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Machine learning applications in vascular neuroimaging for the diagnosis and prognosis of cognitive impairment and dementia: a systematic review and meta-analysis

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Abstract

Background Cerebral small vessel disease (CSVD) is a common neurological condition that contributes to strokes, dementia, disability, and mortality worldwide. We conducted a systematic review and meta-analysis to investigate the use of neuroimaging CSVD markers in machine learning (ML) based diagnosis and prognosis of cognitive impairment and dementia, and identify both methodological changes over time and barriers to clinical translation.

Methods Following the PRISMA guidelines, we systematically searched for original studies that used both neuroimaging CSVD markers and ML methods for diagnosing and prognosing neurodegenerative diseases (preregistration in PROSPERO: CRD42022366767). Each paper was independently reviewed by a pair of reviewers at all stages, with a third consulted to resolve conflicts. We meta-analysed the effectiveness of ML models to distinguish healthy controls from Alzheimer's dementia and cognitive impairment, using area under the curve (AUC) as the performance metric.

Results We identified 75 studies: 43 on diagnosis, 27 on prognosis, and 5 on both. Nearly 60% of studies were published in the past two years, reflecting a growing interest in using CSVD markers in ML-based diagnosis and prognosis of neurodegenerative diseases, especially Alzheimer's dementia. This rising interest may be linked to the strong performance of such models: according to our meta-analysis, ML approaches using CSVD markers perform well in differentiating healthy controls from Alzheimer's dementia (AUC 0.88 [95%-CI 0.85–0.92]) and cognitive impairment (AUC 0.84 [95%-CI 0.74–0.95]). However, the growing interest has not been matched by methodological rigour: only 16 studies met the criteria for inclusion in the meta-analysis due to inconsistent reporting, only five assessed the generalisability of their models on external datasets, and six lacked clear diagnostic criteria.

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Conclusions Interest in incorporating CSVD markers into ML models for neurodegenerative disease classification is on the rise, and their performance suggests that this is worth further exploration. Serious methodological issues, including inconsistent reporting, limited generalisability testing, and other potential biases, are unfortunately common and hinder further adoption. Our targeted recommendations provide a roadmap to accelerate the integration of ML into clinical practice.

Keywords Machine learning, Dementia, Cerebral small vessel disease, Artificial intelligence, Neuroimaging, Cognitive impairment, Alzheimer's dementia, Neurodegenerative diseases

Introduction

Cerebral small vessel disease (CSVD) describes multiple dynamic pathological processes that impair the optimal functioning of perforating arterioles, capillaries, and venules in the brain [1–3]. CSVD is among the most common conditions encountered by neurologists in clinical practice [4] and a significant contributor to major healthcare challenges. CSVD causes 25% of ischaemic strokes, the majority of intracerebral haemorrhages in individuals over 65 years old, and most cases of vascular dementia [2, 3]; contributes to around 45% of all dementia cases worldwide [4]; and leads to mobility and gait issues, neurobehavioural changes, and mood disorders [5]. The relationship between CSVD and Alzheimer's disease (AD) has been recognised since the earliest days of AD research [6], and is now included in the Alzheimer's Society's most recent revised criteria for diagnosing and staging AD [7]. This coexistence between CSVD and AD has taken on a new significance in recent years, as anti-amyloid monoclonal antibody trials have revealed that individuals with cerebral amyloid angiopathy — a form of CSVD — are at risk of developing brain swelling or haemorrhages during the course of the treatment, making CSVD assessments and studies crucial for patient stratification and minimising treatment risks [8].

Although direct assessment of the human cerebral microvasculature in vivo remains challenging with standard imaging technologies, its chronic dysfunction leads to changes that can be detected through magnetic resonance imaging (MRI) and computed tomography (Supplementary BOX 1). Assessing CSVD has traditionally focused on evaluating discrete lesions, such as white matter hyperintensities (WMH), lacunes, cerebral microbleeds, superficial siderosis, perivascular spaces, and small subcortical or cortical microinfarcts, by means of clinical visual ratings and increasingly through quantitative methods [1]. However, advancements in neuroimaging technologies have also revealed that these discrete lesions are not the only consequence, suggesting instead that they often lead to widespread, rather than focal, alterations of microstructure and connectivity [9].

The integration of neuroimaging and machine learning (ML) techniques (Supplementary BOX 2) presents new avenues for understanding the intricate and multifactorial nature of CSVD and vascular contributors to

cognitive impairment and dementia [10]. These possibilities include not only the computational quantification of neuroimaging markers of CSVD (e.g., through segmentation of lesions) [11–13] but also their predictive value for neurodegenerative diseases and dementia, which could ultimately facilitate early detection and personalised treatments. However, the contribution of CSVD to dementia and cognitive impairment using ML appears to be underdeveloped. According to a recent systematic review and meta-analysis conducted by the Imaging Working Group of the international Deep Dementia Phenotyping Network (DEMON) on the application of neuroimaging and ML for dementia diagnosis and prognosis [14], only 2 out of 255 studies focused on vascular forms of dementia. Whilst that review did not consider cognitive changes other than dementia and most included studies leveraged the Alzheimer's Disease Neuroimaging Initiative (ADNI)—a cohort with relatively minimal CSVD burden—it is surprising so few studies had been conducted in this field.

To map the significance of CSVD in ML-based detection of dementia and cognitive impairment more generally, we established a new subgroup of the DEMON Imaging Working group dedicated specifically to this topic. We conducted a systematic review and meta-analysis to (a) determine the use of CSVD neuroimaging markers and ML in the diagnosis and prognosis of cognitive impairment and dementia; (b) identify methodological shifts over time, particularly with recent deep learning advancements; and (c) pinpoint methodological barriers preventing the development and effective deployment of these strategies. Our primary focus was on papers addressing dementia-related diagnosis and prognosis rather than those solely centred on lesion segmentation. We aim for this review to inspire the development of more accurate and validated methods for predicting CSVD-related cognitive impairment, facilitating early detection and intervention.

Methods

Protocol registration

We registered this systematic review protocol with the International Prospective Register of Systematic Reviews (PROSPERO), registration number: CRD42022366767. We conducted this work following the Preferred

Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [15]. The associated PRISMA checklist can be found in the supplementary material.

Search strategy

A medical librarian (VP) searched databases Medline (via Ovid), Embase (via Ovid), Cochrane Library, Emcare (via Ovid), Cinahl (via Ebscohost), PsycInfo (via Ebscohost), BNI (via ProQuest), Web of Science (Core Collection), and Scopus from inception to the date searches were conducted. The search strategy was peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist [16], and evaluated against the PRISMA-S guidelines [17]. Databases were searched separately, rather than multiple databases being searched on the same platform. The search syntax was adapted for each database, and to account for variation between thesaurus terms/controlled vocabulary across each database. Results were limited to the English language in all databases. Results were exported to Endnote 20 for deduplication, using the method outlined by Bramer et al. [18].

All searches were originally conducted on September 20, 2023 and rerun on September 9, 2024 to include any papers published between the initial search and final submission.

PICOS framework

The parameters of this systematic review, as defined by the PICOS framework, were as follows:

- **Participants:** Persons with cognitive impairment or a clinical diagnosis of dementia, as well as people with incident cognitive impairment or dementia.
- **Index:** Neuroimaging-derived CSVD data analysed with ML for diagnosis or prognosis.
- **Comparator:**
 - For diagnostic studies: persons without cognitive impairment or dementia.
 - For prognostic studies: prognostic factor (conversion to cognitive impairment or dementia vs. no conversion).
- **Outcome:** Accuracy of diagnosis or prognosis of cognitive impairment or dementia based on CSVD burden.
- **Study design:** Original cross-sectional or prospective observational studies.

Inclusion and exclusion criteria

To be included, studies had to report on the model performance of the ML methods for the diagnosis or prognosis of cognitive impairment or dementia using imaging markers of CSVD and ML. We deemed eligible original

studies published in English in peer-reviewed journals and excluded in vitro studies or animal studies. We also excluded studies that employed ML solely for image processing such segmentation.

