

Machine Learning Prediction Models for Cognitive Impairment in Cerebral Small Vessel Disease

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Abstract

Background

Early identification of cerebral small vessel disease (CSVD) patients with a higher risk of developing cognitive impairment is essential for timely intervention and improvement of patient prognosis. The advancement of medical imaging and computing capabilities provides new methods for early detection of cognitive disorders. Machine learning (ML) has emerged as a promising technique for cognitive impairment in CSVD. This study aims to conduct a thorough meta-analysis and comparison of published ML prediction models for cognitive impairment in patients with CSVD.

Methods

In September 2024, relevant studies were retrieved from four databases: PubMed, Embase, Web of Science, and the Cochrane Library. The Prediction Model Risk of Bias Assessment Tool (PROBAST) was used to assess the risk of bias of the ML models. The random effects model was used for meta-analysis of C-index, while a bivariate mixed-effects model was used to calculate the pooled sensitivity and specificity with their 95% confidence intervals (CIs). In addition, to limit the influence of heterogeneity, we also performed sensitivity analyses, a meta-regression, and subgroup analysis.

Results

Twenty-one prediction models from thirteen studies, involving 3444 patients met criteria for inclusion. The reported C-index ranged from 0.708 to 0.952. The pooled C-index, sensitivity, and specificity were 0.85 (95% CI 0.82–0.87), 0.82 (95% CI 0.77–0.87), and 0.81 (95% CI 0.73–0.87). As one of the most commonly used ML methods, logistic regression achieved a total merged C-index of 0.81, while non logistic regression models performed better with a total merged C-index of 0.86.

Conclusions

ML models holds significant promise in forecasting the risk of cognitive impairment in patients with CSVD. However, future high-quality research that externally validates the algorithm through prospective studies with larger, more diverse cohorts is needed before it can be introduced into clinical practice.

1. Introduction

Cerebral small vessel disease (CSVD) represents a heterogeneous group of disorders affecting the small blood vessels in the brain, including arterioles, capillaries, and venules (Bos et al., 2018; Li et al., 2022). These conditions are increasingly recognized as significant contributors to vascular cognitive impairment and dementia, posing a major public health challenge as populations age (Pantoni, 2010; Zanon Zotin et al., 2021). Despite its clinical importance, accurately detecting and quantifying cognitive impairment attributable to CSVD remains a complex and challenging task. There is an urgent need for effective strategies to identify individuals at risk of developing cognitive impairment (Das et al., 2019).

The diagnosis of CSVD-related cognitive impairment requires a combination of clinical manifestations, neuropsychological evaluation, and neuroimaging examinations (Rosenberg et al., 2016). Traditional clinical assessments are subject to variability and may fail to capture the nuanced, yet critical changes in cognitive function that may occur in the early stages of disease (Li et al., 2024). Neuropsychological assessment takes a long time and is susceptible to subjective influences from both the subjects and evaluators. Consequently, there is a growing interest in the application of machine learning (ML) approaches that can leverage large datasets to uncover patterns and predict cognitive decline more effectively than conventional methods.

The application of neuroimaging machine learning in CSVD mainly includes assisting diagnosis and disease prediction. Several meta-analyses have demonstrated the efficacy of ML models in predicting cognitive decline across various conditions. For instance, Odusami et al (2024) and Grueso et al (2021) provided comprehensive analysis of ML predicting progression from mild cognitive impairment to Alzheimer's disease, highlighting their potential for early detection. Moreover, Li et al. (2023) illustrated the feasibility of ML in the prediction of post-stroke cognitive impairment. However, ML has limitations and may lead to inaccurate predictions in certain clinical situations. Some researchers found that ML survival or classification models brought little improvement over traditional statistical methods, and the benefits of its assessment should be approached with caution, especially considering the limited sample size and features (R. Li et al., 2023; Noroozi et al., 2024).

Recent work has shown that ML algorithms can classify CSVD and normal patients with high accuracy. Unfortunately, few evidence-based studies of ML models for CSVD-related cognitive impairment are currently available. As a result, this study aims to analyze ML prediction models applied to neuroimaging data combined with other variables to predict cognitive impairment in CSVD and provide a useful reference for clinical practice and future research.

2. Methods

This study was conducted according to the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) 2020 guidelines (Page et al., 2021). It was registered on the PROSPERO website (CRD42024601473).

2.1 Search strategy

Two researchers (QW and JZ) independently conducted a systematic search of the electronic databases MEDLINE (PubMed), Cochrane Library, Embase, and Web of Science, and the retrieval was as of 21 September 2024. The retrieval strategy was as follows: ("cerebral small vessel diseases" OR "subcortical ischemic vascular disease") AND ("cognitive Dysfunction" OR "cognitive impairment") AND ("artificial intelligence" OR "machine learning" OR "neural network" OR "deep learning"). The detailed strategies are available in the **Supplementary Table S1**. In case of disagreement between assessors, consensus was reached through discussion and negotiation. We also identified additional relevant studies by reviewing the reference lists of the retrieved studies and review articles.

This study followed the PICOTS system, recommended by the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist (Palazón-Bru et al., 2020). The key items of our systematic review are described below:

P (Population): Patients with CSVD.

C (Comparator): ML methods as interventions.

O (Outcome): the performance for the prediction and diagnosis of ML models, including model discrimination or concordance index (C-index), specificity, sensitivity, and area under the curve (AUC).

T (Timing): The outcome was predicted after evaluating basic information at admission, clinical scoring scale results, and laboratory indicators.

S (Setting): The use of the ML prediction model is to individualize the prediction of cognitive impairment in patients with CSVD, facilitating the implementation of preventive measures to prevent adverse events.

2.2. Inclusion and exclusion criteria

All studies included had to meet the following criteria: (1) patients diagnosed with CSVD; (2) studies published in English; (3) ML was applied to predict CSVD-related cognitive impairment prediction, with a clear description of the ML models; (4) at least one measure of model performance (discrimination or calibration) was reported. Exclusion criteria were as follows: (1) only analysis of risk factors was conducted, without building complete ML models; (2) publication types such as review articles, case reports, editorials, conference abstracts and animal studies; (3) studies on the accuracy of single-factor prediction models; (4) studies that prediction models were developed, but not validated; (5) the full text could not be retrieved despite contacting the authors via email.

