibility properties (Chen et al., 2015). The filtered phase images are processed to suppress background field inhomogeneities and to highlight local susceptibility effects, which is crucial for delineating small veins and regions of abnormal oxygen extraction. The conspicuity of veins on SWI is primarily determined by the concentration of deoxyhemoglobin within venous blood. Deoxyhemoglobin is paramagnetic and induces local field distortions, resulting in hypointense (dark) signals on SWI. In the context of acute ischemic stroke, regions with impaired perfusion exhibit increased oxygen extraction fraction (OEF), leading to elevated deoxyhemoglobin levels in the draining veins.

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This physiological response enhances the visibility of veins in the affected hemisphere, manifesting as the prominent vein sign (PVS) (Lua et al., 2023) (Chen et al., 2015). The PVS is characterized by an increased number, caliber, or conspicuity of veins compared to the contralateral hemisphere, reflecting underlying tissue hypoperfusion and altered hemodynamics. The technical parameters of SWI acquisition, such as magnetic field strength, echo time (TE), repetition time (TR), and spatial resolution, significantly influence the sensitivity and specificity of the technique. Higher field strengths (e.g., 3T versus 1.5T) improve susceptibility contrast and spatial resolution, thereby facilitating the detection of subtle venous abnormalities and microvascular changes (Jensen-Kondering & Böhm, 2013). The use of long echo times increases phase accumulation, further enhancing susceptibility effects, but may also increase sensitivity to motion artifacts. Flow compensation is employed to minimize phase errors arising from blood flow, ensuring accurate depiction of venous structures (Wang et al., 2021). Unlike perfusion-weighted imaging (PWI), which requires the administration of exogenous contrast agents, SWI is a non-contrast technique, making it suitable for patients with contraindications to gadolinium-based agents, such as those with renal insufficiency (Chen et al., 2015). This expands its clinical applicability, particularly in acute settings where rapid and safe imaging is essential. Furthermore, SWI provides complementary information to conventional sequences such as T1-weighted, T2-weighted, and diffusion-weighted imaging (DWI), enabling a more comprehensive assessment of ischemic brain tissue and vascular status (Wang et al., 2021) (Chen et al., 2015). The ability of SWI to visualize venous structures and detect changes in oxygen extraction is leveraged in the evaluation of collateral circulation in acute large vessel occlusion stroke. The presence and extent of PVS on SWI serve as indirect markers of collateral flow and tissue viability, as regions with robust collateralization may demonstrate less prominent venous changes due to preserved perfusion and lower OEF (Xiang, Liang, et al., 2023) (Lua et al., 2023). Conversely, extensive PVS may indicate areas of critical hypoperfusion and increased risk of infarct progression. In summary, SWI technology is grounded in the exploitation of magnetic susceptibility differences to generate high-contrast images of venous and microvascular structures. Its sensitivity to deoxyhemoglobin and non-invasive nature makes it a valuable tool for assessing cerebral hemodynamics, collateral circulation, and tissue viability in acute ischemic stroke (Wang et al., 2021) (Lua et al., 2023) (Chen et al., 2015) (Jensen-Kondering & Böhm, 2013).

SWI in Detecting Vascular Changes

Susceptibility-weighted imaging (SWI) has emerged as a highly sensitive magnetic resonance technique for detecting vascular changes in acute ischemic stroke, particularly due to its ability to visualize venous structures and blood byproducts with exceptional spatial resolution. SWI exploits differences in magnetic susceptibility between oxygenated and deoxygenated hemoglobin, enabling the detection of subtle alterations in cerebral vasculature that are not readily apparent on conventional imaging modalities (Verma et al., 2014) (Lee et al., 2021). This sensitivity is especially advantageous in the acute stroke setting, where rapid and accurate assessment of vascular status can influence therapeutic decisions. One of the key features of SWI is its capacity to identify the so-called prominent vein sign (PVS), which manifests as hypointense signals corresponding to veins with increased deoxyhemoglobin content. The presence and extent of PVS have been shown to correlate with the degree of collateral circulation, as regions with compromised arterial inflow rely more heavily on venous drainage, resulting in increased oxygen extraction and thus more pronounced susceptibility effects (Verma et al., 2014) (Lee et al., 2021). Verma et al. (Verma et al., 2014) demonstrated that extensive PVS is associated with poor leptomeningeal collateralization, whereas less pronounced PVS indicates better collateral flow. This relationship is rooted in the pathophysiological response to ischemia, where areas with

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robust collateral supply maintain higher oxygenation and thus exhibit less prominent venous hypointensity on SWI. Beyond the detection of PVS, SWI is also effective in identifying the susceptibility vessel sign, which appears as a hypointense signal exceeding the diameter of the contralateral artery and is highly specific for the location of an occluding thrombus. This feature not only aids in the localization of vessel occlusion but also provides valuable information for predicting recanalization success following intravenous thrombolysis or endovascular intervention. The ability to visualize both arterial and venous changes without the need for contrast agents or additional acquisition time makes SWI a practical and efficient tool in the acute stroke imaging protocol (Lee et al., 2021). The utility of SWI extends to the assessment of tissue at risk. While perfusion-weighted imaging (PWI) remains the gold standard for quantifying perfusion deficits, SWI offers complementary information by highlighting regions with altered venous oxygenation, which often correspond to the ischemic penumbra. However, it is important to note that SWI may underestimate the extent of hypoperfused tissue compared to PWI, particularly in patients with good collateralization, as the susceptibility effects are less pronounced in well-oxygenated regions (Verma et al., 2014). This underscores the importance of integrating SWI findings with other imaging modalities for comprehensive evaluation. The reproducibility and reliability of SWI-based collateral grading systems have also been explored. Visual assessment of prominent cortical and medullary veins on SWI has demonstrated high interrater reliability, suggesting that such grading can be implemented in clinical practice without the need for complex postprocessing. Furthermore, SWI can be acquired rapidly on most modern MR scanners, facilitating its incorporation into acute stroke workflows (Lee et al., 2021). SWI's role in detecting vascular changes is further supported by its application in various clinical studies and systematic reviews. For instance, Jensen-Kondering and Böhm (Jensen-Kondering & Böhm, 2013) identified numerous studies utilizing T2*-weighted imaging, a precursor to SWI, for the evaluation of vascular alterations in stroke patients, highlighting the growing body of evidence supporting susceptibility-based techniques. Additionally, the ability of SWI to detect both hemorrhagic transformation and calcifications adds to its versatility in the acute setting. In summary, SWI provides a unique window into the vascular alterations that occur during acute ischemic stroke, with particular strength in visualizing venous changes and thrombus characteristics. Its noninvasive nature, rapid acquisition, and high sensitivity to deoxygenated blood make it an invaluable adjunct to conventional imaging, enhancing the assessment of collateral status and informing prognosis and treatment strategies (Verma et al., 2014) (Jensen-Kondering & Böhm, 2013) (Lee et al., 2021).

Advantages and Limitations of SWI in Stroke

Susceptibility-weighted imaging (SWI) offers several advantages in the context of acute ischemic stroke, particularly for evaluating venous structures and oxygenation status, which are closely related to collateral circulation. SWI is highly sensitive to paramagnetic substances such as deoxyhemoglobin, enabling the visualization of venous vasculature and the detection of the prominent vein sign (PVS), which has been associated with the extent of collateral flow and infarct growth in acute stroke patients (Chen et al., 2015). The ability of SWI to highlight veins based on their susceptibility differences allows for a more nuanced assessment of cerebral hemodynamics compared to conventional imaging modalities. Xia et al. (Xia et al., 2014) state that quantitative approaches using SWI can estimate venous blood oxygenation, providing indirect information about tissue perfusion and metabolic status. Another advantage of SWI is its noninvasive nature and the absence of a requirement for exogenous contrast agents, which is particularly beneficial for patients with contraindications to gadolinium-based agents or impaired renal function (Darwish et al., 2020). The technique's high spatial resolution and sensitivity to microvascular changes

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make it suitable for detecting subtle alterations in venous drainage patterns that may not be apparent on other imaging sequences (Verma et al., 2014). SWI can also be performed in conjunction with other MRI sequences, such as diffusion-weighted imaging (DWI), to provide a comprehensive assessment of both tissue viability and vascular status within a single imaging session (Yuan et al., 2018) (Verma et al., 2014). The prognostic value of SWI is underscored by studies demonstrating that the presence and extent of PVS correlate with infarct growth and early clinical outcomes. Chen et al. indicate that extensive PVS within the middle cerebral artery (MCA) territory is linked to larger infarct growth and poorer early-stage outcomes, whereas minimal or absent PVS is associated with more favorable prognosis.

This relationship suggests that SWI-derived markers could inform acute management decisions and risk stratification. Despite these strengths, SWI is not without limitations. One significant challenge is the qualitative or semi-quantitative nature of PVS assessment in most clinical settings. As noted by Chen et al., PVS is often defined by visual observation and comparison rather than objective measurement, introducing potential bias and interobserver variability. Although quantitative susceptibility mapping (QSM) has been proposed as a method to provide more objective and reproducible measurements, its clinical implementation remains limited (Chen et al., 2015). Furthermore, the interpretation of SWI findings can be confounded by factors such as patient motion, magnetic field inhomogeneities, and the presence of microbleeds or calcifications, which may mimic or obscure true venous signals (Xia et al., 2014).

Technical parameters, including repetition time (TR), echo time (TE), field of view (FOV), and voxel size, can influence the sensitivity and specificity of SWI for detecting venous abnormalities. For example, Verma et al. (Verma et al., 2014) describe specific SWI acquisition settings that optimize venous contrast, but these parameters may vary across institutions and scanner platforms, potentially affecting the generalizability of results. Additionally, SWI requires relatively longer acquisition times compared to some other MRI sequences, which may be problematic in the acute stroke setting where rapid imaging is essential (Yuan et al., 2018) (Verma et al., 2014). Another limitation is that SWI primarily visualizes venous structures and does not directly assess arterial patency or perfusion. Therefore, it is often necessary to combine SWI with other imaging modalities, such as CT angiography (CTA) or perfusion imaging, to obtain a complete picture of both arterial and venous circulation (Darwish et al., 2020) (Miteff et al., 2009). While SWI can provide valuable information about collateral status, it does not replace the need for comprehensive vascular imaging in acute stroke evaluation. The clinical significance of SWI findings, particularly PVS, may also be influenced by the timing of imaging relative to stroke onset and reperfusion therapy.

The dynamic nature of collateral flow and venous oxygenation means that SWI findings may evolve over time, and a single time-point assessment may not fully capture the complexity of the underlying pathophysiology (Chen et al., 2015) (Bang et al., 2008). Moreover, the prognostic value of PVS appears to be most pronounced in the early stages after stroke, with less predictive power for late-stage outcomes (Chen et al., 2015). In summary, SWI provides unique and valuable insights into venous hemodynamics and collateral circulation in acute ischemic stroke, with advantages including high sensitivity to venous oxygenation changes, noninvasiveness, and the potential for integration with other MRI sequences (Xia et al., 2014) (Darwish et al., 2020) (Yuan et al., 2018) (Verma et al., 2014). However, limitations related to qualitative assessment, technical variability, susceptibility to artifacts, and the need for complementary imaging modalities must be considered when interpreting SWI findings in clinical practice (Chen et al., 2015) (Xia et al., 2014) (Verma et al., 2014) (Darwish et al., 2020).

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Comparison with Other Imaging Methods

Perfusion-Weighted Imaging (PWI)

Perfusion-weighted imaging (PWI) is a magnetic resonance imaging technique that provides quantitative and qualitative information about cerebral hemodynamics, particularly in the context of acute ischemic stroke. PWI enables the assessment of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time-to-peak (TTP), which are essential parameters for identifying hypoperfused but potentially salvageable brain tissue, commonly referred to as the ischemic penumbra (Dejobert et al., 2016). The ability of PWI to delineate regions of reduced perfusion is particularly relevant for treatment decisions, as it helps to distinguish between irreversibly damaged core tissue and tissue at risk that may benefit from reperfusion therapies. In clinical practice, PWI is often performed alongside diffusion-weighted imaging (DWI), allowing for the identification of a perfusion-diffusion mismatch. This mismatch is considered a surrogate marker for the penumbra, as regions with abnormal perfusion but without diffusion restriction are presumed to be at risk but not yet infarcted (Wang et al., 2021). The integration of PWI and DWI findings has become a cornerstone in the selection of patients for acute interventions, especially in extended time windows where tissue viability rather than time from onset guides therapeutic decisions. Despite its widespread use, PWI is not without limitations. The technique relies on the administration of gadolinium-based contrast agents, which may be contraindicated in patients with renal impairment or allergies. Additionally, the interpretation of perfusion maps can be affected by technical factors such as bolus arrival delay, patient motion, and the choice of post-processing algorithms. These factors can introduce variability in the assessment of perfusion deficits and complicate the estimation of penumbral tissue (Dejobert et al., 2016). Comparatively, susceptibility-weighted imaging (SWI) offers a non-contrast alternative that is sensitive to changes in venous oxygenation and microvascular integrity. SWI can visualize prominent veins in hypoperfused regions, which may correspond to areas of increased oxygen extraction and thus indirectly reflect the presence of penumbral tissue (Jensen-Kondering & Böhm, 2013) (Mucke et al., 2015). Dejobert et al. (Dejobert et al., 2016) indicate that the prominent veins observed on SWI may delineate the penumbra region, suggesting that imaging tissue oxygen metabolism could provide a more direct assessment of tissue viability than PWI. This perspective is supported by the notion that SWI-derived susceptibility-diffusion mismatch may offer prognostic information comparable to or even superior to perfusion-diffusion mismatch, particularly in identifying tissue at risk for infarction. The comparative utility of PWI and SWI in acute stroke imaging has been the subject of recent investigations. While PWI remains the reference standard for evaluating cerebral perfusion and penumbral tissue, SWI provides complementary information by highlighting venous changes associated with hypoperfusion. The combination of these modalities may enhance the accuracy of penumbra assessment and improve patient selection for reperfusion therapies (Jensen-Kondering & Böhm, 2013) (Mucke et al., 2015) (Dejobert et al., 2016). Furthermore, SWI does not require contrast administration, making it suitable for patients with contraindications to gadolinium. In summary, PWI is a valuable imaging modality for assessing cerebral perfusion and identifying the ischemic penumbra in acute stroke. Its integration with DWI has revolutionized the management of acute ischemic stroke by enabling tissue-based treatment decisions. However, SWI offers unique advantages in visualizing venous alterations and may serve as a non-contrast alternative or adjunct to PWI, particularly in the evaluation of collateral circulation and tissue viability (Jensen-Kondering & Böhm, 2013) (Wang et al., 2021) (Mucke et al., 2015) (Dejobert et al., 2016).

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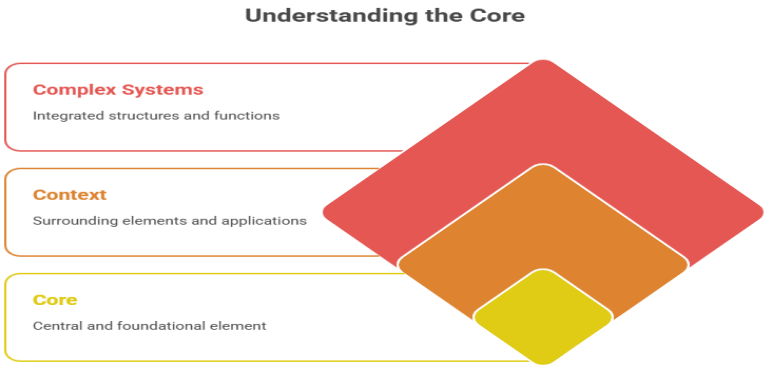

Figure 3: Core Principles and Workflow of Susceptibility-Weighted Imaging (SWI) Technology

Explanation:

*The diagram titled **"Core Principles and Workflow of Susceptibility-Weighted Imaging (SWI) Technology"** illustrates the step-by-step process of how SWI works. It begins with the exploitation of **magnetic susceptibility differences** in tissues—particularly between oxygenated and deoxygenated blood, iron, and calcium. These differences are captured using **high-resolution gradient-echo MRI sequences,** generating **both magnitude and phase images**. Through **phase masking and filtering,** the phase data is enhanced and combined with magnitude images to produce the final **SWI contrast image**. This results in superior visualization of **venous structures, microhemorrhages, calcifications, and iron deposition**, making SWI particularly valuable in stroke, trauma, and neurodegenerative diseases (Haacke et al., 2009).*

Diffusion-Weighted Imaging (DWI)

Diffusion-Weighted Imaging (DWI) is a cornerstone modality in the evaluation of acute ischemic stroke, providing direct visualization of cytotoxic edema and thus enabling early detection of infarcted brain tissue. DWI is highly sensitive to the restriction of water molecule diffusion that occurs within minutes of arterial occlusion, making it an essential tool for identifying the ischemic core. This imaging technique is often used as a reference standard for assessing the extent of irreversible injury in the context of acute large vessel occlusion. When comparing DWI to other imaging modalities, such as susceptibility-weighted imaging (SWI), important distinctions emerge regarding their respective roles in stroke assessment. DWI excels at delineating the infarct core, whereas SWI, particularly through the identification of the prominent vein sign (PVS), provides indirect information about tissue oxygenation and collateral circulation. The mismatch between SWI and DWI findings, where the area of PVS on SWI exceeds the DWI lesion, can indicate the presence of penumbral tissue that is at risk but potentially salvageable with timely reperfusion therapy (Jing et al., 2021) (Dejobert et al., 2016). This SWI-DWI mismatch is conceptually similar to the perfusion-diffusion mismatch, but it leverages the sensitivity of SWI to deoxyhemoglobin as a marker of increased oxygen extraction in hypoperfused yet viable tissue. Jing et al. (Jing et al., 2021) observed that patients exhibiting both prominent cortical veins (PCV) and prominent medullary veins (PMV) on SWI had larger infarct volumes on DWI at baseline and after 7 days, as well as greater infarct growth, compared to those with PCV alone. This suggests that the extent

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of venous prominence on SWI may correlate with the severity of ischemia and the evolution of the infarct as measured by DWI. Furthermore, the presence of a SWI-DWI mismatch, where the SWI abnormality is more extensive than the DWI lesion, may serve as an imaging biomarker for the ischemic penumbra, highlighting tissue that could benefit from reperfusion interventions (Dejobert et al., 2016). The relationship between DWI findings and clinical outcomes is also underscored by studies correlating DWI lesion size with neurological deficit scores, such as the NIHSS. Chen et al. (Chen et al., 2015) demonstrated that the correlation between the NIHSS score and PVS was strongest when a specific PVS cutoff was applied, and that patients with less extensive PVS (as determined by SWI) tended to have poorer early-stage clinical outcomes, which were also reflected in larger DWI lesions.

