

Research Advancements on the Correlation Between Spontaneous Intracerebral Hemorrhage of Different Etiologies and Imaging Markers of Cerebral Small Vessel Disease

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Objective: The purpose of this review is to identify the correlation between ICH and CSVD imaging markers under SMASH-U classification by searching and analyzing a large number of literatures in recent years, laying a theoretical foundation for future clinical research. At the same time, by collecting clinical data to evaluate patient prognosis, analyzing whether there are differences or supplements between clinical trial conclusions and previous theories, and ultimately guiding clinical diagnosis and treatment through the analysis of imaging biomarkers.

Methods: In this review, by searching CNKI, Web of Science, PubMed, FMRS and other databases, the use of “spontaneous intracerebral hemorrhage”, “hypertensive hemorrhagic cerebral small vessel disease”, “cerebral small vessel disease imaging”, “Based cerebral small vessel diseases”, “SMASH the -u classification” and their Chinese equivalents for the main search term. We focused on reading and analyzing hundreds of relevant literatures in the last decade from August 2011 to April 2020, and also included some earlier literatures with conceptual data sources. After screening and ranking the degree of relevance to this study, sixty of them were cited for analysis and elaboration.

Results: In patients with ICH, the number of cerebral microbleeds in lobes, basal ganglia, and the deep brain is positively correlated with ICH volume and independently correlated with neurological functional outcomes; white matter hyperintensity severity is positively correlated with ICH recurrence risk; multiple lacunar infarction independently predict the risk of ICH; severe brain atrophy is an independent risk factor for a poor prognosis in the long term in patients diagnosed with ICH; and the number of enlarged perivascular spaces is correlated with ICH recurrence. However, small subcortical infarct and ICH are the subject of few studies. Higher CSVD scores are independently associated with functional outcomes at 90 days in patients diagnosed with ICH.

Keywords: amyloid angiopathy intracerebral hemorrhage, hereditary cerebral small vessel disease, hypertensive intracerebral hemorrhage, imaging markers of cerebral small vessel disease, SMASH-U classification

Introduction

Spontaneous intracerebral hemorrhage (ICH) is the non-traumatic rupture of intracerebral blood vessels, leading to blood pooling in the brain parenchyma. Its incidence is only secondary to ischemic stroke. Classifying ICH correctly can improve treatment and prognosis, and one common method uses the location of bleeding. Prognosis prediction, however, is not as straightforward based on anatomical location alone. The SMASH-U etiologic classification, the most recent and practical classification for ICH, has been widely accepted for determining the prognosis of patients.^{1,2}

Cerebral small vessel disease (CSVD) represents a type of disease with clinical and imaging manifestations and pathological syndromes involving the cerebral arterioles and their distal branches, arterioles, capillaries, venules, and small veins.³ Approximately one-fourth of strokes are caused by CSVD, and spontaneous ICH is one of the most serious

consequences of CSVD. This proportion has increased with the enhancement of people's living standards and their advancing age. CSVD is associated with the incidence, severity, and prognosis of ICH. However, most of the previous clinical studies were single-etiology, and there was a lack of reviews based on SMASH-U etiologic classification and CSVD imaging markers. In this paper, we review the clinical significance of the correlation between spontaneous ICH of different etiologies and imaging markers of CSVD.

SMASH-U Classification for Spontaneous ICH

The 30-day mortality rate for spontaneous ICH ranges between 35%–52%. Therefore, the most reasonable strategy is to identify high-risk ICH, and to treat and prevent ICH based on the specific etiological classification. The etiology-based SMASH-U classification—structural vascular lesion-related ICH (S), medication-related ICH (M), amyloid angiopathy ICH (A), systemic disease-related ICH (S), hypertension-related ICH (H), and undetermined ICH (U)—is a novel etiological classification for ICH.^{1,2} This classification combines demographic characteristics, relevant risk factors, and clinical data, which are essential for accurate prognostic assessment and optimal treatment.