Study selection

Study selection had two stages. First, each report was screened for eligibility by pairs of independent reviewers based on title and abstract using the screening tool Rayyan (<https://www.rayyan.ai/>). Second, each report that passed the initial filtering was reviewed by pairs of reviewers who independently conducted full-text screening. Conflicts arising at any of these two stages were resolved through discussions, with the assistance of a third independent senior reviewer when necessary.

Data extraction

Data from each included study were extracted independently by pairs of reviewers using a standard template. Once again, conflicts were resolved through discussion, with a third senior reviewer solving any remaining disagreements. The data extraction form captured (a) article information (first/last author, year, journal, country of first/last author's affiliated institution, study type); (b) characteristics of the study population (sample size, age, sex, race/ethnicity, criteria for cognitive impairment and dementia, inclusion and exclusion criteria of study); (c) data analysis (ML approach used, covariates included in model, vascular neuroimaging features used; outcome measure); (d) results (measures of model performance (accuracy, sensitivity, specificity, area under the curve (AUC), positive predictive value, negative predictive value), other metrics reported (e.g. hazard or odds ratios), follow-up period (for prognostic studies only); and (e) risk of bias assessment.

Assessment of risk of bias

We assessed the quality of all individual studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) for diagnostic studies [19] and the Prediction model Risk Of Bias ASsessment Tool (PROBAST) for prognostic studies [20]. Pairs of reviewers independently conducted the critical appraisal of each paper and certainty of evidence rating. Disagreements were resolved through discussion.

Meta-analysis

We conducted a meta-analysis to provide a targeted evaluation of the ML models using vascular neuroimaging features. This meta-analysis focused on the two most common diagnostic tasks identified in the literature we reviewed: distinguishing between healthy controls and AD-dementia or all-cause dementia, as well as between healthy controls and cognitive impairment. Thus, we

compared the performance of the various approaches using the AUC obtained from Receiver Operating Characteristic analyses.

We employed a random-effects model with the DerSimonian and Laird estimation method to calculate the pooled AUC values and confidence intervals. In cases of missing data, such as absent variability measures for the AUC, we reached out to the corresponding authors. In instances where authors did not respond to our inquiries and studies failed to report any measures of variability for the AUC, we estimated the standard error for the AUC based on Hanley and McNeil [21]. If different ML approaches were considered for the same database, we included the analysis utilising the ML model with the best model fit and the largest sample size. We quantified heterogeneity using Cohen's Q statistics and I^2 statistics. The meta-analysis was performed in R version 4.2.1 [22] using the package *metafor* [23].

Results

Search results

Our initial search on September 20, 2023, identified 4,956 potentially relevant records across all databases (Fig. 1). After deduplication using Endnote and Rayyan, we retained 2,630 records. Of these, 256 passed the title and abstract screening, and 62 went on to pass full-text screening and were included in the systematic review [24–85]. On September 9, 2024, we conducted a rerun and identified 845 potentially new relevant records across the same databases (Fig. 1). A total of 546 records remained after deduplication. Screening by title and abstract led to 35 eligible papers, of which 13 passed full-text screening and were included in the systematic review [86–98]. This brought the total number of included records to 75 [24–98]. We contacted the corresponding authors of 36 studies via email to request missing data. Of these, six responded: three provided additional data, while the other three were unable to do so. Finally, a total of 16 studies was suitable for meta-analysis [30, 32, 33, 47, 51, 58, 65, 79, 84, 85, 89, 91, 96, 98], of which seven classified healthy controls versus AD-dementia [30, 32,

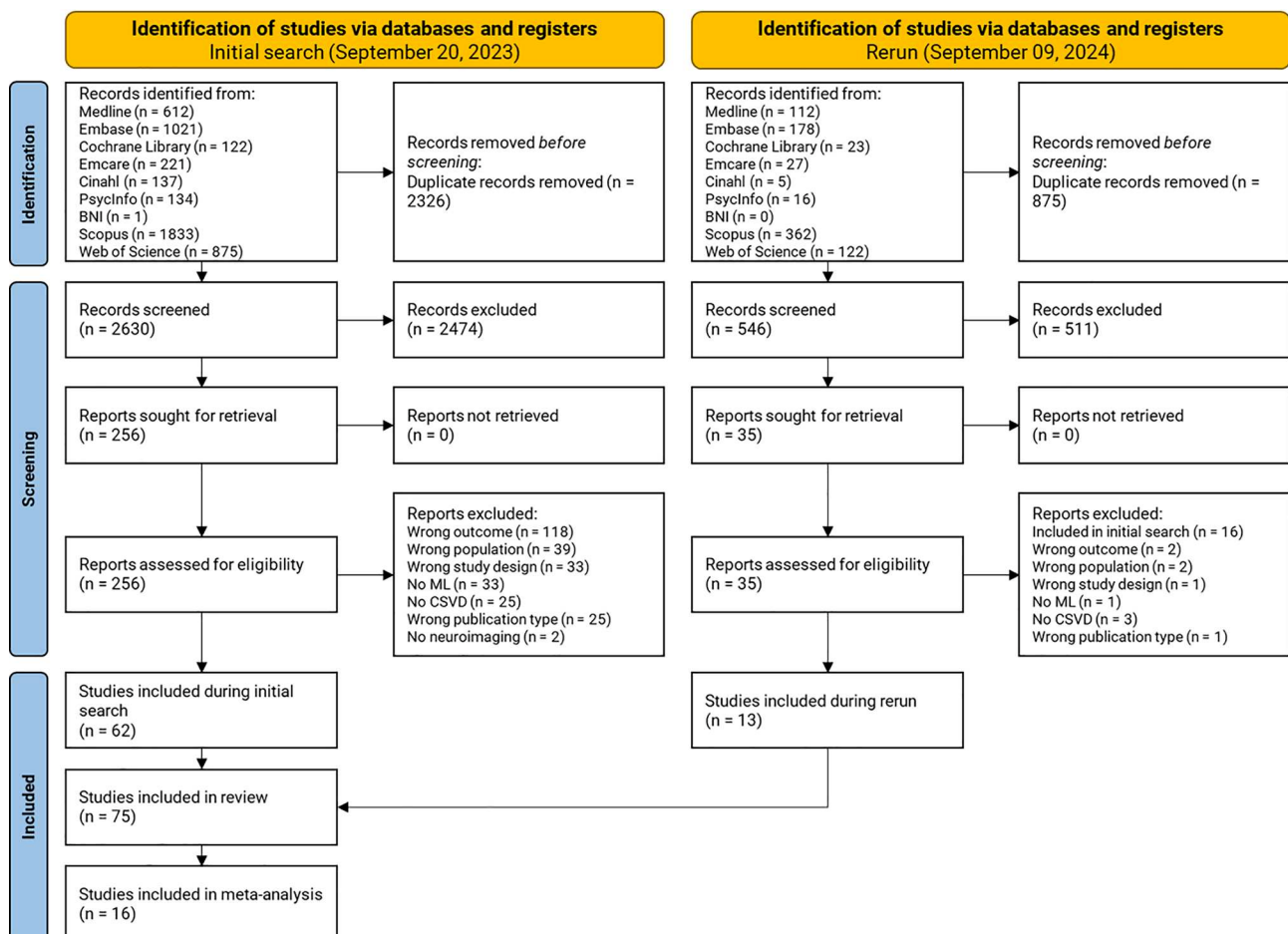


Fig. 1 PRISMA flow chart outlining the number of studies identified, included, and excluded at each stage of the systematic review and meta-analysis

47, 58, 65, 84, 89], and nine healthy controls versus cognitive impairment [32, 33, 51, 58, 79, 85, 91, 96, 98]. A flow chart of the identification and screening process is provided in Fig. 1. Data extraction results can be found in Supplementary data 2.

Study characteristics

Comprehensive details on data extraction related to study characteristics are available in Supplementary Data 2, under the sections “description / metrics paper” and “general description of the study population”.

Origin of studies

According to the affiliations of the first and last authors, the majority of included studies were from China ($n=24$) and the United States of America (USA) ($n=16$). The remaining studies originated primarily from Europe ($n=33$), followed by Asia ($n=7$, excluding China), and North America ($n=3$, excluding the USA). No studies were affiliated with institutions in South America, Africa, or Australia (Fig. 2).