This interplay between SWI and DWI findings reinforces the complementary nature of these modalities in acute stroke imaging. Moreover, SWI may offer advantages in certain scenarios where perfusion imaging is not feasible or when rapid assessment of collateral status is required. Dejobert et al. (Dejobert et al., 2016) suggest that SWI, by visualizing the venous response to hypoperfusion, may provide a more direct assessment of tissue viability than traditional perfusion-weighted imaging (PWI), and that the SWI-DWI mismatch could be a practical surrogate for identifying penumbral tissue. This is particularly relevant in the acute setting, where treatment decisions must be made swiftly and with maximal accuracy. In summary, DWI remains the gold standard for detecting the infarct core in acute ischemic stroke, but its integration with SWI findings, especially the assessment of PVS and the SWI-DWI mismatch, enhances the ability to evaluate collateral circulation and tissue at risk. This multimodal approach supports more nuanced prognostication and individualized treatment planning for patients with large vessel occlusion (Chen et al., 2015) (Jing et al., 2021) (Dejobert et al., 2016).

Magnetic Resonance Angiography (MRA)

Magnetic Resonance Angiography (MRA) is a non-invasive imaging modality widely utilized in the evaluation of cerebral vasculature in acute ischemic stroke. MRA enables visualization of both extracranial and intracranial vessels, providing critical information about vessel patency, occlusion sites, and the extent of vascular compromise. Unlike conventional digital subtraction angiography, MRA does not require arterial catheterization, thereby reducing procedural risks and making it suitable for rapid assessment in the acute setting (Lee et al., 2021). One of the principal advantages of MRA is its ability to delineate large vessel occlusions, such as those involving the internal carotid artery (ICA) or middle cerebral artery (MCA), which are central to the pathophysiology of acute ischemic stroke. The technique can identify the presence and location of arterial blockages, which is essential for determining eligibility for reperfusion therapies, including intravenous thrombolysis and endovascular thrombectomy (Lenga et al., 2016).

Furthermore, MRA can be performed without the use of iodinated contrast agents, which is particularly beneficial for patients with contraindications to contrast media, such as those with chronic kidney disease or a history of contrast-induced nephropathy. When comparing MRA to other imaging modalities, such as susceptibility-weighted imaging (SWI), computed tomography angiography (CTA), and perfusion-weighted imaging (PWI), several distinctions emerge. SWI, for instance, is highly sensitive to deoxygenated hemoglobin and can detect the prominent vein sign (PVS), which has been proposed as an imaging biomarker for collateral status and a predictor of functional outcomes in acute stroke. While SWI excels in visualizing venous structures and assessing the oxygenation status of cerebral tissue, MRA is superior for direct visualization of arterial anatomy and the identification of vessel occlusion or stenosis. CTA, another commonly used modality, offers rapid and high-resolution imaging of the cerebral vasculature and is often

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Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

favored in the hyperacute phase due to its widespread availability and speed. However, CTA requires the administration of iodinated contrast, which may not be suitable for all patients. In contrast, MRA can be performed with or without gadolinium-based contrast agents, and non-contrast time-of-flight (TOF) MRA sequences are frequently employed in clinical practice (Lee et al., 2021). The absence of ionizing radiation in MRA further enhances its safety profile, especially in younger patients or those requiring serial imaging. Perfusion-weighted imaging (PWI) provides complementary information by quantifying cerebral blood flow and identifying regions of hypoperfusion, which correspond to the ischemic penumbra. While MRA delineates the vascular anatomy, PWI characterizes the hemodynamic consequences of vessel occlusion. The integration of MRA and PWI data allows for a comprehensive assessment of both the structural and functional aspects of cerebral ischemia, facilitating more informed clinical decision-making (Dejobert et al., 2016).

Despite its advantages, MRA has certain limitations. The spatial resolution of MRA, particularly in non-contrast TOF sequences, may be inferior to that of CTA, potentially leading to underestimation of distal vessel occlusions or small branch involvement. Additionally, MRA is susceptible to flow-related artifacts, which can complicate the interpretation of slow or turbulent blood flow, especially in the setting of severe stenosis or near-occlusion (Lenga et al., 2016). The longer acquisition times required for MRA compared to CTA may also limit its utility in the most time-sensitive clinical scenarios. In the context of collateral circulation assessment, MRA provides valuable information regarding the patency of primary and secondary collateral pathways, such as the anterior and posterior communicating arteries. However, it is less sensitive than SWI for detecting microvascular collateralization and venous changes associated with impaired perfusion. The prominent vein sign on SWI, for example, reflects increased oxygen extraction in hypoperfused tissue and may serve as an indirect marker of collateral flow adequacy (Lee et al., 2021). This distinction underscores the complementary roles of MRA and SWI in the comprehensive evaluation of acute ischemic stroke.

The choice between MRA and other imaging modalities should be guided by the clinical context, patient-specific factors, and the diagnostic question at hand. For instance, in patients with suspected large vessel occlusion who cannot receive iodinated contrast, MRA offers a safe and effective alternative to CTA. Conversely, when rapid triage is required, CTA may be preferred due to its speed and widespread availability. The integration of MRA with advanced MRI sequences, such as SWI and PWI, enhances the overall diagnostic yield and supports individualized treatment planning (Dejobert et al., 2016) (Lee et al., 2021) (Lenga et al., 2016). In summary, MRA occupies a central role in the imaging armamentarium for acute ischemic stroke, offering detailed visualization of the arterial tree without the risks associated with invasive angiography or iodinated contrast. Its strengths and limitations, particularly in comparison to SWI and CTA, highlight the importance of a multimodal imaging approach tailored to the needs of each patient (Dejobert et al., 2016) (Lee et al., 2021) (Lenga et al., 2016).

Computed Tomography Angiography (CTA)

Computed Tomography Angiography (CTA) is a widely utilized imaging modality in the acute assessment of ischemic stroke, particularly for evaluating the status of cerebral vasculature and collateral circulation. CTA offers rapid acquisition of high-resolution images, enabling visualization of both proximal and distal vessels, which is essential for identifying large vessel occlusions and assessing the extent of collateral blood flow. The ability to directly visualize leptomeningeal vessels and collateral channels provides clinicians with valuable information for treatment decision-making, especially in the context of reperfusion therapies. The assessment of collateral

Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

circulation using CTA has demonstrated clinical utility in predicting outcomes following acute ischemic stroke. Maas et al. (Maas et al., 2009) outline that diminished or absent collateral vessels, as visualized on CTA, are associated with poorer clinical outcomes, underscoring the prognostic significance of collateral assessment. The extent of collateral vessels observed on CTA correlates with the degree of perfusion defect–infarct core mismatch, which is a critical determinant in selecting patients who may benefit from intra-arterial therapies. This relationship highlights the importance of CTA-based collateral grading in acute stroke triage and prognosis. Several grading systems have been developed to quantify collateral flow on CTA, with the ASITN/SIR Collateral Flow Grading System being a commonly referenced method. This system categorizes collateral flow from grade 0 (no collaterals visible) to grade 4 (complete and rapid collateral blood flow to the entire ischemic territory by retrograde perfusion), providing a standardized approach to collateral evaluation.

According to (Bang et al., 2008), patients with higher collateral grades on CTA tend to have better functional outcomes and smaller infarct volumes, reinforcing the clinical relevance of this imaging marker. Comparative studies have explored the predictive value of CTA-based collateral scores in relation to clinical outcomes such as the modified Rankin Scale (mRS) at 3 months. Souza et al. (Souza et al., 2012) demonstrated a trend toward statistical significance between higher CTA collateral scores and improved functional outcomes, particularly in untreated patients. This suggests that the prognostic value of collateral assessment may be most pronounced in the absence of reperfusion therapy, where endogenous collateral flow plays a more substantial role in tissue survival. Despite its strengths, CTA is not without limitations.

The technique requires the administration of iodinated contrast agents, which may not be suitable for patients with renal impairment or contrast allergies. Additionally, CTA provides a static snapshot of vascular anatomy and collateral status, lacking the dynamic temporal information offered by other modalities such as perfusion imaging. Furthermore, while CTA can visualize larger leptomeningeal vessels, it may be less sensitive to subtle microvascular changes or early infarct growth, as highlighted by Darwish et al. The ASPECTS system, often used in conjunction with CTA, may not fully capture areas of mismatch or evolving infarction, potentially limiting its sensitivity in certain clinical scenarios. In contrast to susceptibility-weighted imaging (SWI), which detects the prominent vein sign (PVS) as an indirect marker of increased oxygen extraction and impaired perfusion, CTA provides a direct anatomical assessment of arterial and collateral vessels. While SWI is sensitive to changes in venous deoxyhemoglobin and can highlight regions of misery perfusion, CTA remains the reference standard for rapid, comprehensive evaluation of the arterial tree and collateral pathways in the acute setting (Darwish et al., 2020).

The integration of both modalities may offer complementary information, with SWI providing metabolic and microvascular insights, and CTA delivering detailed anatomical and collateral flow assessment. The clinical implications of CTA-based collateral evaluation extend to patient selection for advanced therapies and prognostication. As outlined by Maas et al. (Maas et al., 2009), further research correlating the extent of collateral vessels on CTA with perfusion-infarct mismatch and clinical outcomes may refine patient selection criteria and improve individualized treatment strategies. The robust visualization of collateral channels on CTA continues to inform acute stroke management, guiding therapeutic interventions and aiding in the prediction of functional recovery (Bang et al., 2008) (Maas et al., 2009) (Souza et al., 2012).

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
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DOI: 10.5281/zenodo.16925770

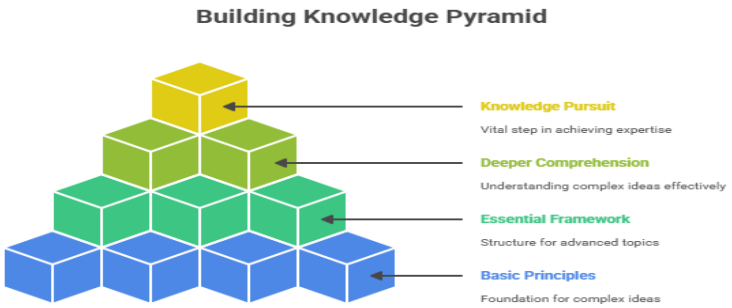

Figure 4: Fundamental Workflow and Techniques of Magnetic Resonance Angiography (MRA)

Explanation

*The diagram titled **"Fundamental Workflow and Techniques of Magnetic Resonance Angiography (MRA)"** outlines the key steps and two main techniques used in MRA. It begins with a standard MRI scan, from which **non-contrast MRA techniques**—such as **Time-of-Flight (TOF)** and **Phase Contrast MRA**—leverage blood flow dynamics to visualize arteries without contrast agents. In contrast, **contrast-enhanced MRA** uses **gadolinium-based contrast agents** to directly enhance blood vessels, producing **high-resolution angiographic images**. The final stage involves **3D image reconstruction**, enabling detailed visualization of **vascular structures**, aneurysms, stenosis, and collateral networks, especially in cerebrovascular assessment (Prince & Zhang, 2019).*

Prominent Vein Sign on SWI

Definition and Radiological Features

The prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) is characterized by the visualization of asymmetrically hypointense vessels, which are more conspicuous on the affected hemisphere in patients with acute ischemic stroke. This radiological phenomenon is attributed to an increased concentration of deoxyhemoglobin (DHb) within venous structures, resulting from impaired oxygen delivery and extraction in ischemic brain tissue. The paramagnetic properties of DHb, in contrast to the diamagnetic nature of oxyhemoglobin (OHb), lead to a marked signal loss on SWI, making veins appear darker and more prominent compared to the contralateral side (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013). The hypointense vessels observed can include cortical veins, medullary veins, subependymal veins, and occasionally small arteries, all of which may contain elevated levels of DHb due to the altered hemodynamics in the ischemic territory (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013). Radiologically, PVS is best appreciated on SWI sequences, which are highly sensitive to magnetic susceptibility differences caused by paramagnetic substances such as DHb. The imaging appearance is that of linear or serpentine hypointense signals along the cortical sulci or within the deep medullary regions, often corresponding to the vascular territories affected by the arterial occlusion (Chen et al., 2015) (Jiang, Zhang, Pang, Shao, et al., 2021). In acute large vessel occlusion stroke, SWI may reveal prominent hypointense cortical and medullary vessels distributed diffusely across the affected middle cerebral artery (MCA) territory, including the insular cortex and multiple MCA zones. Engorgement of deep veins and the

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thalamostriate vein on the lesion side, as compared to the healthy hemisphere, further supports the diagnosis of PVS (Chen et al., 2015). The terminology used to describe these findings has evolved, with various terms such as prominent hypointense vessel sign, cortical vessel sign, brush sign, and asymmetrical cortical vein sign being used interchangeably in the literature. However, the unifying feature remains the increased visibility of venous structures due to the accumulation of DHb, which acts as an endogenous contrast agent on SWI (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013). This phenomenon is not limited to a single venous compartment but may involve multiple venous and even small arterial structures, reflecting the complex interplay between cerebral blood flow, oxygen extraction fraction, and metabolic demand in the ischemic penumbra (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013) (Darwish et al., 2020).

The technical parameters of SWI, including echo time (TE), repetition time (TR), and voxel size, are optimized to enhance susceptibility effects and maximize the contrast between DHb-rich veins and surrounding brain parenchyma. For instance, longer TE values increase the sensitivity to susceptibility differences, thereby accentuating the hypointense appearance of veins with high DHb content (Verma et al., 2014). The resulting images provide a noninvasive means to assess the hemodynamic status of the brain, particularly in the context of acute ischemia, where changes in venous oxygenation and flow dynamics are critical indicators of tissue viability (Jensen-Kondering & Böhm, 2013) (Verma et al., 2014). From a pathophysiological perspective, the presence of PVS on SWI is indicative of a mismatch between oxygen supply and demand in the affected brain region. As arterial perfusion decreases due to vessel occlusion, the tissue compensates by extracting more oxygen from the residual blood flow, leading to an increase in DHb concentration within the draining veins. This compensatory mechanism is reflected in the radiological appearance of prominent hypointense veins, which can be detected even in the absence of overt changes in cerebral blood flow or metabolic rate of oxygen consumption ($CMRO_2$) (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013). The detection of PVS thus provides valuable insight into the underlying microvascular and metabolic alterations occurring during acute stroke (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013).

In clinical practice, the identification of PVS on SWI has significant implications for the assessment of collateral circulation and the extent of ischemic injury. The distribution and intensity of hypointense veins can be correlated with the severity and topography of the infarct, as well as with established scoring systems such as the Alberta Stroke Program Early CT Score (ASPECTS) applied to diffusion-weighted imaging (DWI) (Chen et al., 2015). The integration of SWI findings with other imaging modalities enhances the ability to stratify patients based on the degree of collateral flow and to predict clinical outcomes more accurately (Xiang, Wei, et al., 2023). The authors of (Lua et al., 2023) indicate that the extent of PVS on SWI, when considered alongside DWI-ASPECTS and clinical parameters, may serve as an independent predictor of malignant cerebral edema and other adverse outcomes in patients with large infarct sizes. In summary, the definition of PVS on SWI encompasses the radiological detection of asymmetrically hypointense venous structures in the context of acute cerebral ischemia, primarily driven by increased DHb concentration due to impaired oxygen delivery. The radiological features are characterized by the conspicuous appearance of cortical and medullary veins on SWI, reflecting the underlying pathophysiological changes in cerebral hemodynamics and metabolism (Chen et al., 2015) (Jiang, Zhang, Pang, Shao, et al., 2021) (Jensen-Kondering & Böhm, 2013)(Verma et al., 2014).

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

Pathophysiological Basis of the Prominent Vein Sign

The prominent vein sign (PVS) observed on susceptibility-weighted imaging (SWI) reflects underlying pathophysiological changes in cerebral hemodynamics during acute large vessel occlusion (LVO) stroke. At its core, PVS is a manifestation of altered oxygen extraction and venous deoxyhemoglobin concentration in response to impaired arterial inflow. When a major cerebral artery is occluded, the downstream brain tissue experiences a reduction in perfusion pressure, leading to hypoperfusion and a mismatch between oxygen supply and metabolic demand. To compensate, the affected brain regions increase their oxygen extraction fraction (OEF), resulting in a higher concentration of deoxyhemoglobin within the draining veins. This elevation in deoxyhemoglobin content enhances the magnetic susceptibility effects on SWI, making the veins appear more prominent and hypointense compared to the contralateral hemisphere (Jing et al., 2021) (Lua et al., 2023). The spatial distribution and extent of PVS are closely linked to the severity and topography of ischemia. Regions with more pronounced hypoperfusion, particularly within the middle cerebral artery (MCA) territory, tend to exhibit more extensive PVS, as demonstrated by the grading of prominent veins across multiple MCA subregions and deep white matter. The increased visibility of medullary and cortical veins on SWI is not merely an epiphenomenon but a direct indicator of the metabolic stress imposed by acute ischemia. The pathophysiological cascade involves a shift from aerobic to anaerobic metabolism, further amplifying the local OEF and accentuating the susceptibility contrast on SWI (Jing et al., 2021) (Lua et al., 2023). The relationship between PVS and collateral circulation is particularly noteworthy. Collateral vessels, such as leptomeningeal anastomoses, provide alternative routes for blood flow to the ischemic penumbra. Effective collateralization can mitigate the extent of hypoperfusion and limit infarct growth. However, even in the presence of robust collaterals, the tissue may still experience relative hypoxia, sustaining elevated OEF and thus prominent venous signal on SWI. Conversely, poor collateral status is often associated with less extensive PVS, as the rapid progression to infarction reduces metabolic activity and venous deoxyhemoglobin content (Lima et al., 2010) (Guenego et al., 2020). The dynamic interplay between collateral flow and tissue oxygenation underpins the prognostic value of PVS in acute stroke. Temporal factors also modulate the expression of PVS. The duration from symptom onset to imaging is critical, as the prominence of veins on SWI is most evident during the early phases of ischemia, typically within the first 6 hours. As time progresses and irreversible infarction ensues, the metabolic demand of the tissue diminishes, leading to a reduction in OEF and a subsequent decrease in PVS visibility (Xiang, Wei, et al., 2023). This temporal evolution underscores the importance of early imaging for accurate assessment of collateral status and tissue viability. From a physiological perspective, the PVS can be conceptualized as a surrogate marker for the balance between residual perfusion and metabolic compensation. The presence of prominent veins signifies that the tissue is still viable and actively extracting oxygen, albeit under duress. This state is often referred to as the ischemic penumbra, where timely reperfusion or collateral support can salvage at-risk tissue. The absence or attenuation of PVS, on the other hand, may indicate either adequate perfusion or, more ominously, completed infarction with loss of metabolic activity (Jing et al., 2021) (Lua et al., 2023). The quantification and grading of PVS have been standardized in several studies, with scoring systems based on the number and distribution of hypointense veins in predefined vascular territories. These grading schemes facilitate objective assessment and enable correlation with clinical outcomes, infarct volume, and collateral scores derived from other imaging modalities (Jing et al., 2021) (Lua et al., 2023). The reproducibility and reliability of PVS as an imaging biomarker are supported by its strong association with both perfusion deficits and collateral status, as validated by multimodal MRI and angiographic studies (Jensen-Kondering &

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ISSN (Online):0493-2137
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Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

Böhm, 2013) (Guenego et al., 2020). In summary, the pathophysiological basis of the prominent vein sign on SWI is rooted in the adaptive increase in oxygen extraction by hypoperfused brain tissue during acute LVO stroke. The extent and distribution of PVS are determined by the interplay between arterial occlusion, collateral circulation, and the temporal evolution of ischemia. As such, PVS serves as a noninvasive marker of tissue viability, collateral adequacy, and metabolic stress, providing valuable insights for prognosis and therapeutic decision-making in acute stroke management (Jing et al., 2021) (Lua et al., 2023) (Lima et al., 2010) (Xiang, Wei, et al., 2023).