Imaging Markers of CSVD

Recent small subcortical infarct (RSSI), presumed vasogenic lacuna (LA), presumed vasogenic white matter hyperintensity (WMH), enlarged perivascular space (EPVS), cerebral microbleed (CMB), and brain atrophy (BA) are the main imaging features of CSVD.⁴

RSSI

RSSI refers to recent small infarcts that occurred in the region of the perforating arterial vessel within the last four weeks, with a maximum axial diameter of 20 mm, accounting for approximately 25% of acute ischemic stroke.^{3,5} Most lesions are found in the posterior limbs of the internal capsules, centrum semiovale, lenticular nucleus, anterolateral thalamus, and the subtentorial region (brainstem and cerebellum). It is characterized by low signals on T1WI sequences and high signals on T2WI, FLAIR, and DWI sequences.⁴ A study by Arboix et al⁶ showed that, recent small subcortical infarcts usually cause classic or atypical lacunar syndromes.

Presumed Vasogenic LA

Presumed vasogenic LA, also known as “lacunar infarction (LI)”, refers to the small cavity remaining in the brain tissue after the necrotic tissue of the subcortical infarct has been cleared; it is secondary to subcortical small infarction, and can result in progressive neurological functional decline. It appears as round or oval cavities in the subcortical area, internal capsules, centrum semiovale, or brainstem on magnetic resonance imaging (MRI), similar to cerebrospinal fluid signals. It has a diameter of 3–15 mm and exhibits low signals on T1-weighted imaging (T1WI), high signals on T2WI, a low-signal center surrounded by high-signal loop on fluid attenuated inversion recovery (FLAIR) sequences, and no high signals on diffusion-weighted imaging (DWI).⁴ Internationally, experts recommend noting the location of each lesion and the total number of lesions, and grading numerically: grade 0 = normal; grade 1 = 1–3 lesions; grade 2 = 4–10 lesions; grade 3 $\geq$ 10 lesions.⁷

Presumed Vasogenic WMH

WMH is characterized by essentially symmetrical, spot-like, or patchy abnormal signals in the white matter region of the brain, with varying sizes and blurred boundaries. Small cap-like lesions in the frontal lobe and occipital angle expand to the subcortical white matter area and fuse with the lesions at the basal ganglia and the white matter region of the thalamus. They exhibit equal or low signals on T1WI sequences, and high signals on T2WI and FLAIR sequences.⁴ Currently, WMH severity is measured using the Fazekas grading scale, which evaluates the aggregate of the paraventricular and deep WMH, with a score of 0–6.⁸ It is typically classified as periventricular white matter hyperintensity (PVH) grading and deep brain white matter hyperintensity (DWMH) grading. PVH grading: 0 = none; 1 = “cap-like” or “pencil-like” lining; 2 = smooth “halo”; 3 = irregular PVH extending to deep white matter. DWMH grading: 0 = none; 1 = spot-like lesion; 2 = lesions beginning to fuse; 3 = lesions fused into larger areas.⁹

EPVS

EPVS is an enlarged gap that surrounds and travels along blood vessels. On MRI, it appears as a linear shape around vessels moving in parallel and as a circular or oval shape around vessels moving vertically, with similar signals to the cerebrospinal fluid. It exhibits low signals on T1WI and FLAIR sequences and high signals on T2WI, with a typical diameter < 3 mm. PVS is more prevalent in the basal ganglia, subcortical area, and brainstem than in the cerebellum.⁴ A 4-level rating scale is normally used, and the aspect with the most abundant perivascular spaces in the basal ganglia, hippocampus, and centrum semiovale is selected for severity grading:¹⁰ none (0 = none); mild (1 = ≤ 10 lesions); moderate (2 = 11–20 lesions); severe (3 = 21–40 lesions) and extremely severe (4 = > 40 lesions). In general, the number of perivascular spaces refers to the number of lesions on one side of the brain tissue; if the number of lesions on the two sides is unequal, the side with the higher number prevails.^{11,12}

CMBs

CMBs are microscopic hemorrhages caused by microvascular lesions of the brain, located primarily in the cortex and subcortical or deep gray and white matter, with a maximum diameter of 10 mm and a minimum diameter of 2–5 mm. Small, round, or oval homogeneous no-signal lesion with well-defined boundaries can be observed in susceptibility-weighted imaging (SWI). These lesions appear and disappear abruptly at different aspects, but are not visible on FLAIR, T1WI, and T2WI sequences.⁴ The currently known grading criteria for CMB are:¹³ grade 0 = none; grade 1 = 1–4 lesions; grade 2 = 5–9 lesions; grade 3 = ≥ 10 lesions.