Study focus

Among the 75 included studies, 43 (57%) focused on diagnosis, 27 (36%) on prognosis, and five (7%) on both (Supplementary Table 1). More than two-thirds (70%) of the studies used private or local datasets ($n=35$ diagnosis, $n=16$ prognosis, $n=2$ both). When publicly available datasets were used ($n=12$ for diagnosis, $n=14$ for prognosis, $n=4$ for both), ADNI was the most frequent choice ($n=17/30$). Only 14 studies included two or more cohorts in their analyses ($n=7$ for diagnosis, $n=5$ for prognosis, $n=2$ for both). ADNI was the most commonly used dataset in these cases ($n=9/14$).

Participant demographics

The mean age of participants was 71.7 years (standard deviation (SD) 8.5), with a mean age of 69.9 years (SD 9.3) in diagnostic studies and 72.1 years (SD 8.3) at baseline in prognostic studies. There was a relatively balanced representation of men and women across the studies, with women making up 54% of participants overall (48.1% in diagnostic studies and 55% in prognostic studies).

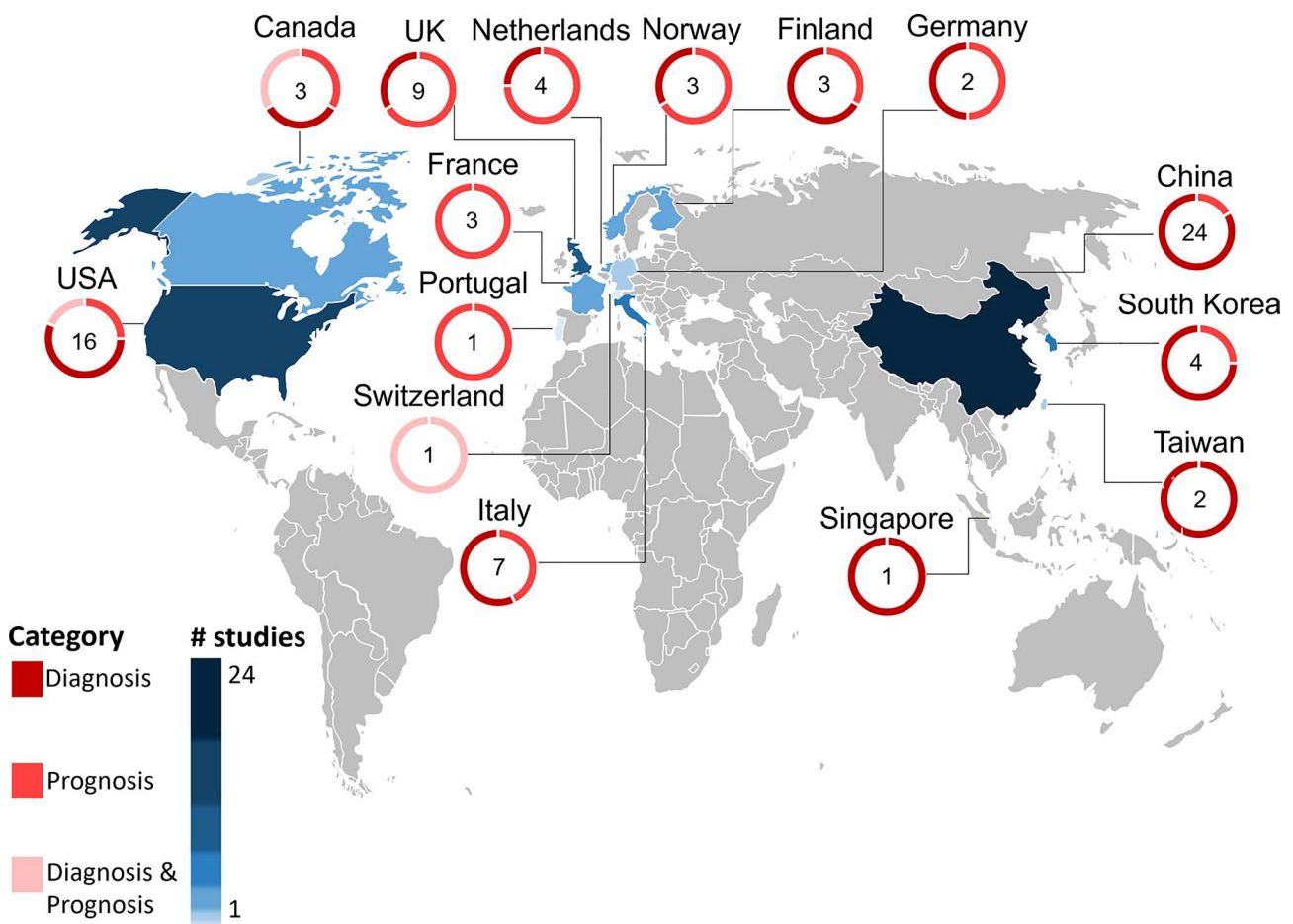


Fig. 2 Countries of institutional affiliation for the first and last authors of each included publication. Note that the first and last authors had different affiliations in eight papers. The numbers on the map thus sum to 83 rather than 75 (total number of included studies)

Only six studies (8%) provided race or ethnicity information ($n=3$ diagnosis, $n=3$ prognosis). In those studies, 6217 (79%) participants were reported as White ($n=1$ diagnosis, $n=3$ prognosis), 209 (3%) as Asian ($n=2$ diagnosis), 934 (12%) as Black ($n=1$ prognosis), and 476 (6%) as “other” ($n=2$ diagnosis, $n=2$ prognosis).

ML methods

Detailed information on the ML methods used in each study can be retrieved from Supplementary Data 2, specifically from the section “ML method used”.

Application of ML methods

A total of 23 different ML methods were employed for the diagnosis or prognosis of cognitive impairment and dementia based on vascular neuroimaging features (Fig. 3). These methods spanned eight categories (Supplementary BOX 2). For diagnosis (Fig. 3A), the most popular ML categories were instance-based, regression, and ensemble algorithms, with support vector machines (SVM, instance-based), logistic regression (regression), and random forest (ensemble) being the most commonly used models. For prognosis (Fig. 3B), the top three categories remained the same, with Cox regression (regression), SVM (instance-based), and random forest (ensemble) being the most frequently used models.

Logistic regression, was the most popular ML method, appearing in 28 (37%) of the 75 papers reviewed [24, 27, 41, 44, 50, 53, 54, 58–60, 63, 64, 66, 67, 72, 74–76, 81–83, 86, 87, 91, 93, 94, 96, 98]. It was followed closely by SVM which was used in 26 (35%) papers [25, 28, 33, 35–40, 45, 46, 48–52, 72, 79, 82, 84, 85, 90, 93, 94, 97, 98]. These two methods were applied almost twice as often as the next most common methods, namely Cox regression and random forest, which were featured in 15 (20%) [42, 55, 62, 68–70, 73, 75, 77, 78, 80, 88, 89, 92, 99] and 14 (19%) papers [32, 34, 50, 56, 57, 61, 72, 76, 82, 89, 91, 93, 97, 98], respectively. Other methods were much less common. Strikingly, despite the growing prominence of deep learning over the past decade, its application in diagnosing and predicting cognitive impairment and dementia based on vascular neuroimaging features remains limited. Only four (5%) of the papers employed deep learning [29, 30, 43, 47], with three of them using convolutional neural networks (CNNs) [30, 43, 47]. Three studies employed Bayesian methods [39, 91, 98] and three discriminant analysis [45, 71, 91], all exclusively applied for diagnostic purposes.

Popularity over time

The application of ML techniques for diagnosis and prediction of cognitive impairment and dementia based on vascular neuroimaging features has experienced a significant growth over the past decade (Fig. 3C). Cox

regression was the first technique we identified that used any CSVD feature, namely WMH, to predict dementia [99]. Logistic regression and SVM have remained popular and widely used since their first application in 2007 and 2010, respectively. The application of random forests, on the other hand, was first identified in 2015 and has only recently reached its highest level of usage, as it was used in around one-third of the works in 2023 (36%). Neural networks and eXtreme Gradient Boosting (XGBoost) appeared only in 2022.