2.3. Literature screening

EndNote 20 software (Clarivate Analytics, Philadelphia, PA, USA) were employed to manage the studies and remove duplicate items. Three investigators (QW JZ and PL) conducted literature screening and ensured that all studies met the inclusion criteria. Each selected article has been screened at least twice. Any disagreement was dissolved by consulting a third reviewer (XZ).

2.4. Data extraction

The data extracted from each article was categorized into two groups: (1) Basic information: name of the first author, publication year, country, study design, sample size, age, diagnostic criteria for cognitive impairment, number of model variables and modeling variables. (2) Model information: variable selection method, handling of missing value, ML algorithms, model validation method, model performance measures. The extraction of information was performed by one reviewer, then checked by another reviewer to ensure accuracy and consistency.

2.5. Quality and Bias Assessments

The Prediction Model Risk of Bias Assessment Tool (PROBAST) was used to assess the risk of bias and applicability of the included study. The PROBAST consists of 20 signaling questions in four distinct domains, namely participants, predictors, outcome, and analysis (Moons et al., 2019). Each signaling question can be answered as "yes", "probably yes", "no", "probably no" or "no information". If at least one signaling question in a domain is answered as "no" or "probably no", that domain should be considered at high risk of bias. Only when all domains are judged as low

risk of bias, the overall bias can be considered low risk (Fu et al., 2024). Two independent researchers (QW and JZ) evaluated the quality and the bias risk of the included studies. Any disagreements will be resolved by consensus by a third researcher (CH).

2.6. Outcome measures

We extracted the C-index as the primary outcome measure, which can be used to reflect the overall accuracy of ML models. However, this indicator alone may not fully reflect the predictive accuracy of ML models. Therefore, sensitivity and specificity were included as complementary outcome measures to evaluate the predictive accuracy of ML in CSVD-related cognitive impairment.

2.7. Data synthesis and statistical analysis

Stata version 15.1 (StataCorp LP, College Station, TX, USA) were used to conduct the meta-analyses. Given the differences in modeling variables and parameters, the C-index was preferred to be pooled using a random effects model using a random effects model while a bivariate mixed-effects model was used to calculate the pooled sensitivity and specificity. If the C-index did not report 95% CIs and standard error (SEs), we estimated the SEs using the methods by Debray (Debray et al., 2019). C-index is similar to the AUC (Nezic, 2020), indicates its diagnostic or prognostic discrimination ability as low (C-index ≤ 0.5), modest (C-index > 0.6 to 0.7), good (C-index > 0.7 to 0.8), or strong (C-index > 0.8) (Snell et al., 2018). Cochrane Q-test and I^2 statistics were performed to examine heterogeneity. The I^2 statistics provides a measure of heterogeneity, with values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity respectively (Higgins et al., 2003).

Subgroup analyses, meta-regression and sensitivity analysis were also performed to gain insight into potential sources of heterogeneity. The C-index of the different ML algorithms for predicting cognitive impairment in patients with CSVD are discussed in the subgroup Analysis section. Sensitivity analysis was conducted by sequentially excluding each individual study and subsequently recalculating the pooled effect size for the remaining dataset. Publication bias was evaluated using Egger's test, with $p > 0.05$ indicating a low publication bias (Egger et al., 1997).

3. Results

3.1. Study selection

The study search process is illustrated in the PRISMA flowchart (Fig. 1). In total, 5603 records were obtained by performing electronic and manual searches. After removing duplicates and screening titles and abstracts, 89 articles remained. On the basis of full-text review, thirteen articles were included in the study.

3.2. Study characteristics

Table 1 summarizes the design and participant characteristics of the included studies. The publication years of the article ranged from 2016 to 2024; 5 out of 13 (38%) were published in 2024 (Chen et al., 2024; Huang et al., 2024; Li et al., 2024; Zhang et al., 2024; Zhu et al., 2024). Of the thirteen eligible studies, ten were conducted in China (H. F. Chen et al., 2020; Chen et al., 2023; Huang et al., 2024; Li et al., 2024; M. Liu et al., 2022; Qin et al., 2023; Wang et al., 2021; L. Zhang et al., 2022; Zhang et al., 2024; Zhu et al., 2024), one in Italy (Ciulli et al., 2016), and two in the UK (Chen et al., 2024; R. Li et al., 2023). In the studies we included, eight were prospective (including three multicenter study) (Li et al., 2024; M. Liu et al., 2022; L. Zhang et al., 2022; Zhang et al., 2024; Zhu et al., 2024), and five were retrospective (H. F. Chen et al., 2020; Chen et al., 2023; Chen et al., 2024; Ciulli et al., 2016; Huang et al., 2024; R. Li et al., 2023; Qin et al., 2023; Wang et al., 2021), all conducted in single centers. The source data for ML training were mostly obtained from clinical hospitals; some also included public database. Among the 13 studies, the most commonly used diagnostic criteria for cognitive impairment were Montreal Cognitive Assessment (MoCA) ($n = 6$), followed by Mini-Mental State Examination (MMSE) ($n = 2$) and Diagnostic and Statistical Manual of Mental Disorders (DSM) ($n = 2$).

