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Review

Multimodal Artificial Intelligence in Cerebral Small Vessel Disease: From Risk Prediction to Personalised Management

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ABSTRACT: Cerebral small vessel disease (CSVD) is a major substrate for cerebrovascular and neurodegenerative conditions. However, its subtle and diffuse lesions hinder early detection and timely intervention. This clinically oriented review examines applications of artificial intelligence (AI) in CSVD, focusing on the integration of imaging with clinical, molecular or digital data. It covers three clinical areas: risk stratification and prognosis, diagnosis and quantitative assessment, and personalised management. We distinguish between findings in CSVD cohorts, evidence from other populations and proposed applications. We consider internal and external validation and evidence of clinical impact. Prediction models have been developed for CSVD screening and for estimating the risk of lesion progression, cognitive decline and vascular events. Selected studies have evaluated automated lesion quantification across multiple centres. Imaging and digital measures have also been used to assess current cognitive and gait impairment. AI-assisted treatment selection, remote monitoring and rehabilitation remain at an early stage, and their clinical benefits in CSVD have yet to be established. We discuss key requirements for clinical translation, including harmonised data acquisition, annotation aligned with neuroimaging standards, external validation and prospective evaluation of safety, equity and value in clinical practice. The review emphasises CSVD-specific phenotypes and longitudinal management, with outcomes extending beyond imaging to cognition, gait, affect and independence in activities of daily living. Future studies should establish whether these approaches improve clinical assessment and patient outcomes compared with current practice.

Keywords: Cerebral small vessel disease, machine learning, deep learning, artificial intelligence, clinical decision support, risk stratification

1. Introduction

Cerebral small vessel disease (CSVD) is a common, age-related syndrome caused by pathological injury to the cerebral microvasculature [1-3]. It is highly prevalent, affecting around 5% of individuals aged 50 years and becoming nearly universal in nonagenarians [4]. CSVD often progresses without obvious symptoms. Chronic hypoperfusion, endothelial injury, blood-brain barrier (BBB) disruption, and

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neuroinflammation can gradually impair brain function [5]. Over time, these processes contribute to stroke, cognitive impairment, gait disturbance, and mood symptoms [6-8]. The Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) guidelines describe a set of magnetic resonance imaging (MRI) markers. These include white matter hyperintensities (WMH), recent small subcortical infarcts (RSSIs), intracerebral haemorrhage (ICH), lacunes, enlarged perivascular spaces (EPVS), cerebral microbleeds (CMBs), and brain atrophy [9,10]. CSVD substantially increases the risk of severe and often irreversible neurological outcomes [11,12]. Epidemiologically, CSVD is a major contributor to vascular and mixed dementia [13,14]. Parkinsonism, dementia, or both develop in over a quarter of patients with CSVD [15]. Moreover, approximately 25% of strokes are directly attributable to CSVD-related vascular lesions [16].

Given this burden, earlier and more targeted intervention in CSVD may help reduce the risk of downstream cerebrovascular and neurodegenerative outcomes [11]. However, heterogeneous clinical manifestations, the lack of clinically validated circulating biomarkers, and limited standardisation of imaging surrogates hinder current management [17]. Clinicians therefore face several practical questions: which patients need closer follow-up, how to measure lesion burden consistently, and how to adapt management as the disease progresses. Artificial intelligence (AI) offers methods to extract quantitative information from imaging and combine it with clinical, molecular, or digital data. In CSVD, prognostic studies have combined clinical and imaging variables to predict stroke or death, while automated lesion analysis has been evaluated across multiple centres [18,19]. These approaches address risk prediction and the measurement of lesion burden. Applications in treatment selection, remote monitoring, and rehabilitation are less well evaluated in CSVD.

Clinical adoption is constrained by heterogeneity in data acquisition, insufficient external validation, limited model interpretability, and unresolved concerns about privacy, accountability, and regulatory oversight [20,21]. Prospective evidence on clinical benefit and implementation in routine care remains limited. This review therefore examines three clinical domains: (i) risk stratification and prognosis, (ii) diagnosis and quantitative assessment, and (iii) personalised management. We distinguish between findings in CSVD cohorts, evidence from other populations and proposed applications. For each application, we consider technical feasibility, model validation, and evidence of clinical impact in relation to its intended clinical purpose and the populations studied.

2. AI Methods and Their Evolution in CSVD Research

In CSVD, AI has been adopted to address small, diffusely distributed and often clinically silent lesions, substantial heterogeneity in disease manifestation, and class imbalance within clinical datasets. These features challenge conventional statistical models and rule-based image analysis, and their impact is compounded by multicentre variation and label noise. Early studies in the 2010s relied on hand-crafted features with machine learning (ML) to automate WMH segmentation on fluid-attenuated inversion recovery (FLAIR). Semi-automated pipelines incorporating support vector machines (SVMs) were also developed to identify candidate CMBs on susceptibility-weighted imaging (SWI) [22,23]. Since the mid-2010s, deep learning (DL), particularly convolutional neural networks (CNNs), has been applied to lesion segmentation and detection in CSVD research [24,25]. Applications have since expanded to lacune detection and automated quantification of EPVS. Beyond single-task lesion analysis, multimodal AI combines different types of data to address a common task [26,27]. In CSVD, this may involve multiple MRI sequences or imaging combined with clinical, molecular or digital data. For example, a single model may learn from MRI and clinical data together, or the outputs of separate imaging and clinical models may be combined at a later stage. Using several predictors or algorithms does not, by itself, constitute multimodal integration.

ML, a major subfield of AI, has primarily been used in CSVD for two purposes: (i) automated analysis of STRIVE phenotypes on neuroimaging and (ii) prediction using imaging-derived and clinical features. Supervised methods, including SVMs and random forests (RF), can perform effectively when applied to hand-crafted imaging features, particularly with limited data [28]. However, challenges such as limited labelled data and heterogeneous acquisition protocols have driven the adoption of semi-supervised, weakly supervised, and transfer learning strategies. These approaches may improve task-relevant performance when labelled data are limited. As a methodological example, a deformation-aware semi-supervised DL model was used to segment small cerebral vessels on 7 T magnetic resonance angiography (MRA). In a manually annotated region, its Dice score was 18.98% higher than that of the corresponding model without deformation-aware learning [29]. Data-driven dimensionality reduction and ML have also been combined to characterise multidimensional CSVD phenotypes. Principal component analysis identified a common component spanning cognition, apathy and gait, while random forest analysis evaluated the relative importance of associated neuroimaging features [30]. Although routine neuroimaging markers

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remain essential, ML models still struggle to capture the full heterogeneity of CSVD and may be biased by non-representative datasets [31]. Consequently, successful clinical translation requires rigorous attention to data curation, clinically meaningful endpoints, and bias mitigation.

As a subset of ML, DL algorithms can learn feature representations directly from data, thereby reducing the need for manual feature engineering [32]. Common DL architectures include CNNs for image-based feature extraction, recurrent neural networks for sequential data, and transformer models for longer-range dependencies. DL is now widely used for image-based CSVD phenotyping and supports automated analysis across multiple STRIVE phenotypes [33,34]. For instance, an integrated model combining Mask R-CNN with a multi-instance learning classifier was developed to automate the detection of CMBs on SWI and the classification of CSVD. On an external test set, the model achieved a lesion-level intersection-over-union of 0.52 for CMB detection and a weighted-average area under the curve (AUC) of 0.91 for CSVD subtype classification [18]. In a separate study, a 3D CNN built to identify Fazekas grade-I CSVD from non-contrast brain MRI reported accuracies of 0.93 on 2D axial slices and 0.86 on 3D image stacks [35]. These examples indicate potential gains in detection and grading, although differences in task setup and reporting level (slice versus patient) limit direct comparability. More broadly, CNN-based methods, including U-Net architectures, have been used to quantify WMH and EPVS burden; two-stage pipelines incorporating candidate generation followed by false-positive reduction have also been used for CMB detection on susceptibility-sensitive MRI [36-38]. DL systems have achieved strong segmentation performance and favourable precision-recall trade-offs for detection, while automated analysis may reduce inter-reader variability. However, these models are not universally reliable, particularly when exposed to shifts in data distribution or deployed across heterogeneous environments [39]. To facilitate integration into clinical decision workflows, models should report how confident they are in each prediction, and whether predicted probabilities match observed event rates, alongside discrimination performance.

3. Risk Stratification and Prognosis with AI in CSVD

Models address both the identification of existing disease and the prediction of subsequent structural or functional deterioration [40]. Conventional analyses often focus on prespecified associations [41,42]. AI and related data-driven methods offer complementary approaches to combining demographic, vascular, laboratory, and imaging information and exploring interactions among these features (Fig. 1).

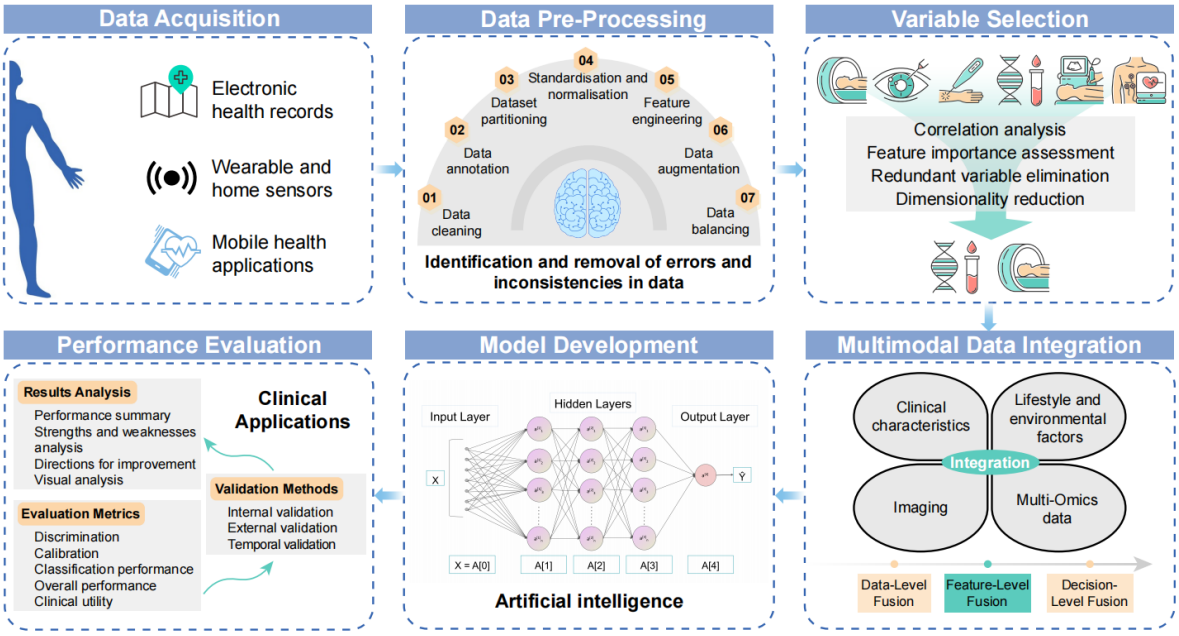


Figure 1. End-to-end multimodal AI workflow for cerebral small vessel disease. The schematic outlines key stages of AI-enabled model development, spanning multimodal data acquisition and pre-processing, model development and fusion, validation and performance evaluation, and clinical implementation. Particular emphasis is placed on internal and external validation, interpretability, and real-world clinical relevance. Data-, feature- and decision-level fusion can be used as alternative or complementary strategies at different stages of model development.