Validation and generalisation

A rigorous evaluation of both performance and generalisability of ML prediction algorithms is essential for the translation into real-world clinical settings, as even the most promising models may fail when exposed to previously unseen data. The authors' approaches to validation are outlined in Supplementary Data 2, under the section “Validation strategy”. A representative illustration of the importance of using an independent hold-out test set is provided in a paper included in this review [91], where the authors showed that the model with the highest performance on the training set also exhibited the poorest generalisation, with an AUC of 100 [95% CI: 100, 100] in training and 50.0 [95% CI: 50.0, 50.0] in an independent test set. Despite this, only five out of 75 studies assessed the generalisation capabilities of their models using held-out external datasets ($n=4$ diagnosis; $n=1$ prognosis) [47, 48, 61, 88, 91]. Although limited access to multiple datasets clearly presents a challenge for assessing generalisability, a total of ten studies had data from multiple sources and were therefore well-positioned to validate their models on independent cohorts ($n=5$ diagnosis [31, 47, 48, 90, 91]; $n=3$ prognosis [88, 93, 94]; $n=2$ both [76, 89]).

When reported clearly, studies relied to a large extent on cross-validation ($n=28$ diagnosis; $n=10$ prognosis). Some studies also split a single or pooled dataset into training and testing sets from the start ($n=3$ diagnosis; $n=3$ prognosis) [43, 47, 48, 61, 69, 88, 91] and one diagnostic study also used bootstrapping [71]. Unfortunately, the absence of any form of validation—or a lack of clear reporting on whether it was conducted—was strikingly common, especially in prognostic analyses, where over 55% of studies were affected by this issue ($n=12$ diagnosis; $n=18$ prognosis).

Neuroimaging modalities and features

Data extracted regarding neuroimaging modalities and features can be found in Supplementary Data 2, under the sections “specific details for datasets” and “vascular neuroimaging features used”. Studies leveraged structural, diffusion, and functional MRI (fMRI), as well as computed tomography and positron emission

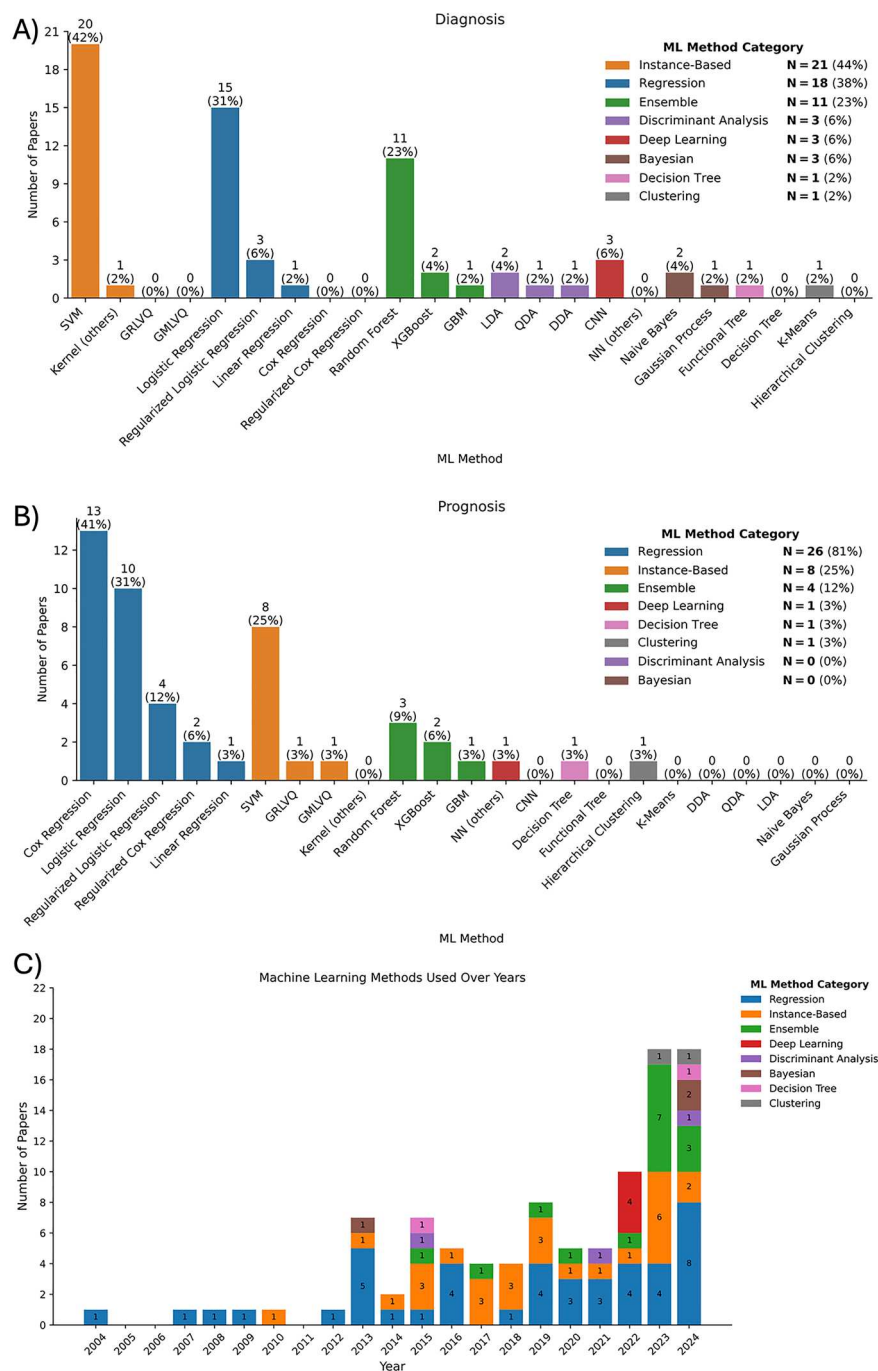


Fig. 3 Number of papers using each machine learning (ML) method in our review, faceted by **A)** diagnosis or **B)** prognosis, and **C)** use of different ML categories over time. Different colours correspond to different ML categories. Note that as one paper may use multiple ML methods/categories, the percentages in **A)** and **B)** may not sum up to 100%. Kernel (others) = Kernel methods other than SVM; NN (others) = Neural networks other than CNN

tomography (Fig. 4). Structural MRI was by far the most widely used neuroimaging modality, appearing in 67 (89%) studies, whereas computed tomography was the least used, appearing in only one (1%) paper. A total of 27 (36%) studies leveraged two or more imaging modalities. When this occurred, structural MRI and diffusion-based

MRI were the most common combination, used in 19 out of 27 (70%) papers.

Diagnosis

Around 40% of the diagnostic studies ($n=20$) leveraged vascular neuroimaging features obtained from structural

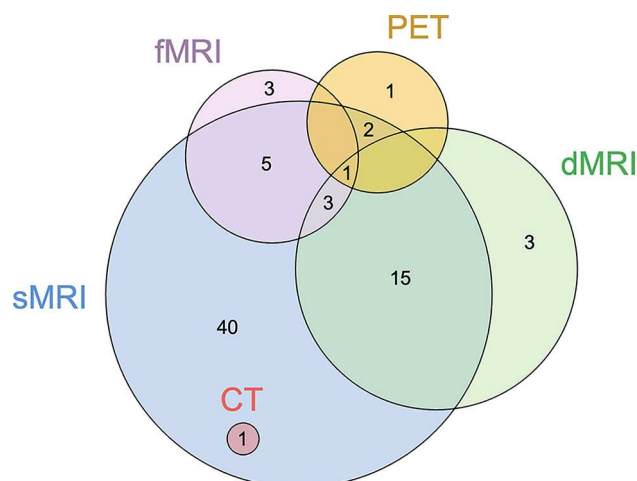


Fig. 4 Neuroimaging techniques used to extract vascular neuroimaging features in the studies included in the review. Abbreviations: CT=computed tomography; dMRI=diffusion-based MRI; fMRI=functional MRI; sMRI=structural MRI; PET=positron emission tomography

MRI sequences. Every study that used structural MRI quantified WMH. Other neuroimaging features were less frequently considered: perivascular spaces ($n=2$) [41, 82], cerebral microbleeds ($n=2$) [41, 82], lacunes ($n=3$) [41, 81, 82], and stroke lesion volume or subtype ($n=2$) [54, 67].