Table 1
Overview of basic data of the included studies

Author (year)	Country	Data source	Study design	Age, years	Sample size, n	Diagnostic criteria for cognitive impairment	Included variables	Model evaluation metrics
Zhang, L (2022)	China	Neurology department of a hospital	Retrospective study	71.06 ± 9.88	159	MoCA score < 26 (an additional 1 point for education < 12 years)	hypertension, homocysteine, total CSVD MRI burden, and years of schooling	C-index, AUC
Huang (2024)	China	Clinical hospital	Prospective study	57.28 ± 1.37	304	mild-CSVD: MoCA score 18–26; sever-CSVD: MoCA score < 17	Hippocampal textures	AUC, Sensitivity Specificity, Accuracy, PPV, NPV
Zhang, Y (2024)	China	Neurology department of a hospital	Retrospective study	65.91 ± 7.90	71	MoCA score < 26	BEN, BEN/ALFF, and BEN/ReHo	AUC, Sensitivity Specificity, Accuracy
Li, N (2024)	China	Neurology department of a hospital	Retrospective cross-sectional study	NR	377	MoCA score < 25	Age, hypertension, total CSVD burden, ApoA1	AUC, Sensitivity Specificity, Accuracy, PPV, NPV
Zhu (2024)	China	Neurology department of a hospital	Retrospective study	66.7 ± 6.99	227	MoCA score < 26 (an additional 1 point for education < 12 years)	Age, homocysteine, hypertension, lacunar infarct score, total CSVD burden	C-index
Chen (2024)	UK	Multicentre (UKB, SCANS, RUN DMC)	Prospective cohort study	NR	761	NR	Demographic factors (n = 3), Cognitive scores (n = 3)	C-index

Table 1
(continued)

Author (year)	Country	Data source	Study design	Age, years	Sample size, n	Diagnostic criteria for cognitive impairment	Included variables	Model evaluation metrics
Liu, M (2022)	China	Neurology department of a hospital	Retrospective cohort study	50–80	197	neuropsychological tests scores fallen beyond ± 1.5 standard deviations (SDs) from the mean;	multiscale features of the brain functional interactions	AUC, Sensitivity, Specificity, Accuracy
Li (2023)	UK, Netherland, Singapore	Multicentre (SCANS, RUN DMC, HARMONISATION)	Prospective cohort study	NR	889	DSM	Demographic features (n = 7), Imaging features (n = 5 Cognitive features (n = 3)	AUC, Sensitivity, Specificity, Accuracy, Precision
Wang (2021)	China	Neurology department of a hospital	Prospective study	64.71 $\pm$ 6.94	113	MoCA score, MMSE score, neuropsychological tests scores: 1.5 standard deviations below the normative mean	DTI features (n = 8), CBF features (n = 5)	AUC, Sensitivity, Specificity, Accuracy
Qin (2023)	China	Multicentre (3 hospitals)	Prospective cohort study	64.8 $\pm$ 7.8	136	DSM-IV; CDR of ≥ 0.5 on at least one domain and a global score ≥ 0.5	DTI features, rsfMRI features, clinical features Neuropsychological measures	Sensitivity, Precision, Specificity, Accuracy
Chen, X (2023)	China	Neurology department of a hospital	Prospective study	70.25	100	Shanghai Manual of Cohort Studies on Cerebral Small Vessel Diseases	HBP, DM, HLP, Smoke, Drink	AUC, Sensitivity, Specificity, Accuracy, PPV, NPV
Chen, H (2020)	China	Neurology department of a hospital	Prospective cross-sectional study	64.8 $\pm$ 1.57	70	Beijing version of the MoCA (MoCA-BJ), MMSE	DTI features: AD, FA, MD, RD	Sensitivity, Specificity, Accuracy
Ciulli (2016)	Italy	Clinical hospital	Prospective, randomized, single-blind	75.3 $\pm$ 6.8	40	TMT-B	MD, FA	Sensitivity, Specificity, Accuracy
Abbreviations: NR: not reported, RF: random forests; AUC: area under the receiver operating characteristic curve; PPV: positive predictive value; NPV: negative predictive value; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; CDR, clinical dementia rating; DSM: Diagnostic and Statistical Manual of Mental Disorders; BEN: brain entropy, ALFF: amplitude of low frequency fluctuation, ReHo: regional homogeneity; SCANS: St George's Cognition and Neuroimaging in Stroke; RUN DMC: Radboud University Nijmegen Diffusion Tensor and MRI Cohort; HARMONISATION: A memory clinic study in Singapore; DTI: diffusion tensor imaging; rsfMRI: resting-state fMRI CBF: cerebral blood flow; HBP: high blood pressure; DM: diabetes mellitus; HLP: hypercholesterolemia; TMT: Trail Making Test Part B								

Table 2 provides the model information in the included studies. There were 21 models in the included studies, among which 17 models reported AUC or C-statistic values, ranging from 0.708 to 0.952, and 10 models reported sensitivity and specificity. In the 13 studies, the logistic regression (LR) (38.4%; n = 5) was the most universally used algorithm, followed by the support-vector machine (SVM) (23%; n = 3). Besides, seven studies also assessed the performance of other ML algorithms: random forest (RF), k-nearest neighbors (KNN), decision trees (DT), connectome-based prediction model (CPM), DS-GAN (diffusion scalar generative adversarial network), Reg-Logistic, generalised matrix learning vector quantisation (GMLVQ), generalised relevance learning vector quantisation (GRLVQ), and unsupervised machine learning model. For measuring deep learning performance, AUC and the Youden index were most commonly used.

Table 2
Methodological characteristics of the included machine learning models

Author (year)	Missing value processing	Validation set generation method [internal validation/external validation]	Variable screening/ feature selection method	ML algorithms	Model performance (C-index/ Sensitivity, Specificity)
Zhang, L (2022)	NR	Bootstrapping	Univariate significance level, multivariate logistic regression with stepwise regression (Forward: LR)	LR	C-index: 0.806 (0.735–0.877)
Huang (2024)	Median interpolation	5-fold cross-validation	Spearman correlation, LASSO regression	KNN	C-index: 0.818 (0.673–0.96) Sensitivity: 0.538 Specificity: 0.947
Zhang, Y (2024)	ML method	leave-one-out cross validation	SVM classifier	SVM	C-index: 0.824(0.750–0.899), Sensitivity: 0.865, Specificity: 0.618
Li, N (2024)	NR	10-fold cross validation	multivariate logistic regression analysis, LASSO regression	LR	C-index: 0.852 (0.781–0.923) Sensitivity: 0.769, Specificity: 0.74
Zhu (2024)	Median interpolation	Bootstrapping	Univariate analysis, binary logistic regression	LR	C-index: 0.867(0.788–0.947)
Chen (2024)	NR	External validation	Information value	DS-GAN (consist of 2 deep learning models: a generator and a discriminator)	SCANS: C-index:0.828 (0.733, 0.923),0.903(0.828–0.978) RUN DMC: C-index:0.845(0.800–0.890),0.858(0.815–0.901)
Liu, M (2022)	NR	5-fold cross-validation	SVM classifier, GCN	CPM (with SVM as the classifier) and GCN	C-index: 0.821(0.747–0.895), Sensitivity: 0.818, Specificity: 0.823