BA

BA is characterized by a decrease in brain volume and is unrelated to a local decrease in volume caused by damage such as traumatic brain injury and cerebral infarction.⁴ It is characterized radiographically by symmetrical or asymmetrical decrease in brain volume, ventricular enlargement, widening of the sulcus and gyrus, and decrease in the specific gray or white matter volume, which is associated with decreased cognitive function, particularly executive function.¹⁴ BA is primarily evaluated using T1WI, and the clinical assessment of BA includes linear measurement, area measurement, visual rating scale (VRS), and automatic volumetric measurement, with VRS classification and automatic volumetric measurement evaluation being widely used.¹⁵ Although various BA grading scales have been used in clinical studies and are regarded as having some diagnostic power, they have not been widely used in clinical practice.^{16,17}

Correlation Between Spontaneous ICH and CSVD Imaging Markers

SMASH-U classifies spontaneous ICH as comprising hypertensive ICH (HICH), amyloid angiopathy ICH, and undetermined ICH. The first two causes are the most prevalent, accounting for 78–88% of spontaneous ICH cases. The rupture of atherosclerotic arterioles leads to HICH, which is frequently confined to the deep brain. The rupture of small and medium-sized arteries in the cortex and pia mater regions, resulting in lobar hemorrhage, is the primary cause of amyloid angiopathy ICH. Undetermined ICH is determined when the other five causes and other unidentified causes have been ruled out, and patients should not be classified as having this type if multiple possible causes coexist.

Spontaneous HICH and CSVD Imaging Markers

Spontaneous ICH is a common neurological disorder, ranking second among stroke subtypes, with spontaneous HICH being the most prevalent cause.¹⁸ Based on epidemiological studies, spontaneous HICH accounts for 18.8–47.6% of all strokes in China, which is significantly higher than that in Western countries, and most patients diagnosed with spontaneous HICH are in critical condition, with a high mortality and disability rate.¹⁹

Spontaneous HICH Combined with LI

Xu et al discovered that patients diagnosed with HICH having multiple LI and were at higher risk of recurrent ICH.²⁰ Small vessel hypertensive lesions are associated with deep spaces (basal nucleus, medial and external capsule areas, thalamus). In contrast, Sato et al discovered no significant correlation between the number of LI and the prognostic

outcome in patients diagnosed with HICH.²¹ Few studies have examined the combination of LI with HICH, and the results are limited. Also, relevant clinical features, recurrence, and prognosis need to be clarified.

Spontaneous HICH Combined with WMH

Xu et al hypothesized that the severity of WMH is positively correlated with the risk of recurrence of HICH.²⁰ The likelihood of ICH recurrence increases as lesion severity increases. Sato et al and Sykora et al discovered that the degree of WMH was positively correlated with the mortality of patients with HICH.^{21,22} Kaffashian et al discovered that the overall score of white matter lesions was correlated with the risk of first ischemic and hemorrhagic stroke.²³ Uniken et al discovered that the severity of white matter lesions was independently associated with adverse neurological outcomes at discharge and 90-day prognosis following stroke.²⁴ A comprehensive analysis of most studies suggests that the severity of WMH is positively associated with the risk of recurrence of ICH and adverse neurological outcomes after ICH.