Non-lesion measurements were also common in many diagnostic studies. These included assessments of microstructural integrity from regional white matter ($n=13$) [32, 34, 36–39, 51, 54, 61, 65, 71, 79, 83], fMRI or diffusion MRI-based connectivity ($n=8$) [33, 35, 45, 49, 51, 76, 84, 85], or other, less conventional imaging features ($n=7$), such as tissue textures ($n=2$) [56, 89], white matter density ($n=1$) [65], fMRI-derived amplitude of low-frequency fluctuation ($n=3$) [53, 61, 96], ^{18}F -fluorodeoxyglucose/positron emission tomography derived “metabolic cognitive signature” ($n=1$) [47], and iron deposition ($n=1$) [40].

Of the 48 studies reporting diagnostic analyses, most used quantitative assessments of vascular neuroimaging features ($n=40$). Nine (19%) employed clinical visual ratings, of which two relied solely on visual ratings.

Prognosis

Twenty-four (75%) prognostic studies used vascular neuroimaging features derived from structural MRI. WMH were assessed in every study. Other neuroimaging features, including lacunes ($n=7$) [42, 46, 55, 63, 80, 94, 95], perivascular spaces ($n=5$) [42, 80, 86, 92, 95], cerebral microbleeds ($n=5$) [42, 72, 92, 94, 95], and stroke lesion volume or subtype ($n=2$) [24, 25], were less relatively common.

Non-lesion measurements were less common in prognostic than in diagnostic studies. Five studies used

diffusion tensor imaging [29, 62, 78, 88, 94] and no studies investigated other diffusion-based signal modeling. Two studies investigated connectivity measures: one using diffusion-based structural connectivity [76], and one using WMH-based disconnectome measures [50]. Other vascular markers used in prognosis studies included tissue texture analysis ($n=2$) [69, 70], and susceptibility-weighted imaging-based markers such as iron deposition ($n=1$) [40].

Visual ratings were used in half of studies reporting prognostic results (16 out of 32). Most ratings were conducted on WMH burden, with one study reporting solely perivascular space ratings. Nine studies included additional quantitative measures alongside visual ratings, while the remaining relied solely on visual ratings ($n=7$). There was significant variation in the rating scales used across studies. For example, the six prognostic publications that used visual ratings of WMH employed a range of methods, including binary measures with different cut-offs as well as grading scales with 3, 4, 10, and 11 points.

Temporal changes in vascular neuroimaging features

Studies using diffusion-based indices (e.g., fractional anisotropy and mean diffusivity) have decreased in recent years. Before 2020, diffusion imaging studies made up 41% of studies ($n=16$), compared to just 17% of studies published between 2020 and 2024 ($n=6$). Recent years have witnessed the adoption of novel techniques including graph theory, pattern analyses, and other methods of connectivity assessment, amplitude of low-frequency fluctuation, and composite brain signatures, making up a fifth (19%; $n=7$) of studies published in 2020–2024. Studies relying solely on clinical visual ratings have not changed in recent years ($n=5$ before 2020, $n=4$ since 2020).

MRI scanner strength

MRI scanner strength details were reported in 65 (84%) studies ($n=40$ diagnostic, $n=26$ prognostic, $n=5$ both). Diagnostic studies were primarily carried out on 3 Tesla (T) scanners. Most studies used a consistent scanner strength across participants and scans ($n=33$), with 3T being the most common ($n=27$), followed by 1.5T ($n=5$), and one study using a 4T scanner. A few studies ($n=7$) used scanners of different field strengths; six of these combined 1.5T and 3T scanners, while one study used both 1T and 1.5T scanners.

Most prognostic studies, on the other hand, were conducted on 1.5T scanners. Among the 27 prognostic studies that reported scanner strength, the majority used only 1.5T scanners ($n=15$), with about half as many relying exclusively on 3T scanners ($n=7$). A few studies ($n=5$) employed a mix of scanner strengths; two combined 0.5T

and 1.5T scanners, and three studies used both 1.5T and 3T scanners.

The use of higher field strength scanners has increased over time. Before 2020, more than half of the studies (59%) relied predominantly on 1.5T scanners ($n=23$). Since 2020, reliance on 1.5T scanners has declined, with only 14% of studies using 1.5T scanners ($n=4$), while 62% ($n=18$) used 3T scanners exclusively.

Harmonisation

Since data acquisition often takes place across multiple sites using potentially different MRI scanners and protocols, harmonisation becomes crucial to deal with inter-scanner variability and ensure comparability across sites. We identified 19 studies that, in principle, would have benefited from harmonisation due to the use of different MRI scanners [25, 27, 32, 34, 39, 42, 48, 56–58, 69, 73, 77, 86, 88–91, 93]. Among these, five studies reported implementing any form of harmonisation: intensity normalisation across scanners [32], principal component analysis to isolate disease-relevant principal components while reducing scanner effects [39], manual correction of segmentation maps to mitigate inter-scanner variability [56, 57], and statistical harmonisation using ComBat [90].

Dementia

Extracted data relevant to dementia diagnosis and prognosis are available in Supplementary Data 2, under the sections “diagnosis or prognosis” and “general description of the study population”. We identified 47 studies that focused on dementia, with 26 (55%) targeting diagnosis, 17 (36%) prognosis, and four (9%) both. Remarkably, despite the review’s strong emphasis on vascular aspects, diagnostic studies predominantly concentrated on AD ($n=24$) [27, 28, 30, 32, 34, 36, 39, 47, 48, 52, 56–58, 60, 65, 66, 71, 74, 76, 82, 84, 89, 90, 97]. Other forms of dementia were also examined but with less frequency: vascular dementia ($n=4$) [43, 45, 66, 82], frontotemporal dementia ($n=3$) [82, 83, 90], Lewy body dementia ($n=3$) [56, 57, 90], behavioural variant frontotemporal dementia ($n=1$) [83], post-stroke dementia ($n=1$) [47], progressive non-fluent aphasia ($n=1$) [83], and semantic dementia ($n=1$) [83]. Prognostic studies also focused largely on AD ($n=13$) [26, 50, 52, 55, 59, 60, 63, 68–70, 76, 89, 94], with vascular dementia following ($n=6$) [26, 46, 55, 73, 78, 94]. Mixed dementias were each examined by four prognostic studies [59, 63, 73, 75], and a single prognostic study also explored frontotemporal dementia [73].

Assessment criteria

Dementia diagnosis was primarily relied on published clinical criteria or via consensus diagnosis by experienced neurologists based on clinical evaluations, including cognitive tests, general neurological exams, and collateral

information. Studies of AD employed no less than six different diagnostic criteria, namely Diagnostic and Statistical Manual of Mental Disorders (DSM versions III-R, IV or V) [100], National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS or NINCDS-ADRDA) [101], National Institute on Aging and Alzheimer’s Association (NIA-AA) [102, 103], National Institute on Aging–Alzheimer’s Disease Centers (NIA-ADRC), National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN) [104], and Alzheimer’s Disease Diagnostic and Treatment Centers (ADDTC) [105].

In addition to the diagnostic variability, six studies did not specify the criteria for diagnosing dementia ($n=4$ diagnosis, $n=2$ prognosis) and six diagnostic studies determined dementia diagnoses without adhering to standard criteria. Instead, they relied on specific thresholds from cognitive tests, including the Mini-Mental State Examination (MMSE) ($n=1$), the Clinical Dementia Rating scale (CDR) ($n=1$), the Montreal Cognitive Assessment (MoCA) scores ($n=1$), and various combinations of these test ($n=3$).

Cognitive impairment

Information related to the diagnosis and prognosis of cognitive impairment, as extracted from the included studies, is provided in Supplementary Data 2 under the sections “diagnosis or prognosis” and “general description of the study population”. We identified 45 articles addressing cognitive impairment (without a specific dementia diagnosis), with 26 (58%) focusing on diagnosis, 14 (31%) on prognosis, and five (11%) assessing both diagnosis and prognosis. The definition, subtype, and potential aetiology of cognitive impairment varied substantially across the studies.