3.1 Early Risk Stratification and Screening

Early screening and risk stratification may help prioritise neuroimaging in individuals at risk of CSVD and inform further clinical assessment in patients with established disease. A useful screening model must therefore rely on information available when that decision is made. Performance should be judged at clinically relevant decision thresholds, with attention to calibration and clinical utility as well as discrimination (Fig. 2) [43-45].

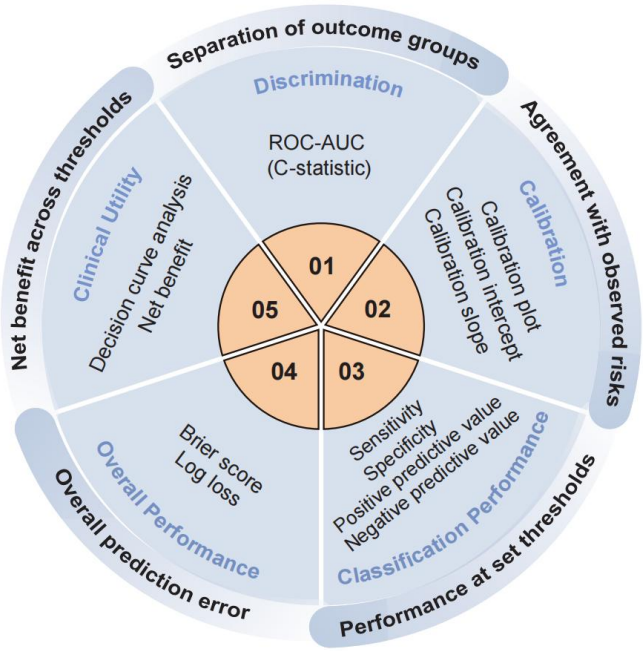


Figure 2. Performance evaluation of AI-enabled prediction models in CSVD. Selected measures illustrate the assessment of classification and risk prediction models across five domains. Metric selection and interpretation depend on the outcome type and model output. Classification performance is evaluated at specified thresholds, while decision curve analysis assesses net benefit across clinically relevant thresholds. For binary outcomes, ROC-AUC is equivalent to the C-statistic. Abbreviations: AI: artificial intelligence; CSVD: cerebral small vessel disease; ROC-AUC: area under the receiver operating characteristic curve; C-statistic: concordance statistic.

Within this framework, routinely available clinical and laboratory variables may provide useful inputs for first-line risk stratification. Age, blood pressure variability, homocysteine (Hcy), albuminuria, and renal dysfunction have each been associated with CSVD imaging markers or white matter hyperintensity burden [46-50]. These variables are candidate predictors rather than stand-alone diagnostic tests. Their value for screening depends on whether they improve case identification beyond age and vascular history alone. For instance, binary logistic regression identified five independent predictors of cognitive impairment associated with CSVD: age, hypertension, Hcy, lacunar infarction (LI) score, and total CSVD burden. The model showed good apparent discrimination, with a C-index above 0.8, suggesting that an interpretable prediction model is feasible [51]. These conventional statistical models provide clinically interpretable baselines against which more complex ML approaches should be evaluated.

Higher neutrophil-to-lymphocyte ratios and metabolic syndrome have also been associated with greater CSVD burden [27,52]. In one cross-sectional study, least absolute shrinkage and selection operator (LASSO) regression was used for variable selection, followed by logistic regression. The resulting model included age, metabolic syndrome, neutrophil-to-lymphocyte ratio, Hcy, cystatin C, uric acid, smoking status, and prognostic nutritional index. For classification of total CSVD imaging burden, the model achieved a receiver operating characteristic (ROC)-AUC of 0.85, a precision-recall AUC of 0.81, and a Brier score of 0.15 [27]. Another retrospective study used LASSO and multivariable logistic regression to reduce 88 candidate variables to nine predictors, including previous stroke, hypertension, creatinine, and Hcy. The resulting nomogram distinguished patients with and without CSVD, with ROC-AUCs of 0.85 and 0.86 in the training and internal validation sets, respectively [53].

Molecular biomarkers may provide additional information for patient stratification. A six-protein serum panel, selected through regularised feature selection and validated by enzyme-linked immunosorbent assay, combined with age, distinguished patients with CSVD from controls [54]. These proteins largely reflect the complement and coagulation pathways, providing biological plausibility for their association with vascular injury. A separate CSVD case-control study analysed plasma biomarkers together with clinical and MRI features using regularised logistic regression and RF. Myeloperoxidase (MPO) was an important model feature and was elevated particularly in patients with LI. Model analyses also identified CXCL4 and MPO–DNA complexes as features associated with CSVD [55]. Candidate discovery has also been explored in Fabry disease (FD), a hereditary disorder that can affect cerebral small vessels. An in silico systems-biology and ML model prioritised CAMK2A, ILK, LMNA and KHSRP as candidate markers of vascular or neuronal injury [56]. These findings concern candidate generation; the proteins have not been tested as inputs to CSVD screening models.

Opportunistic imaging can refine risk when scans obtained for other indications are already available. In a retrospective CSVD study, an XGBoost model combined clinical risk factors with carotid perivascular fat density and radiomic features from head and neck computed tomography (CT) angiography to predict subsequent MRI-defined progression [57]. Such estimates may help identify patients who warrant closer reassessment. Where prior MRI is available, automated measurements can characterise existing lesion burden. In a multicentre study, mcPVS-Net segmented perivascular spaces (PVS) on 3D T1-weighted images acquired across different scanner vendors, achieving a mean Dice coefficient of 0.80 against manual masks in the test dataset. The resulting volumes correlated with visual ratings; separate analyses examined associations with age, hypertension and WMH [58]. These measurements may complement clinical severity assessment, although the study did not evaluate prediction of later deterioration.

Much of this evidence concerns the detection of existing CSVD or the assessment of current imaging burden and cognitive impairment. To support early screening, these models need evaluation in patients being considered for MRI referral. A useful screening model should identify more cases at a given referral rate, or reduce the number of scans without increasing missed disease. Among patients with established CSVD, additional biomarkers and automated measurements need to improve decisions about further assessment or follow-up beyond those informed by routine clinical and MRI findings. Comparisons with conventional models using the same predictors would clarify whether any improvement comes from the algorithm or simply from access to additional data.

3.2 Disease Trajectory and Outcome Prediction

3.2.1 Forecasting Structural Progression and Vascular Events

CSVD may progress through gradual white matter injury or discrete vascular events, with consequences that depend on lesion location, brain reserve and comorbidity [26,59]. Prognostic modelling therefore needs to distinguish structural progression from subsequent ischemic stroke or ICH. The clinical value of these estimates depends on whether they improve decisions about follow-up imaging and vascular risk management.

DL has been used to model the spatial evolution of WMH. The Disease Evolution Predictor predicted where WMH would enlarge, regress or remain stable over one year from baseline FLAIR-derived maps in a post-stroke cohort [60]. A subsequent study incorporated stroke lesion information into a probabilistic U-Net to refine these estimates [61]. Both used the same dataset acquired on a single scanner, demonstrating feasibility within that setting. Spatial information could complement total WMH volume by indicating where lesions may progress, particularly near pathways involved in cognition or motor function. Agreement in total WMH volume does not necessarily imply accurate prediction of the spatial distribution of WMH change. Whether these forecasts improve prediction of subsequent clinical deterioration remains to be established.

A related task is to estimate the risk of future ischemic stroke or ICH using MRI lesion burden, blood biomarkers and clinical variables. A conventional regression study in patients with primary ICH linked MRI-defined CSVD burden to subsequent functional outcome and stroke recurrence [62]. In cerebral amyloid angiopathy (CAA)-related ICH, adding acute-phase blood neurofilament light chain (NfL) to MRI-derived burden increased the C-index for recurrent haemorrhage from 0.77 to 0.88 in an internally validated Cox model [63]. This combination suggests a role for molecular markers alongside structural imaging, although NfL measured soon after ICH may also reflect injury from the index haemorrhage. Because the prognostic implications of small-vessel and large-vessel disease are not interchangeable [64], vascular aetiology should be considered when developing and evaluating prognostic models. In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a random survival forest combining demographic, clinical and MRI variables achieved a mean five-year time-dependent AUC of 0.77 for stroke or death under nested cross-validation

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[19]. Cox regression performed comparably when LASSO feature selection was applied, indicating that predictor selection contributed to performance. A neural network using MRI-derived parameters in a separate CSVD cohort reported an AUC of 0.93 for stroke within three years [65]. Differences in study populations, endpoints and prediction horizons limit direct comparison of these AUCs.