Spontaneous HICH Combined with CMB

Park et al discovered that the number of CMA in the basal ganglia and deep nucleus was positively correlated with the bleeding amount and adverse neurological outcomes in patients diagnosed with HICH.²⁵ Suo and Boulouis et al discovered that CMB in lobes and non-lobes was associated with the increase in hematomas, whereas the number of CMB foci was positively correlated with the enlargement of hematomas.^{26,27} Studies by Lioutas and Charidimou et al have revealed that when there are more than 10 CMB foci, the risk of hematoma volume enlargement is increased and the risk of recurrence of ICH is significantly increased concurrently.^{28,29} Pasi et al investigated the imaging features of ICH and discovered that the incidence of cerebellar hemorrhage increased in patients with supratentorial microhemorrhage, and that most patients with cerebellar hemorrhage had hypertensive CSVD, primarily microangiopathy.³⁰

Spontaneous HICH Combined with EPVS

In a study of the correlation between perivascular space and the risk of stroke, the degree of EPVS was positively correlated with the risk of new-onset ICH, especially EPVS in the basal ganglia and hippocampus, which was significantly correlated with the risk of HICH, but not with the risk of acute cerebral infarction.³¹ Suo et al discovered that moderate to severe EPVS is correlated with hematoma enlargement.²⁶ Xu et al discovered that EPVS in the basal ganglia or centrum semiovale did not increase the risk of ICH recurrence.²⁰ Lau et al discovered that patients diagnosed with HICH having more than 20 EPVS in the basal ganglia not only had poor prognosis, but also had correspondingly increased risk of recurrent bleeding.³²

Spontaneous HICH Combined with RSSI

At present, there are few studies on the relationship between RSSI and HICH. One study showed that a recent small subcortical infarction can cause lacunar syndrome (hemorrhagic lacunar stroke), and patients with lacunar syndrome are more likely to have hypertension and deep internal capsule lesions, and the prognosis is better than that of other intracerebral hemorrhage groups. As reported in the clinical series of this disease, there is general Future research must investigate lly no in-hospital death, and 22.8% of cases are asymptomatic at discharge.³³

Spontaneous HICH Combined with BA

Few studies have been conducted on BA and HICH, but studies have demonstrated that the symptoms of BA in patients diagnosed with CSVD are closely related to WMH, and that WMH manifestations are often accompanied by cognitive decline. Combined evaluation of BA and WMH is superior to WMH alone in predicting cognitive functional changes, but the pathophysiological mechanism underlying the correlation between BA in different regions and WMH requires further exploration.¹⁵ Currently, there are few studies on the correlation between RSSI and HICH, hence it is not elaborated specifically.

Amyloid Angiopathy ICH and CSVD Imaging Markers

Cerebral amyloid angiopathy (CAA) is an age-related CSVD characterized by gradual deposition of β -amyloid in the cortex, subcortex, and leptomeningeal artery walls, manifested primarily by recurrent lobar hemorrhage and cognitive decline.³⁴ CAA-associated ICH (CAAH) accounts for 15–40% of nontraumatic ICH.³⁵ It is the second most common cause of ICH. The gold standard for diagnosing CAA has been histopathological confirmation of brain tissue sample, but

invasive biopsies carry certain risks. Therefore, clinical and neuroimaging examinations are currently mainly relied upon. The Boston Standard is the most commonly used diagnostic criterion for CAA in clinical practice. In 2022, Charidimou et al released version 2.0 of the Boston Standard and validated it both internally and externally;³⁶ compared with the traditional Boston Standard, the diagnostic sensitivity is enhanced without reducing diagnostic specificity.³⁷

Amyloid Angiopathy ICH Combined with LI

CAA is one of the causes of LI, which is caused by occlusion of the deep perforating branch of cerebral arteries. A large-scale study confirmed the correlation between LI in the lobes and CAA. Patients with CAA typically have lesions in the semiovale centrum and cortical-subcortical lobes. Recent studies have demonstrated that the presence of lobar LI can predict the risk of CAAH in patients independently, and LI may become an important diagnostic and prognostic marker for patients diagnosed with CAAH.³⁸

Amyloid Angiopathy ICH Combined with WMH

In patients diagnosed with CAA, the vascular amyloid destroys the integrity of blood vessels and the blood-brain barrier, resulting in occlusive small vessel disease and cerebral hypoperfusion; furthermore, chronic ischemic and hypoxia can damage the white matter. CAA-associated white matter lesions generally involve posterior white matter.³⁹ A study discovered that WMH and LI were associated with the risk of ICH, with WMH being more strongly associated with vascular injury and vascular risk factors; grade 3 to 4 WMH is an independent risk factor for long-term prognosis in patients diagnosed with CAAH.²¹