Most diagnostic studies (52%) that studied cognitive impairment examined cognitive impairment linked to CSVD ($n=11$) [32, 33, 35, 38, 53, 54, 61, 71, 81, 91, 96], such as WMH ($n=4$) [33, 35, 85, 91], subcortical ischemic vascular disease ($n=4$) [32, 53, 71, 81], and vascular cognitive impairment ($n=3$) [38, 54, 81]. However, a notable proportion of them (62%) also targeted mild cognitive impairment (MCI) ($n=12$) [32, 37, 40, 41, 45, 49, 51, 58, 76, 87, 89, 98] or its amnesic and non-amnesic subtypes ($n=3$) [27, 34, 79]. Cognitive impairment associated with Parkinson’s disease ($n=1$) [44] and coronary artery disease ($n=1$) [51] was also examined. Prognostic studies mainly investigated either the progression of MCI to dementia ($n=14$) [40, 50, 52, 55, 59, 60, 69, 73, 76, 86, 89, 92, 93, 95], including progression to vascular dementia ($n=1$) [73], mixed dementia ($n=1$) [73], and AD ($n=6$) [50, 52, 60, 69, 76, 86].

Assessment criteria

While there was some consistency across studies, the diagnostic criteria consisted of a variety of definitions of cognitive impairment. Most papers that focused on cognitive impairment relied on neuropsychological tests ($n=18$ diagnosis, $n=11$ prognosis). For example, performance below 1.5 standard deviations from the mean on cognitive tests was deemed indicative of MCI. A significant variability in the choice of cognitive tests was noted. Some papers adopted established clinical criteria, such as those proposed by Petersen et al. [106, 107] or the DSM-5 [100], or utilised consensus diagnoses from multiple neurologists ($n=1$ diagnosis, $n=4$ prognosis). In the other instances, a combination of neuropsychological tests and clinical criteria was used ($n=5$ diagnosis, $n=2$ prognosis) with some studies also incorporating vascular neuroimaging measures, such as including WMH burden to support MCI diagnosis ($n=5$ diagnosis, $n=1$ prognosis). Three papers did not specify the criteria used to identify MCI.

Results meta-analysis

Healthy controls versus Alzheimer's dementia

Seven studies reported AUC measures for classifying AD-dementia versus healthy controls (see Fig. 5A). Of these, five did not report any measures of variability; the standard error for these AUC values was therefore estimated. The pooled AUC was 0.88 [95% confidence interval (CI) 0.85–0.92] (Fig. 5A), with significant heterogeneity across studies.

Healthy controls versus cognitive impairment

Nine studies used ML algorithms to classify cognitive impairment versus healthy controls (see Fig. 5B). Only two of these studies reported measures of variability, therefore all other standard errors for the AUC were estimated. The pooled AUC was 0.84 [95% CI 0.74–0.95], with significant heterogeneity among studies (Fig. 5B) [32, 33, 51, 58, 79, 85, 91, 96, 98].

Healthy controls versus all-cause dementia

Nine studies utilised ML methods to diagnose all-cause dementia versus healthy controls, of which two studies (Chan et al. 2023 [32] and Lee et al. 2022 [47]) made multiple comparisons. Here we selected the comparisons with the largest sample sizes included. Of these studies, three reported measures of variability for the AUC, the standard error for all remaining AUC values were therefore estimated. The pooled AUC was 0.88 [95% CI 0.83–0.93] (Supplementary Fig. 1A), with significant heterogeneity across studies. Including the other two comparisons of Chan et al. 2023 [32] and Lee et al. 2022 [47] in the meta-analysis yielded similar results (Supplementary Fig. 1B).

Risk of bias assessment

Diagnosis

For diagnostic studies, we conducted risk of bias assessment using the QUADAS-2 framework to establish potential biases regarding patient selection, index method bias, reference accuracy, blinding, consistency of references, participant inclusion, and method applicability (Supplementary Fig. 2A and Table 2A). Approximately 40% of the papers exhibited a low risk of bias across the aforementioned domains (flow and timing: $n=21$; reference standard: $n=28$; index test: $n=31$; patient selection: $n=32$). The patient selection domain had by far the highest risks of bias ($n=19$), with studies either using case-control designs or failing to adequately disclose patient selection details. Concerns about method applicability in diagnostic studies were minimal, with 83% of studies having low risk of bias.

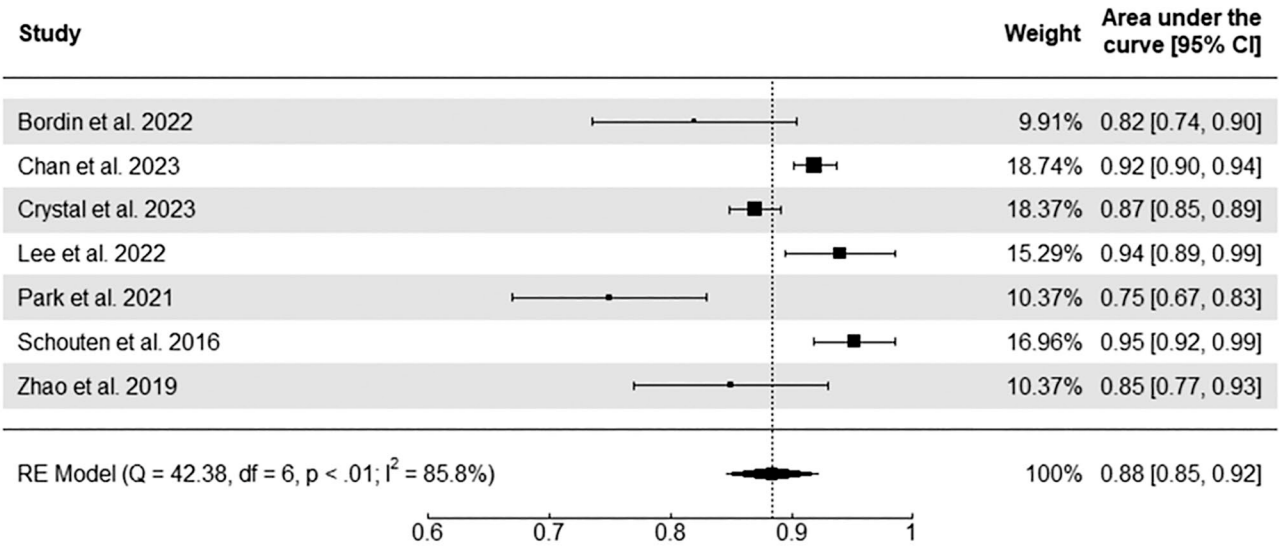
Prognosis

For prognostic studies, we conducted risk of bias assessment using the PROBAST framework to establish potential biases in prediction models regarding patient selection, predictor measurement, outcome measurement, and analysis and model evaluation (Supplementary Fig. 2B and Table 2B). Nine out of the 32 prognostic studies were rated as having a low risk of bias across all evaluated domains (participants: $n=23$; predictors: $n=29$; outcome: $n=26$; analysis: $n=11$). The analysis domain stood out as the most frequent source of concern, with 14 studies rated as having a high risk of bias. The primary reasons were unclear exclusion criteria from prognostic analyses and lack of clarity regarding how model overfitting and optimism in model performance were addressed. Concerns about applicability were minimal, with 94% of the studies showing low concerns.