The distinction between ischaemic and haemorrhagic outcomes is particularly relevant to follow-up in CSVD. A model developed to predict one outcome may not reliably predict the other, and death can preclude either outcome. Before predictions guide follow-up, absolute risk estimates need to be assessed for calibration at the intended time horizon and validated in independent cohorts representative of the intended clinical population. For binary outcomes, earlier studies suggested at least 100 events and 100 non-events, with approximately 200 of each for flexible calibration assessment. Sample sizes should be planned according to the anticipated event rate and required precision of performance estimates [66-68]. Even adequately powered external validation may reveal poor performance when the validation population differs from the development cohort [69]. Further evaluation should examine reproducibility across scanners and populations, changes in calibration over time and net benefit at thresholds relevant to follow-up decisions.

3.2.2 Predicting Long-Term Functional Outcomes and Decline

Beyond the structural and vascular outcomes considered above, long-term prognosis in CSVD also encompasses cognition, mobility and independence. Cognitive decline has received the most attention, but gait impairment and apathy may affect everyday function before dementia develops. Studies of current impairment can identify candidate predictors, but longitudinal evaluation is needed to determine whether these features also predict decline.

Clinical and imaging studies provide several such candidates. A LASSO-selected logistic model incorporating vascular risk factors, CSVD imaging burden and apolipoprotein A1 identified existing cognitive impairment with AUCs of 0.87 and 0.85 in the training and validation sets [70]. WMH texture may provide additional information. In a recent multicentre study, a Transformer-based radiomics model achieved external AUCs of 0.86 and 0.75 for current cognitive impairment, while a longitudinal analysis linked a selected WMH textural feature to subsequent cognitive decline [46]. The reported classification AUCs, however, reflect detection of current impairment.

Longitudinal evidence also supports the use of microstructural measurements derived from routine MRI. A DL model trained using UK Biobank data synthesised fractional anisotropy and mean diffusivity maps from T1-weighted images, with image synthesis evaluated in four CSVD cohorts [71]. Dementia prediction was examined in St George's Cognition and Neuroimaging in Stroke (SCANS) and Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort (RUN DMC) over 5 and 14 years, respectively. Synthetic mean diffusivity yielded C-indices of 0.82 and 0.81, compared with 0.53 and 0.71 for WMH volume alone. Here, DL generated the imaging marker, and Cox regression assessed its prognostic value. Such approaches may extend access to informative measurements when diffusion sequences are unavailable. The choice of outcome model is a separate issue. A comparison across three CSVD cohorts found that more complex ML methods offered little improvement over Cox or logistic regression using the same predictors; regularised models performed well, and baseline global cognition was particularly informative [72]. Together, these studies suggest that obtaining better measurements may be at least as important as increasing algorithmic complexity.

Retinal imaging offers a further, less invasive source of information, although its prognostic evidence currently comes from populations not selected for CSVD. In a memory-clinic cohort, the DL-derived retinal ageing marker RetiPhenoAge was associated with cognitive decline after adjustment for clinical variables, with a subdistribution hazard ratio of 1.34 per standard deviation increase [73]. Its association with incident dementia was replicated in UK Biobank. Associations with CSVD imaging markers and plasma proteins were examined separately. These findings support further investigation in CSVD, although the study did not evaluate a prognostic model combining retinal, MRI and protein data.

For mobility, longitudinal imaging studies have identified changes associated with gait decline. Longitudinal analyses of RUN DMC linked white matter atrophy and deterioration in diffusion measures to declining stride length over 5.4 years. Baseline CSVD imaging markers showed no robust association with later gait decline after correction for multiple testing [74,75]. Digital gait assessment could complement imaging during follow-up. An SVM combining gait and surface electromyography features classified Timed Up and Go-defined fall-risk groups in covert CSVD with an AUC of 0.99 [76]. Smartphone and video methods have also quantified gait during prescribed walking tasks [77]. These approaches assess current gait characteristics and functional performance. Their ability to predict actual falls or new dependence in daily activities requires prospective evaluation.

Apathy may provide additional prognostic

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information. In SCANS and RUN DMC, baseline apathy was associated with incident dementia after adjustment for age, education and baseline cognition. Depressive symptoms showed no such association. In SCANS, increasing apathy during follow-up was also associated with dementia [78]. This supports considering apathy separately from depression when selecting prognostic features. Across cognitive, motor and behavioural studies, however, loss of independence is less directly assessed than dementia diagnosis or test performance. Prognostic analyses should account for death as a competing event. Models that update predictions during follow-up may also need to incorporate recurrent stroke and treatment changes. Transitions to dependence or institutional care could be evaluated as distinct outcomes. Future studies should establish whether additional measurements improve prediction beyond baseline cognition, gait and routine MRI findings.

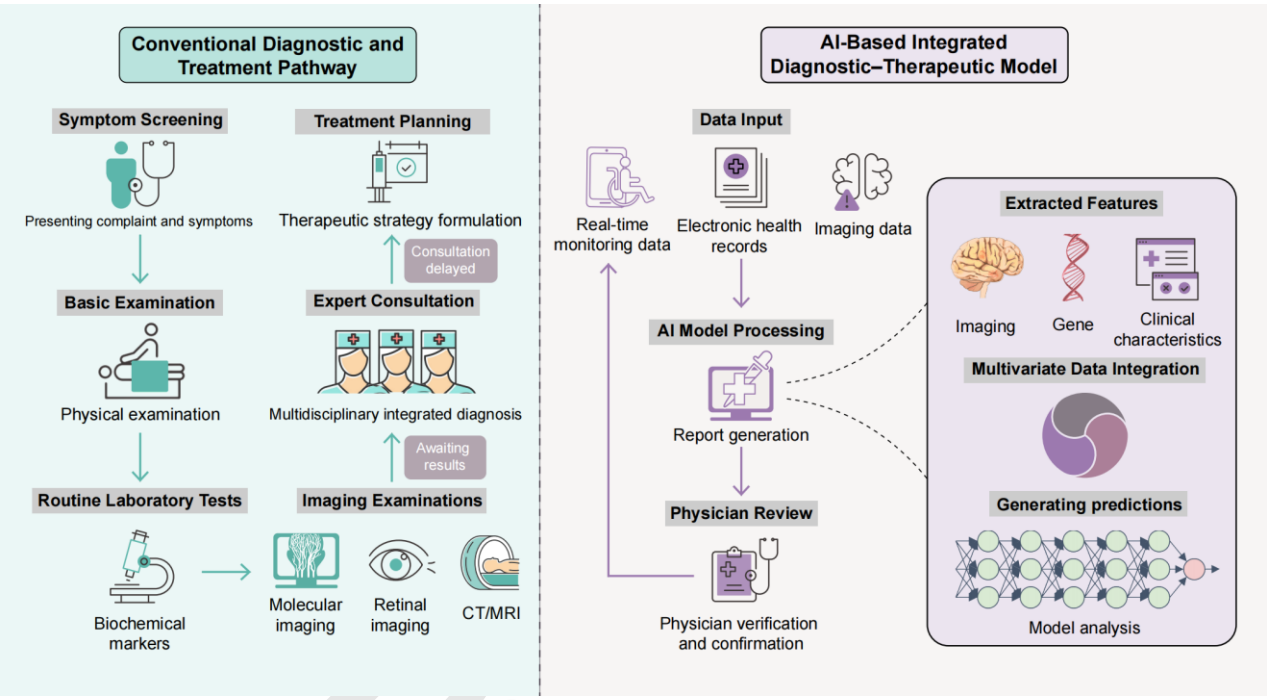


Figure 3. Conventional care versus an AI-integrated pathway for cerebral small vessel disease. The schematic contrasts a traditional, linear care pathway with an AI-enabled model linking data capture, analysis, and decision support. In conventional care, symptom-led screening, examination, routine tests, and imaging proceed in discrete stages, with results accumulated before expert consultation and treatment planning, often delaying feedback. In the AI-integrated pathway, routinely collected clinical and imaging data are aggregated with other care-related data streams, followed by automated feature extraction, multimodal integration, and model inference to generate risk estimates and structured reports. Clinicians verify outputs and incorporate them into multidisciplinary planning.

4. Diagnosis and Quantitative Assessment with AI in CSVD

The clinical assessment of CSVD continues to rely predominantly on indirect markers [79,80]. Consequently, clinicians infer overall disease burden from downstream manifestations such as WMH, lacunes, CMBs, EPVS, cortical superficial siderosis, and atrophy [9,10]. This interpretative process is labour-intensive, influenced by reader experience, and subject to variability across imaging platforms and institutions, which can hinder consistent diagnosis and longitudinal assessment. Current AI systems are not designed to replace expert interpretation but rather to standardise three clinically important functions: (i) automated lesion detection and volumetric quantification; (ii) structured phenotyping and subtyping of CSVD to link imaging patterns to likely aetiological pathways and clinical risk profiles; and (iii) differential diagnosis in cases where CSVD overlaps radiologically with other white matter or microvascular disorders. Representative methods are summarised in Table 1, and conventional and AI-enabled diagnostic pathways for CSVD are outlined in Figure 3.

Table 1. Representative AI applications relevant to CSVD assessment, progression prediction and functional phenotyping.