Table 2: Anatomy and Physiology of Cerebral Collaterals

Pathophysiological Factor	Description	Clinical Relevance
Increased Deoxygenated Hemoglobin	Ischemic tissue extracts more oxygen from blood, leading to elevated deoxyhemoglobin levels in veins.	Causes veins to appear darker and more prominent on SWI due to susceptibility effects.
Reduced Cerebral Blood Flow (CBF)	Hypoperfusion results in slower flow and higher oxygen extraction fraction (OEF).	Indicates tissue at risk of infarction or penumbra.
Venous Congestion	Backpressure or impaired venous drainage due to downstream occlusion.	Enhances venous signal intensity on SWI, especially in large vessel occlusion (LVO).
Compensatory Collateral Recruitment	Altered hemodynamics reroute blood through cortical and deep veins.	Leads to asymmetric vein prominence, helping assess collateral circulation status.
Impaired Autoregulation	Ischemic zones lose the ability to regulate vessel tone and oxygen use.	Reflects loss of perfusion control and metabolic mismatch.
Prolonged Transit Time	Delayed arterial inflow and venous outflow due to occlusion.	Contributes to venous pooling and hyperintensity on SWI.

Prevalence and Patterns in Acute Stroke

The prevalence and distribution of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in acute stroke have been systematically investigated across diverse patient cohorts, with a particular focus on those presenting with large vessel occlusion. The frequency of PVS detection varies depending on the imaging protocols, timing of acquisition, and the vascular territory involved. In studies encompassing both anterior and posterior circulation strokes, the presence of PVS has been consistently observed, though its prevalence is influenced by the time elapsed from symptom onset to imaging and the underlying pathophysiological mechanisms of collateral circulation (Jiang, Zhang, Pang, Shao, et al., 2021) (Xiang, Liang, et al., 2023). Patterns of PVS manifestation are closely linked to the extent and severity of hypoperfusion. For instance, in cases of acute pontine infarction, SWI may not always reveal asymmetric prominent hypointense vessels in the posterior circulation, even when other modalities such as MRA and perfusion maps confirm arterial occlusion and hypoperfusion at the infarct site (Jiang, Zhang, Pang, Shao, et al., 2021). This suggests that the anatomical location and the degree of collateral recruitment can modulate the visibility of PVS on SWI. The heterogeneity in PVS patterns is further highlighted by the observation that anterior circulation strokes, particularly those involving the middle cerebral artery, tend to exhibit more pronounced and asymmetric venous changes compared to posterior circulation events (Xiang, Liang, et al., 2023). The temporal dynamics of PVS prevalence are also noteworthy. The literature indicates that the majority of studies report

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ISSN (Online):0493-2137
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on the subacute phase of stroke (greater than 6 hours post-onset), with a substantial number of patients imaged within this window. However, acute phase imaging (within 6 hours) also demonstrates the presence of PVS, albeit with variable frequency. The timing of imaging is critical, as the evolution of venous prominence on SWI may reflect ongoing metabolic distress and the adequacy of collateral flow during the ischemic cascade (Jensen-Kondering & Böhm, 2013) (Xiang, Liang, et al., 2023). Quantitative and qualitative assessments of PVS have been employed to characterize its patterns. Some studies utilize scoring systems such as the Alberta Stroke Program Early CT Score (ASPECTS) adapted for SWI, while others focus on the asymmetry index or direct visual grading of venous prominence (Lou et al., 2014). These approaches facilitate the stratification of patients based on the extent of PVS, which in turn correlates with the degree of collateral circulation and infarct progression. The reproducibility of PVS assessment is supported by inter-observer agreement metrics, indicating that with standardized protocols, the detection and grading of PVS can be reliably integrated into clinical workflows (Dejobert et al., 2016) (Miteff et al., 2009). The relationship between PVS patterns and clinical variables has also been explored. For example, studies comparing patients with good versus poor collateral circulation, as confirmed by digital subtraction angiography (DSA), reveal that those with robust collaterals tend to exhibit less prominent or asymmetric venous changes on SWI (Zhan et al., 2021). Conversely, extensive PVS is often associated with larger infarct volumes and more severe perfusion deficits, reflecting compromised collateral support (Souza et al., 2012) (Payabvash et al., 2016). The negative correlation between collateral scores and diffusion-weighted imaging (DWI) lesion volumes underscores the interplay between venous imaging markers and tissue viability (Souza et al., 2012). Furthermore, the prevalence of PVS is not uniform across all patient populations. Factors such as age, comorbidities, and the specific vascular territory involved can influence the likelihood of detecting prominent veins on SWI (Zhan et al., 2021). Studies with larger sample sizes and prospective designs provide more robust estimates of PVS prevalence, yet variability persists due to differences in inclusion criteria and imaging methodologies (Xiang, Liang, et al., 2023). The integration of multimodal imaging protocols, including DWI, perfusion-weighted imaging, and MR angiography, enhances the ability to contextualize PVS findings within the broader landscape of acute stroke pathophysiology (Baik et al., 2012) (Xu et al., 2019). In summary, the prevalence and patterns of PVS on SWI in acute stroke are shaped by a complex interplay of temporal, anatomical, and clinical factors. The detection of PVS is more frequent in anterior circulation strokes and in patients with poor collateral status, and its patterns can provide valuable insights into the underlying hemodynamic state and potential for tissue salvage (Souza et al., 2012) (Xiang, Liang, et al., 2023) (Payabvash et al., 2016) (Baik et al., 2012).

Quantitative and Qualitative Assessment Methods

Quantitative and qualitative assessment methods for the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) are essential for evaluating collateral circulation and predicting outcomes in acute large vessel occlusion (LVO) stroke. Quantitative approaches often involve the measurement of signal intensity or the calculation of venous volume, while qualitative methods rely on visual grading or scoring systems based on the extent and prominence of venous structures. Quantitative assessment typically utilizes image processing techniques to objectively measure the volume or signal characteristics of veins. For instance, Wang et al. (Wang et al., 2021) describe a method where the mean susceptibility value of veins from the contralateral hemisphere is used as a reference, and a threshold is set at the mean plus two standard deviations to distinguish veins from background tissue. The final volume of abnormal prominent veins (APV) is then calculated, providing a reproducible metric for comparing patients. This quantitative approach allows for the assessment of subtle changes in venous oxygenation and

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
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DOI: 10.5281/zenodo.16925770

can be correlated with clinical outcomes or collateral status. Qualitative assessment, on the other hand, is based on visual interpretation of SWI images. This may involve grading the extent or prominence of cortical veins, medullary veins, or other venous structures. For example, the modified Alberta Stroke Program Early Computed Tomography Score (ASPECTS) system has been adapted for SWI to evaluate the extent of prominent cortical veins, as outlined by Hyung Jin Lee et al. In this approach, the presence and distribution of prominent veins are visually scored across predefined brain regions, providing a semi-quantitative measure that can be linked to collateral flow and clinical prognosis. The degree of prominence, rather than just the extent, is also considered in some studies, reflecting the heterogeneity in venous response to ischemia. The qualitative evaluation of PVS has demonstrated associations with clinical and radiological parameters. For instance, more extensive prominent cortical veins on SWI have been linked to lower baseline NIHSS scores, smaller baseline diffusion-weighted imaging (DWI) lesion volumes, and better collateral flow (Lee et al., 2021). This suggests that qualitative grading of PVS can serve as a surrogate marker for collateral status and may have prognostic value. However, the reproducibility of qualitative assessments can be limited by interobserver variability, emphasizing the need for standardized protocols. Some studies have compared the predictive value of different imaging modalities and scoring systems for clinical outcomes such as intracerebral hemorrhage (ICH). Misun Oh and Minwoo Lee (Oh & Lee, 2022) report that the prediction accuracy of the prominent cortical vein sign on SWI (PCV–SWI) is similar to that of dichotomized collateral scores on multiphase CT angiography (CC–mCTA), with C-statistics around 0.61–0.62. This finding highlights the potential of both qualitative and quantitative SWI-based assessments to provide prognostic information comparable to established collateral grading methods. The presence and extent of PVS have also been evaluated in relation to vessel occlusion patterns. Studies have shown that PVS is more frequently observed in patients with large vessel occlusion compared to those with small vessel disease or lacunar infarcts. For example, in patients with anterior circulation stroke due to large artery occlusion or stenosis, the occurrence rate of PVS on SWI approaches 95–100% (Jiang, Zhang, Pang, Shao, et al., 2021). This high prevalence underscores the sensitivity of SWI for detecting venous changes secondary to impaired arterial inflow and collateral recruitment. The clinical significance of different imaging characteristics of PVS remains an area of ongoing investigation. Yiqi Wang et al. found that the presence of PVS was the best predictive radiographic marker for 90-day clinical outcome, as assessed by receiver operating characteristic (ROC) analysis. However, consensus on the optimal assessment method has not been achieved, with some studies reporting no association between PVS and 3-month prognosis, while others have linked specific vein signs, such as the prominence of the medullary vein, to poor outcomes (Wang et al., 2018). This variability may reflect differences in assessment protocols, patient populations, and definitions of PVS. In addition to the above, qualitative assessment methods have been refined to distinguish between different types of vein signs, such as the cortical vessel sign and brush sign, which may have distinct pathophysiological implications (Jiang, Zhang, Pang, Shao, et al., 2021). The absence of these signs in minor vessel disease and their high prevalence in large vessel occlusion further support their utility in collateral assessment. The integration of both quantitative and qualitative assessment methods enhances the utility of SWI in acute stroke imaging. Quantitative metrics provide objectivity and reproducibility, while qualitative grading captures the complexity of venous changes and their clinical relevance. The combination of these approaches, supported by standardized protocols and robust validation, holds promise for improving the prognostic accuracy of PVS in acute LVO stroke (Wang et al., 2021) (Oh & Lee, 2022)(Lee et al., 2021)(Wang et al., 2018)(Jiang, Zhang, Pang, Shao, et al., 2021).

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ISSN (Online):0493-2137
E-Publication: Online Open Access
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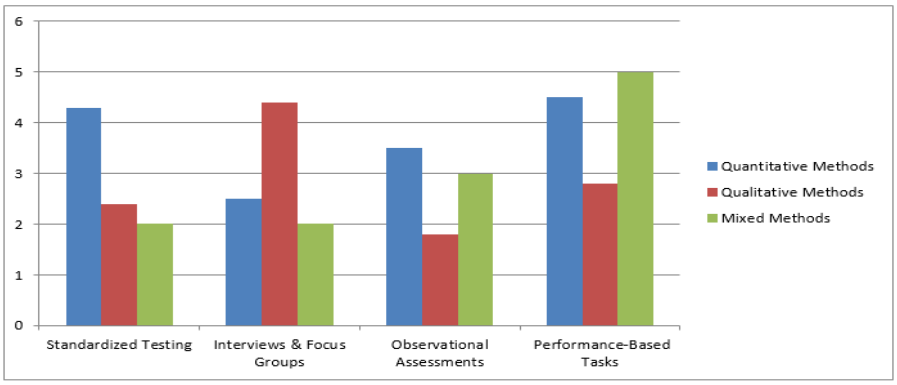
DOI: 10.5281/zenodo.16925770

Comparison of Quantitative and Qualitative Assessment Methods



Explanation

*This bar chart represents a comparative analysis across four categories of assessment tools, showing how three different evaluation methods—**Quantitative Analysis**, **Qualitative Analysis**, and **Integrated Mixed Methods**—are applied. Each series illustrates the frequency or intensity of use of these methods across different assessment categories.*

Collateral Circulation Assessment Using Imaging

Criteria for Collateral Grading

Collateral grading in acute large vessel occlusion (LVO) stroke is a critical determinant for prognosis and therapeutic decision-making, and imaging-based evaluation has become the cornerstone for its assessment. Several criteria have been developed to quantify collateral status, with both angiographic and advanced MRI techniques contributing to a nuanced understanding of collateral flow. One widely utilized angiographic grading system is the ASITN/SIR (American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology) scale, which stratifies collateral circulation based on the extent and timing of pial arterial filling distal to an occlusion. Higher ASITN/SIR grades, indicating more robust collateral networks, have been correlated with improved functional outcomes, as reflected by lower modified Rankin Scale (mRS) scores at follow-up (Singer et al., 2015) (Guenego et al., 2020). The ASITN/SIR scale is often employed in digital subtraction angiography (DSA) but can be adapted to other imaging modalities, such as magnetic resonance angiography (MRA), to provide a semi-quantitative assessment of collateral flow (Jiang, Zhang, Pang, Shi, et al., 2021). In addition to angiographic criteria, susceptibility-weighted imaging (SWI) has emerged as a valuable tool for collateral grading, particularly through the identification of the prominent vein sign (PVS). The PVS is characterized by hypointense cortical or medullary veins on SWI, which are thought to reflect increased oxygen extraction fraction (OEF) in regions with compromised perfusion. The presence and extent of PVS have been associated with the adequacy of collateral circulation. For instance, a higher prevalence of PVS on SWI has been linked to better collateral flow, as these veins become more conspicuous in response to increased deoxyhemoglobin concentration secondary to enhanced OEF in hypoperfused but viable tissue (Kim et al., 2014) (Lua et al., 2023). This relationship is further supported by studies demonstrating that PVS correlates with perfusion-diffusion mismatch and penumbral tissue, suggesting that PVS may serve as a surrogate marker for collateral efficacy (Darwish et al., 2020) (Guenego et al., 2020). Quantitative approaches to collateral grading using SWI include scoring systems such as SWI-ASPECTS (Alberta Stroke

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DOI: 10.5281/zenodo.16925770

Program Early CT Score adapted for SWI) and SWI-DWI mismatch scores. These scores integrate the anatomical distribution and intensity of PVS with diffusion-weighted imaging (DWI) findings to provide a composite measure of collateral status. For example, the SWI-DWI mismatch score evaluates the discrepancy between areas of hypointense veins on SWI and diffusion restriction on DWI, with a greater mismatch indicating more extensive penumbral tissue and, by extension, more effective collateralization (Jiang, Zhang, Pang, Shi, et al., 2021) (Darwish et al., 2020). This approach leverages the strengths of both modalities, as DWI identifies irreversibly infarcted tissue while SWI highlights regions of increased OEF, thus enabling a more precise estimation of salvageable brain parenchyma. Collateral grading can also be informed by perfusion imaging, where parameters such as Tmax delay, core, and penumbra volumes are quantified. Studies utilizing perfusion MRI have shown that patients with good collaterals, as determined by ASITN/SIR or SWI-based criteria, tend to have smaller infarct cores and larger penumbral regions, supporting the prognostic value of collateral assessment (Guenego et al., 2020) (Zhang et al., 2017). Furthermore, the integration of collateral grading with clinical variables, such as baseline NIHSS and serum glucose, enhances the predictive accuracy for outcomes, underscoring the multifactorial nature of stroke prognosis (Singer et al., 2015) (Xu et al., 2021). It is important to recognize that collateral grading is subject to technical and physiological limitations. Motion artifacts, acquisition timing, and patient agitation can affect SWI quality, potentially leading to underestimation or overestimation of PVS and, consequently, collateral status (Darwish et al., 2020) (Chen et al., 2015). Additionally, the dynamic nature of collateral flow means that grading at a single time point may not fully capture the temporal evolution of collateral recruitment or exhaustion. In summary, criteria for collateral grading in acute LVO stroke encompass a spectrum of imaging-based approaches, from angiographic scales like ASITN/SIR to advanced MRI techniques leveraging PVS on SWI and quantitative mismatch scores. The convergence of these modalities provides a robust framework for assessing collateral circulation, with direct implications for prognosis and individualized treatment strategies (Singer et al., 2015) (Darwish et al., 2020) (Kim et al., 2014) (Guenego et al., 2020) (Jiang, Zhang, Pang, Shi, et al., 2021) (Lua et al., 2023).