Table 2
(continued)

Author (year)	Missing value processing	Validation set generation method [internal validation/external validation]	Variable screening/ feature selection method	ML algorithms	Model performance (C-index/ Sensitivity, Specificity)
Li (2023)	Complete case analysis	5-fold cross-validation External validation	Sparse logistic regression classifier, LASSO regression, feature ranking	LR, SVM, Reg-Logistic, GMLVQ, GRLVQ	C-index: LR 0.860 (0.826–0.894), Reg-Logistic 0.870(0.837–0.903) SVM 0.858(0.824–0.892) GMLVQ 0.817 (0.779–0.856) GRLVQ 0.868 (0.835–0.901)
Wang (2021)	NR	leave-one-out cross validation	Sparse logistic regression classifier, LASSO regression	SLR	C-index: 0.708 (0.667–0.740), Sensitivity: 0.77, Specificity: 0.641
Qin (2024)	Remove highly missing variables, fill missings with model	Internal validation External validation	LASSO regression	Unsupervised machine learning model	Sensitivity: 0.795, Specificity: 0.962 Sensitivity: 0.711, Specificity: 0.938
Chen, X (2023)	Complete case analysis	1,000 times cross-validation	Statistical analysis, k-means clustering	DT	C-index: 0.952 (0.911–0.993) Sensitivity: 0.981, Specificity: 0.896
Chen, H (2020)	imputation	Bootstrapping	Spearman correlation, RF	RF	Sensitivity: 0.818, Specificity: 0.79
Ciulli (2016)	NR	leave-one-out cross validation	Averaging Mean Diffusivity (MD) and Fractional Anisotropy (FA) maps within 50 Regions of Interest (ROIs)	SVM	Sensitivity: 0.895, Specificity: 0.714
Abbreviations: NR: not reported, ML: machine learning; LASSO: Least Absolute Shrinkage and Selection Operator; RF: random forest; KNN: k-nearest neighbors; CPM: connectome-based prediction model; GCN: graph convolutional network; LR: logistic regression; SVM: support-vector machine; Reg-Logistic: regularised logistic regression with elastic net penalty; GRLVQ: generalised relevance learning vector quantisation; GMLVQ: generalised matrix learning vector quantisation; DT: decision tree; SLR: sparse logistic regression DS-GAN: diffusion scalar generative adversarial network					

Table 3
Results of subgroup analyses of C-index by study design, validation set generation method and machine learning type

Subgroups	Models	Pooled C-index (95%CI)	P Value	I ² (%)
Overall	17	0.85 (0.82, 0.87)	P < 0.001	81.6
Study design				
Retrospective	5	0.83 (0.80, 0.87)	P = 0.792	0
Prospective	12	0.85 (0.82, 0.88)	P < 0.001	86.9
Validation method				
Internal validation	8	0.83 (0.76, 0.91)	P < 0.001	91
External validation	9	0.86 (0.84, 0.87)	P = 0.515	0
Model type				
Logistic regression	5	0.81 (0.74, 0.89)	P < 0.001	89.8
Non-logistic regression	12	0.86 (0.84, 0.89)	P < 0.001	63.5

Feature selection is an important step for ML training. Some researchers favored features that are statistically correlated and easily obtainable with CSVD (i.e., structural MRI, demographic, and cognitive results), whereas others incorporated factors based on established knowledge from

previous models. In the included studies, 4 studies used DTI (diffusion tensor imaging) data as input features (H. F. Chen et al., 2020; Ciulli et al., 2016; Qin et al., 2023; Wang et al., 2021), 3 studies used rs-fMRI (resting-state functional MRI) data as input features (M. Liu et al., 2022; Qin et al., 2023; Zhang et al., 2024), and one used a radiomics model with hippocampal texture features (Huang et al., 2024).

3.3. Model validation

In the included studies, all ML models were internally or externally validated. Among them, internal validation was conducted in ten studies using random split, k-fold cross-validation or bootstrapping, while the remaining three conducted external validation. Models that only developed without validation were not included.

3.4. Quality assessment

Five studies had a high risk of bias (38.4%), while only three studies had low risk (23%). In the participant domain, two studies were considered to have a moderate risk of bias primarily due to the use of inappropriate data sources and controversial criteria (Chen et al., 2024; R. Li et al., 2023), while bias in the other studies were low. In the predictor domain, one study had an unclear risk of bias due to lack of information on how predictive factors are defined or measured (Li et al., 2024). The bias of outcome in one study was unclear due to no standard for diagnosing cognitive impairment described (Chen et al., 2024), and three was high because multiple predictive factors form part of the outcome of cognitive impairment (H. F. Chen et al., 2020; Li et al., 2024; Wang et al., 2021). In the analysis domain, the method of converting continuous variables into categorical variables in the two studies was not mentioned (H. F. Chen et al., 2020; Huang et al., 2024). six studies where missing data has not been properly processed (Chen et al., 2024; Ciulli et al., 2016; Li et al., 2024; M. Liu et al., 2022; Wang et al., 2021; L. Zhang et al., 2022), four studies did not consider model overfitting and underfitting (Chen et al., 2024; Ciulli et al., 2016; Qin et al., 2023; Wang et al., 2021). Therefore, these attributes should be improved in subsequent model construction. More details of the risk of bias are shown in **Supplementary Table S2**.