Intended use	Input modality	Methods	Study population	Study design	Sample size	Outcome	Internal validation	External validation	Calibration	Key results	Refs
WMH quantification and CHIPS grading	FLAIR MRI	2D U-Net; template-based CHIPS scoring	Silent cerebrovascular disease	Cross-sectional	Participants: 564	Current WMH and CHIPS ≥5	325 training; 139 test; manual CHIPS reference	100 participants; different scanner	NR	External AUC 0.87 (95% CI 0.82–0.92); sensitivity 86.50%, specificity 81.30%	[81]
Lesion quantification	T1, T2*, FLAIR and DWI MRI	U-Net-based CNN	Stroke/TIA with ≥1 CSVD marker	Cross-sectional	Participants: 1,500 development; 30 reader test	WMH, lacune, recent subcortical infarct and CMB masks	Expert-mask reference; development split unclear	Independent reader set; centre separation unclear	NA	Mean Dice: WMH 0.67, lacunes 0.50, infarcts 0.73, CMBs 0.50; processing time: AI 4.40 versus readers 636.00 s/case	[82]
DMV quantification	SWI; structural MRI for associations	3D U-Net; component counting; multivariable linear regression	CSVD	Retrospective cross-sectional	Participants: 305	DMV masks/counts and current CSVD burden	189 training; 30 validation; 86 test; manual reference	None	NA	Dice 0.46 ± 0.07; count ICC 0.76	[83]
CMB detection and localisation	QSM MRI	FRST candidates; V-Net false-positive reduction; CycleGAN augmentation	CSVD	Retrospective cross-sectional	Participants: 393	Current CMBs and locations	280 training; 35 validation; 78 test; random split	None	NA	Test set: 326 CMBs; lesion-level sensitivity 88.90%; 2.87 false positives/participant	[38]
PVS quantification and serial measurement	3D T1 MRI; T2/FLAIR reference	mcPVS-Net (nnU-Net); multivariable linear regression	ADNI-3 and community adults	Cross-sectional; serial measurement analysis	Participants: 55 development; 1,020 application; 90 serial; 173 external	PVS masks/volumes; serial measurement consistency	40 training; 15 test; 2-year serial MRI assessment	Community cohort/new scanner; manual masks in 5 participants	NA	Dice: internal 0.80 ± 0.09; external 0.67; serial volume ICC 0.97	[58]
Lesion quantification	T1, FLAIR and SWI/SWAN MRI	Multi-output U-Net; EfficientNet encoder	Arteriolosclerotic CSVD	Cross-sectional	Participants: 163	WMH, CMB, lacune and EPVS masks/volumes	105 development; participant-stratified nested 5-fold CV	58 participants; temporal/scanner test at the same institution	NA	Test Dice: WMH 0.78, CMBs 0.64, lacunes 0.77, EPVS 0.73; lesion-level sensitivity: CMBs 61.90%, lacunes 76.50%, EPVS 68.90%	[84]
Structural progression prediction	Carotid CTA fat density/radiomics; clinical variables	Elastic-net feature selection; XGBoost	CSVD; carotid stenosis <30%	Retrospective longitudinal	Participants: 294	MRI-defined CSVD progression; MRI interval ≥3 months	160 training; 69 test	65 participants; separate hospital	NR	AUC: internal 0.81 (95% CI 0.69–0.91); external 0.81 (95% CI 0.68–0.92)	[57]
Atrophy classification	NCCT	2D ResNet measurements; logistic regression; 3D CNN comparator	CSVD	Retrospective cross-sectional	Participants: 385 (107 no, 185 mild, 93 severe atrophy)	Current atrophy: binary and three-class severity	308 training; 77 test; 5-fold CV for tuning	None	NR	Binary AUC: 2D 0.95, 3D 0.94 (P = 0.25); three-class weighted κ: 0.73/0.61, respectively	[85]
Haemorrhage detection and localisation	NCCT; report-derived training labels	EfficientNet-B2; attention-based bidirectional LSTM; NLP labelling	Patients undergoing head CT	Retrospective cross-sectional	Scans: 10,699 training; 7,243 internal test; 491 external	Current intracranial haemorrhage; slice localisation	Participant-disjoint hold-out; reader/localisation subsets	CQ500; 41.80% haemorrhage	NR	External scan-level AUC 0.96 (95% CI 0.96–0.97), PPV 89.30%; slice-level localisation AUC 0.82; heatmap Dice 0.64	[86]
WMH detection from retinal images	Fundus photographs; MRI reference	DenseNet-201; EfficientNet-B7	Adults with paired fundus/MRI data	Retrospective cross-sectional	Participants: 1,892 (3,726 photographs); grading:	Current WMH presence and Fazekas grade	Participant-disjoint stratified 10-fold CV	None	NR	Photograph-level AUC: 0.74 ± 0.03/0.72 ± 0.03; grade accuracy: 41.40%/39.60%,	[87]

					462 (905 photographs)					respectively	
Retinal vascular phenotyping	OCTA; MRI and clinical covariates	OCTANet vessel segmentation; multivariable linear regression (GEE)	Neurologically normal adults aged ≥50 years	Cross-sectional	Participants: 139	Retinal features associated with current lacunes/WMH	Association analysis only; no diagnostic classifier	None	NA	DVC fractal dimension–lacunes: β = 0.58 (P < 0.01); SVC tortuosity–deep WMH: β = 0.31 (P = 0.03)	[88]
WMH quantification from PET	^{18}F-FDG PET; FLAIR reference masks	WhyperGAN; H-DenseUNet comparator	Cognitively impaired adults	Retrospective cross-sectional	Participants: 150	Current WMH masks/volumes	105 training; 45 test; FLAIR-derived masks	None	NA	Dice (WhyperGAN/H-DenseUNet): WMH >60 mL, 0.75/0.56; ≤60 mL, 0.36/0.24	[89]
Biomarker discovery and classification	Serum LC–MS/MS proteomics; age; MRI reference	LASSO feature selection; SVM-RFE; protein-network and panel ROC analyses	High-burden CSVD (score ≥3); MRI-normal controls	Case–control	Participants: 96 discovery (58 cases); 54 ELISA verification (27 cases)	Current high-burden CSVD; protein differences	70:30 feature-selection split; final panel ROC subset unclear	ELISA protein verification; no fixed-model external validation	NR	Six proteins plus age: AUC 0.95 (95% CI 0.90–0.98); 4/6 proteins differed in the ELISA sample	[54]
Biomarker classification	Plasma biomarkers; clinical and diagnostic MRI features	RF; KNN; regularised logistic regression	Mild VCI; lacunar stroke; controls	Case–control	Participants: 118 (36 VCI, 44 lacunar stroke, 38 controls); 114 analysed	Current CSVD versus controls; feature importance	RF: 91 training, 23 test; logistic regression: 76 training, 38 test	None	NR	All-input RF: accuracy 78.30%, sensitivity 100.00%, specificity 28.60%; regularised logistic regression AUC 0.73	[55]
CSVD burden stratification	Clinical/laboratory variables; MRI reference	LASSO feature selection; logistic regression; ML comparators	CSVD	Cross-sectional	Participants: 508 (194 high burden)	Current high CSVD burden (score 3–4)	75:25 training/test split; CV for tuning	None	Calibration plot	Logistic regression: AUC 0.85, PR-AUC 0.81; sensitivity 69.40%, specificity 82.30%; Brier score 0.15	[27]
CSVD detection	Clinical/laboratory variables; MRI reference	LightGBM; recursive/forward feature selection; SHAP	Community adults aged >40 years	Retrospective cross-sectional	Participants: 1,204	Current MRI-defined WMH and/or lacunes	572 development; 80:20 training/test split; nested 5-fold CV; selection/SMOTE within training folds	632 participants; separate geographic region	Calibration plots; evaluation cohort unclear	AUC: internal 0.86 (95% CI 0.80–0.93); external 0.76 (95% CI 0.72–0.80)	[90]
Cognitive classification	Scanned clock drawings	CNN; saliency maps and Grad-CAM	Cognitively impaired adults and controls	Cross-sectional	Drawings: 7,009 total; 3,282 for CNN analysis	Current cognitive impairment	Drawing-level stratified 5-fold CV	None	NR	Drawing-level accuracy 75.65 ± 1.10%; AUC 0.83 ± 0.01	[91]
Functional assessment and cognitive classification	Eye tracking; gait video; age and education	AI eye/gait measurements; bidirectional LSTM; logistic regression	Hospital CSVD; community presumed early CSVD	Cross-sectional (prospective recruitment)	Participants: 513 (194 hospital; 319 community)	Current MoCA-defined cognitive impairment	Not performed; apparent AUCs	Community model refitted; no fixed-model external validation	NR	AUC adjusted for age and education: hospital 0.79; community 0.81	[92]

Abbreviations: 2D: two-dimensional; 3D: three-dimensional; ADNI: Alzheimer's Disease Neuroimaging Initiative; AI: artificial intelligence; AUC: area under the receiver operating characteristic curve; CHIPS: Cholinergic Pathways Hyperintensities Scale; CI: confidence interval; CMBs: cerebral microbleeds; CNN: convolutional neural network; CSVD: cerebral small vessel disease; CT: computed tomography; CTA: computed tomography angiography; CV: cross-validation; DMVs: deep medullary veins; DVC: deep vascular complex; DWI: diffusion-weighted imaging; ELISA: enzyme-linked immunosorbent assay; EPVS: enlarged perivascular spaces; FDG: fluorodeoxyglucose; FLAIR: fluid-attenuated inversion recovery; FRST: fast radial symmetry transform; GEE: generalised estimating equations; Grad-CAM: gradient-weighted class activation mapping; ICC: intraclass correlation coefficient; KNN: k-nearest neighbours; LASSO: least absolute shrinkage and selection operator; LC–MS/MS: liquid chromatography–tandem mass spectrometry; LightGBM: Light Gradient Boosting Machine; LSTM: long short-term memory; ML: machine learning; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; NA: not applicable; NCCT: non-contrast computed tomography; NLP: natural language processing; NR: not reported; OCTA: optical coherence tomography angiography; PET: positron emission tomography; PPV: positive predictive value; PR-AUC: area under the precision–recall curve; PVS: perivascular spaces; QSM: quantitative susceptibility mapping; RF: random forest; ROC: receiver operating characteristic; SHAP: Shapley additive explanations; SMOTE: synthetic minority oversampling technique; SVC: superficial vascular complex; SVM-RFE: support vector machine recursive feature elimination; SWAN: susceptibility-weighted angiography; SWI: susceptibility-weighted imaging; TIA: transient ischaemic attack; VCI: vascular cognitive impairment; WMH: white matter hyperintensities; XGBoost: extreme gradient boosting.

4.1 Imaging Modalities and Markers

4.1.1 MRI

MRI remains the reference modality for CSVD and has been the main focus of AI-based imaging research. Manual WMH scoring, CMB counting and EPVS grading are time-consuming and may vary between readers. In a comparison of 10 classifiers for WMH segmentation across four datasets with different MRI sequence combinations, an RF model using MRI intensity and spatial location features performed best, with mean Dice coefficients of 0.66–0.72 [28]. RF also outperformed the other classifiers when FLAIR was unavailable, although omitting this sequence reduced segmentation accuracy. DL has also been applied to EPVS quantification [93]. A 3D convolutional regression network estimated basal ganglia EPVS burden, with intraclass correlation coefficients of 0.74 for agreement with expert visual scores and 0.93 for scan–rescan reproducibility [94]. In community-cohort participants, DEEPMIR distinguished CMBs from non-haemorrhagic iron deposits using multimodal MRI. CMB detection achieved sensitivities of 0.84–0.88 and precision of 0.40–0.59 under leave-one-out cross-validation [95]. These approaches provide quantitative measures of lesion burden to complement visual assessment [96].