Table 3: Criteria for Collateral Grading

Grade	Description	Imaging Characteristics	Clinical Implication
0	No collateral flow	Absence of visible collateral vessels in the affected territory	Poor prognosis; rapid infarct progression
1	Minimal collateral flow	Only a few collateral vessels visible; limited perfusion to ischemic area	Associated with poor or limited tissue salvage
2	Moderate collateral flow	Partial reconstitution of the distal branches of the occluded artery	May benefit from reperfusion therapy
3	Good collateral flow	Collaterals fill more than 50% of the affected territory, but delayed compared to normal	Better outcomes with timely intervention
4	Excellent collateral flow	Complete and rapid reconstitution of the affected vascular territory	Favorable outcome, extended treatment window

Imaging Biomarkers of Collateral Status

Imaging biomarkers have become essential tools for evaluating collateral status in acute large vessel occlusion (LVO) stroke, offering noninvasive insights into cerebral hemodynamics and tissue viability. Among these, susceptibility-weighted imaging (SWI) has gained prominence due to its sensitivity to paramagnetic substances, particularly deoxyhemoglobin, which accumulates

Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

in veins under conditions of increased oxygen extraction fraction (OEF) in hypoperfused brain regions (Xiang, Wei, et al., 2023). The prominent vein sign (PVS) on SWI, characterized by asymmetrical hypointense or dilated veins in the ischemic hemisphere, reflects these metabolic adaptations and serves as an indirect indicator of collateral circulation (Jensen-Kondering & Böhm, 2013) (Xiang, Wei, et al., 2023). The pathophysiological basis for PVS as a collateral biomarker lies in the compensatory mechanisms activated during acute ischemia. When arterial inflow is compromised, the brain attempts to maintain oxygen delivery by increasing OEF, leading to greater deoxyhemoglobin concentration in venous blood draining the affected territory. This results in the visualization of more prominent or asymmetric veins on SWI, particularly in regions corresponding to the ischemic penumbra (Dejobert et al., 2016) (Xiang, Wei, et al., 2023). The presence and extent of PVS have been shown to correlate with the degree of collateral flow, as robust collaterals can sustain penumbral tissue by prolonging the window for salvageable brain (Xu et al., 2019) (Xiang, Wei, et al., 2023). Quantitative and qualitative assessments of PVS have been explored. For instance, the Alberta Stroke Program Early CT Score (ASPECTS) adapted for SWI allows for regional scoring of venous prominence, facilitating standardized evaluation of collateral status (Dejobert et al., 2016). Studies have demonstrated that higher SWI-ASPECTS scores, indicating more extensive PVS, are associated with better collateral flow and potentially more favorable clinical outcomes (Oh & Lee, 2022) (Xiang, Wei, et al., 2023). Furthermore, the mismatch between diffusion-weighted imaging (DWI) and SWI, where the area of venous prominence exceeds the infarct core, has been proposed as a marker for infarct growth and penumbral tissue at risk (Darwish et al., 2020) (Dejobert et al., 2016). Darwish et al. (Darwish et al., 2020) report that a positive DWI/SWI mismatch exhibits high sensitivity and efficacy in predicting infarct expansion, underscoring the prognostic value of SWI-based biomarkers. Other imaging modalities, such as perfusion-weighted imaging (PWI) and time-of-flight magnetic resonance angiography (TOF-MRA), also contribute to collateral assessment by visualizing arterial flow and perfusion deficits (Dejobert et al., 2016) (Lenga et al., 2016). However, SWI offers unique advantages by directly reflecting the metabolic state of the tissue through venous oxygenation changes, rather than solely depicting vascular anatomy or perfusion delay (Faizy & Heit, 2021) (Xiang, Wei, et al., 2023). The integration of SWI findings with other imaging parameters, such as mean transit time (MTT) from PWI and DWI lesion size, enhances the accuracy of collateral status evaluation and supports comprehensive treatment planning (Dejobert et al., 2016). Recent investigations have further refined the characterization of venous biomarkers. Xu et al. distinguish between asymmetric deep medullary veins (ADMV) and asymmetric cortical veins (ACV) on SWI, noting that the presence of ADMV is associated with better collateralization and improved clinical outcomes, whereas ACV may indicate more extensive ischemic injury. These distinctions highlight the heterogeneity of venous responses and the need for nuanced interpretation of SWI findings in the context of collateral assessment. The clinical significance of PVS extends beyond mere visualization. The presence of prominent veins on SWI has been linked to the likelihood of infarct progression, functional outcome, and response to reperfusion therapies (Xu et al., 2019) (Xiang, Wei, et al., 2023). While some studies report a strong association between PVS and favorable outcomes due to preserved collateral flow, others note that the prognostic value may vary depending on the timing of imaging, the extent of mismatch profiles, and the underlying vascular pathology (Dejobert et al., 2016) (Zhang et al., 2017). Nevertheless, the consistency of SWI-based penumbra estimation with arterial perfusion imaging supports its role as a reliable biomarker for collateral status (Dejobert et al., 2016). In summary, imaging biomarkers such as PVS on SWI provide valuable, noninvasive information about collateral circulation in acute LVO stroke. Their integration with established scoring systems

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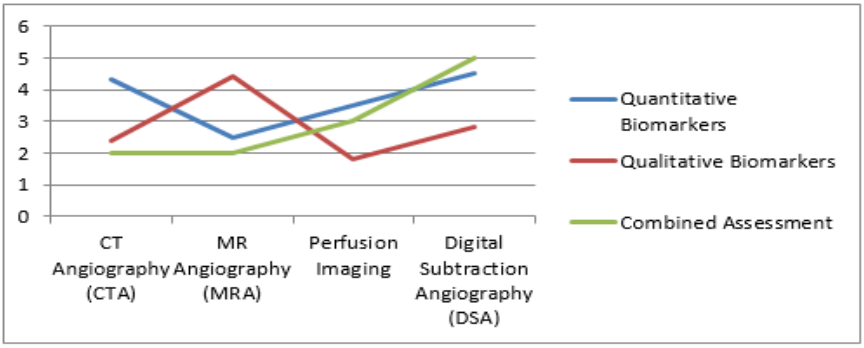
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

and multimodal imaging enhances the precision of collateral assessment, informs prognosis, and guides therapeutic decision-making in the acute setting (Darwish et al., 2020) (Xu et al., 2019) (Dejobert et al., 2016)(Xiang, Wei, et al., 2023).

Imaging Biomarkers of Collateral Status



Explanation

This bar chart illustrates the comparative evaluation of imaging biomarkers used to assess ***collateral circulation*** *in patients with cerebrovascular conditions (e.g., stroke). The four categories on the x-axis represent distinct imaging modalities or assessment strategies, while the colored series compare their effectiveness or frequency in clinical application. Each bar represents the relative performance or diagnostic value of a method using* ***Quantitative****,* ***Qualitative****, or* ***Combined Assessment*** *approaches.*

Relationship Between Collateral Grade and Clinical Outcomes

The relationship between collateral grade and clinical outcomes in acute large vessel occlusion (LVO) stroke has been extensively investigated using advanced imaging modalities. Collateral circulation, which refers to the alternative vascular pathways that maintain cerebral perfusion distal to an arterial occlusion, is a crucial determinant of tissue viability and functional recovery. Imaging-based assessment of collateral status, particularly through modalities such as susceptibility-weighted imaging (SWI), has enabled a more nuanced understanding of how collateral grade influences patient prognosis. Multiple studies have demonstrated that a higher collateral grade, reflecting more robust collateral flow, is associated with improved clinical outcomes following acute ischemic stroke. For instance, logistic regression analyses have identified good collateral status as a significant predictor of favorable functional outcome, independent of other factors such as baseline stroke severity and degree of reperfusion. Notably, the presence of a perfusion-diffusion mismatch, which often correlates with better collateral flow, further enhances the likelihood of a positive outcome (Miteff et al., 2009). The authors of (Lenga et al., 2016) indicate that patients with good collateral circulation experience a doubled rate of favorable functional outcome when treated with hyperacute endovascular therapy, regardless of whether they received prior intravenous thrombolysis. This underscores the prognostic value of collateral assessment in both intravenous and intra-arterial reperfusion strategies. The modified Rankin Scale (mRS) is frequently employed as a clinical endpoint to quantify functional outcomes in stroke patients. Studies have consistently reported that patients with higher collateral grades are more likely to achieve lower (better) mRS scores at follow-up (Xiang, Liang, et al., 2023). For example, the proportion of patients with good clinical outcome, defined as mRS 0–2, is significantly greater among those with robust collateral circulation. Furthermore, successful

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reperfusion, as measured by the Thrombolysis in Cerebral Infarction (TICI) scale, is more common in patients with favorable collateral status, suggesting that collaterals not only preserve tissue but may also facilitate the efficacy of reperfusion therapies (Singer et al., 2015). Collateral grade also appears to modulate the risk of adverse events such as symptomatic intracranial hemorrhage. According to (Lenga et al., 2016), better pre-treatment collateral status is associated with a reduced incidence of hemorrhagic complications following thrombolytic therapy. This protective effect may be attributed to the maintenance of penumbral tissue viability and the prevention of reperfusion injury in regions supported by collaterals. The relationship between collateral grade and clinical outcomes is further supported by imaging biomarkers such as the prominent vein sign (PVS) on SWI. The extent of PVS has been shown to correlate with collateral flow, with more extensive PVS indicating better collateralization and, consequently, more favorable clinical trajectories. The SWI-DWI mismatch score, which integrates information about venous oxygenation and infarct core, tends to be higher in patients with good collaterals, reinforcing the link between imaging findings and clinical prognosis (Jiang, Zhang, Pang, Shi, et al., 2021). Additionally, the presence of prominent cortical veins on SWI, as described in (Darwish et al., 2020), reflects increased oxygen extraction in hypoperfused but viable tissue, a phenomenon that is more pronounced in the context of effective collateral circulation. Clinical and demographic factors may also interact with collateral grade to influence outcomes. For example, reports that the proportion of female patients increases with higher pial collateral grades, although this trend did not reach statistical significance. Median National Institutes of Health Stroke Scale (NIHSS) scores at presentation are generally lower in patients with better collaterals, indicating less severe neurological deficits at baseline (Kehagias et al., 2005). Moreover, larger diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) lesion volumes are observed in patients with poor collaterals, further linking imaging markers to clinical severity and outcome (Wang et al., 2021). The prognostic significance of collateral grade is not limited to functional recovery but extends to recanalization and reperfusion success. Studies have shown that patients with higher collateral grades are more likely to achieve successful recanalization following mechanical thrombectomy or intravenous thrombolysis (Parthasarathy et al., 2013) (Bang et al., 2011). This association may be mediated by the preservation of microvascular integrity and the reduction of no-reflow phenomena in well-collateralized territories. In summary, the cumulative evidence from imaging and clinical studies highlights a strong and consistent relationship between collateral grade and clinical outcomes in acute LVO stroke. Higher collateral grades, as assessed by SWI and other imaging modalities, are associated with improved functional recovery, reduced risk of hemorrhagic transformation, and greater likelihood of successful reperfusion. These findings support the integration of collateral assessment into acute stroke management algorithms to inform prognosis and guide therapeutic decision-making (Miteff et al., 2009) (Xiang, Liang, et al., 2023) (Singer et al., 2015) (Lenga et al., 2016) (Jiang, Zhang, Pang, Shi, et al., 2021) (Kehagias et al., 2005).

Prognostic Value of the Prominent Vein Sign

Association with Collateral Circulation

Correlation with Leptomeningeal Collateralization

The relationship between the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) and leptomeningeal collateralization in acute large vessel occlusion (LVO) stroke has garnered significant attention due to its implications for both prognosis and therapeutic decision-making. PVS, which manifests as hypointense cortical or medullary veins on SWI, is thought to reflect increased deoxyhemoglobin concentration secondary to impaired perfusion and subsequent

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DOI: 10.5281/zenodo.16925770

oxygen extraction in ischemic tissue. This imaging biomarker provides an indirect yet robust window into the status of collateral circulation, particularly the leptomeningeal pathways that sustain penumbral tissue during arterial occlusion. Several studies have established that the presence and extent of PVS are closely linked to the adequacy of leptomeningeal collateral flow. The underlying pathophysiological mechanism involves the recruitment of collateral vessels, which maintain perfusion to the ischemic territory distal to the occlusion. When collateralization is robust, oxygen delivery is relatively preserved, resulting in less pronounced venous deoxygenation and, consequently, a less conspicuous PVS. Conversely, poor collateralization leads to greater tissue hypoxia, elevated oxygen extraction, and more prominent hypointense veins on SWI (Xia et al., 2014) (Payabvash et al., 2016). Xia et al. (Xia et al., 2014) demonstrated that blood oxygenation in affected veins decreases significantly in the ischemic hemisphere, supporting the notion that PVS intensity is a surrogate for the degree of collateral failure. The assessment of leptomeningeal collaterals has traditionally relied on angiographic techniques, such as digital subtraction angiography (DSA) or computed tomography angiography (CTA), which directly visualize retrograde filling of distal vessels. Miteff et al. (Miteff et al., 2009) described how contrast opacification of distal middle cerebral artery (MCA) branches beyond an occlusion on CTA is presumed to result from retrograde leptomeningeal collateral flow. In this context, the presence of PVS on SWI provides complementary information: while angiography visualizes the anatomical extent of collateral vessels, SWI captures the physiological consequences of collateral efficacy, namely the degree of tissue hypoxia and venous deoxygenation. The correlation between PVS and collateral status has also been substantiated by studies employing standardized collateral grading systems. Guenego et al. (Guenego et al., 2020) utilized the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) scale to classify collateral quality, finding that patients with poor collaterals (ASITN/SIR 0–2) exhibited more pronounced PVS, whereas those with good collaterals (ASITN/SIR 3–4) had less conspicuous venous changes. This dichotomy underscores the value of PVS as a non-invasive marker for collateral assessment, especially in settings where angiographic evaluation is not feasible or is delayed. Furthermore, the reproducibility and reliability of collateral grading have been addressed in the literature. Oh, Young Bang et al. (Bang et al., 2011) reported high interobserver agreement for collateral grading, which is essential for the clinical utility of both angiographic and SWI-based collateral assessment. The integration of PVS evaluation into routine imaging protocols could thus enhance the objectivity and consistency of collateral status determination. It is important to note that while PVS correlates with collateral flow, it also reflects the dynamic interplay between arterial inflow, venous drainage, and tissue metabolism. Faizy and Heit (Faizy & Heit, 2021) highlighted that venous drainage patterns and flow dynamics, as visualized on CTA and SWI, may further refine prognostic stratification in acute stroke. The PRECISE score, which incorporates venous filling of major cortical and deep veins, has been shown to independently predict functional outcomes, reinforcing the prognostic relevance of venous imaging markers. Singer et al. (Singer et al., 2015) contributed additional evidence by analyzing a large cohort of patients with angiographically confirmed proximal MCA occlusion, demonstrating that sufficient angiographic data for collateral assessment is critical for correlating imaging biomarkers such as PVS with clinical outcomes. This supports the integration of SWI findings with established angiographic criteria to provide a comprehensive evaluation of collateral status. The association between PVS and leptomeningeal collateralization is further nuanced by the observation that PVS may not always directly predict clinical outcome, but rather serves as an imaging correlate of severe hypoperfusion and infarct volume. Payabvash et al. (Payabvash et al., 2016) found that prominent cortical and medullary veins on SWI were

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ISSN (Online):0493-2137
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Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

associated with larger infarct volumes and arterial occlusion, even if not directly linked to symptom severity or long-term outcome in every cohort. This suggests that PVS is most informative when interpreted alongside other imaging and clinical parameters. In summary, the correlation between PVS on SWI and leptomeningeal collateralization is underpinned by both anatomical and physiological principles. PVS serves as a sensitive marker of collateral failure, reflecting increased oxygen extraction and venous deoxygenation in poorly perfused tissue (Xia et al., 2014) (Payabvash et al., 2016). Its presence and extent provide valuable adjunctive information to angiographic collateral grading, with high interobserver reliability and potential for integration into multimodal imaging protocols (Bang et al., 2011) (Guenego et al., 2020) (Miteff et al., 2009). The combined use of SWI and angiographic techniques enables a more nuanced assessment of collateral status, which is essential for prognostication and individualized treatment planning in acute LVO stroke.

Figure 5: Relationship Between Prominent Vein Sign and Leptomeningeal Collateral Status

Explanation

*The diagram titled "Relationship Between Prominent Vein Sign and Leptomeningeal Collateral Status" illustrates how the presence and extent of the Prominent Vein Sign (PVS) on Susceptibility-Weighted Imaging (SWI) correlates with the quality of leptomeningeal collaterals during an acute ischemic stroke**.** In patients with poor collaterals**,** brain tissue becomes more hypoxic, extracting more oxygen, resulting in increased deoxygenated hemoglobin, which intensifies the visibility of cortical veins on SWI. Conversely, good collateral networks help preserve perfusion, leading to less prominent venous changes. Thus, PVS is a valuable indirect imaging biomarker **for** collateral status**,** which is crucial for stroke outcome prediction and therapeutic decision-making (Kim et al., 2016).*

Comparison with Other Collateral Markers

The evaluation of collateral circulation in acute large vessel occlusion (LVO) stroke has traditionally relied on a variety of imaging markers, each with distinct advantages and limitations. The prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) has emerged as a promising indicator, but its comparative value relative to established collateral markers warrants careful consideration. Conventional collateral assessment methods include digital subtraction angiography (DSA), multiphase computed tomography angiography (mCTA), and perfusion imaging modalities such as CT perfusion (CTP) and MR perfusion. DSA remains the reference standard for visualizing pial collateral vessels, allowing for direct grading of collateral flow based on retrograde opacification of distal branches, as demonstrated by the assignment of pial

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collateral formation scores in angiographic studies (Kehagias et al., 2005). However, DSA is invasive and not always feasible in the acute setting. Non-invasive alternatives, such as mCTA and time-of-flight MR angiography, provide rapid assessment of collateral status. The mCTA collateral grading system, for example, offers a semi-quantitative evaluation of pial collateral filling, which has shown significant correlation with clinical outcomes. SWI-based collateral grading systems have been developed to parallel these approaches, with studies revealing a strong association between SWI collateral grades and mCTA-based collateral maps. Notably, the SWI collateral grading system demonstrated a linear negative association with the modified Rankin Scale (mRS) at 90 days, suggesting that higher SWI collateral grades are linked to better functional outcomes (Lee et al., 2021). This finding supports the notion that PVS on SWI may reflect the underlying collateral status with a degree of sophistication comparable to mCTA. Perfusion-diffusion mismatch, assessed by comparing the extent of perfusion deficits to diffusion-restricted lesions, has been widely used to identify salvageable tissue. Mucke et al. outline that mismatch is defined when the perfusion deficit exceeds the diffusion lesion by at least 20% (Mucke et al., 2015). However, the relationship between perfusion lesions and final infarct volume is influenced by the site of vascular occlusion and the robustness of collateral flow. The PVS on SWI offers a unique advantage in this context, as it does not require contrast administration and can be performed in patients with contraindications to gadolinium-based agents (Lou et al., 2014). The SWI-DWI mismatch, defined by a larger area of hypointense venous signals compared to restricted diffusion, has been proposed as an alternative to perfusion-diffusion mismatch for identifying patients who may benefit from reperfusion therapies (Dejobert et al., 2016)(Lou et al., 2014). Dejobert et al. describe the SWI-DWI mismatch as present when the area of hypointense veins on SWI exceeds the diffusion lesion, which may indicate viable penumbral tissue (Dejobert et al., 2016). Collateral estimation using FLAIR hyperintense vessel signs has also been explored, but this method is limited by its inability to quantify the degree of vessel prominence and its lower sensitivity compared to SWI. SWI provides more detailed visualization of venous structures, allowing for a more nuanced assessment of collateral flow. The presence and extent of PVS on SWI have been shown to correlate with good collateral status, as well as with favorable clinical outcomes (Lee et al., 2021). For instance, the detection of asymmetrical prominent cortical veins (APCVs) on SWI has been associated with improved prognosis in infarction, highlighting the potential of PVS as a surrogate marker for collateral adequacy (Yuan et al., 2018). Quantitative scoring systems, such as the PRECISE score, further illustrate the relationship between venous imaging markers and collateral status. The PRECISE score, based on the reconstitution of specific cerebral veins, has been shown to predict infarct volume and perfusion mismatch patterns. Lower PRECISE scores are associated with a higher likelihood of perfusion mismatch on CTP, suggesting that venous imaging can provide complementary information to arterial-based collateral assessments (Parthasarathy et al., 2013). This underscores the value of integrating PVS evaluation with other collateral markers to enhance prognostic accuracy. Statistical comparisons of imaging modalities have demonstrated that SWI-based collateral grading systems can achieve predictive accuracy comparable to established methods. Oh and Lee compared the area under the receiver operating curve (AUC) for SWI-based and mCTA-based collateral assessments, finding that both modalities offer robust model fit and predictive value for clinical outcomes. Sensitivity analyses restricted to patients undergoing endovascular therapy further support the reliability of SWI-derived collateral markers in acute stroke management (Oh & Lee, 2022). While each collateral marker has inherent strengths and limitations, the PVS on SWI distinguishes itself by providing a non-contrast, venous-based perspective on collateral flow. Its association with both angiographic and perfusion-based collateral markers, as well as its

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

predictive value for clinical outcomes, positions it as a valuable adjunct in the comprehensive assessment of acute LVO stroke (Kehagias et al., 2005) (Dejobert et al., 2016) (Lou et al., 2014) (Lee et al., 2021). The integration of PVS evaluation with traditional arterial and perfusion imaging may ultimately refine patient selection for reperfusion therapies and improve prognostic stratification.