3.5. Performance of ML Models for predicting cognitive impairment in CSVD

Meta-analysis showed that the overall pooled C-index for ML models predicting cognitive impairment in CSVD was 0.85 (95% CI 0.82–0.87; $P < 0.001$; $I^2 = 81.6\%$; $n = 17$); the pooled sensitivity was 0.82 (95% CI 0.77–0.87; $P = 0.07$; $I^2 = 43.51\%$; $n = 10$) and the pooled specificity was 0.81 (95% CI 0.73–0.87; $P < 0.001$; $I^2 = 72.15\%$; $n = 10$). Forest plots of the above results are presented in Figs. 2, 3.

The results of meta-regression showed that four items including country where the data were collected, publication year, study design, and ML methods used did not significant affect the C-index ($p > 0.05$; **Supplementary Table S3**).

3.6. Subgroup analysis

We performed the subgroup analysis of C-index based on study design, validation set generation method and model type. For study design, the pooled C-index of retrospective and prospective studies was 0.83 (95%CI 0.80–0.87, $n = 5$) and 0.85 (95%CI 0.82–0.88, $n = 8$), respectively. For validation set generation method, the pooled C-index of internal and external validation studies was 0.83 (95%CI 0.76–0.91, $n = 8$) and 0.86 (95%CI 0.84–0.87, $n = 9$), respectively. For ML algorithms, 5 prediction models were established applying the LR algorithms (Li et al., 2024; R. Li et al., 2023; Wang et al., 2021; L. Zhang et al., 2022; Zhu et al., 2024), and the overall pooled C-index for the LR models was 0.81 (95% CI 0.74–0.89). The overall pooled C-index for non-LR models was 0.86 (95% CI 0.84–0.89), the highest value among these subgroups. Forest plots of the above results are presented in supplemental file **Figure S1-3**.

3.7. Sensitivity analysis and publication bias

The sensitivity analysis excluding studies one by one showed that the meta-analysis results of predictive value of ML for cognitive impairment in CSVD were stable and reliable (**Supplementary Figure S4**). Egger's test result ($P = 0.439$) and a symmetrically distributed funnel plot suggested no publication bias (**Supplementary Figure S5**).

4. Discussion

Although the increasing use of ML in predicting cognitive impairment in CSVD, the quality of studies varies, and the results also differ. It is necessary to perform a meta-analysis for a unified evaluation. This study is the first to systematically explore the application of the latest ML prediction models for cognitive impairment in CSVD.

4.1. Principal findings

In our study, the overall pooled estimation of 13 studies showed that ML models achieved high accuracy in early recognition of CSVD patients, with a C-index of 0.85 (95% CI 0.82–0.87) and sensitivity and specificity of $> 80\%$. These results underscore the ability of ML algorithms to integrate complex data from various sources, such as neuroimaging, clinical assessments, and genetic markers, offering potential advantages. Although ML methods may not provide greater benefit than current available screening strategies, they do possess an advantage in allowing for a preferred trade-off between sensitivity and specificity (Z. Zhang et al., 2022). It was reported that common cognitive screening tests have similar predictive accuracy in CSVD-related cognitive impairment (Pasi et al., 2021). Research has shown that the MoCA has superior sensitivity of

cognitive function than other screening tools, but its specificity is less than desirable (Jia et al., 2021; Szcześniak et al., 2021). However, our findings showed that ML has considerably high and balanced predictive accuracy (c-index, sensitivity, and specificity) in CSVD-related cognitive impairment and is robust for future clinical implementation.

Based on the subgroup analysis, models developed utilizing non-LR methods achieved the highest C-index, implying that researchers should consider testing a broader range of candidate models to potentially identify superior predictive performance. Li et al (R. Li et al., 2023) developed five common ML methods (i.e., LR, SVM, Reg-Logistic, GMLVQ, GRLVQ) to predict the occurrence of CSVD-related cognitive impairment, with a data set of 889 patients. Reg-Logistic and GRLVQ were the two models with the best diagnostic accuracy in that study (C-index 0.868–0.87). Regarding the ML methods used to predict the risk of cognitive impairment in the context of CSVD, LR is the most commonly used type of model, since LR models are suitable for simple data with linear relationships between variables and outcomes (Boehm-Sturm et al., 2017; B. Liu et al., 2022; Montine et al., 2021). Ensemble methods like RF have achieved high precision in predicting cognitive trajectory types using longitudinal by aggregating the results of multiple decision trees, thus reducing overfitting and increasing robustness (Mohammadiarvekeh et al., 2023). Moreover, SVM and KNN have more advantages in image recognition and segmentation for predicting mild cognitive impairment (Al-Qazzaz et al., 2018; Zhang et al., 2021). Deep learning exhibits significant potential in the realm of image classification, attributed to its capability to automatically extract low to high-level features. Studies have demonstrated the utility of deep learning models in analyzing MRI sequence to identify subtle changes subcortical vascular cognitive impairment (Q. Chen et al., 2020; Wang et al., 2019).