Automated MRI measurements have also been used to characterise imaging phenotypes and explore clinical associations [41]. In small-vessel occlusion stroke, a U-Net-based model quantified periventricular and deep WMH volumes separately [97]. Another study used nnU-Net to segment CMBs from SWI and filtered phase images, with mean Dice scores of 0.73 in internal validation and 0.46 in external validation. The resulting CMB counts were analysed using linear regression in a separate clinical dataset of patients with suspected cognitive impairment. These counts were associated with age, hypertension, WMH burden and Mini-Mental State Examination (MMSE) scores [98]. Semi-supervised ML applied to arterial spin labelling MRI identified three CSVD perfusion subgroups that differed in lacunes, periventricular WMH and total CSVD burden [99]. Another DL model combined slice-wise CMB detection with scan-level classification of arteriolosclerotic CSVD, CAA and CADASIL. In an external test set of 28 patients, CMB detection recall was 0.71, while subtype classification achieved a weighted-average AUC of 0.91 and an accuracy of 0.82 [18].

Another clinically valuable application of AI is facilitating the differential diagnosis of CSVD from other white matter pathologies, particularly when vascular and inflammatory lesions are radiologically indistinguishable. DL models trained on FLAIR features, using transfer learning and attention mechanisms, have been developed to distinguish CSVD from multiple sclerosis. Reported performance included a mean balanced accuracy of 0.86 and a mean ROC-AUC of 0.99 [100]. This capability is particularly valuable at referral interfaces, where AI-assisted differentiation may prompt timely neuroinflammatory evaluation when multiple sclerosis is plausible, or reduce unnecessary escalation when imaging is more consistent with CSVD. Resting-state functional MRI extends assessment to functional networks. In CSVD, k-means clustering of dynamic connectivity patterns revealed network differences associated with executive function and processing speed [101]. Prospective multicentre studies are needed to establish the additional diagnostic value of these and related methods alongside clinical assessment and expert image interpretation.

4.1.2 CT

CT remains the first-line brain imaging modality in many acute and subacute cerebrovascular presentations because it is rapid, low-cost, and widely available. Its diagnostic value in CSVD has historically been limited by lower sensitivity for subtle white matter change and CMBs compared with MRI [17], as well as by interpretative challenges arising from age-related atrophy and imaging artefacts. However, AI methods may help narrow this gap by extracting quantitative markers of parenchymal injury and vascular risk from routine CT in forms that are more amenable to broader deployment.

One major application is automated structural analysis of non-contrast CT. In a CSVD pilot study, an automated 2D pipeline combining CNN-based linear measurements with logistic regression was compared with an end-to-end 3D CNN. In a held-out internal test set of 77 participants, the models achieved AUCs of 0.95 and 0.94 for detecting atrophy, respectively. For classification into no, mild or severe atrophy, weighted kappa values against expert annotations were 0.73 and 0.61 [85]. This provides a basis for structured grading of CT-visible atrophy. A CNN evaluated using ten-fold cross-validation produced CT-derived white matter lesion volumes that correlated with FLAIR-derived volumes ($r = 0.94$). Mean Dice overlap was 0.43 overall and 0.68 in the Fazekas 3 group [102]. These results suggest that CT-derived volumes can approximate MRI-defined lesion burden, although spatial agreement was limited and was better in patients with extensive lesions. Haemorrhage detection and characterisation are another active area. A systematic review of AI systems for ICH detection on non-contrast CT or MRI reported overall sensitivity and specificity above 0.92 [103]. This is particularly relevant for CSVD because spontaneous deep or lobar haemorrhage is a

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defining clinical presentation of arteriolosclerotic disease and CAA. Early and reliable identification of haemorrhage burden and location provides critical information for prognosis, acute management, and antithrombotic strategy.

Vascular CT is also beginning to benefit from automation. DL applied to CT angiography has enabled automated 3D segmentation of the carotid arteries [104]. Although these applications are not specific to CSVD, they may still provide useful contextual information in patients in whom macrovascular atherosclerosis coexists with small-vessel disease [105]. These applications support further evaluation of automated CT measurements in CSVD, particularly where MRI access is limited.

4.1.3 Retinal Imaging

The retinal vasculature shares key developmental and structural features with cerebral small vessels, and observational as well as mechanistic studies have linked retinal microvascular alterations to CSVD [106-108]. These findings provide a basis for investigating retinal measurements as indirect markers of cerebral small-vessel injury. AI has been used to extract quantitative features from colour fundus photography (FP) and optical coherence tomography angiography (OCTA), and to assess their relationships with MRI-defined CSVD burden.

Fundus-based DL has been used to estimate MRI-defined WMH, with one study reporting a mean ROC-AUC of 0.74 under ten-fold cross-validation [87]. In a cross-sectional community cohort of 180 older adults without stroke or dementia, a retinal image model reported patient-level sensitivity of 0.93 and specificity of 0.98 for high WMH burden. Validation used internal resampling and cross-validation, and estimated WMH volumes correlated with MRI measurements [109]. Related work extended retinal image analysis to estimating WMH burden in individual brain regions [110]. FP has also been used to examine retinal microvascular changes in FD. DL-based vessel segmentation enabled quantitative assessment of retinal vascular morphology. The arteriolar asymmetry ratio was inversely correlated with WMH and lacune scores, total CSVD burden and global cortical atrophy scores [111]. These cross-sectional associations were observed in a hereditary vasculopathy; their relevance to sporadic CSVD requires further study.

OCTA extends these capabilities by enabling the quantitative assessment of retinal capillary features [112]. A lower vascular orientation distribution value in the superficial capillary plexus was associated with lacunar rather than non-lacunar ischaemic stroke in adjusted logistic regression [113]. The study used AI for vessel quantification and logistic regression to examine the association with stroke subtype. FP and OCTA provide quantitative retinal measurements that could be investigated alongside MRI, although their place in routine CSVD screening remains to be defined.

4.1.4 Molecular Neuroimaging

Molecular neuroimaging with positron emission tomography (PET) and single-photon emission computed tomography (SPECT) may help characterise perfusion failure, microvascular dysfunction, and glial activation [114,115]. When interpreted alongside structural MRI, these signals may highlight molecular and perfusion changes and neurovascular inflammation associated with white matter injury, cognitive decline, and gait disturbance, particularly when conventional MRI does not fully explain the clinical picture. In selected patients, this additional information may support diagnostic clarification and more individualised follow-up planning.

In ADNI participants with mixed vascular and amyloid-related risk factors, DL segmentation and spectral clustering identified distinct WMH spatial patterns. Parietal WMH burden was independently associated with florbetapir PET measures of cerebral amyloid accumulation [116]. These findings illustrate the use of automated WMH measurements alongside amyloid PET to investigate mixed pathology in older adults. SPECT provides complementary haemodynamic information by measuring cerebral perfusion. In a single-centre study, a deep CNN automated vascular region-of-interest placement on dynamic chest images for deriving the input functions used in brain perfusion SPECT quantification. Automated and manual time–activity curve integrals were closely correlated ($r = 0.97–0.98$) [117]. Automating this step may make perfusion quantification more practical in stroke and memory services, where manual processing can be time-consuming. This is potentially relevant to CSVD, in which chronic cerebral hypoperfusion and regional hemodynamic vulnerability have been implicated in WMH progression and subcortical cognitive dysfunction.

Despite these advantages, the widespread use of PET and SPECT remains limited by cost, limited access to tracers, and specialised infrastructure requirements. These modalities may complement MRI in selected cases where identifying coexisting amyloid pathology or clarifying cerebral perfusion addresses a specific diagnostic question. As AI-driven quantification becomes more standardised across centres, molecular imaging could complement MRI and retinal imaging within an integrated, multiscale diagnostic workflow for selected CSVD populations.

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4.2 Fluid Biomarkers

Fluid biomarkers may complement MRI by providing information on vascular and tissue injury [11,118]. Plasma S100B has been studied alongside MRI measures of cerebrovascular disease and BBB function in relation to cognition in older adults [119]. Serum NfL has also been associated with WMH and diffuse white matter damage in sporadic CSVD and CADASIL [120]. Routine measures, including the neutrophil-to-lymphocyte ratio and Hcy, have also been evaluated alongside clinical variables in regression and ML models for classifying CSVD imaging burden [27]. These routine measures provide accessible inputs, although they do not specifically measure cerebral injury.

Plasma extracellular vesicle (EV) proteomics provides a recent CSVD-specific example. In a multicentre study of patients with MRI-defined CSVD and moderate-to-severe WMH, RF models selected candidate proteins for targeted mass spectrometry in a separate dataset. XGBoost then evaluated combinations of proteins showing consistent expression patterns across the two datasets. HNRNPU and RPL38 distinguished cognitively normal patients with CSVD from controls (AUC 0.85), whereas ATP6V1F and HNRNPU distinguished patients with and without cognitive impairment within CSVD (AUC 0.90). These results were obtained in randomly partitioned test sets. Adding demographic and vascular risk variables improved discrimination between cognitively normal patients with CSVD and controls; clinical or MRI variables did not improve classification of cognitive status within CSVD. RPL38 was also associated with WMH burden and white matter integrity [121].

Complementary evidence comes from cerebrospinal fluid proteomics. In BioFINDER-2, which included cognitively unimpaired individuals and patients with mild cognitive impairment (MCI) or dementia, network-based clustering identified protein modules linked to vascular, immune and neuronal processes. Conventional regression related protein abundance to WMH, CMBs and infarcts. Matrix metalloproteinase-12 was increased across these manifestations, while lobar and deep CMBs showed partly distinct profiles [122]. In FD, systems biology and ML identified a 17-protein plasma signature distinguishing patients from controls [123]. The model classified FD status; it did not establish a marker panel for cerebral small-vessel involvement.

Biological specificity remains important. The EV study sampled total circulating vesicles and did not assess amyloid status in CSVD participants. Its signature may therefore reflect systemic processes or coexisting neurodegenerative pathology [121]. These panels remain potential adjuncts to MRI and should be interpreted alongside the lesions and clinical features assessed.