Amyloid Angiopathy ICH Combined with CMB

Lobar hemorrhage and microbleeds, which occur in the cerebral cortex and subcortex, particularly the parietal-occipital lobe, are the most important imaging characteristics of CAAH. Multiple lobular, ventricular, subarachnoid, and subdural hemorrhages are possible manifestations. However, CMB in the lobar region has been used as a diagnostic criterion for CAA. Cranial SWI is highly sensitive to microbleeds in the brain, with an almost 100% diagnosis rate. This imaging feature allows for the early diagnosis of CAA. The results of another study found that CAAH imaging diagnosis was linked to CMB in the superficial regions of the cerebellum (gray matter, vermis).⁴⁰

Amyloid Angiopathy ICH Combined with EPVS

The perivascular space is an important cerebrospinal fluid drainage channel, and the deposition of β -amyloid in patients diagnosed with CAA blocks the drainage of cerebrospinal fluid through the perivascular space and EPVS. Studies have shown that EPVS in the centrum semiovale is associated with CAAH, and the number of EPVS is correlated with the histopathological severity of CAA as well as the number of microbleeds in the brain and iron deposits on the surface of the brain.⁴¹ EPVS in the centrum semiovale and iron deposition on the cortical surface were found to be independent predictors of ICH recurrence in a study of patients diagnosed with CAAH.⁴²

Amyloid Angiopathy ICH with BA

BA is an important mediator of cognitive impairment and functional outcomes. BA is a better predictor of the severity of CAA than WMH.^{43,44} Vascular amyloid protein destroys blood vessels, causing microaneurysms or fibrinoid necrosis of the vascular wall, and long-term ischemia and hypoxia cause white matter demyelination and BA, impacting brain connectivity and plasticity.⁴⁵ Kwon et al discovered that patients with moderate volume basal ganglia hemorrhage benefit from mild or moderate BA.⁴⁶ In a recent study measuring a higher proportion of frontal lobes and shorter distance between the Sylvian fissure of the third ventricle, however, severe BA was found to be an independent risk factor for long-term prognosis.⁴⁷ Also, the study found that patients diagnosed with CAAH exhibited a small lump effect when the hematoma was located in superficial areas such as the cortex and subcortical region. Conversely, in patients with large hematomas and deep ICH, mild or moderate atrophy may partially offset the mechanical damage caused by the mass effect due to hematoma, edema, increased intracranial pressure, and herniation, which is more pronounced in the early stages of ICH.⁴⁸

Amyloid Angiopathy ICH Combined with RSSI

Acute cortical microinfarction and EPSV are two recently reported imaging features associated with CAAH. In recent years, several studies have demonstrated that CAA-induced vascular wall damage not only causes IC but may also result in cerebral blood flow self-regulation dysfunction and acute cortical microinfarction. However, standard clinical examination methods cannot easily detect this pathological change. The prevalence of acute cortical microinfarcts was positively correlated with the presence of more severe amyloid-related vasculopathy in CAA patients.^{49,50}

Undetermined ICH and CSVD Imaging Markers

According to the available literature, 19% of ICH cases have an unknown cause. This number includes patients who have not completed the examinations and those who still have an unknown cause after routine examination. CSVD is the most common cause of ICH, among which hereditary CSVD is also prone to stroke-like lesions, but most cases are difficult to diagnose due to the lack of relevant genetic testing or pathological biopsy. Currently, the most prevalent hereditary CSVD (hCSVD) is a group of rare cerebrovascular diseases caused by single gene mutations, primarily consisting of cerebral autosomal dominant angiopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive angiopathy with subcortical infarcts and leukoencephalopathy (CARASIL), cathepsin A-related arteriopathy with stroke and leukoencephalopathy (CARASIL), Fabry disease, and type IV collagen A 1/2 cerebral arteriopathy (COL4A1/A2).⁵¹ MRI changes vary between different types of hCSVD, but WMHs, LI, EPVS, CMB, and BA are almost always present. Currently, there is no definite classification standard, hence they are classified as undetermined ICH, and elaborated based on the following categories.