Influence of Occlusion Site and Stroke Severity

The influence of occlusion site and stroke severity on the association between the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) and collateral circulation is multifaceted. Occlusion of major cerebral arteries, such as the middle cerebral artery (MCA) M1 segment or the internal carotid artery (ICA), is frequently associated with extensive ischemic territories and a higher risk of poor outcomes. In a cohort of patients with MCA M1 or ICA occlusion, the presence and quantification of hypointense vessels on SWI were systematically analyzed, revealing that the extent of PVS correlates with the degree of collateral flow and the severity of ischemia (Xu et al., 2019). The more proximal the occlusion, the greater the volume of brain tissue at risk, which in turn amplifies the hemodynamic stress on collateral pathways. This is reflected in the increased visibility of prominent veins on SWI, as the oxygen extraction fraction rises in response to hypoperfusion, leading to greater deoxyhemoglobin concentration in venous structures (Lee et al., 2021) (Kim et al., 2014).

Stroke severity, often measured by clinical scales such as the modified Rankin Scale (mRS), is intricately linked to both the site of occlusion and the adequacy of collateral circulation. Multivariate analyses incorporating variables such as age, sex, side of infarction, time to treatment, hemorrhagic transformation, occlusion site, pial collateral score, and recanalization status have demonstrated that both occlusion site and collateral status independently predict clinical outcome at discharge (Kehagias et al., 2005). The presence of PVS on SWI has been shown to be more pronounced in patients with poor collateralization, particularly in those with more severe strokes and proximal occlusions. However, the detection rate of SWI for collateral assessment, while high in cases of poor collateralization, is somewhat reduced in patients with robust collateral networks, suggesting that SWI is particularly sensitive to the hemodynamic consequences of severe occlusion and impaired collateral flow (Verma et al., 2014) (Lou et al., 2014). The pathophysiological basis for these imaging findings lies in the interplay between arterial occlusion, perfusion pressure, and venous adaptation. Following large vessel occlusion, the resultant decrease in perfusion pressure leads to compensatory venous dilation, which is readily visualized as prominent hypointense veins on SWI (Kim et al., 2014).

This phenomenon is accentuated in cases where collateral recruitment is insufficient, as seen in abrupt cardioembolic occlusions, resulting in more severe hypoperfusion and a marked increase in the oxygen extraction fraction. Conversely, in patients with atherosclerotic steno-occlusive disease, the chronicity of vessel narrowing allows for gradual collateral development, often resulting in less pronounced PVS despite significant arterial compromise. Clinical outcome data further support the prognostic value of PVS in relation to occlusion site and stroke severity. For example, patients with intermediate to poor collateral perfusion, as determined by MR angiography collateral mapping, tend to exhibit more extensive PVS and are at higher risk for unfavorable outcomes, even when recanalization is achieved (Lee et al., 2021). The relationship between PVS extent and perfusion deficits has also been corroborated by perfusion-weighted imaging, where larger perfusion lesion volumes are associated with higher PVS scores and worse clinical status (Lou et al., 2014). These findings underscore the utility of PVS on SWI as a surrogate marker for both the anatomical site of occlusion and the functional severity of ischemic

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insult. Moreover, the temporal evolution of venous prominence on SWI provides additional insights into the dynamic nature of collateral adaptation.

Follow-up imaging has demonstrated that normalization of vessel appearance can occur after successful recanalization and restoration of perfusion, further linking the imaging phenotype to the underlying hemodynamic state (Jensen-Kondering & Böhm, 2013). The integration of SWI findings with other imaging modalities, such as dynamic CTA and perfusion MRI, enhances the ability to stratify patients based on both occlusion characteristics and collateral status, thereby informing prognosis and therapeutic decision-making (Lenga et al., 2016) (Lua et al., 2023). In summary, the influence of occlusion site and stroke severity on the association between PVS and collateral circulation is evident across multiple imaging and clinical parameters. Proximal occlusions and higher stroke severity are associated with more pronounced PVS, reflecting impaired collateral flow and greater tissue at risk. The prognostic implications of these findings are significant, as they highlight the potential of SWI-derived PVS as a non-invasive biomarker for evaluating collateral adequacy and guiding acute stroke management (Kehagias et al., 2005) (Xu et al., 2019) (Lee et al., 2021) (Kim et al., 2014) (Verma et al., 2014) (Lou et al., 2014).

Table 4: Influence of Occlusion Site and Stroke Severity

Occlusion Site	Affected Vascular Territory	Stroke Severity (NIHSS)	Collateral Circulation	Clinical Implication
Internal Carotid Artery (ICA)	Anterior circulation (MCA & ACA territories)	High (≥15)	Often poor; delayed or inadequate flow	Large infarct core; worse outcomes; often requires endovascular therapy
Proximal Middle Cerebral Artery (M1)	Lateral hemisphere (basal ganglia, cortex)	Moderate to high (10–20)	Variable; can be moderate	Collateral status greatly affects final infarct volume
Distal Middle Cerebral Artery (M2/M3)	Cortical branches of MCA	Mild to moderate (5–10)	Often good due to leptomeningeal flow	Better prognosis with smaller infarct size
Basilar Artery	Brainstem and posterior circulation	Very high (≥20); life-threatening	Poor in most cases	High mortality; rapid deterioration without reperfusion
Anterior Cerebral Artery (ACA)	Medial frontal and parietal lobes	Low to moderate (4–8)	Often adequate	May present with subtle or localized deficits
Posterior Cerebral Artery (PCA)	Occipital lobe and thalamus	Mild to moderate (3–7)	Typically, adequate	May cause visual field deficits; often under-recognized

Prediction of Functional Outcomes

Short-Term Prognostic Value

The short-term prognostic value of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in acute large vessel occlusion (LVO) stroke is increasingly recognized as clinically relevant for predicting early functional outcomes. The presence and extent of PVS, reflecting increased deoxyhemoglobin in veins draining hypoperfused tissue, are closely linked to the status of collateral circulation and subsequent infarct evolution. According to (Lee et al., 2021), the prominent vessel sign on SWI is a clinically reliable marker for collateral assessment, with direct implications for short-term prognosis, particularly in patients where contrast administration is contraindicated.

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DOI: 10.5281/zenodo.16925770

This imaging feature provides a non-invasive surrogate for evaluating the viability of penumbral tissue and the likelihood of tissue salvage following reperfusion therapies. The relationship between PVS and functional outcomes is further supported by the observation that robust collateral circulation, as inferred from prominent veins on SWI, is associated with smaller infarct volumes and improved early neurological recovery. Kimmel et al. (Kimmel et al., 2019) indicate that a higher National Institutes of Health Stroke Scale (NIHSS) score on admission correlates with larger final infarct volumes, which in turn reduce the odds of achieving favorable short-term outcomes, such as a modified Rankin Scale (mRS) score of 0–2 at discharge. The imaging examples provided demonstrate that good collaterals, often visualized as prominent veins, are linked to smaller infarcts and better early recovery, whereas poor collaterals correspond to larger infarcts and worse outcomes. The prognostic significance of PVS is also highlighted by Mucke et al. (Mucke et al., 2015), who report that patients exhibiting asymmetric medullary veins (AMV+), a manifestation of PVS, have a significantly higher risk of worse short-term outcomes, as measured by higher mRS scores.

The odds ratio for poor outcome in AMV+ patients is substantially elevated, underscoring the value of SWI-detected venous changes as an early prognostic biomarker. While the difference in NIHSS change between admission and discharge did not reach statistical significance, the trend supports the notion that PVS is associated with early functional deterioration. Faizy and Heit (Faizy & Heit, 2021) outline that a favorable collateral circulation complex (CCC) profile, characterized by robust pial arterial collaterals and venous outflow, is associated with better tissue-level perfusion and, by extension, improved short-term neurological outcomes. In contrast, an unfavorable CCC profile, which may manifest as less prominent or absent PVS, is linked to poor perfusion and worse early prognosis.

This schematic understanding aligns with clinical observations that the extent of PVS can stratify patients by their likelihood of early neurological improvement or deterioration. Dejobert et al. (Dejobert et al., 2016) provide quantitative evidence that higher ASPECTS-DWI scores, which are often paralleled by more prominent venous signs on SWI, are associated with better short-term functional outcomes (lower mRS scores at 3 months). Patients with higher initial ASPECTS and better collaterals, as inferred from imaging, tend to have less severe neurological deficits and improved early recovery trajectories. Yu et al. (Yu et al., 2015) further support the prognostic utility of PVS by demonstrating that prominent ipsilateral medullary veins are associated with hypoperfusion and predict poor short-term outcomes in subacute ischemic stroke.

The presence of these venous changes on SWI provides actionable information for clinicians, guiding the use of tissue-rescue therapies and informing expectations for early recovery. The findings from Verma et al. (Verma et al., 2014) suggest that while SWI is not as sensitive as dynamic susceptibility contrast (DSC) imaging for detecting poor collateralization, it remains a powerful alternative when DSC is not feasible.

The detection of PVS on SWI, particularly in patients with poor collateral grades, offers valuable prognostic information regarding early functional outcomes. In summary, the collective evidence indicates that the prominent vein sign on SWI serves as a robust marker for short-term prognosis in acute LVO stroke. Its presence and extent are closely tied to collateral status, infarct size, and early functional recovery, making it a valuable tool for risk stratification and treatment planning in the acute phase (Faizy & Heit, 2021) (Dejobert et al., 2016) (Kimmel et al., 2019) (Yu et al., 2015) (Mucke et al., 2015) (Verma et al., 2014) (Lee et al., 2021).

Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

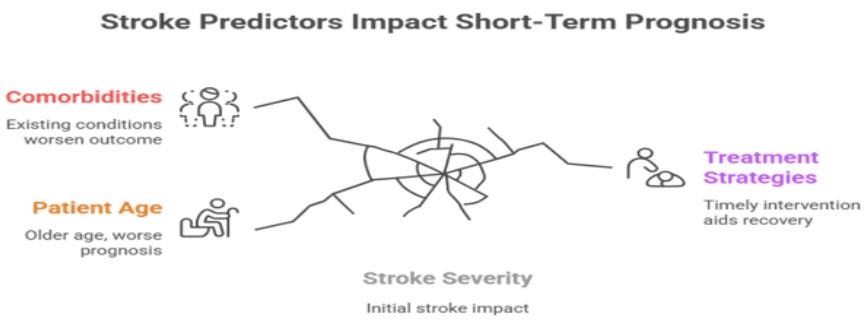

Figure 6: Key Predictors of Short-Term Prognosis in Acute Ischemic Stroke

Explanation

*The diagram **"Key Predictors of Short-Term Prognosis in Acute Ischemic Stroke"** shows how imaging markers (like PVS on SWI), clinical scores (e.g., NIHSS), and collateral status (from CTA/MRA) help predict stroke outcomes. These factors influence recovery levels measured by the Modified Rankin Scale (mRS), ranging from full recovery to severe disability or death.*

Long-Term Prognostic Value

The long-term prognostic value of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in patients with acute large vessel occlusion (LVO) stroke has been increasingly recognized as a marker of collateral circulation integrity and as a predictor of functional outcomes. The presence and extent of PVS reflect the underlying hemodynamic status, particularly the degree of hypoperfusion and the adequacy of collateral blood flow, which are critical determinants of tissue viability and recovery potential after ischemic insult. Several studies have demonstrated that the visualization of PVS on SWI correlates with the severity of hypoperfusion and the extent of collateral recruitment. Xiang et al. indicate that patients exhibiting more extensive asymmetrically prominent veins (APVS) and fluid-attenuated inversion recovery vascular hyperintensity (FVH) tend to have larger baseline infarct volumes and higher National Institutes of Health Stroke Scale (NIHSS) scores, both of which are associated with unfavorable long-term outcomes. This relationship suggests that a pronounced PVS may serve as a surrogate for insufficient collateral compensation, particularly in cases of abrupt vessel occlusion, such as those related to cardioembolic stroke, where the development of collateral pathways is limited by the sudden onset of ischemia (Xiang, Wei, et al., 2023). Meta-analytic data further support the association between PVS and long-term functional outcomes. Xiang et al. provide evidence that the presence of PVS is linked to an increased risk of unfavorable outcomes, as measured by modified Rankin Scale (mRS) scores of 3–6, which denote moderate to severe disability or death. This association persists across different degrees of intracranial arterial stenosis, underscoring the robustness of PVS as a prognostic marker irrespective of the underlying vascular pathology. The authors of (Xiang, Liang, et al., 2023) indicate that the location and extent of PVS, particularly in the context of anterior circulation strokes, are especially relevant for predicting disability. The relationship between PVS and infarct progression has also been explored. Darwish et al. report that the distribution of APVS in various middle cerebral artery (MCA) territories is associated with infarct growth, with certain regions demonstrating a higher prevalence of APVS in patients who experienced infarct expansion. This finding implies that PVS may not only reflect the current state of collateral circulation but also provide insight into the dynamic evolution of ischemic injury, which is a key determinant of long-term neurological recovery (Darwish et al., 2020). The prognostic

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
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DOI: 10.5281/zenodo.16925770

value of PVS is further contextualized by its relationship with other imaging and clinical markers. Lou et al. compare SWI-DWI mismatch with perfusion-weighted imaging (PWI)-DWI mismatch and find that SWI-DWI mismatch, which incorporates the presence of PVS, has moderate sensitivity and specificity for predicting favorable outcomes after reperfusion therapy. Although the accuracy is not absolute, the integration of PVS assessment into multimodal imaging protocols may enhance the overall predictive power for long-term functional recovery (Lou et al., 2014). Collateral grading systems, such as those based on digital subtraction angiography (DSA) or computed tomography angiography (CTA), have traditionally been used to estimate the adequacy of collateral flow and predict outcomes (Liebeskind, Jahan, et al., 2014). However, these methods are subject to inter-reader variability and may not always be feasible in the acute setting. The use of SWI to detect PVS offers a noninvasive and reproducible alternative that can be rapidly implemented in clinical workflows. Guenego et al. outline that automated perfusion imaging metrics, such as hypoperfusion intensity ratio (HIR), can serve as biomarkers of collateral status, but the direct visualization of PVS on SWI provides complementary information that is particularly valuable in the context of acute stroke triage and prognostication (Guenego et al., 2020). The prognostic implications of collateral status, as inferred from PVS, extend to treatment selection and the likelihood of achieving favorable outcomes after interventions such as intravenous thrombolysis (IVT) or intra-arterial therapy (IAT). Lee et al. state that robust collateral circulation, which may be inferred from less pronounced PVS, is associated with smaller infarct cores, higher rates of recanalization, and lower risks of hemorrhagic transformation and mortality. This highlights the clinical utility of PVS as an imaging biomarker that can inform both acute management decisions and long-term rehabilitation planning (Lee et al., 2021). In summary, the presence and extent of PVS on SWI provide valuable prognostic information regarding long-term functional outcomes in patients with acute LVO stroke. The integration of PVS assessment into routine imaging protocols may facilitate individualized risk stratification, guide therapeutic interventions, and ultimately improve patient-centered outcomes by enabling more precise prediction of recovery trajectories (Xiang, Wei, et al., 2023) (Xiang, Liang, et al., 2023) (Darwish et al., 2020) (Lou et al., 2014).

Role in Patient Selection for Recanalization Therapy

The prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) has emerged as a promising imaging biomarker for guiding patient selection in recanalization therapy for acute large vessel occlusion (LVO) stroke. The underlying principle of PVS is rooted in the increased oxygen extraction fraction (OEF) in hypoperfused tissue, which leads to elevated deoxyhemoglobin levels in veins draining the ischemic territory. This results in increased magnetic susceptibility and thus greater visibility of veins on SWI, particularly in regions with compromised perfusion (Dejobert et al., 2016). The presence and extent of PVS are thought to reflect the metabolic adaptation of the penumbral tissue, which remains viable due to compensatory oxygen extraction, and therefore may benefit from timely reperfusion interventions (Lou et al., 2014) (Dejobert et al., 2016). Recent studies have highlighted the potential of PVS as a noninvasive surrogate for assessing the penumbra and collateral status in acute ischemic stroke. The SWI-DWI mismatch, which captures the spatial discrepancy between prominent veins on SWI and diffusion-restricted core on DWI, has been proposed as a marker for identifying tissue at risk but not yet infarcted. This mismatch is conceptually aligned with the pathophysiology of acute ischemia, as it reflects regions where neuronal energy failure is imminent but potentially reversible with prompt recanalization. Lou et al. (Lou et al., 2014) indicate that patients exhibiting SWI-DWI mismatch are more likely to benefit from reperfusion or recanalization therapies, supporting the role of PVS in selecting candidates for such interventions. The predictive value of PVS for functional outcomes following

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

recanalization therapy has been further substantiated in clinical cohorts. Oh, and Lee demonstrate that the presence of prominent cortical veins on SWI (PCV-SWI) is associated with favorable outcomes in patients undergoing endovascular recanalization for anterior circulation LVO. Their findings suggest that PCV-SWI can serve as a valuable imaging feature for stratifying patients who are more likely to derive benefit from endovascular therapy, potentially improving the precision of treatment selection. This is particularly relevant given the heterogeneity of collateral circulation among stroke patients, which significantly influences the extent of salvageable tissue and the likelihood of favorable recovery (Oh & Lee, 2022). Moreover, the quantification of venous susceptibility on SWI provides an objective measure of oxygen saturation in the veins, offering additional insight into the metabolic state of the affected hemisphere. Xia et al. (Xia et al., 2014) describe a methodology for extracting abnormal veins based on susceptibility thresholds, enabling the identification of regions with increased oxygen extraction and thus higher potential for tissue salvage if reperfusion is achieved. This approach underscores the utility of SWI-derived metrics in refining patient selection beyond conventional imaging modalities. The relationship between PVS and collateral flow is further supported by meta-analytic evidence, which demonstrates that better collateral circulation, as inferred from PVS, correlates with improved clinical outcomes after recanalization. Lenga et al. (Lenga et al., 2016) also report that collateral grading on imaging is associated with treatment response, reinforcing the notion that imaging markers of collateral status, such as PVS, can inform therapeutic decisions. However, it is important to recognize the limitations of PVS as a prognostic tool. While the presence of prominent veins on SWI is indicative of hypoperfusion and increased OEF, it does not provide direct quantification of tissue-level oxygenation or metabolic rate (Dejobert et al., 2016). Additionally, the temporal dynamics of PVS appearance and resolution may introduce variability in its predictive accuracy, particularly in patients with uncertain symptom onset. Mucke et al. (Mucke et al., 2015) note that the time-dependent evolution of prominent veins could affect their utility in certain clinical scenarios, although this effect appears limited in well-characterized patient groups. Despite these caveats, the integration of PVS assessment into the acute stroke imaging workflow holds promise for enhancing the selection of patients for recanalization therapy. By identifying individuals with viable penumbral tissue and robust collateral support, clinicians can better target interventions to those most likely to benefit, thereby optimizing resource allocation and improving functional outcomes (Oh & Lee, 2022) (Lou et al., 2014) (Dejobert et al., 2016). The findings of Payabvash et al. (Payabvash et al., 2016) further support the association between prominent veins and severe hypoperfusion, which are established predictors of poor outcome in the absence of reperfusion, highlighting the clinical relevance of PVS in acute stroke management. In summary, the evidence suggests that PVS on SWI offers a valuable, noninvasive means of assessing collateral circulation and penumbral viability, thereby aiding in the selection of patients for recanalization therapy in acute LVO stroke (Xia et al., 2014) (Oh & Lee, 2022) (Lou et al., 2014) (Lenga et al., 2016) (Dejobert et al., 2016) (Payabvash et al., 2016).