4.3 Neurocognitive and Behavioural Assessment

4.3.1 Cognitive Function

Cognitive impairment in CSVD commonly affects processing speed, attention and executive function, although memory and other domains may also be involved [124,125]. Brief instruments such as the MMSE and the Montreal Cognitive Assessment (MoCA) provide a global assessment [126,127]. Digital methods can extend this assessment by quantifying aspects of performance that are not captured by a total test score.

Direct CSVD evidence comes from AI-assisted oculomotor and gait assessment. The EyeKnow and ReadyGo systems measured eye movements and video-based gait features in a hospital cohort with CSVD and a community cohort with presumed early CSVD. Anti-saccade accuracy, stride velocity and swing velocity, combined with age and education in logistic regression models, identified MoCA-defined cognitive impairment with AUCs of 0.79 in the hospital cohort and 0.81 in the community cohort [92]. AI-assisted systems provided the quantitative measurements, while cognitive classification used conventional regression. These findings concern current cognitive status, rather than the prediction of subsequent decline.

Automated analysis of conventional tests has also been evaluated in cohorts not selected for CSVD. A CNN analysed scanned clock drawings to classify cognitive impairment, with explainability methods highlighting regions that contributed to classification [91]. This illustrates automated interpretation of test performance. Speech analysis offers a different source of information. In a memory-clinic study across the Alzheimer's disease spectrum, ML models used acoustic features from spontaneous speech to classify cognitive status and estimate performance in individual cognitive domains under cross-validation [128-130]. The analysis concerned acoustic properties of speech, rather than linguistic content.

Natural language processing (NLP) has also been applied to clinical documentation. A DL model detected references to cognitive decline in notes written before an MCI diagnosis. It achieved an AUC above 0.99 in a set of 2,000 unfiltered note sections, of which 69 contained manually annotated evidence of decline [131]. This evaluation concerned documented symptoms in individual text sections within one healthcare system. The study did not assess patient-level diagnostic accuracy for CSVD-related cognitive impairment.

4.3.2 Gait Patterns

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Gait abnormalities may emerge before overt functional limitations are acknowledged and may be present even without self-reported imbalance [132,133]. For instance, WMH have been linked with slower gait speed, reduced cadence, prolonged stride time, and extended stance phase. Lacunes may contribute to gait dysfunction partly through their association with impaired attention and executive control. Basal ganglia EPVS are specifically associated with reduced gait speed [134]. A brief, standardised gait assessment at first presentation can document motor impairment alongside the routine neurological examination. Visual observation, however, may miss subtle abnormalities and can be influenced by examiner experience.

AI-driven quantitative gait analysis converts raw movement into objective, reproducible metrics. Using wearable sensors or camera-based platforms, spatiotemporal parameters, including stance-to-swing ratio, gait speed, and stride variability, can be recorded during routine walking [135,136]. These systems enable automated extraction of numerous gait features within minutes, outside specialised motion laboratories, thereby reducing examiner dependence and facilitating longitudinal tracking across clinical settings [137-139]. Under controlled conditions, smartphone-based sensors can also yield reliable gait measurements comparable to those obtained with reference-grade devices [140]. Data-driven analysis can also relate quantitative gait patterns to imaging burden. In 720 community participants without diagnosed neurological disease, sparse sliced inverse regression identified a wearable-derived gait pattern associated with high CSVD burden on MRI (odds ratio 1.25, 95% CI 1.01–1.55). The pattern included slower walking, longer stance and double-support phases, smaller gait angles and greater variability [141]. These findings describe an association between quantitative gait measurements and existing imaging burden. Beyond feature extraction, DL has been used to classify walking ability in broader stroke populations. In a six-centre study, OpenPose-derived pose data were used to classify Functional Ambulation Category groups, with an accuracy of 0.90 in an internal test set created by a random 80:20 training–test split [142]. The model reproduced clinically assigned severity categories, providing evidence for automated gait grading within the studied stroke population.

Gait abnormalities are not specific to CSVD and may also reflect parkinsonism, peripheral neuropathy or musculoskeletal disease. For clinical use, validation should include these common comorbidities, and individual gait parameters need clear definitions and appropriate reference ranges.

4.3.3 Affective Function

Neuropsychiatric symptoms are frequently observed in CSVD, commonly presenting as apathy, depressive mood, anxiety, and irritability [143]. These symptoms can affect everyday function but may receive limited attention during routine assessment. In patients with CSVD and depressive symptoms, diffusion tensor imaging (DTI) and network analyses have identified abnormalities in white matter microstructure and emotion-related structural networks [144]. Cognitive slowing and reduced verbal fluency in CSVD may complicate symptom reporting and the use of standard mood questionnaires.

AI has been explored through two approaches to neuropsychiatric assessment. The first is language analysis. NLP systems can quantify emotional tone in short texts. In adult samples not selected for CSVD, sentiment derived from brief, open-ended responses predicted changes in depressive symptoms over three weeks after accounting for current mood [145]. A separate study analysed 428 diaries from 91 app users, using labels based on symptom scales and clinician review. A fine-tuned GPT-3.5 model with chain-of-thought prompting achieved an accuracy of 0.90, specificity of 0.96 and sensitivity of 0.64 under five-fold cross-validation [146]. Their usefulness in CSVD remains uncertain, particularly when cognitive or language impairment affects self-report.

The second approach involves integrating neuroimaging, laboratory results, and clinical features to identify a vascular depression phenotype, a late-life depressive syndrome associated with underlying small vessel pathology. In a multicentre study comparing older adults with vascular depression and non-depressed controls, an interpretable LightGBM model combined WMH score, lacune count, age and five circulating biomarkers. It achieved an AUC of 0.90 (95% CI 0.84–0.94) in an independent cohort of 171 participants, with SHAP outputs describing the contribution of individual predictors [147]. These findings support multimodal characterisation of the study-defined vascular depression phenotype. Assessment of apathy would require a separate model, since reduced motivation is not equivalent to depressed mood.

5. Personalised Management of CSVD Enabled by AI

Current management of CSVD still relies largely on generalised vascular risk control, despite wide variation in individual trajectories. Some patients remain stable for years, whereas others develop gait instability, subcortical cognitive slowing, and mood disturbance despite similar baseline blood pressure and imaging findings. This heterogeneity likely reflects differences in the pace and combination of underlying microvascular injury processes, rather than a single uniform pathway. AI may

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help combine clinical and imaging information to support treatment review and reassessment as the disease evolves.

5.1 Therapeutic Discovery and Prediction

Drug discovery in CSVD requires experimental models that capture injury to the cerebral microvasculature. AI can help prioritise compounds for these models, although most applications discussed here were developed outside CSVD.

Direct CSVD research has provided biological leads. Random forest and regularised regression analyses identified neutrophil and platelet markers associated with CSVD [55]. These associations point to pathways worth pursuing; they do not show that blocking the corresponding targets would alter the disease. AI-based phenotypic screening offers a way to investigate compound mechanisms [148,149]. MitoReID used DL to analyse mitochondrial image sequences in a cell-based platform developed outside CSVD. It identified cyclooxygenase-2 inhibition as a mechanism of epicatechin, which was confirmed in vitro [150]. In an in vitro BBB model using angiotensin II-exposed endothelial cells, harpagoside reduced barrier permeability and oxidative stress alongside lower cyclooxygenase-2 expression [151]. These findings provide a rationale for investigating cyclooxygenase-2-related mechanisms in CSVD. A more disease-specific experimental platform used patient-derived induced pluripotent stem cells carrying HTRA1 or COL4A1/2 mutations to construct endothelial–mural cell models. Three of 13 matrix metalloproteinase inhibitors restored BBB permeability to control levels [152]. This screen was not AI-guided. It nevertheless provides a monogenic CSVD assay in which computationally ranked compounds could be tested.

For compounds intended to act within brain tissue, predicting BBB penetration is another important step. MegaMolBART encoded simplified molecular-input line-entry system (SMILES) strings describing molecular structure, and XGBoost used the resulting features to predict BBB penetration. The model achieved an AUC of 0.88 on held-out test data. Selected predictions were examined in human BBB spheroids [153]. This general molecular model could support screening for agents intended to act within brain tissue. Predicted BBB penetration alone is insufficient to establish adequate target exposure or efficacy against small-vessel injury. In parallel, a DL framework combined propensity score estimation with inverse probability weighting to identify drug repurposing candidates in coronary artery disease [154]. This approach offers a methodological precedent for investigating repurposing candidates in CSVD.

These approaches support different stages of discovery (Fig. 4). Their contribution to CSVD will depend on testing computationally prioritised compounds in experiments that establish their effects on cerebral microvascular injury.

5.2 Decision Support for Personalised Treatment

CSVD management still relies largely on vascular prevention, but coexisting ischaemic and haemorrhagic risks complicate treatment selection [125,155]. A useful AI output should inform a specific treatment decision, with benefit weighed against harm [156]. Most drug-response and treatment-effect models discussed here were developed in broader stroke, atrial fibrillation (AF) or hypertensive populations. Their use to guide prescribing has not been established in CSVD.

Studies relevant to antiplatelet selection have examined imaging phenotypes and laboratory drug response. In CSVD cohorts, DL applied to SWI has detected CMBs and helped distinguish arteriolosclerotic CSVD from CAA [18]. ML models incorporating genetic and clinical information have separately estimated laboratory aspirin resistance in broader stroke cohorts [157,158]. These studies address haemorrhage-related imaging features and laboratory non-response, respectively. A PICASSO post-hoc analysis found fewer cerebral haemorrhages with cilostazol than aspirin in patients with ischaemic stroke and multiple CMBs (hazard ratio 0.08, 95% CI 0.01–0.60), whereas no significant difference was observed in those with prior ICH [159]. Whether combining AI-derived phenotypes with response predictions improves antiplatelet selection has not been tested in these studies.