The most commonly used features in ML models are neuroimaging biomarkers such as white matter hyperintensities (WMHs), cerebral microbleeds (CMBs) lacunar infarction (LI), enlarged perivascular spaces (EPVS) and total CSVD burden. The preliminary research on neuroimaging biomarkers provides the imaging basis of CSVD for machine learning and can serve as primary features for input. In addition, DTI and rs-fMRI are widely applied in the study of CSVD, primarily focusing on the early identification and progression of cognitive impairment (Egle et al., 2022). Based on DTI and rs-fMRI parameters, structural and functional brain networks can be constructed separately. The fractional anisotropy (FA) score of DTI in CSVD patients decreases, while the mean diffusivity (MD) increases (Biesbroek et al., 2017), and these changes are associated with clinical outcomes such as cognitive impairment (Tuladhar et al., 2015), gait abnormalities (van der Holst et al., 2018), and emotional disorders (van Uden et al., 2015). Research based on rs-fMRI has found that CSVD patients exhibit abnormal functional activity in the prefrontal cortex, subcortical region, cingulate gyrus, and hippocampus (Li et al., 2012; Yi et al., 2012). Ciulli et al. utilized the mean MD value as a feature and employed a machine learning strategy combining a linear support vector machine with leave-one-out cross validation to predict the executive function of CSVD patients with mild cognitive impairment, in which sensitivity, specificity, and accuracy all reached a high level (Ciulli et al., 2016). Furthermore, Pantoni et al. used traditional imaging biomarkers and the fractal dimension (FD) of gray and white matter as input features to predict different neuropsychological test scores. They found that the FD value of white matter was the most commonly used feature, and FD may be an important marker for predicting cognitive decline in CSVD, which can supplement traditional imaging biomarkers (Pantoni et al., 2019). Our study also finds that radiomics features are frequently used as predictors in ML models for CSVD-related cognitive impairment. A recent study validated the superior accuracy and specificity of radiomics models utilizing hippocampal texture features in identifying CSVD patients with severe cognitive impairment (Huang et al., 2024).

As for validation methods, 8 studies selected cross-validation, with different folding or iteration times. Cross-validation splits the samples into training set and testing set. This division can average the accuracy of each iteration to obtain a more robust model performance, rather than validating the model on just one test sample. 13 studies chose leave-one-out cross validation, in which case the model is trained using all data except for one data point, and then it attempts to classify the missing data points and applies the same operation to the rest of the sample in subsequent iterations. 2 studies used bootstrapping as a validation method. The model in most studies primarily relied on internal validation rather than external validation. The lack of external validation of the obtained results is considered a major limitation of current prediction models (van Kempen et al., 2021). The reason for this phenomenon may be due to the insufficient sample sizes for external validation. Subgroup analysis according to different validation methods showed that the pooled C-index of the external validation group were higher than those of the internal validation. This may be because the dataset used for external validation is large, allowing ML algorithms to be fully learned and trained.

4.2. Limitations and strengths

This study has several potential limitations. First, non-English studies were not included in the meta-analysis, which might lead to selection bias. Second, a significant proportion of the included studies were conducted in mainland China, which may limit the generalizability of the findings to Western populations. Therefore, it is crucial for future research to develop models for cognitive impairment in CSVD patients across diverse populations to ensure their relevance and applicability in varied clinical settings. Thirdly, the heterogeneity in study designs, sample sizes, outcome measures, and a diverse array of feature selection methods across the included studies introduced potential biases and may affect the performance and applicability of ML models. Lastly, the number of validated studies and models included is relatively low, with only 3 models have external validation. Internal validation of data can result in overfitting or spectrum bias, thereby potentially overestimating the performance of machine learning models (Hu et al., 2023; Kuo et al., 2022).

Despite the aforementioned limitations, this study can still offer valuable guidance for future research and clinical practice. In the first place, the major strength of our study lies in the rigorous literature search methodology and sufficiently detailed meta-analysis to be reproducible. We

performed a quantitative synthesis, unprecedented in prior research, to systematically compare the models in question and described the characteristics of the validated ML models. In addition, the novel PROBAST was used to assess the risk of bias of the included predictive models. We conducted a thorough examination of more details of the model, such as data sources, processing, feature selection, and model validation (Di Tanna et al., 2020). Finally, we found that 5 studies had a high risk of bias in methodological quality, which may lead to overfitted prediction models. Potential biases may be prevented if studies adhere to the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) initiative in their reporting (Collins et al., 2015).

4.3. Future perspectives

In order to make ML algorithms more robust in clinical implementation, there are some important issues that should be addressed in future research. Firstly, the multimodal imaging research of CSVD has gradually shifted from structural imaging biomarkers, to parameter analysis based on DTI and rs-fMRI, and then to constructing brain networks, leading people's understanding of CSVD from local to global. In the future, multimodal data including DTI and fMRI can be conducted to further explore the occurrence and development patterns of CSVD. Secondly, studies that achieved higher accuracy have in common the use of multidimensional and multimodal data, as well as increasingly complex classification methods. However, a balance is needed between the algorithms that achieve the higher performance, and the data and methods that more easily obtainable data in the clinical practice. In addition, although these algorithms are useful in distinguishing the brain features of CSVD, their performance is far from specific enough to hand over a complete diagnosis to automated methods. Nevertheless, when implemented in clinical practice, computer-aided diagnosis will provide a faster, easier to perform, and earlier detection method to predict the potential progression of CSVD patients to cognitive impairment. Consequently, it is recommended that clinicians enhance their capability to apply ML techniques to improve the accuracy of their diagnoses (Nagendran et al., 2020; Wu et al., 2023). Finally, the effectiveness and performance of machine learning are closely related to the size of the dataset. Therefore, Future research should prioritize the development of novel models that leverage larger sample sizes and employ rigorous study designs. Emphasis should be placed on multicenter external validation to ensure the generalizability and robustness of findings across diverse populations.

5. Conclusion

This study shows the potential of ML algorithms predictive performance for cognitive impairment in patients with CSVD and can be used as a potential tool for early identification of cognitive impairment in this population. The development and validation of ML models tailored to CSVD-related cognitive impairment could facilitate earlier diagnosis and personalized treatment strategies, potentially improving patient outcomes.

This study also analyzed the classification algorithms and feature source used in the selected studies, making diverse methodologies available to researchers. Our research findings also emphasize that the main limitation of the current prediction model is the lack of external validation. Additionally, this meta-analysis excluded studies that only developed models without validation and did not report model performance metrics. Overall, while the study provides important insights into the potential of machine learning for diagnosing cognitive impairment in patients with CSVD, more research is needed to fully explore and validate these approaches.