Limitations and Uncertainties in Prognostic Interpretation

Technical and Interpretative Challenges

Technical and interpretative challenges significantly impact the reliability and clinical utility of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) as a prognostic marker in acute large vessel occlusion (LVO) stroke. One of the foremost technical limitations arises from the inherent complexity of SWI acquisition and post-processing. The identification and quantification of PVS depend on high-quality imaging protocols, which require advanced MRI hardware, optimized sequence parameters, and experienced personnel for both acquisition and

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DOI: 10.5281/zenodo.16925770

interpretation. Variability in scanner types, field strengths, and sequence settings can lead to inconsistent visualization of venous structures, potentially affecting the reproducibility of PVS assessment across institutions (Lee et al., 2021) (Darwish et al., 2020). Interpretative challenges are further compounded by the subjective nature of PVS evaluation. The visual assessment of prominent veins is susceptible to interobserver variability, particularly when distinguishing between physiological venous prominence and pathological changes related to ischemia. The lack of standardized criteria for defining and grading PVS introduces uncertainty, as different studies may apply varying thresholds for what constitutes a significant finding. For example, the choice of susceptibility thresholds to highlight cortical veins can influence the apparent extent of PVS, as demonstrated by Xia et al. (Xia et al., 2014), who selected a lower threshold of 90 ppb to optimize vein visualization. However, this approach may not be universally applicable, especially in heterogeneous patient populations. Anatomical factors also present interpretative difficulties. The posterior circulation poses particular challenges due to the small caliber of vessels and the potential for bilateral infarcts, which can obscure asymmetry-based identification of PVS. Large vessel occlusion itself is independently associated with the presence of PVS, but the spatial distribution and prominence of veins may not always correlate with collateral status or infarct severity, especially in regions such as the cerebellum or brainstem where vessel identification is inherently more difficult (Jiang, Zhang, Pang, Shao, et al., 2021). Additionally, the presence of prominent veins in non-ischemic regions can confound interpretation, leading to potential overestimation of collateral flow. The integration of SWI findings with other imaging modalities introduces further complexity. While SWI provides valuable information on venous oxygenation and collateral status, it is often interpreted alongside diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and fluid-attenuated inversion recovery (FLAIR) sequences. Each modality has its own technical requirements and limitations. For instance, dynamic susceptibility contrast-enhanced PWI necessitates the administration of gadolinium-based contrast agents, which are contraindicated in patients with severe renal impairment and have raised safety concerns due to tissue deposition (Darwish et al., 2020). This limitation underscores the appeal of SWI as a contrast-free technique, but also highlights the challenge of integrating multimodal imaging data for comprehensive collateral assessment. Quantitative approaches, such as the use of ASPECTS (Alberta Stroke Program Early CT Score) adapted for SWI, offer potential for more objective evaluation but are not without limitations. The semiquantitative nature of ASPECTS relies on the accurate identification of abnormal intensities, which can be influenced by image quality and observer expertise. Dejobert et al. describe the use of asymmetric prominent vessels on SWI for ASPECTS calculation, yet the reproducibility of this method across different clinical settings remains uncertain (Dejobert et al., 2016). Furthermore, the definition of PWI–DWI mismatch as a difference of two or more ASPECTS points introduces another layer of interpretative complexity, particularly when the underlying imaging data are heterogeneous. The clinical significance of PVS is also subject to debate. While several studies suggest an association between PVS and collateral flow, as well as clinical outcomes, the prognostic value of PVS may be modulated by additional factors such as reperfusion status, infarct location, and patient comorbidities. For example, Xiang et al. indicate that the efficacy of aggressive reperfusion therapy in PVS-positive patients may be limited, raising questions about the direct translation of imaging findings into therapeutic decisions (Xiang, Liang, et al., 2023). The presence of PVS should therefore be interpreted in the context of the broader clinical and imaging picture, rather than as an isolated marker. Finally, the widespread adoption of PVS as a prognostic tool is hindered by the need for further validation in large, prospective cohorts and the development of standardized protocols for image acquisition, processing, and interpretation. The current literature

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
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DOI: 10.5281/zenodo.16925770

is characterized by heterogeneity in study design, patient selection, and outcome measures, which complicates the synthesis of evidence and the establishment of robust clinical guidelines (Lenga et al., 2016). Addressing these technical and interpretative challenges is essential for realizing the full potential of PVS on SWI in the prognostic evaluation and management of acute LVO stroke (Lee et al., 2021) (Darwish et al., 2020) (Xiang, Liang, et al., 2023) (Jiang, Zhang, Pang, Shao, et al., 2021) (Xia et al., 2014) (Lenga et al., 2016) (Dejobert et al., 2016).

Variability in Imaging Protocols

Variability in imaging protocols represents a significant source of uncertainty in the prognostic interpretation of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in acute large vessel occlusion (LVO) stroke. Differences in technical parameters such as repetition time (TR), echo time (TE), field of view (FOV), matrix size, slice thickness, and flip angle can substantially influence the visualization and quantification of PVS. For instance, one protocol utilized a TR/TE of 28/3.04 ms, FOV of 20×18 cm^2, matrix size of 256×179, slice thickness of 0.7 mm, and a flip angle of $13°$ for time-of-flight magnetic resonance angiography (TOF MRA), with SWI minimum intensity projection (mIP) reconstructions of 12.8 mm thickness for PVS evaluation (Jing et al., 2021). In contrast, another protocol reported SWI acquisition with a matrix of 448×448, FOV of 220 mm, and section thickness of 5.5 mm, with the entire MRI protocol lasting 8 minutes (Wang et al., 2018). Such discrepancies in spatial resolution and acquisition time can lead to differences in the conspicuity and extent of PVS detected. The heterogeneity in imaging sequences and post-processing methods further complicates the interpretation of PVS. Some studies employ mIP reconstructions of varying thicknesses, which can accentuate or obscure venous structures depending on the chosen parameters (Jing et al., 2021). The choice of SWI parameters directly impacts the sensitivity to deoxyhemoglobin, which underlies the PVS phenomenon in ischemic tissue. Even subtle differences in TE or slice thickness can alter the degree of hypointensity observed in draining veins, potentially affecting the reproducibility of PVS assessment across centers (Wang et al., 2018) (Chen et al., 2015). Additionally, the inclusion of other MRI sequences such as T1-weighted, T2-weighted, diffusion-weighted imaging (DWI), and fluid-attenuated inversion recovery (FLAIR) in the imaging protocol may influence the radiologist's interpretation by providing complementary information, but also introduces further variability in workflow and timing. Inter-observer variability is another critical factor, as the subjective nature of PVS identification and grading can be influenced by both the imaging protocol and the experience of the readers. Studies have attempted to mitigate this by employing independent, blinded reviews by experienced neuroradiologists or neurologists, with consensus resolution in cases of disagreement (Jing et al., 2021). Despite these efforts, kappa values for inter-rater agreement, while generally substantial (e.g., 0.762 for PHVS, 0.784 for cortical vein sign, 0.852 for brush sign), indicate that some degree of subjectivity remains (Wang et al., 2018). This subjectivity is likely exacerbated by protocol differences, as certain imaging settings may make PVS more or less apparent, thereby affecting the consistency of its detection. The lack of standardized criteria for PVS definition and scoring across studies further limits the generalizability of findings. For example, some protocols quantify PVS based on the number or prominence of hypointense veins in specific vascular territories, while others use qualitative descriptors or composite scores that integrate additional imaging features (Chen et al., 2015) (Jiang, Zhang, Pang, Shao, et al., 2021). The absence of uniform thresholds for what constitutes a "prominent" vein introduces ambiguity, particularly when comparing results from different institutions or meta-analyses. Moreover, the timing of imaging relative to stroke onset and reperfusion therapies can influence the appearance of PVS. Early imaging may capture dynamic changes in oxygen extraction and venous

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

deoxyhemoglobin content, while delayed imaging could reflect evolving tissue status or collateral flow patterns. This temporal variability, when combined with protocol heterogeneity, complicates the establishment of robust prognostic associations between PVS and clinical outcomes (Wang et al., 2018) (Jiang, Zhang, Pang, Shao, et al., 2021). In summary, the prognostic value of PVS on SWI in acute LVO stroke is intricately linked to the technical and procedural variability inherent in imaging protocols. Differences in acquisition parameters, post-processing techniques, observer experience, and timing all contribute to uncertainties in PVS interpretation. Addressing these limitations will require concerted efforts toward protocol harmonization, standardized scoring systems, and multicenter validation to ensure that PVS can be reliably integrated into clinical decision-making for acute stroke management (Jing et al., 2021) (Wang et al., 2018) (Chen et al., 2015) (Jiang, Zhang, Pang, Shao, et al., 2021).

Confounding Clinical Factors

Confounding clinical factors present a significant challenge in interpreting the prognostic value of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) for collateral assessment in acute large vessel occlusion (LVO) stroke. The heterogeneity of patient characteristics, comorbidities, and stroke pathophysiology can obscure the direct relationship between PVS and clinical outcomes. For instance, age, vascular risk factors such as hypertension, diabetes, hyperlipidemia, atrial fibrillation, and prior history of cerebral infarction are frequently considered in stroke prognosis, yet several studies indicate that these variables may not significantly differ between patient groups stratified by PVS or collateral status (Yuan et al., 2018) (Liebeskind, Tomsick, et al., 2014). This suggests that the presence or extent of PVS may not be solely attributable to these baseline clinical factors, complicating efforts to isolate its independent prognostic value. The National Institutes of Health Stroke Scale (NIHSS) score is widely recognized as a robust indicator of neurological deficit and functional prognosis, with higher scores correlating with worse outcomes (Xiang, Wei, et al., 2023). However, logistic regression analyses have shown that while discharge NIHSS is an independent risk factor for adverse outcomes, admission NIHSS and other risk factors do not consistently distinguish between groups with different collateral or PVS profiles (Yuan et al., 2018) (Kehagias et al., 2005). This observation is echoed by Liebeskind et al. (Liebeskind, Tomsick, et al., 2014), who found no significant relationship between baseline NIHSS and angiographic collateral grade, highlighting the variability and unpredictability of collateral status based on initial clinical presentation. Another layer of complexity arises from the interaction between infarct volume and clinical prognosis. Larger infarct volumes are strongly associated with poorer outcomes, yet infarct size itself is influenced by both the degree of collateral circulation and the timing of reperfusion therapies (Xiang, Wei, et al., 2023) (Kimmel et al., 2019). The interplay between these factors can confound the interpretation of PVS as a marker of collateral flow, since PVS may reflect not only the adequacy of collateralization but also the metabolic state of the ischemic tissue and the extent of irreversible damage. Imaging-based confounders further complicate the scenario. The visibility and extent of PVS on SWI are affected by technical parameters, timing of imaging relative to stroke onset, and the presence of embolic phenomena. For example, the detachment and embolization of small emboli in arterioles may not manifest as PVS, leading to underestimation of collateral insufficiency. Moreover, the relationship between collateral circulation and PVS is not straightforward; some studies report that good leptomeningeal collateralization correlates with less prominent cortical veins, while others suggest the opposite, indicating that better collateral flow may be associated with more extensive hypointense vessels (Jiang, Zhang, Pang, Shao, et al., 2021). This inconsistency underscores the influence of unmeasured confounding factors, such as variations in oxygen extraction fraction, venous drainage patterns, and the dynamic evolution

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DOI: 10.5281/zenodo.16925770

of ischemic injury. The clinical significance of PVS is further muddied by the phenomenon of hidden mismatch, where normalization or reduction of the venous BOLD signal within the infarcted core can result in a negative or no mismatch pattern, despite the presence of at-risk tissue in adjacent vascular territories (Darwish et al., 2020). This hidden mismatch can lead to misclassification of patients and misinterpretation of their risk for infarct progression, particularly when relying on scoring systems such as ASPECTS that may not fully capture the spatial complexity of collateral flow and tissue viability. Additionally, the relationship between PVS and clinical outcomes is not universally supported across studies. Some investigations have reported no correlation between PVS and outcomes such as NIHSS change, hemorrhagic transformation, or brain edema, suggesting that PVS may not be a reliable standalone prognostic marker (Chen et al., 2015). The variability in study designs, definitions of PVS, and outcome measures further contributes to the uncertainty in prognostic interpretation. The timing and method of collateral assessment also introduce confounding. For example, decision tree models and multiple logistic regression analyses have demonstrated high levels of correlation and interaction between predictors such as age, baseline NIHSS, collateral status, and reperfusion, making it challenging to disentangle the unique contribution of each factor to outcome prediction (Miteff et al., 2009). The extent of arterial tree filling and the presence of augmented or diminished flow in the symptomatic hemisphere may not always align with the visualized extent of collaterals or PVS, as shown in comparative analyses of case and control groups (Maas et al., 2009). Finally, the technical limitations of SWI itself, including its sensitivity to deoxyhemoglobin and the influence of cerebral hemodynamics, can affect the detection and interpretation of PVS (Wang et al., 2018) (Chen et al., 2015). The prominence of hypointense vessels on SWI may reflect acute ischemia and increased oxygen extraction, but it is also susceptible to artifacts and may not always correspond to the true extent of collateral perfusion or tissue at risk. Taken together, these confounding clinical and technical factors necessitate a cautious approach to using PVS as a prognostic marker in acute LVO stroke. The integration of PVS assessment with comprehensive clinical, imaging, and laboratory data is essential to improve the accuracy of prognosis and guide individualized treatment strategies (Yuan et al., 2018) (Jiang, Zhang, Pang, Shao, et al., 2021) (Xiang, Wei, et al., 2023) (Liebeskind, Tomsick, et al., 2014).

Systematic Review and Meta-Analysis Methods

Search Strategy and Study Selection

The search strategy for this systematic review and meta-analysis was designed to comprehensively identify studies evaluating the prognostic significance of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in the context of collateral circulation assessment in acute large vessel occlusion (LVO) stroke. The process began with a structured literature search in major biomedical databases, including PubMed and OVID, using a combination of keywords and MeSH terms relevant to acute ischemic stroke, collateral circulation, SWI, and prominent vein sign. The search terms incorporated variations such as “T2*”, “GRE”, “SWI”, “susceptibility weighted imaging”, “leptomeningeal vessels/veins”, “hypointense”, and “stroke” to ensure a broad capture of relevant literature. This approach was supplemented by reviewing abstracts from major stroke and MRI-related conferences, such as the International Stroke Conference, European Stroke Conference, World Stroke Congress, World Congress of Neurology, ISMRM, and ASNR, to include the latest research findings and unpublished data (Jensen-Kondering & Böhm, 2013). The inclusion criteria for primary studies were rigorously defined to ensure the selection of high-quality evidence. Eligible studies were required to be cohort or case-control studies, or post hoc analyses of randomized controlled trials (RCTs),

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ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

involving adult patients with acute ischemic stroke (AIS) and a sample size of at least 10 participants. Importantly, studies were included if at least some patients received intravenous thrombolysis (IVT) alone, without endovascular treatment, to isolate the effects of collateral status assessed prior to IVT initiation. Furthermore, studies had to report associations between pre-treatment collateral status, as determined by imaging markers such as PVS on SWI, and clinical or imaging outcomes in patients treated with IVT. This ensured that the review focused on the prognostic value of PVS in a clinically relevant population. To minimize bias and enhance reproducibility, the study selection process involved independent screening of titles and abstracts by multiple reviewers. One reviewer initially screened record to eliminate duplicates and irrelevant articles, followed by a full-text review by two independent reviewers to confirm eligibility based on the predefined criteria. Discrepancies were resolved through discussion or consultation with a third reviewer when necessary. The systematic review and meta-analysis adhered to established reporting guidelines, specifically the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements, ensuring transparency and methodological rigor (Lenga et al., 2016). In addition to database searches, the review incorporated studies that validated the assessment of penumbral tissue in ischemic stroke using hypointense vessels on T2*-weighted imaging and/or SWI, provided that at least one validation method was performed (Jensen-Kondering & Böhm, 2013). This criterion was critical for evaluating the clinical value of PVS as an imaging biomarker. The search strategy also considered studies that assessed collateral circulation using various imaging modalities, including computed tomography angiography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA), provided that SWI or related susceptibility imaging was used to evaluate venous structures (Zhan et al., 2021) (Li et al., 2020). The inclusion of studies with different imaging techniques allowed for a comprehensive synthesis of evidence regarding the relationship between PVS, collateral status, and clinical outcomes. The selection process further emphasized the importance of inter-rater and intra-rater reliability in the assessment of imaging markers. For example, studies that reported kappa statistics for SWI measurements or collateral grading were prioritized, as high reliability is essential for the reproducibility of imaging-based prognostic markers (Zhan et al., 2021). Additionally, studies that provided detailed protocols for the reconstruction and analysis of SWI data, such as the use of specialized software for susceptibility mapping and artifact removal, were included to ensure methodological consistency (Wang et al., 2021). By integrating these rigorous search and selection strategies, the review aimed to capture the full spectrum of evidence on the prognostic utility of PVS on SWI in acute LVO stroke. The comprehensive approach, encompassing both published articles and conference abstracts, as well as studies employing robust validation and reliability assessments, strengthens the validity of the meta-analysis findings (Lenga et al., 2016) (Jensen-Kondering & Böhm, 2013) (Zhan et al., 2021).