For patients with CSVD and AF, anticoagulation decisions involve balancing ischaemic prevention against haemorrhagic risk. In a retrospective AF cohort receiving direct oral anticoagulants (DOACs), a random forest model predicted bleeding requiring hospitalisation within one year with an AUC of 0.76, compared with 0.57 for HAS-BLED [160]. The cohort was not selected for CSVD and excluded patients with previous significant bleeding. PRESTIGE-AF illustrates the competing risks: DOACs reduced ischaemic stroke but increased recurrent ICH in survivors of ICH with AF [161]. In its prespecified imaging analysis, cortical superficial siderosis was associated with recurrent ICH, although the risk estimate was imprecise [162]. CMB count alone should not determine whether anticoagulation is stopped [163]. Assessment should consider the treatment indication, previous ICH, CMB burden and distribution, blood pressure control and concomitant medication [163,164]. Predicting bleeding risk does not establish whether withholding anticoagulation or reducing its dose would improve outcomes.

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Blood pressure studies show why the population and endpoint matter. In older hypertensive adults with MRI-defined WMH, INFINITY found less WMH progression with intensive ambulatory blood pressure control over three years, without significant differences in gait or cognition [165]. PRESERVE enrolled patients with symptomatic LI and confluent WMH; intensive and standard lowering did not differ significantly in the primary DTI measure of white matter change over two years [166]. Neither trial established a functional benefit from intensive lowering. An XGBoost model using electronic health record data from a broader hypertensive population predicted blood pressure control within 12 months, with an AUC of 0.76 [167]. This model predicted the likelihood of achieving blood pressure control, rather than the effects of choosing a particular treatment target. Models estimating the relative effects of intensive and standard control address a different question. A post-hoc analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) combined phenomapping with XGBoost to estimate variation in cardiovascular benefit from intensive versus standard control. The model was tested externally in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial. Adjusted hazard ratios for intensive versus standard control were 0.70 (95% CI 0.55–0.90) in the group with higher predicted benefit and 1.05 (95% CI 0.84–1.32) in the group with lower predicted benefit (interaction P = 0.02) [168]. The cardiovascular endpoint limits its application to CSVD. A separate SPRINT MRI analysis used DL to quantify WMH and PVS in hypertensive adults without diabetes or prior stroke, finding less progression of a composite small-vessel injury measure with intensive control [169]. Here, DL supplied measurements for a conventional treatment comparison.

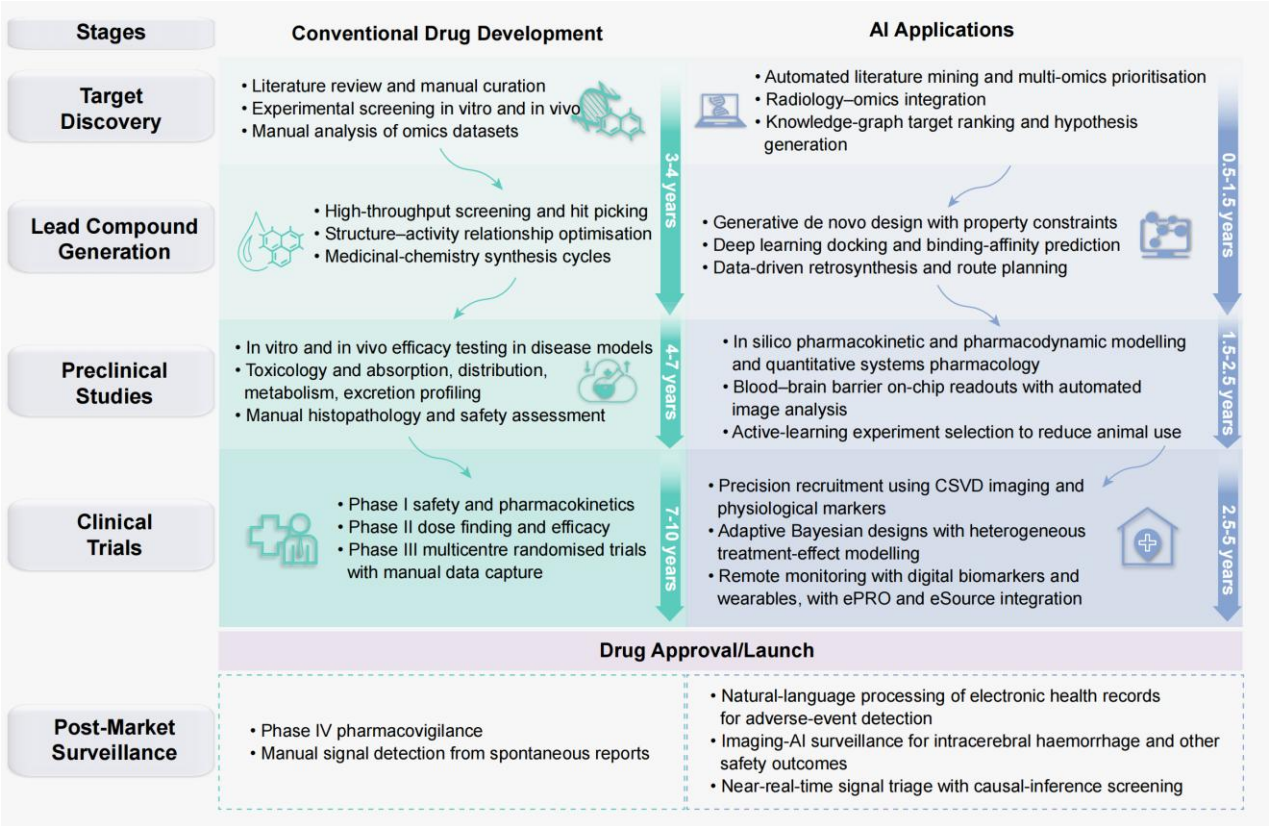


Figure 4. Potential applications of AI across drug development in CSVD. The schematic presents conventional drug development alongside potential AI applications, from target discovery to post-marketing surveillance. These applications draw on broader biomedical research and require validation in CSVD. Cumulative development times are schematic estimates and should not be interpreted as validated CSVD timelines or measured time savings attributable to AI. Abbreviations: AI: artificial intelligence; CSVD: cerebral small vessel disease; ePRO: electronic patient-reported outcome; eSource: electronic source data.

Dose adjustment offers a more defined application. A deep reinforcement learning model developed from AF trial data recommended warfarin adjustments using serial international normalised ratio (INR) measurements and dosing information, aiming to maintain an INR of 2.0–3.0. The model was evaluated retrospectively and did not direct prescribing. In an external trial dataset, greater agreement at centre level between actual prescribing and

model recommendations was associated with more time in the therapeutic range and a lower incidence of a composite outcome comprising stroke, systemic embolism and major haemorrhage. Similar associations were observed with an established rules-based dosing algorithm [170].

Current prevention guidance remains the basis for prescribing, including lipid lowering after lacunar ischaemic stroke [171]. AI recommendations should be evaluated within this framework. In MRI-characterised CSVD cohorts, the relevant test is whether model-guided care improves ischaemic prevention without unacceptable haemorrhagic harm, while preserving cognition and mobility.

5.3 Real-Time Monitoring and Patient Feedback

Brief clinic visits may miss variation in blood pressure, gait stability and daily activity. Home-based devices offer a way to collect these observations between appointments [172,173].

Gait assessment, in particular, can now be performed outside specialist laboratories. In a CSVD cohort, smartphone accelerometry and video analysis using OpenPose identified differences in step regularity and posture during brief normal, dual-task and fast walking tasks [77]. These assessments were conducted in hospital corridors. Complementary evidence comes from a post-stroke feasibility study in which a single RGB-D camera was compared with instrumented 3D gait analysis. The reported intraclass correlation coefficients were 0.94 for both walking velocity and cadence, but only 0.47 for step width [174]. These findings support measurement of selected gait parameters, although accuracy varies by parameter.

Daily activity recordings may also provide information about apathy. Seven-day actigraphy in CSVD showed lower daytime activity in patients with apathy, with activity levels negatively correlated with apathy severity [175]. Another study found that greater MRI-defined CSVD burden was associated with lower rest–activity rhythm amplitude and greater fragmentation of activity within the day [176]. Both studies used conventional actigraphy analyses. These measurements could be evaluated as inputs to models of changes in activity or motivation over time, but reduced activity can also reflect impaired mobility or fatigue. Changes in activity therefore need to be interpreted alongside symptoms and daily circumstances.

Trials in stroke and hypertensive populations have evaluated remote blood pressure monitoring and feedback. A randomised feasibility trial after ischaemic stroke found that Bluetooth-enabled home monitoring with additional clinical contact improved measurement adherence, without a significant between-group difference in mean blood pressure [177]. In the SMART-BP trial, patients with uncontrolled hypertension receiving app-based feedback had a greater reduction in home systolic blood pressure at 24 weeks than those undertaking self-monitoring alone (22.4 versus 17.2 mmHg; $P = 0.02$) [178,179]. These trials tested remote monitoring and feedback; they did not evaluate whether AI provides additional benefit in CSVD. Repeated home readings can quantify day-to-day variability; assessment of nocturnal patterns requires measurements taken overnight.

Patient-reported outcomes remain essential for assessing clinical effectiveness. The CADASIL Patient-Reported Outcome questionnaire covers emotional symptoms, attention and executive difficulties, motor function and daily activities. It was validated for use in CADASIL, although further development was required for other forms of CSVD [180]. An international CADASIL survey also identified fatigue as a frequent and particularly troublesome symptom [181]. Such findings help define what remote follow-up should capture beyond movement and blood pressure. Digital questionnaires could record these concerns alongside sensor measurements [182,183]. Summarising free-text symptom reports with NLP is another potential application, but its clinical value in CSVD remains untested [184].

The clinical value of monitoring depends on whether the changes detected can inform an appropriate response. Neither agreement with laboratory measurements nor associations with current disease burden define how large or sustained a change should be to warrant clinical review. CSVD studies should test whether feedback leads to appropriate reassessment and improves outcomes such as falls, treatment adherence or everyday function. Consent to ongoing monitoring and clear responsibility for responding to alerts are also essential, particularly for patients who need help using the devices.