Discussion

This systematic review and meta-analysis summarised 75 studies examining the role of CSVD neuroimaging markers in ML-based diagnosis and prognosis of cognitive impairment and dementia. The field has grown substantially over the past two decades, with nearly 60% of studies being published in the last two years. Key findings reveal a mix of insights. Positively, most studies used datasets with balanced sex representation. Negatively, even though ML models leveraging CSVD features achieved high diagnostic performance, many lacked external validation and showed limited transparency regarding overfitting. Unexpectedly, most studies focused on AD rather than vascular dementia. Additionally, while XGBoost and neural networks are gaining traction, traditional methods like Cox regression, logistic regression, and SVM remain dominant. The following

A: Healthy controls versus Alzheimers Dementia



B: Healthy controls versus cognitive impairment

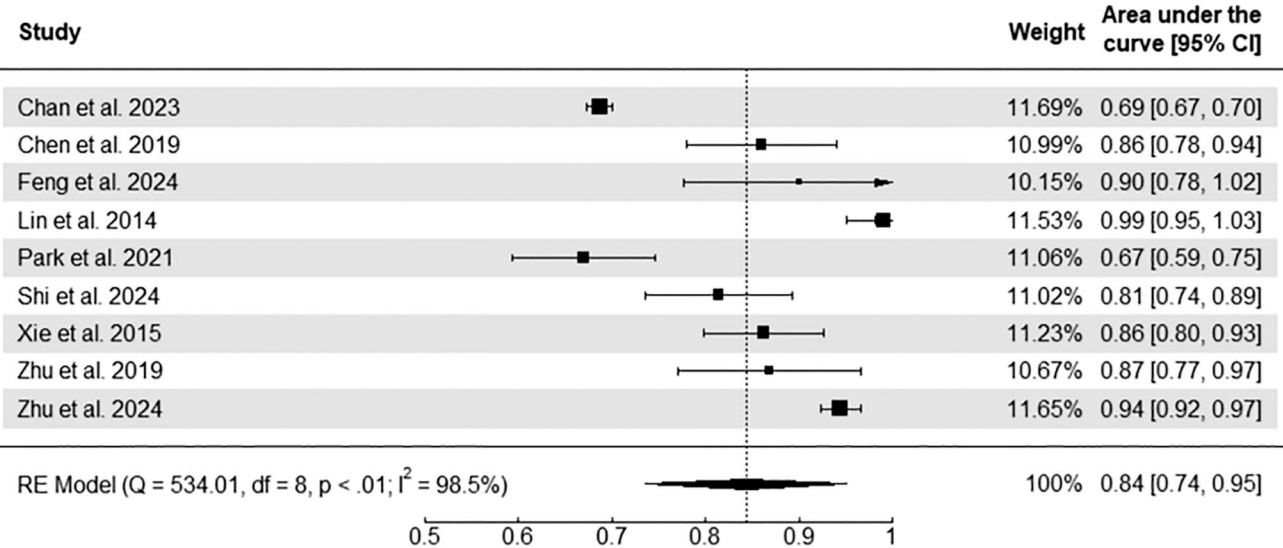


Fig. 5 Meta-analysis of studies targeting the classification of **(A)** Alzheimer's dementia versus healthy controls and **(B)** cognitive impairment versus healthy controls. Pooled AUC values and their corresponding confidence intervals (CI) were computed using a random-effects model. Weights represent each study's relative contribution to the overall pooled estimate. Confidence intervals might exceed 1.00 because standard errors have been estimated due to missing data

sections expand on these findings and place them within a broader context.

Vascular neuroimaging and its contributions to neurodegeneration

Most studies on dementia diagnosis and prognosis focused on AD (23/30 diagnostic; 10/21 prognostic) rather than vascular dementia (4/30 diagnostic; 6/21 prognostic). For example, seven of the nine studies that compared all-cause dementia with healthy controls in the

meta-analysis focused on AD-related dementia. These seven studies that incorporated vascular features in ML models demonstrated strong performance (AUC 0.88 [95%-CI 0.85, 0.92]). This indicates not only the benefit of including CSVD in AD diagnostic classifiers, but also reflects a growing interest in the role of CSVD and vascular neuroimaging in dementia, particularly in AD-related dementia.

The focus on AD surprised us, given the review's emphasis on vascular neuroimaging and CSVD, though

aspects discussed in the literature may help explain this trend. AD is the leading cause of dementia, and CSVD is one of the most common conditions in clinics [4]. It is therefore expected that CSVD co-occurs and interacts with AD as well as other neurodegenerative disorders [108–113]. The role of vascular risk factors in the pathogenesis and progression of AD is well established [114], extending beyond their mere coexistence [115]. Potential mechanisms include impairment of the neurovascular unit [116, 117], disruption of the glymphatic system [118], and hypoperfusion and hypoxia [116, 119]. This coexistence is now formally recognised in the most recently proposed AD diagnostic and staging criteria, where vascular biomarkers are identified as indicators of non-AD co-pathology that may accelerate symptom progression [7].

Considering vascular risk factors in the progression of neurological conditions such as vascular dementia and AD creates opportunities for prevention [116, 120]. Modifiable CSVD risk factors, including diabetes, hypertension, smoking, obesity, and high low-density lipoprotein cholesterol, can be addressed with cost-effective treatments, such as hypertensive medications and lifestyle changes [121]. These measures may reduce vascular risks and delay or prevent cognitive decline, potentially alleviating the societal burden of dementia. Recent studies in birth cohorts show a decline in cerebrovascular pathology [122], which may explain the decrease in age-adjusted dementia incidence [123–125]. Understanding and identifying CSVD features associated with AD using ML approaches may therefore support early diagnosis and risk prediction, permitting early effective preventive strategies.

Underuse of CSVD markers beyond WMH

WMH—whether assessed through clinical visual ratings or computational methods—was by far the most consistently utilised CSVD marker, appearing in *all* structural MRI-based diagnostic and prognostic studies. While the emphasis on WMH is not inherently problematic, it represents a clear missed opportunity. The marked underrepresentation of other clinically relevant CSVD markers—such as lacunes, perivascular spaces, cerebral microbleeds, cortical superficial siderosis, and cortical cerebral microinfarcts—limits the capacity of ML models to fully capture the complexity of vascular contributions to neurodegenerative diseases. This overreliance on WMH may stem from the widespread availability of tools for its automated segmentation, combined with the lack of openly validated systems—either commercial or research-based—that offer comprehensive analysis of all neuroimaging CSVD markers [126].

BOX 1 Recommendations to move toward clinically useful, machine learning methods applied to vascular neuroimaging for cognitive impairment and dementia

Reporting:

- Inclusion of measures of variance and/or confidence intervals for all performance metrics
- Full disclosure of all results, including those that do not reach statistical significance

Generalisability:

- Use of external independent datasets for validation

From curated to real-world datasets

- Inclusion of diverse populations
- Investigation of a broad spectrum of neurodegenerative diseases, including a greater focus on vascular dementia

Fairness and representativeness

- Exploration of sex-specific and race/ethnicity-specific contributions of vascular features for neurodegeneration

Recommendations

We have identified several limitations of the field and present corresponding recommendations, as summarised in BOX 1.

Reporting

Many studies did not report variances or confidence intervals for model performance, making it challenging to combine their findings in a meta-analysis. For future studies, *we strongly recommend the inclusion of confidence intervals for all performance metrics, following established reporting standards such as the TRIPOD+AI guideline* [127]. Careful consideration should also be given to the choice of metrics. For instance, in cases of pronounced class imbalance, reporting sensitivity and specificity alongside AUC can be crucial. Additionally, *we advocate for the full disclosure of all results, including those that do not achieve statistical significance, to enhance the completeness and unbiased representation of study findings.*

Generalisability

Despite achieving high accuracy metrics, the translation of predictive ML algorithms to real-world clinical settings requires extensive external validation. Despite this, our systematic review suggests that generalisability remains largely neglected, with less than 10% of the studies included in this review evaluating their models on hold-out external datasets. It is clear that datasets containing subjects with the exact pathology of interest are limited in availability. However, we also identified five additional studies that, despite having access to multiple datasets—and thus the opportunity to assess generalisability—chose to train and test their models on the pooled data instead of using separate datasets for independent validation. Many studies leveraged cross-validation, a method for evaluating model performance by dividing data into

subsets, training on some and testing on others. While this approach helps estimate a model's performance on unseen data, inherent similarities between the training and test sets mean it does not entirely eliminate the risk of overfitting. A recent study by Chekroud and colleagues found that, even with adequately cross-validated algorithms, the performance of these ML models was consistently lower in external datasets [128]. *We thus recommend the validation on external datasets to properly assess the true performance of these algorithms.* An ML model, whether simple or complex, could still become “tuned” to the specific folds in the cross-validation process and fail to generalise to genuinely new data beyond the validation set.