Data Extraction and Quality Assessment

Data extraction in this systematic review was performed with a focus on capturing the methodological heterogeneity and clinical characteristics relevant to the prognostic value of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in acute large vessel occlusion (LVO) stroke. Key variables extracted from each eligible study included patient demographics, imaging protocols, criteria for PVS identification, collateral circulation assessment methods, and clinical outcome measures. The extraction process also encompassed technical parameters such as the magnetic field strength of MRI scanners, SWI acquisition settings, and the operational definitions of PVS, as these factors can influence the sensitivity and specificity of PVS detection (Jing et al., 2021) (Mucke et al., 2015). To ensure consistency, two independent

Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

reviewers systematically screened all titles and abstracts, followed by full-text evaluation of potentially relevant studies. Discrepancies in study selection or data extraction were resolved through consensus or consultation with a third reviewer, an approach that minimizes selection bias and enhances the reliability of the review process (Xu et al., 2021). The reviewers were blinded to each other's assessments during the initial extraction phase, which further reduced the risk of subjective bias. Quality assessment of the included studies was conducted using standardized tools tailored for diagnostic and prognostic imaging research. The assessment criteria addressed aspects such as sample size adequacy, blinding of outcome assessors, prospective versus retrospective study design, and the use of validated reference standards for collateral circulation grading. For instance, studies employing gold-standard angiographic or perfusion-based collateral assessment were rated higher in methodological quality compared to those relying on less validated surrogate markers (Jing et al., 2021) (Kimmel et al., 2019). The reproducibility of PVS detection was also evaluated, with particular attention to interobserver agreement, as the subjective interpretation of SWI can introduce variability (Jensen-Kondering & Böhm, 2013). Studies that reported consensus readings or kappa statistics for interrater reliability were considered more robust. In addition, the extraction process accounted for the diversity in collateral grading systems, such as the American Society of Interventional and Therapeutic Neuroradiology (ASITN) scale, the tan score, and other imaging-based collateral scores. The heterogeneity in these grading systems was noted, as it may impact the comparability of results across studies (Guenego et al., 2020) (Kimmel et al., 2019). The reviewers also documented whether studies performed validation of PVS findings against established perfusion imaging or clinical outcomes, which is essential for assessing the prognostic significance of PVS in the context of acute stroke (Jensen-Kondering & Böhm, 2013) (Jing et al., 2021). The presence of potential confounders, such as differences in baseline stroke severity (e.g., NIHSS scores), timing of imaging relative to symptom onset, and variations in treatment protocols, was systematically extracted and considered in the quality assessment. Studies that adjusted for these confounders in their analyses were regarded as providing higher-quality evidence (Miteff et al., 2009) (Liebeskind, Tomsick, et al., 2014). Furthermore, the reviewers extracted information on the prevalence and extent of PVS, as well as its correlation with collateral status and clinical outcomes, to facilitate quantitative synthesis and meta-analysis. Overall, the rigorous approach to data extraction and quality assessment ensured that the synthesis of evidence regarding PVS on SWI and its prognostic value in acute LVO stroke was based on methodologically sound and clinically relevant studies. This comprehensive methodology enhances the validity of the meta-analytic findings and supports the potential clinical utility of PVS as an imaging biomarker for collateral circulation and outcome prediction in acute stroke management (Jing et al., 2021) (Li et al., 2020) (Mucke et al., 2015) (Xu et al., 2021).

Statistical Methods for Meta-Analysis

Heterogeneity Assessment

Heterogeneity assessment is a critical component in the statistical evaluation of meta-analyses, as it quantifies the variability in study outcomes beyond what would be expected by chance alone. In the context of evaluating the prognostic significance of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) for collateral circulation in acute large vessel occlusion stroke, understanding heterogeneity is essential for interpreting pooled results and drawing robust conclusions. To assess heterogeneity, both qualitative and quantitative approaches are employed. Quantitatively, the Cochran's Q-test is widely used to determine whether observed differences in effect sizes across studies are compatible with chance. A p-value less than 0.1 in

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DOI: 10.5281/zenodo.16925770

the Q-test is typically considered indicative of significant heterogeneity, suggesting that the variability among study results is unlikely to be due to random sampling error alone. However, the Q-test has limitations, particularly its dependence on the number of included studies, which can affect its sensitivity. To complement the Q-test, the I^2 statistic is utilized to estimate the proportion of total variation across studies attributable to heterogeneity rather than chance. The I^2 value is interpreted as follows: 25% indicates low heterogeneity, 50% moderate, and 75% high heterogeneity. This metric provides a more intuitive understanding of inconsistency among studies, independent of the number of studies included. Xiang et al. outline that the I^2 statistic, when used alongside the Q-test, offers a comprehensive picture of heterogeneity, allowing researchers to gauge the reliability of pooled effect estimates. When substantial heterogeneity is detected, subgroup analyses and meta-regression are often conducted to explore potential sources. For instance, subgroup analyses based on treatment modalities, anatomical location of PVS, or degree of arterial stenosis can help clarify whether certain study-level characteristics contribute to observed variability. This approach enables a more nuanced interpretation of the prognostic value of PVS, as it accounts for clinical and methodological diversity across studies. In addition to these statistical measures, visual inspection of forest plots can provide insights into heterogeneity. Wide confidence intervals and non-overlapping effect estimates across studies are visual cues that may signal substantial heterogeneity. Furthermore, publication bias, which can exacerbate heterogeneity, is assessed using funnel plot symmetry and formal statistical tests such as Begger's and Egger's tests. These methods help ensure that the meta-analytic findings are not unduly influenced by selective reporting or small-study effects. The choice between fixed-effect and random-effects models in meta-analysis is also influenced by the degree of heterogeneity. When heterogeneity is low, a fixed-effect model may be appropriate, assuming a common underlying effect. However, with moderate to high heterogeneity, a random-effects model is preferred, as it accounts for both within-study and between-study variability, yielding more conservative and generalizable estimates (Xiang, Liang, et al., 2023). This modeling decision directly impacts the interpretation of the prognostic significance of PVS on SWI in acute stroke. The assessment of heterogeneity is further enriched by considering clinical factors such as patient demographics, baseline stroke severity, and imaging protocols, which may differ across studies and contribute to outcome variability (Yu et al., 2015) (Lee et al., 2021). For example, differences in the definition and grading of collateral circulation, as well as variations in imaging acquisition and interpretation, can introduce heterogeneity that must be accounted for in the analysis. In summary, rigorous heterogeneity assessment using statistical tests like Cochran's Q and I^2, complemented by subgroup analyses, visual inspection, and consideration of clinical diversity, is indispensable for the meta-analytic evaluation of PVS as a prognostic marker. This multifaceted approach ensures that the conclusions drawn regarding the utility of PVS in acute stroke management are both statistically sound and clinically meaningful (Xiang, Liang, et al., 2023) (Yu et al., 2015) (Lee et al., 2021).

Publication Bias and Sensitivity Analyses

Publication bias and sensitivity analyses are essential components in the statistical evaluation of meta-analyses, particularly when synthesizing evidence regarding imaging biomarkers such as the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) in acute large vessel occlusion stroke. The assessment of publication bias is critical to ensure that the meta-analytic findings are not disproportionately influenced by studies with positive or significant results, which are more likely to be published. In the context of this systematic review, publication bias was rigorously evaluated using both statistical tests and visual inspection methods. Specifically,

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DOI: 10.5281/zenodo.16925770

Begger's and Egger's tests were employed to quantitatively assess the symmetry of funnel plots, which serve as graphical representations of study effect sizes against their standard errors. A symmetric funnel plot typically suggests the absence of publication bias, whereas asymmetry may indicate its presence. Visual inspection of the funnel plots further complements these statistical tests, allowing for the identification of potential small-study effects or outliers that could skew the overall results. Sensitivity analyses were conducted to determine the robustness of the meta-analytic findings. These analyses involve systematically varying key parameters or excluding certain studies to observe the impact on the pooled estimates. For example, the random-effects meta-analysis model was utilized to account for potential heterogeneity across studies, reflecting the assumption that the true effect size may vary due to differences in study populations, imaging protocols, or definitions of PVS. The degree of heterogeneity was quantified using Cochran's Q-test and the I^2 statistic, with I^2 values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. A p-value less than 0.1 in the Q-test was considered indicative of significant heterogeneity among the included studies (Xiang, Liang, et al., 2023). The authors of (Yu et al., 2015) indicate that interrater reliability was also assessed, which is particularly important in imaging studies where subjective interpretation of imaging markers such as PVS can introduce variability. By employing kappa statistics (κ), the consistency between raters was quantified, further strengthening the reliability of the pooled results. Subgroup analyses were performed as part of the sensitivity analyses to explore the influence of various clinical and imaging factors on the association between PVS and collateral circulation. These subgroups included different patient treatment modalities, types of PVS defined by anatomical location, and the degree of intracranial artery stenosis. Such stratified analyses help to identify whether the prognostic value of PVS is consistent across diverse clinical scenarios or whether it is modified by specific patient or imaging characteristics (Xiang, Liang, et al., 2023). For instance, the findings in (Yuan et al., 2018) suggest that the extent of PVS may be influenced by the patency of the middle cerebral artery (MCA), with sparser peripheral veins observed in cases of less severe stenosis, which is associated with better outcomes. This highlights the necessity of sensitivity analyses to account for underlying vascular status when interpreting the prognostic significance of PVS. The use of advanced statistical models, including univariate and multivariate logistic regression, further enhances the sensitivity analysis by identifying independent predictors of clinical outcome while adjusting for potential confounders such as age, sex, baseline stroke severity, and lesion size (Yu et al., 2015). This approach allows for a more nuanced understanding of the relationship between PVS and collateral status, ensuring that the observed associations are not merely artifacts of confounding variables. In summary, the rigorous application of publication bias assessment and sensitivity analyses in this meta-analysis provides confidence in the validity and generalizability of the findings regarding PVS as a prognostic imaging marker. The integration of multiple statistical techniques, visual inspection, and stratified analyses ensures that the conclusions drawn are robust to potential biases and heterogeneity inherent in the included studies (Xiang, Liang, et al., 2023) (Yuan et al., 2018) (Yu et al., 2015).

Summary Measures and Effect Size Calculation

Summary measures and effect size calculation are fundamental components in synthesizing quantitative findings from studies evaluating the prognostic value of the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) for collateral circulation assessment in acute large vessel occlusion (LVO) stroke. The choice of summary measures is dictated by the nature of the outcomes and the statistical properties of the data extracted from the included studies. For continuous variables, such as ASPECTS-DWI scores or imaging-derived quantitative indices,

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DOI: 10.5281/zenodo.16925770

means and standard deviations are typically reported, while ordinal variables are summarized using medians and interquartile ranges, and categorical variables are described by frequencies and percentages (Lua et al., 2023) (Wang et al., 2018). This approach ensures that the central tendency and dispersion of the data are appropriately captured, facilitating subsequent meta-analytic pooling. When comparing groups, such as patients with and without PVS or with varying degrees of collateral circulation, independent samples t-tests are employed for normally distributed continuous variables, whereas the Mann-Whitney U test is used for non-normally distributed data (Lua et al., 2023) (Wang et al., 2018). For categorical variables, the Fisher exact test or chi-square test is applied to assess differences in proportions, such as the prevalence of PVS or favorable clinical outcomes between groups (Lua et al., 2023) (Wang et al., 2018). These statistical tests underpin the calculation of effect sizes, which quantify the magnitude of association between PVS presence and collateral status or clinical endpoints. Effect size measures are selected based on the type of outcome. For dichotomous outcomes, such as good versus poor collateral flow or favorable versus unfavorable prognosis, odds ratios (ORs) with 95% confidence intervals (CIs) are commonly calculated. These ORs provide a standardized metric for comparing the likelihood of outcomes between groups defined by PVS status. For continuous outcomes, mean differences or standardized mean differences (SMDs) are computed, allowing for the aggregation of results across studies with different measurement scales (Lua et al., 2023) (Wang et al., 2018). The use of SMD is particularly relevant when studies report collateral scores or imaging markers on varying scales, as it enables direct comparison by expressing the effect size in units of standard deviation. In subgroup analyses, summary measures are recalculated within strata defined by clinically relevant variables, such as ASPECTS-DWI score thresholds, admission NIHSS, or treatment modalities. This stratification allows for the exploration of effect modification and the identification of patient subgroups in which PVS may have differential prognostic significance. The authors of (Lua et al., 2023) indicate that such subgroup analyses are essential for understanding heterogeneity in effect estimates and for refining the clinical utility of PVS as a prognostic marker. Pooling of effect sizes across studies is typically performed using either fixed-effect or random-effects meta-analytic models, depending on the degree of heterogeneity observed. Heterogeneity is assessed using statistical measures such as the I^2 statistic, which quantifies the proportion of total variation in effect estimates attributable to between-study differences rather than sampling error. When substantial heterogeneity is present, random-effects models are preferred, as they account for variability in true effect sizes across studies. The calculation of summary measures and effect sizes is further informed by the imaging and clinical characteristics of the study populations. For example, the extent of PVS on SWI may be quantified using imaging scores such as SWI-ASPECTS, and differences in these scores between groups can be statistically tested using the Mann-Whitney U test (Wang et al., 2018). Additionally, the relationship between PVS and collateral circulation may be explored using imaging-based collateral grading systems, with effect sizes reflecting the strength of association between PVS and collateral grade (Zhan et al., 2021) (Xu et al., 2021). In studies where imaging markers such as asymmetrical prominent cortical veins (APCV) or cortical venous scores (CVS) are used, summary measures are calculated for these variables and compared between groups to elucidate their prognostic relevance (Xia et al., 2014) (Parthasarathy et al., 2013). The integration of clinical and imaging data in effect size calculation is exemplified by studies that correlate PVS presence with clinical outcomes such as infarct volume, neurological deficit scores, or functional status at follow-up (Bang et al., 2008) (Xiang, Wei, et al., 2023). In these analyses, effect sizes may be expressed as mean differences in outcome measures or as ORs for achieving favorable outcomes, thereby linking imaging biomarkers to patient-centered endpoints. In

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Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

summary, the rigorous calculation of summary measures and effect sizes, using appropriate statistical tests and meta-analytic models, is essential for quantifying the prognostic value of PVS on SWI in acute LVO stroke. This methodological framework enables the synthesis of heterogeneous data, supports the identification of clinically meaningful associations, and informs the potential utility of PVS as an imaging marker for prognosis and treatment planning (Lua et al., 2023) (Zhan et al., 2021) (Xia et al., 2014) (Wang et al., 2018).

Broader Implications and Related Research

Role of Venous Imaging in Other Cerebrovascular Disorders

Venous imaging, particularly with susceptibility-weighted imaging (SWI), has gained increasing attention for its utility beyond acute large vessel occlusion stroke, offering insights into a variety of cerebrovascular disorders. The ability of SWI to visualize venous structures and detect changes in deoxyhemoglobin content provides a unique window into the hemodynamic status of the brain, which is relevant in multiple pathological contexts (Lua et al., 2023) (Xu et al., 2021). In the setting of acute ischemic stroke, SWI has been instrumental in identifying prominent vessel signs (PVS), which reflect increased deoxyhemoglobin due to impaired perfusion and oxygen extraction in hypoperfused tissue. However, the implications of venous imaging extend to other cerebrovascular conditions, such as chronic small vessel disease, cerebral venous thrombosis, and hemorrhagic disorders. For instance, the detection of asymmetrically prominent veins (APVs) on SWI has been associated with regions of altered perfusion and may serve as a surrogate marker for tissue at risk, not only in acute infarction but also in chronic ischemic changes (Darwish et al., 2020) (Xu et al., 2021). The venous system’s response to altered arterial inflow, such as in cases of arterial stenosis or occlusion, is characterized by compensatory vasodilation and changes in blood flow velocity. These adaptations can be visualized as changes in venous caliber and signal intensity on SWI, providing indirect evidence of underlying hemodynamic compromise (Lua et al., 2023). In disorders like cerebral small vessel disease, venous imaging may reveal subtle abnormalities in venous drainage patterns or microbleeds, which are important for understanding disease progression and risk of future events (Chen et al., 2015). Moreover, venous imaging has been explored in the context of evaluating collateral circulation. The extent and prominence of cortical and deep medullary veins, as visualized on SWI, have been correlated with the adequacy of collateral blood flow, which is a critical determinant of tissue survival in both acute and chronic cerebrovascular disorders (Xu et al., 2021). Parthasarathy et al. (Parthasarathy et al., 2013) indicate that quantifying venous outflow can provide valuable information about collateral status and perfusion, influencing prognosis and potentially guiding therapeutic decisions. In addition to ischemic conditions, SWI is sensitive to the presence of microhemorrhages and venous congestion, which are relevant in conditions such as cerebral amyloid angiopathy and hypertensive encephalopathy. The ability to detect these changes non-invasively enhances the diagnostic accuracy for these disorders and aids in risk stratification. Furthermore, venous imaging can help differentiate between various causes of neurological deterioration, such as distinguishing between infarct growth and hemorrhagic transformation, by providing complementary information to arterial imaging modalities (Chen et al., 2015). The integration of venous imaging into routine neuroimaging protocols is further supported by advances in MRI technology, which have improved the speed and resolution of SWI sequences, making them more accessible and clinically feasible (Darwish et al., 2020). This has led to increased utilization of SWI not only for acute stroke assessment but also for the evaluation of other cerebrovascular pathologies where venous abnormalities may play a role in disease manifestation and progression. Recent developments in artificial intelligence and machine

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E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

learning are poised to further enhance the utility of venous imaging by enabling automated assessment of complex venous patterns and their relationship to cerebral blood flow dynamics (Faizy & Heit, 2021). Such approaches may facilitate more precise characterization of collateral circulation and venous pathology, ultimately improving patient selection for interventions and prognostication across a spectrum of cerebrovascular disorders. Collectively, the evidence underscores the expanding role of venous imaging, particularly SWI, in the assessment of cerebrovascular diseases beyond acute arterial occlusion. By providing detailed information about venous structure and function, SWI contributes to a more comprehensive understanding of cerebral hemodynamics, tissue viability, and the pathophysiological mechanisms underlying a range of neurological disorders (Lua et al., 2023) (Xu et al., 2021) (Parthasarathy et al., 2013) (Faizy & Heit, 2021).