Cerebral Autosomal Dominant Angiopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

CADASIL is the most prevalent single-gene dominant hCSVD caused by NOTCH3 gene mutation, and typically manifests as migraine, repeated minor strokes, mental and emotional disorders, vascular cognitive impairment, and gait abnormalities, typically between the ages of 40 and 50. Common MRI findings include progressively exacerbating bilateral cerebral WMHs, LI, CMB, and EPVS, which typically precede clinical onset. Long regarded as classic symptoms of the disease, anterior temporal WMHs and EPVS vary in their association with cognition depending on the anatomical region involved. LI, the most important MRI marker for CADASIL, is linked to worse clinical outcomes and cognitive performance. BA has been associated with diminished cognitive ability and increased disease severity. However, CMBs do not appear to have a direct correlation with disease severity.⁵² It is not possible to definitively determine whether or to what extent ICH in CADASIL is caused by arterial hypertension or CADASIL-specific vascular disease. The interaction of genetic and acquired factors may result in hemorrhagic lesions, and ICH is a possible but uncommon manifestation of CADASIL.⁵³

Cerebral Autosomal Recessive Angiopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL)

Homozygous or compound heterozygous mutations in the HTRA1 gene cause CARASIL, which typically manifests between the ages of 30 and 40. The MRI results of the brain reveal diffuse WMHs involving bilateral frontal lobes, temporal lobes, external capsules, thalamus, and pons.⁵⁴ After progression, BA, LI, and CMBs can be observed, but not as clearly as CADASIL. ICH can also occur in some patients diagnosed with CARASIL.

Type IV Collagen α 1/2 Cerebral Arteriopathy (COL4A1/A2)

The type IV collagen gene α 1 and type IV collagen gene α 2 encoding the α 1 and α 2 chains of type IV collagen, are located on human chromosome 13, respectively. The results of a study revealed that COL4A1/A2 gene mutations lead to poor stability of the vascular basement membrane, providing a pathological basis for the development of hemorrhagic cerebrovascular disease and increasing the risk of ICH.⁵⁵ MRI manifestations include all types of ICH, including microbleeds, with up to 60% of patients exhibiting lateral periventricular and deep WMHs, EPVS, LI, and BA.⁵⁶ CSVD biomarkers indicate a high prevalence of CMB, primarily located in the periventricular white matter, basal ganglia, thalamus, and brainstem. COL4A1/A2 gene variants may influence the prognosis of sporadic ICH. Therefore, clinical screening for COL4A1/A2 gene variants may be helpful for secondary prevention and acute treatment.

Fabry Disease

Fabry disease is an X-linked lysosomal storage disease caused by mutation in the GLA gene. About 20% of patients diagnosed with Fabry disease have ischemic stroke, and a small number of them develop ICH and cerebral vein thrombosis. MRI typically reveals progressively worsening WMHs, while LI, CMB, and EPVS can also be seen, and BA is rarely observed.^{57,58}

Total Burden Scores of CSVD Imaging and Relationship with Spontaneous ICH

Staals et al proposed a scoring table that can comprehensively assess the total burden of CSVD imaging, including the four most prevalent CSVD imaging manifestations, namely LI, WMH, CMB, and PVS, with a score of 0 to 4 points.⁵⁹ The following four criteria represent 1 point each: (1) ≥ 1 LI; (2) Fazekas scores of medium and deep WMH ≥ 2 points and/or paraventricular WMH ≥ 3 points; (3) ≥ 1 deep or subtentorial CMB; (4) Moderate to severe (grade 2–4) PVS in the basal ganglia. Since many of the typical findings of CSVD do not occur in isolation, the total burden score of CSVD imaging may be more suitable to assess the overall impact of CSVD. The CSVD total burden score predicts the incidence of ischemic stroke, mortality, lesion outcome, functional outcomes after stroke, and postoperative complications, and is indicative of disease severity based on evaluation scores.⁶⁰ A study found that the adverse neurological functional outcome and recurrence risk of patients diagnosed with HICH was proportional to the total burden score of CSVD; a higher total CSVD burden is independently associated with neurological functional outcome at 90 days in patients diagnosed with CAAH.⁶¹ Currently, there is no correlation between the total burden and the prognosis of ICH caused by CSVD with a single genotype. There are few relevant studies, therefore, additional data and research are required for clarification.