From curated to real-world datasets

Neuropathological studies often show a complex constellation of brain pathologies across neurodegenerative dementias [129], which may exist to varying degrees alongside cerebrovascular disease [130]. These mixed or multiple pathologies can make it challenging for ML algorithms to accurately classify cases and predict disease progression, in turn lowering the robustness and generalisability of ML models. Hence, training ML algorithms that assess cerebrovascular disease in the presence of other neuropathological indicators, using features derived from well-characterised, multimodal datasets across neurodegenerative dementias, is highly desirable. *This underscores the importance of leveraging more representative, deeply phenotyped, real-world datasets that include diverse types of dementias.* As we move closer towards individualised, precision medicine approaches, such a strategy will optimise the translation of ML algorithms in clinical settings while ensuring their applicability across ethnically and socioeconomically diverse populations worldwide.

Fairness and representativeness

Many included studies used case-control designs, which, while useful for comparisons, often introduce selection bias, especially when controls are not well-matched to cases [19]. Additionally, several studies lacked clear inclusion/exclusion criteria, undermining replicability and generalisability. Six studies also failed to clearly specify diagnostic criteria, further impacting repeatability and reliability. Although there was a balanced representation of men and women in the included studies, only one study assessed sex differences in the classification of dementia [72]. It is well-established that women are at higher risk of developing dementia and WMH [131, 132]. Similarly, while ethnicity can modulate developing dementia [133], only six studies reported the race or ethnicity of their participants. The inconsistent reporting of demographic factors, such as race or ethnicity, raises

concerns about diversity in dementia research, given that most dementia cohorts tend to be well educated, and of higher socioeconomic status than what would be expected based on census data [134, 135]. This has important implications for accurately predicting dementia risk, especially since race, ethnicity, socioeconomic background, and education are important factors that can modulate an individual's cumulative risk for developing dementia [136–138]. Non-representative samples may limit the applicability of the findings to broader, more diverse populations. *We recommend that future cohort studies seek to collect and consistently report data from diverse populations, and that studies explore sex- and race/ethnicity-specific classifications of dementia.*

Strengths and limitations

This work has major strengths. We performed a systematic search across nine databases to provide a comprehensive summary of the existing evidence on the application of vascular neuroimaging in ML-based diagnosis and prognosis of cognitive impairment and dementia. Our approach followed a carefully structured methodology to ensure both transparency and reproducibility. This included pre-registering our protocol and adhering to PRISMA guidelines. All papers included in the title and abstract screening, full-text screening, data extraction, and risk of bias assessment phases—during both the initial review and the re-run—were independently reviewed by multiple reviewers, with each paper evaluated by two reviewers and a third consulted to resolve any outstanding conflicts. We systematically assessed the risk of bias and the overall quality of the studies using established quality assessment tools, specifically QUADAS-2 and PROBAST, to ensure a robust evaluation of the evidence included in our review. Through these rigorous standards, we aimed to synthesise high-quality evidence that can guide future research to accelerate the integration of ML into clinical practice.

This work has three main limitations. First, a limitation of our meta-analysis is the significant variation in covariates and sample sizes across studies, which may have led to heterogeneity in the predictive models and potentially affected AUC comparability (see Supplementary data 2). Second, we did not assess the added value of neuroimaging markers of CSVD in diagnosing or predicting dementia, as only a few studies compared the performance of ML models with and without CSVD markers. Third, the risk of bias assessment tools used here were not designed for AI studies, and while recent efforts have been made, such tools are still in their infancy [127, 139]—the rationale for using accepted risk of bias tools for the tasks, QUADAS-2 and PROBAST.

Future of ML and vascular neuroimaging

Neuroimaging

The majority of studies in our review relied on structural MRI data, with only a single study using computed tomography. A significant shift in this trend is unlikely in the coming years, though it is probable that new and advanced imaging methods will begin to appear more frequently in the literature. While assessing the human cerebral microvasculature in vivo using conventional imaging technologies remains challenging, advancements in MRI with higher field strengths (7T and above) as well as other imaging technologies help us get closer to detecting subtle vascular changes and visualising small-calibre blood vessels [140, 141].

The recent incorporating of non-lesional outcomes into the assessment of CSVD in the STRIVE II criteria (Standards for Reporting Vascular Changes on Neuroimaging) will likely enrich our understanding of CSVD and its contributions to neurodegenerative diseases. Investigating functional markers, such as those derived from fMRI [142], could enable determining the extent to which CSVD leads to impaired neurovascular coupling and neural network communication, and ultimately contributes to cognitive decline [143].

Harmonisation

A major challenge in developing large multimodal datasets lies in harmonising data. This is important because data acquired from different MRI scanners or imaging sites can introduce systematic variability—such as differences in intensity scaling, resolution, or noise characteristics—that is unrelated to the condition of interest. Without appropriate harmonisation, these scanner- or site-specific effects can confound statistical analyses, reduce model generalisability, compromise reproducibility and comparability across studies or cohorts. The fact that only a quarter (26%) of studies using data from multiple scanners or sites applied any form of harmonisation indicates that there is still considerable scope for wider adoption of such techniques to improve the reliability and translational impact of neuroimaging research.

Treatments

Identifying and quantifying CSVD is relevant for the selection and stratification of dementia treatments, as illustrated in anti-amyloid therapies (e.g. Lecanemab or Donanemab). As CSVD markers play a pivotal role in the diagnosis of cerebral amyloid angiopathy [144], a major risk factor for adverse treatment outcomes [144–147], accurate identification of patients who are not at increased risks of adverse events and therefore will benefit most from treatment is crucial. AI-based predictions could provide clinicians with valuable tools to tailor therapeutics, thus enhancing safety and efficacy while

facilitating precision medicine approaches for patients [148].

Conclusion

CSVD markers are playing an increasing role in ML-based diagnosis and prognosis of dementia and cognitive impairment, with models leveraging these markers already demonstrating strong performance in distinguishing individuals with and without cognitive impairment and dementia. However, challenges remain of reporting standards, generalisability, and fairness that hinder the widespread adoption of these approaches. As the cerebrovascular interest subgroup of the international DEMON Network Imaging Working Group, we have collaboratively developed a set of targeted recommendations to drive progress in this field over the next decade. We firmly believe that adopting these recommendations will greatly accelerate the integration of ML methods into clinical practice, delivering meaningful benefits for patients.

Abbreviations

AD	Alzheimer's diseases
ADDTCT	Alzheimer's Disease Diagnostic and Treatment Centers
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRDA	Alzheimer's Disease and Related Disorders Association
AUC	Area under the curve
CDR	Clinical Dementia Rating
CNN	Convolutional neural network
CSVD	Cerebral small vessel diseases
DEMON	Network The Deep Dementia Phenotyping Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	Functional magnetic resonance imaging
HARNES	HARmoNizing Brain Imaging METHodS for VaScular Contributions to Neurodegeneration
MCI	Mild cognitive impairment
ML	Machine learning
MRI	Magnetic resonance imaging
NIA-AA	National Institute on Aging and Alzheimer's Association
NIA-ADRC	National Institute on Aging-Alzheimer's Disease Centers
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NINDS-AIREN	National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROBAST	Prediction model Risk Of Bias ASsessment Tool
PROSPERO	International Prospective Register of Systematic Reviews
QUADAS-2	QQuality Assessment of Diagnostic Accuracy Studies
SD	Standard deviation
STRIVE	Standards for Reporting Vascular Changes on Neuroimaging
SVM	Support vector machines
T	Tesla
TRIPOD + AI	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis + Artificial Intelligence
USA	United States of America
WMH	White matter hyperintensities
XGBoost	eXtreme Gradient Boosting

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

VL, AB, TR, SW, and JB conceptualised the study. The literature search was conducted by VP, VL, AB, FED, GC, HGM, AK, RL, AL, CM, AM, OP, US, SYWT, ST, SW, and JB screened the literature and extracted the data. The statistical analysis was conducted by VL, ST, and SW. VL, AB, DJL, TR, SW, and JB supervised the study. All authors interpreted the data, drafted and approved the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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