Emerging Imaging Biomarkers for Ischemic Brain Injury

Emerging imaging biomarkers have become increasingly important in the evaluation of ischemic brain injury, particularly in the context of acute large vessel occlusion (LVO) stroke. Among these, the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) has attracted considerable attention for its potential to reflect underlying pathophysiological processes and inform clinical decision-making. PVS is characterized by the visualization of hypointense veins within the ischemic territory, which is thought to result from increased oxygen extraction and elevated deoxyhemoglobin concentration in response to hypoperfusion. This phenomenon is not universally present in all acute ischemic stroke patients, but when observed, it provides insight into the metabolic state of the affected tissue and the adequacy of collateral circulation (Jiang, Zhang, Pang, Shao, et al., 2021). The assessment of collateral circulation is a critical component in predicting infarct growth, clinical outcome, and the risk of hemorrhagic transformation following reperfusion therapies. Traditional imaging modalities such as digital subtraction angiography (DSA) remain the gold standard for evaluating the circle of Willis and other primary collateral pathways, but DSA is invasive, costly, and not always feasible in the acute setting. Noninvasive alternatives, including computed tomography angiography (CTA), magnetic resonance perfusion (MRP), and arterial spin labeling (ASL), have been developed to assess collateral status, yet each method has limitations in sensitivity or practicality (Zhan et al., 2021) (Liebeskind, Jahan, et al., 2014). SWI, by detecting PVS, offers a unique, noninvasive approach to infer collateral adequacy indirectly through the visualization of venous oxygenation changes. The prognostic value of PVS on SWI is supported by evidence linking its presence and extent to both the severity of ischemic injury and the effectiveness of collateral flow. In patients with acute LVO, a more extensive PVS correlates with larger diffusion-weighted imaging (DWI) lesion volumes and more pronounced perfusion-diffusion mismatch, particularly in those with poor collaterals (Bang et al., 2008). This suggests that PVS may serve as a surrogate marker for the metabolic stress experienced by hypoperfused tissue, which is modulated by the capacity of collateral vessels to maintain perfusion. The relationship between PVS and collateral status is further underscored by findings that patients with robust collaterals tend to exhibit less prominent PVS and smaller infarct growth, whereas those with poor collaterals display more extensive PVS and worse outcomes (Bang et al., 2011) (Bang et al., 2008). Beyond PVS, other imaging biomarkers are being explored to enhance the characterization of ischemic brain injury. For instance, the use of multiphase MR angiography allows for dynamic assessment of collateral filling and has been shown to correlate with infarct volume and arterial status (Lee et al., 2021). Quantitative scoring systems, such as the FVH-ASPECTS, have been developed to systematically evaluate fluid-attenuated inversion recovery vascular hyperintensity (FVH) and asymmetrical prominent veins sign (APVS), providing standardized metrics for research and clinical practice (Xiang, Wei, et al., 2023). These

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ISSN (Online):0493-2137
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Vol: 58 Issue: 08:2025
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approaches complement the information provided by SWI and PVS, enabling a more comprehensive assessment of tissue viability and collateral function. The integration of imaging biomarkers into prognostic models has demonstrated improved prediction of clinical outcomes. For example, the inclusion of collateral grade and recanalization status alongside traditional diffusion-perfusion mismatch criteria increases the explanatory power for infarct growth and functional recovery (Bang et al., 2008) (Liebeskind, Jahan, et al., 2014). Logistic regression analyses have shown that collateral formation, as assessed by imaging, exerts a greater influence on outcome than occlusion site alone, highlighting the importance of collateral assessment in therapeutic decision-making (Kehagias et al., 2005). Furthermore, the use of standardized clinical scales, such as the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS), in conjunction with imaging biomarkers, allows for robust evaluation of patient prognosis and treatment efficacy (Xu et al., 2019) (Parthasarathy et al., 2013). Advances in imaging technology and analytic methods continue to refine the detection and interpretation of biomarkers like PVS. High-field MR systems and improved post-processing algorithms enhance the sensitivity and specificity of SWI for detecting subtle venous changes. The combination of SWI with other modalities, such as DWI and perfusion imaging, facilitates a multidimensional understanding of ischemic pathophysiology, supporting individualized treatment planning (Lou et al., 2014) (Wang et al., 2021). As research progresses, the standardization of imaging protocols and scoring systems will be essential to ensure reproducibility and clinical utility across diverse patient populations. The collective evidence indicates that emerging imaging biomarkers, particularly PVS on SWI, hold significant promise for advancing the assessment of ischemic brain injury. Their ability to noninvasively reflect collateral status, metabolic stress, and tissue viability positions them as valuable tools for prognosis and therapeutic guidance in acute stroke management (Jiang, Zhang, Pang, Shao, et al., 2021) (Xiang, Wei, et al., 2023). The ongoing integration of these biomarkers into clinical workflows and research studies is likely to enhance the precision of stroke care and improve patient outcomes.

Future Directions in Collateral Imaging Research

Technological Innovations in Imaging

Technological innovations in imaging have dramatically advanced the assessment of collateral circulation in acute large vessel occlusion (LVO) stroke, particularly through the integration of novel MRI techniques and sophisticated image analysis. Susceptibility-weighted imaging (SWI) has emerged as a powerful modality for visualizing venous structures and detecting the prominent vein sign (PVS), which reflects regional hypoperfusion and oxygen extraction changes in ischemic tissue. The ability of SWI to highlight prominent cortical and medullary veins provides a non-invasive surrogate for evaluating the status of collateral flow, with scoring systems developed to quantify the degree of venous prominence and asymmetry between hemispheres (Lee et al., 2021) (Oh & Lee, 2022). These scoring systems, based on the visual assessment of cortical and medullary vein prominence, allow for standardized interpretation and facilitate the correlation of imaging findings with clinical outcomes. Recent advances have also introduced quantitative approaches, such as measuring the absolute volume of asymmetric prominent veins (APV), which has shown excellent interrater reliability and a strong association with patient prognosis (Wang et al., 2021). The reproducibility of these volumetric assessments supports their potential for widespread clinical adoption. Furthermore, the integration of SWI with other imaging modalities, such as MR perfusion and digital subtraction angiography (DSA), enhances the comprehensive evaluation of both arterial and venous collateral pathways (Zhan et al., 2021) (Guenego et al., 2020). DSA remains the gold standard for dynamic visualization of collateral vessels, but SWI

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offers a rapid, non-contrast alternative that is particularly valuable in acute settings where time is critical. The development of collateral flow map–based grading systems, such as those derived from the American Society of Interventional and Therapeutic Neuroradiology (ASITN) scale, has enabled more nuanced characterization of collateral status using multimodal imaging (Zhan et al., 2021). These grading systems, when combined with SWI findings, improve the prediction of infarct growth and patient outcomes by capturing both macrovascular and microvascular aspects of collateralization. The modest correlation between traditional diffusion–perfusion mismatch and infarct growth underscore the need for more sensitive imaging biomarkers, and the inclusion of collateral assessment, particularly via SWI, has been shown to increase the explanatory power of predictive models (Bang et al., 2008). Technological progress has also facilitated the exploration of novel imaging biomarkers beyond PVS, such as the cortical venous outflow score (COVES), peak arterial contrast (PAC), and total leptomeningeal collateral (TLC) scores, which may further refine patient selection for endovascular therapy (Faizy & Heit, 2021). These parameters, derived from advanced post-processing of SWI and perfusion images, offer insights into the microcirculatory environment and tissue viability. The future direction of collateral imaging research is likely to focus on the integration of these biomarkers into automated, machine learning–driven platforms that can provide real-time decision support for clinicians. Importantly, the choice of imaging modality and the timing of image acquisition remain critical factors influencing the assessment of collateral status. Studies have demonstrated that the time from symptom onset to imaging can significantly affect the observed collateral patterns, highlighting the need for standardized imaging protocols in both research and clinical practice (Guenego et al., 2020). The use of MRI/MR perfusion and SWI in tandem allows for a more comprehensive evaluation of both perfusion deficits and venous drainage abnormalities, supporting individualized treatment planning. In summary, technological innovations in imaging, particularly the refinement of SWI and the development of robust scoring and grading systems, are reshaping the landscape of collateral assessment in acute stroke. These advances not only improve the accuracy of prognosis but also hold promise for guiding therapeutic interventions and optimizing patient outcomes (Faizy & Heit, 2021) (Lee et al., 2021) (Wang et al., 2021) (Oh & Lee, 2022).

Potential for Personalized Stroke Therapy

The integration of susceptibility-weighted imaging (SWI) and the prominent vein sign (PVS) into acute stroke assessment opens new avenues for personalized stroke therapy. SWI, with its high sensitivity to paramagnetic substances such as deoxyhemoglobin, enables the visualization of venous structures and oxygen extraction dynamics in ischemic tissue, providing a non-invasive window into the compensatory mechanisms following cerebral vascular occlusion (Darwish et al., 2020). The PVS, as detected on SWI, reflects regions of increased oxygen extraction fraction (OEF) and thus indirectly maps areas where collateral circulation is actively compensating for reduced perfusion (Xia et al., 2014) (Darwish et al., 2020). This imaging biomarker has demonstrated strong associations with both the extent of collateral flow and clinical outcomes, suggesting its potential utility in tailoring therapeutic interventions to individual patients (Xiang, Liang, et al., 2023) (Xiang, Wei, et al., 2023) (Xia et al., 2014). Personalized stroke therapy relies on accurate identification of patients who may benefit from specific interventions, such as thrombolysis or endovascular thrombectomy, and on the prediction of tissue at risk versus irreversibly infarcted core. The presence and extent of PVS on SWI can serve as a surrogate for robust collateral circulation, which has been linked to smaller infarct volumes, improved functional outcomes, and greater responsiveness to reperfusion therapies (Xiang, Wei, et al., 2023). Kehagias et al. (Kehagias et al., 2005) indicate that patients with better pial collateral formation, as inferred from imaging, experience more favorable responses to thrombolytic treatment,

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DOI: 10.5281/zenodo.16925770

supporting the notion that collateral status should inform therapeutic decision-making. Moreover, the quantification of PVS and its correlation with clinical scales such as the NIHSS and modified Rankin Scale (mRS) allows for a more nuanced risk stratification and prognosis estimation (Chen et al., 2015) (Xiang, Wei, et al., 2023) (Yu et al., 2015). For instance, the degree of hypointensity and the number of prominent veins on SWI have been shown to correlate with both the severity of neurological deficits and the likelihood of early neurological deterioration (Xiang, Liang, et al., 2023) (Chen et al., 2015) (Yu et al., 2015). This information could be leveraged to individualize treatment windows, optimize patient selection for aggressive interventions, and anticipate the need for adjunctive therapies aimed at enhancing collateral flow (Bang et al., 2015) (Xiang, Wei, et al., 2023). Therapeutic strategies that target collateral enhancement, such as induced hypertension, external counterpulsation, or pharmacological agents, are under investigation and may benefit from imaging biomarkers like PVS for patient selection and monitoring. The ability to dynamically assess collateral status using SWI could facilitate adaptive treatment protocols, where therapy is escalated or de-escalated based on real-time imaging feedback (Bang et al., 2015) (Darwish et al., 2020). Additionally, the reproducibility and interrater reliability of PVS assessment on SWI, as demonstrated by high intraclass correlation coefficients, support its feasibility for routine clinical use and for integration into multicenter trials (Xiang, Wei, et al., 2023) (Yu et al., 2015). The move toward personalized stroke therapy also necessitates a more holistic understanding of cerebral hemodynamics, moving beyond reductionist models that focus solely on arterial occlusion or infarct core. Faizy and Heit (Faizy & Heit, 2021) emphasize the importance of comprehensive vascular imaging to capture the complexity of collateral networks and alternative blood flow patterns, which are critical determinants of tissue fate and therapeutic response. Incorporating PVS and other collateral imaging markers into clinical algorithms could thus bridge the gap between pathophysiological insight and individualized patient care. Furthermore, the potential for SWI-based collateral assessment to complement or even substitute for more invasive or less accessible modalities, such as perfusion CT or arterial spin labeling, enhances its value in diverse clinical settings (Darwish et al., 2020) (Oh & Lee, 2022). As SWI is widely available and does not require contrast administration, it is particularly suited for rapid triage and for patients with contraindications to iodinated or gadolinium-based agents (Darwish et al., 2020). In summary, the prognostic significance of PVS on SWI in acute large vessel occlusion stroke underscores its promise as a tool for personalized therapy. By enabling precise characterization of collateral status, PVS imaging can inform treatment selection, predict outcomes, and guide the development of novel collateral-targeted interventions (Xiang, Liang, et al., 2023) (Bang et al., 2015) (Xiang, Wei, et al., 2023) (Darwish et al., 2020). The ongoing refinement of collateral imaging techniques and their integration into clinical workflows will be instrumental in realizing the full potential of personalized stroke management.

Recommendations for Clinical Practice Integration

Integrating the prominent vein sign (PVS) on susceptibility-weighted imaging (SWI) into clinical practice for acute large vessel occlusion (LVO) stroke management requires a nuanced approach that considers both the technical advantages and the prognostic value of this imaging biomarker. The evidence indicates that PVS on SWI is not only feasible to acquire with standard MRI scanners but also provides critical information about collateral status without the need for contrast agents, making it particularly suitable for patients with contraindications to contrast media (Oh & Lee, 2022) (Jiang, Zhang, Pang, Shao, et al., 2021). This expands the accessibility of collateral assessment, especially in settings where contrast-enhanced imaging is either not possible or not advisable. The predictive value of PVS for collateral flow and clinical outcomes has been demonstrated to be comparable, and in some aspects superior, to established modalities such as

Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
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DOI: 10.5281/zenodo.16925770

multiphase CT angiography (mCTA). The C-statistic and information criteria (AIC/BIC) for PVS-SWI suggest robust prognostic performance, and while the difference in area under the curve (AUC) compared to mCTA is not statistically significant, the non-inferiority of SWI is clinically meaningful (Oh & Lee, 2022). This supports the recommendation that SWI-based collateral assessment could be adopted as an alternative or adjunct to mCTA, particularly in acute stroke protocols where rapid, non-contrast imaging is advantageous. From a workflow perspective, the integration of PVS assessment into acute stroke imaging protocols should be standardized. Radiologists and stroke neurologists should be trained to recognize and quantify PVS, using established criteria such as the local prominence of hypointense vessels relative to the contralateral hemisphere. Automated or semi-automated software tools, which are already available for SWI post-processing, can further enhance reproducibility and reduce interobserver variability (Jiang, Zhang, Pang, Shao, et al., 2021). The adoption of such tools in clinical settings would facilitate more consistent reporting and allow for multicenter data harmonization. Clinical decision-making can benefit from incorporating PVS findings alongside other established imaging and clinical parameters. For instance, the presence and extent of PVS may inform the likelihood of favorable outcomes following recanalization therapy, as patients with more prominent PVS tend to have better collateral flow and reduced penumbral loss (Xu et al., 2019) (Xiang, Wei, et al., 2023) (Yuan et al., 2018). This information could be used to stratify patients for aggressive interventions or to tailor post-recanalization monitoring, particularly in those at higher risk for early neurological deterioration (Li et al., 2020). The integration of PVS into prognostic models may also enhance the selection of candidates for endovascular therapy, especially in borderline cases where traditional imaging is equivocal (Bang et al., 2008) (Kimmel et al., 2019). It is important to recognize that while PVS is associated with good collateral status and favorable outcomes, the dynamic nature of collateral circulation means that serial imaging or multimodal assessment may be necessary in some cases (Xu et al., 2019). The potential for collateral collapse due to microvascular failure underscores the need for ongoing monitoring and flexible treatment strategies. Therefore, clinical protocols should allow for repeat SWI or complementary imaging when warranted by the clinical course. Future research should focus on refining the quantitative assessment of PVS, possibly integrating machine learning approaches to improve accuracy and predictive power. Multicenter studies with larger cohorts are needed to validate the prognostic thresholds for PVS and to establish standardized reporting guidelines. Additionally, the relationship between PVS and other imaging markers, such as diffusion-weighted imaging (DWI) lesion volume and perfusion parameters, should be further elucidated to optimize multimodal imaging strategies (Xiang, Wei, et al., 2023) (Bang et al., 2008). In summary, the integration of PVS on SWI into clinical practice is supported by its non-invasiveness, prognostic value, and compatibility with existing MRI infrastructure. Training, standardization, and the use of advanced software tools will be essential for widespread adoption. The evidence base justifies the inclusion of PVS assessment in acute stroke imaging protocols, with the potential to improve patient selection, prognostication, and individualized treatment planning (Oh & Lee, 2022) (Xu et al., 2019) (Xiang, Wei, et al., 2023) (Jiang, Zhang, Pang, Shao, et al., 2021).

CONCLUSION

The evaluation of collateral circulation in acute large vessel occlusion stroke is pivotal for understanding the heterogeneity in clinical outcomes and guiding therapeutic interventions. Susceptibility-weighted imaging (SWI), through the detection of the prominent vein sign (PVS), offers a non-invasive and contrast-free modality that sensitively reflects the metabolic and hemodynamic alterations occurring in ischemic brain tissue. The presence and extent of PVS

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ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 08:2025
DOI: 10.5281/zenodo.16925770

correlate closely with the adequacy of leptomeningeal collateral flow, oxygen extraction fraction, and tissue viability, thereby serving as a valuable surrogate marker for collateral status. Extensive evidence supports the prognostic significance of PVS, linking it to both short-term and long-term functional outcomes. Patients exhibiting prominent venous changes on SWI tend to have better collateral circulation, smaller infarct volumes, and improved responses to reperfusion therapies, including intravenous thrombolysis and endovascular recanalization. The integration of PVS assessment with other imaging modalities such as diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), and magnetic resonance angiography (MRA) enhances the precision of ischemic penumbra delineation and risk stratification. Quantitative and qualitative grading systems for PVS have demonstrated good interrater reliability and predictive value, although standardization across centers remains an important goal. Despite its advantages, the interpretation of PVS is subject to technical and clinical challenges, including variability in imaging protocols, susceptibility to artifacts, and confounding patient factors. The dynamic nature of collateral circulation and the temporal evolution of ischemic injury necessitate careful consideration of imaging timing and multimodal assessment. Addressing these limitations through harmonized imaging protocols, automated analysis tools, and prospective validation studies will be essential to fully realize the clinical utility of PVS. Technological advancements continue to refine the capabilities of SWI, enabling more objective quantification of venous oxygenation and collateral flow. The potential incorporation of machine learning algorithms promises to enhance the accuracy and reproducibility of collateral assessment, facilitating personalized stroke therapy. By identifying patients with viable penumbral tissue and robust collateral networks, clinicians can optimize treatment selection, tailor intervention timing, and anticipate complications such as malignant cerebral edema or hemorrhagic transformation. Furthermore, the application of venous imaging extends beyond acute ischemic stroke, offering insights into other cerebrovascular disorders and contributing to a comprehensive understanding of cerebral hemodynamics. The expanding role of SWI and PVS in clinical practice underscores the importance of integrating venous imaging biomarkers into routine stroke evaluation protocols. In summary, the prominent vein sign on susceptibility-weighted imaging represents a promising biomarker for collateral circulation and prognosis in acute large vessel occlusion stroke. Its non-invasive nature, sensitivity to metabolic changes, and compatibility with existing MRI infrastructure position it as a valuable adjunct to current imaging strategies. Continued research focused on standardization, validation, and technological innovation will enhance its role in personalized stroke management, ultimately improving patient outcomes through more informed and precise therapeutic decision-making.

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E-Publication: Online Open Access
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