Declarations

Author contributions

XZ and HC contributed to the study concept and design. QW and JZ retrieved and filtered the articles. QW and JZ extracted the data. QW and JZ analyzed the data. JZ, QW, and PL interpreted the data. JZ and QW drafted the manuscript. XZ and HC contributed to the critical revision of the manuscript. All authors contributed to the paper and approved the submitted version.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

Not applicable

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Figures

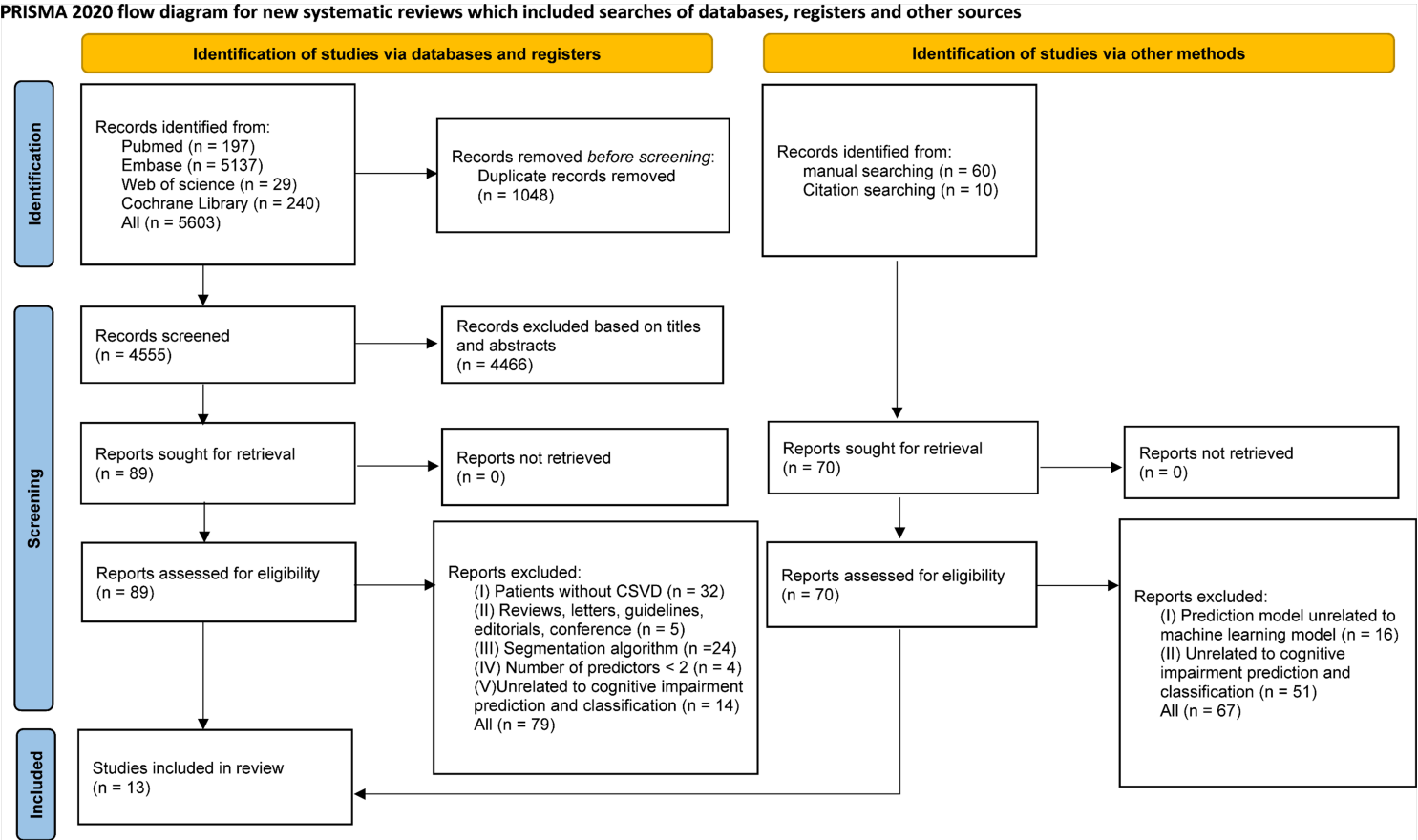


Figure 1

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the retrieval process

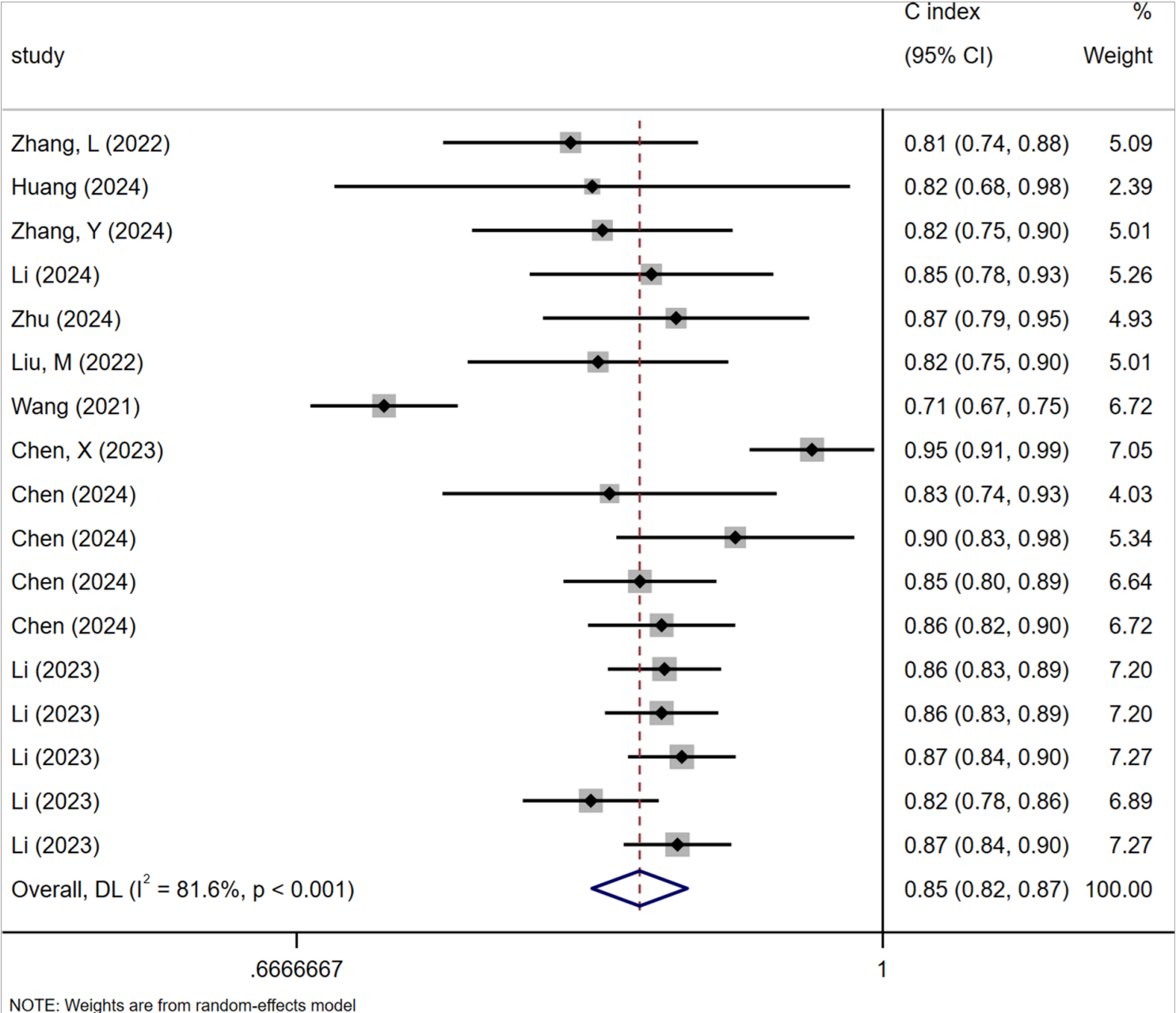


Figure 2
Forest plot of pooled C-index

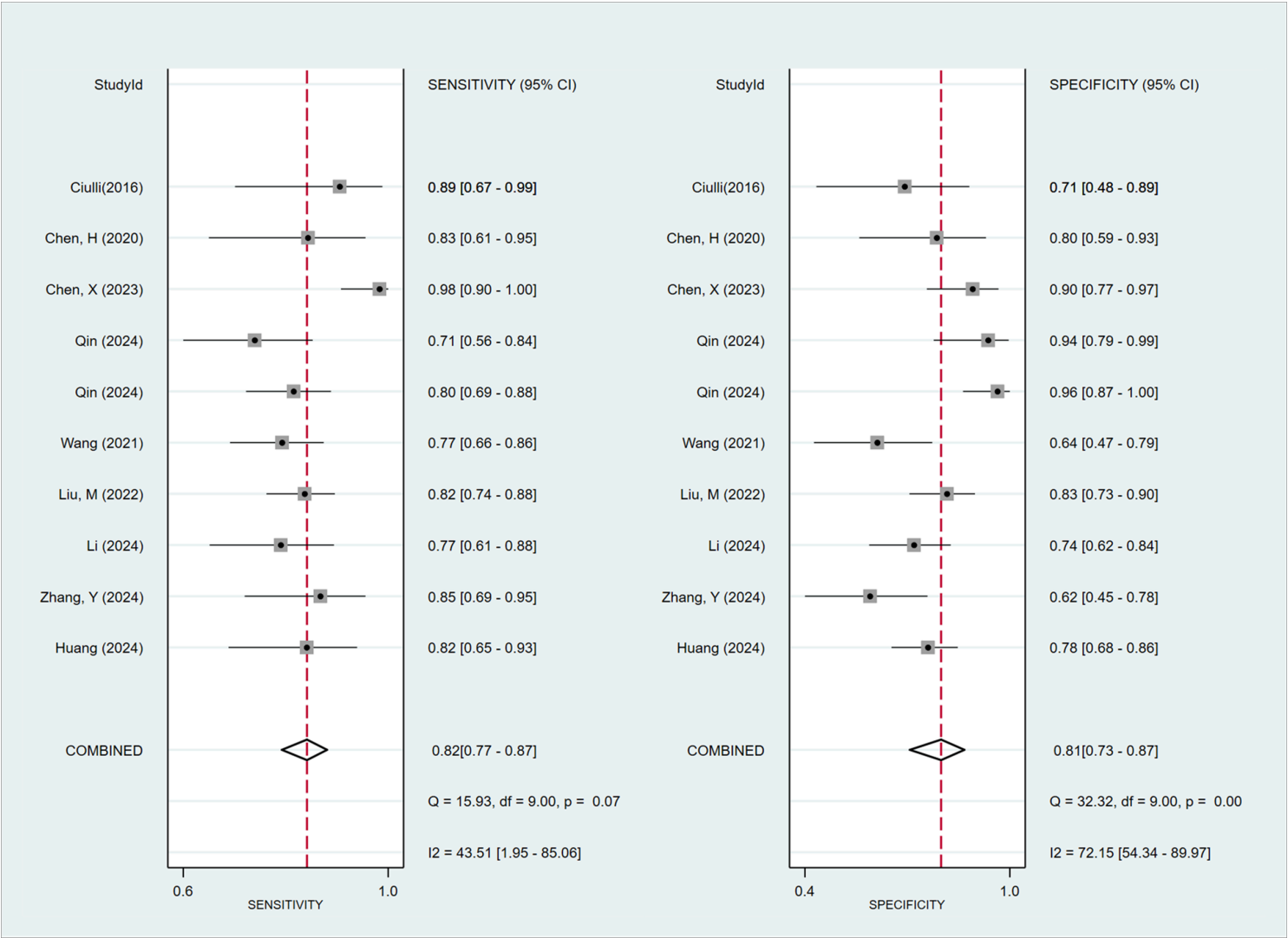


Figure 3
Forest plot of pooled sensitivity and specificity

Supplementary Files

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- [Supplementary.docx](#)