Discussion

SMASH-U classification has been demonstrated to be an effective predictor of long-term functional prognosis and mortality after ICH. Targeting the ICH prognosis etiology system can aid clinicians in providing targeted therapy.⁶² In summary, most studies have demonstrated that the number of CMBs in basal ganglia and deep region is positively correlated with the ICH volume in patients diagnosed with HICH, which can predict poor prognosis; CMB in the lobar region can be used as diagnostic criteria for CAAH, which is independently correlated with neurological functional outcomes. The severity of WMH is positively correlated with the risk of HICH recurrence, and grade 3–4 WMH is an independent risk factor for the long-term prognosis of patients diagnosed with CAAH. Multiple LIs increase the risk of recurrent ICH in patients diagnosed with HICH, and the presence of lobar LA can predict the risk of developing ICH in patients diagnosed with CAA independently. There are few studies on BA and HICH, however, BA can affect long-term prognosis in combination with WMH, and severe BA is an independent risk factor for long-term poor prognosis in patients diagnosed with CAAH. EPVS in the basal ganglia and hippocampus correlates significantly with the risk of new-onset HICH, and the number of EPVS correlates significantly with ICH recurrence. EPVS in the semiovale centrum are an independent predictor of recurrence of CAAH. The prognosis of RSSI with HIGH is better. The presence of RSSI is positively correlated with the poor prognosis of CAAH patients. The undetermined spontaneous ICH discussed in this article is hereditary CSVD caused by a single gene, and six imaging markers are present in most cases. However, the relationship between each marker and the disease is not nearly identical. The correlation between unknown ICH and imaging markers requires additional research and evidence. The greater the total burden scores of CSVD, the greater the likelihood of a poor prognosis and recurrence of ICH. In addition, higher CSVD scores correlate independently with the 90-day functional outcome. CSVD is one of the primary causes of poor prognosis of ICH. Imaging is one of the most important diagnostic tools and understanding the imaging manifestations and prognosis of ICH of different etiologies can guide clinical treatment and prognosis assessment.

Although imaging examination methods are relatively convenient and accurate non-invasive methods in clinical practice, there are still some shortcomings: 1. The conclusions drawn solely based on imaging features are relatively single, and further exploration is needed to determine whether blood, biomarkers, and other unknown factors will synergistically affect research outcomes and associations. 2. Currently, there is no clear classification standard for

unexplained cerebral hemorrhage in the literature reviewed, and there is no clear conclusion on its association with imaging markers of CSVD. Future research must investigate the value of imaging in the early diagnosis and prognostic assessment of CSVD to provide a more accurate foundation for clinical treatment. And it is also necessary to study the relationship between neuroimaging and biomarkers in the direction of adverse outcomes of ICH such as cognitive impairment.

Abbreviation

ICH, intracerebral hemorrhage; CSVD, cerebral small vessel disease; RSSI, recent small subcortical infarct; LA, lacune; WMH, white matter hyperintensity; CMB, cerebral microbleed; BA, brain atrophy; LI, lacunar infarction; VRS, visual rating scale; HICH, hypertensive intracerebral hemorrhage; CAA, cerebral amyloid angiopathy; CAAH, cerebral amyloid angiopathy hemorrhage; hCSVD, hereditary cerebral small vessel disease; COL4A1, collagen type IV α 1; COL4A2, collagen type IV α 2; SMASH-U, Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined; MRI, magnetic resonance imaging; T1WI, T1-weighted images; T2WI, T2-weighted images; SWI, susceptibility-weighted imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery.

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