5.4 Rehabilitation Management and Emerging Technologies

Rehabilitation in CSVD should address both executive dysfunction and impaired gait or balance [185,186]. In CSVD, AI has mainly been evaluated for functional assessment; evidence for AI-guided rehabilitation remains limited. Smartphone sensors and OpenPose video analysis have characterised single- and dual-task gait in CSVD [77], while AI-assisted oculo-gait measurements have identified features associated with cognitive impairment [92]. In broader gait-validation studies, markerless measurements of speed, step time and step length showed good to excellent agreement (intraclass correlation

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coefficients 0.81–0.98), with weaker results for some joint angles [187]. Their reliability for measuring dual-task cost and gait variability, and their ability to detect changes during CSVD rehabilitation, require further evaluation.

Rehabilitation triage raises a different question. In an internally validated small-artery occlusion stroke study, regression and ML models estimated the need for rehabilitation assessment within 48 hours of admission. Clinical variables supplied most of the predictive information; adding WMH burden and laboratory markers did not improve discrimination, and complex algorithms performed comparably to logistic regression [188]. Such models need to demonstrate added value over routine neurological and gait assessments before they are used to prioritise referrals.

Training trials illustrate the importance of assessing cognitive and motor outcomes separately. Cog-VACCINE enrolled patients with subcortical vascular cognitive impairment without dementia and MRI-defined small-vessel lesions. Seven weeks of computerised training, with difficulty adjusted by accuracy-based rules, improved MoCA scores relative to an active control; the executive-function endpoint showed no significant between-group improvement [189]. A 12-month resistance-training trial in MRI-confirmed CSVD with MCI found a small cognitive benefit over balance and tone exercises (Cohen's d = 0.18), without a significant between-group difference in dual-task Timed Up and Go at completion [190]. A virtual reality meta-analysis in broader MCI populations reported cognitive benefits, but its subgroup findings on immersion and training schedules do not establish CSVD dosing [191]. The added benefit of ML-guided adjustment of task difficulty over rule-based adaptation remains unclear in CSVD.

Stimulation trials provide another setting in which AI-guided parameter selection could be evaluated. CSVD trials reported improvements in gait and executive function after transcranial direct current stimulation [192], and in Timed Up and Go performance after accelerated intermittent theta burst stimulation; the latter trial showed no significant group-by-time interaction for the MoCA total score [193]. Task-based functional MRI also guided individual prefrontal targets for repetitive transcranial magnetic stimulation, with cognitive benefits at three months [194]. These studies evaluated stimulation protocols or image-guided targeting, rather than AI-selected parameters. In healthy adults, personalised Bayesian optimisation selected home-based transcranial random noise stimulation intensity using baseline attention and head circumference. The overall effect of stimulation was not significant; benefits were observed only among participants with lower baseline performance [195]. CSVD-specific trials would need to compare algorithm-selected settings with standard protocols and assess both clinical benefits and adverse effects.

Brain-computer interfaces (BCIs) use trained decoders to translate neural activity into commands for rehabilitation devices. In chronic stroke, ML decoding of motor attempts triggered functional electrical stimulation and improved arm recovery [196]. A meta-analysis of BCI-controlled functional electrical stimulation found a moderate effect on upper-limb motor function (standardised mean difference 0.50, 95% CI 0.26–0.73) [197]. These stroke studies offer a precedent for rehabilitation after LI with residual arm impairment, but do not validate executive–gait training in diffuse CSVD. A stroke telerehabilitation trial also supports home delivery of arm therapy [198], although it did not evaluate an AI-guided program.

Programs guided by AI models should be compared with otherwise equivalent rehabilitation programs to establish whether AI improves functional recovery. Dual-task assessments must measure cognitive performance alongside gait, because an increase in walking speed may be accompanied by poorer performance on the cognitive task. Follow-up should include falls and activities of daily living to assess whether benefits extend beyond supervised sessions.

6. Challenges and Future Directions

Multicentre data quality remains a major obstacle to CSVD modelling [26,199]. Variation in scanners, sequences and protocols can affect CMB detection and WMH quantification. STRIVE recommendations provide a common framework for defining and annotating imaging markers [9,10]. ComBat and related harmonisation methods can reduce site effects in derived measurements but cannot recover information that was not acquired [200,201]. Studies should specify the required sequences for each imaging task and how incomplete imaging will be handled.

Data-sharing restrictions can limit centralised pooling of MRI, retinal and wearable data. Federated learning allows institutions to train a shared model while retaining raw data locally, but does not automatically resolve differences in acquisition or labelling [202,203]. Missing inputs also require attention. SWI, retinal images or wearable recordings may be unavailable because of limited access, disability or clinical selection. Randomly removing inputs during training may not reproduce these patterns. Models should be evaluated using the combinations of inputs available in routine practice, with performance reported for each combination and calibration assessed for risk estimates. Versions designed for fewer inputs require their own validation, and systems should flag when missing data prevent a reliable result.

Mixed pathology is particularly relevant in older

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patients. Arteriolosclerotic CSVD may coexist with CAA, Alzheimer-type pathology or large-vessel disease. In symptomatic CSVD, cerebrospinal fluid biomarker profiles suggesting Alzheimer pathology or neurodegeneration were associated with poorer cognition [204]. Models trained in selected cohorts should therefore be tested in patients with coexisting pathology. The presence of CSVD on MRI should not be assumed to account fully for cognitive or gait impairment. Relevant co-pathologies should be recorded where available. External validation should examine performance by co-pathology and vascular risk profile and, for imaging-based models, scanner type and sequence [205]. Longitudinal assessment introduces further challenges. Scanner upgrades, changing treatment patterns and shifts in disease prevalence can affect measurement consistency and risk calibration [206]. Performance should be monitored over time, with scanner and model versions recorded. Criteria for recalibration or retraining should be specified in advance. Changes in output following scanner or software updates should be checked for technical effects before they are interpreted as disease progression.

Interpretability should help clinicians recognise errors. Saliency maps can be unstable and should not replace inspection of the underlying image [207]. There should be a documented process for reviewing uncertain or implausible outputs, and model failures should be recorded for audit. Negative and inconclusive findings should be reported alongside positive results. Prediction studies should follow TRIPOD+AI reporting guidance, with PROBAST+AI used to assess quality, risk of bias and applicability. Reports and protocols of randomised trials evaluating AI interventions should follow CONSORT-AI and SPIRIT-AI, respectively [208-211].

Regulatory frameworks now codify many of these expectations. Under the EU AI Act, AI-enabled medical devices meeting the relevant criteria are classified as high risk and will be subject to requirements for risk management, data quality, human oversight and post-market monitoring. The European Health Data Space establishes a legal framework for the secondary use of health data in secure environments with audit trails. In the United States, the US Food and Drug Administration guidance on Predetermined Change Control Plans describes how adaptive updates to AI-enabled device software functions can be pre-specified and audited. For multinational CSVD studies, these frameworks enable safer iteration; however, they also introduce non-trivial compliance and documentation work.

Access to these tools may differ across patients and care settings. Recruitment and evaluation should include patients across a range of ages, ethnic backgrounds and socioeconomic circumstances [206]. Variation in scanner capabilities and limited imaging access in rural services also need consideration. Home monitoring depends on device ownership, digital literacy and, sometimes, help from carers. Evaluation should examine uptake, reasons for exclusion, subgroup performance and, for risk models, calibration. Patients unable to provide optional measurements should retain access to appropriate CSVD assessment. Integration into routine care requires information exchange with existing clinical systems, staff training and clear responsibility for reviewing outputs [212-214]. Support with device use and alternatives such as face-to-face assessment should be available when digital access is not feasible.

Finally, robust economic evidence remains limited. A study illustrates that diagnostic accuracy alone does not determine cost-effectiveness [215]. Budget impact depends on infrastructure, model maintenance, and periodic revalidation. All of these incur high costs in multimodal CSVD programs involving imaging, sensors, and home monitoring. Consequently, payers and hospitals require transparent cost models and prospective service evaluations rather than extrapolations from retrospective performance [216]. Economic evaluation should be linked to service-level endpoints (scan utilisation, referral volume, follow-up intensity, and patient-relevant outcomes) rather than diagnostic accuracy alone.

7. Limitations

The evidence reviewed is uneven across clinical applications. CSVD studies provide the clearest support for automated imaging assessment, whereas several treatment and rehabilitation examples draw on broader stroke populations or other research settings. Findings in hereditary CSVD may not transfer directly to sporadic disease because the underlying vasculopathies differ. These differences limit the extent to which the findings can inform routine care for sporadic CSVD. Studies vary in design, disease definitions and outcome assessment, making reported performance estimates difficult to compare. We therefore did not pool performance estimates or undertake a quantitative comparison of algorithms. Studies also differ in how they use AI. Some integrate several patient-level data sources within one model; others use AI-derived measurements in conventional statistical analyses. When both the input data and the modelling method change, the source of any performance improvement is difficult to determine. The added clinical value of multimodal integration therefore remains uncertain. In particular, the available reports do not consistently show whether collecting additional modalities improves a specific clinical decision enough to justify the extra time, cost and burden for patients.

8. Conclusion

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Given the established role of CSVD as a substrate for later cerebrovascular and neurodegenerative syndromes, earlier and more precisely targeted intervention may help mitigate irreversible clinical decline. For risk stratification and prognosis, models combining clinical information with imaging or digital measurements have been studied for screening and estimating later cognitive or vascular outcomes. Comparative studies suggest that better measurements may be at least as important as greater algorithmic complexity. AI research in CSVD has progressed furthest in automated lesion detection and quantitative imaging assessment. ML and DL have supported measurement of WMH, CMBs, lacunes and EPVS, with multicentre evaluation in selected studies. More standardised measurements may support serial follow-up and help relate structural injury to clinical manifestations. For personalised management, existing studies identify roles for AI in compound screening, treatment review and rehabilitation assessment. Studies in related populations provide methods for further investigation, while disease-specific treatment studies define the clinical questions those methods need to address. Evidence that model-guided management improves outcomes in CSVD remains limited. Clinical translation will depend on standardised acquisition, rigorous external validation and service evaluations that assess safety, equity and value when model outputs are used to guide defined clinical decisions. For multimodal systems, this also means establishing when the combined information changes a decision beyond what routine assessment can provide. In ageing populations, the goal is to preserve cognition, mobility and independence while reducing vascular events. Ultimately, sustained focus on clinical relevance over technological novelty will determine whether AI delivers better outcomes for people living with CSVD.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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