Original Article

Predictive value of machine learning in diagnosing cognitive impairment in patients with Parkinson's disease: a systematic review and meta-analysis

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Background: The current process used to diagnose cognitive impairment in patients with Parkinson's disease (PD) is unsatisfactory. More and more researchers had introduced machine learning into this field in recent years. This study explored the application of machine learning and its diagnostic performance in this field.

Methods: Since Parkinson's concurrent cognitive impairment is currently divided into different periods, most studies focus on the prodromal or early stages of Parkinson's cognitive impairment, and a few focuses on the dementia stage of Parkinson's. To ensure comprehensiveness, and model stability, we included patients with Parkinson's concurrent cognitive impairment in different periods who met the nadir criteria. A comprehensive literature search was carried out of the PubMed, Cochrane, Embase, and Web of Science databases. We used Prediction Model Risk of Bias Assessment Tool (PROBAST) to assess the risk of bias for the machine learning models covered by the included original studies. The outcome indicators included the concordance-index (C-index), sensitivity, and specificity. A meta-analysis using the random-effects model was conducted to determine the C-index, and a double variable mixed-effects model was used to determine the sensitivity and specificity. The meta-analysis in this article was completed in STATA.

Results: A total of 32 articles, comprising 10,778 patients and 51 prognostic models [summary c-statistic: 0.857, 95% confidence interval (CI) (0.842–0.873)], met the selection criteria and were included in this analysis. The total sensitivity and specificity of all models were 0.77 (95% CI: 0.72–0.81) and 0.83 (95% CI: 0.80–0.85), respectively, and those of the testing test were 0.85 (95% CI: 0.79–0.89), and 0.74 (95% CI: 0.70–0.78), respectively. A large part of the model showed a high risk of bias mainly because the study design was almost retrospective investigation.

Conclusions: This study constitutes a detailed mapping and assessment of the machine learning for prediction in PD patients with cognitive decline, which may provide stronger discriminative performance and can be used as a potential tool for early diagnosis.

Keywords: Machine learning; cognitive impairment; Parkinson's disease (PD); PD diagnosis

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Introduction

Parkinson's disease (PD) is a common disorder of neurodegeneration. It has a reported prevalence of >6 million worldwide, a figure that is 2.5 times larger than that of the past generation, and it has become a major cause of neurological disability (1,2). The incidence rate of PD is not high in those aged <50 years; however, it increases rapidly as age increases, and a study has reported that the incidence rate is the highest among those aged 80 years (3). The median age-standardized incidence of PD in developed countries is 14 per 100,000 people per year, and most PD patients are aged 65 years or older (4). The prevalence of age-adjusted PD has been reported to be lower in Africa than in Europe and the Americas (5-7); however, that of Asia has been found to be identical to that of Europe and the Americas (8). There are some differences in incidence depending on location; however, patients with PD experience a deterioration in body function, and a decline in mobility and cognition, which requires multidisciplinary management, such as drug treatments and rehabilitation therapies (9,10). The decreasing body function, declin mobility and cognition, drug treatments and rehabilitation therapies all of these create a heavy social and financial burden, especially among the elderly (11).

Cognitive decline, which, depending on the severity, ranges from PD with mild cognitive impairment to PD with dementia, is the most common and essential non-motor symptom of PD (12). Recent studies report that the prevalence of dementia is 46% at 10, even 6 years within the progression of PD (13,14). Thus, the early identification of PD patients with a cognitive defect in clinical practice would achieve prompt interventions.

Currently, in clinical practice, the cognitive impairments were mainly diagnosed via clinical interviews by experienced neurologists, which performs unsatisfactorily, and some other related tools, such as individual biomarkers and imaging evidence (15). The underlining reason may be these tools present different part of features of PD-CI. Given the heterogeneity of PD-CI, it may be difficult to replace these tools with each other, not to mention the specific contribution of each of these tools to predicting PD-CI with traditional analysis methods respectively. Due to the complexity and enormity of cognitive scores and image results, it is also hard to handle these data by traditional analysis methods. Recently, machine learning has been applied to the medical field for pre-diagnosis, and some investigators have used this advanced method to predict PD with cognitive impairment (PD-CI). ML can precisely model the relationship between inputs and outputs, and thus generate invisible data. On the other hand, ML make the analysis easier when dealing with complicated and huge data. However, machine learning includes multiple models with differential variables, which leads to certain heterogeneity. Consequently, debate continues as to whether machine learning should be used to diagnose PD-CI (16). The current systematic review and meta-analysis sought to provide a direction for the development and update of the scoring systems used in the diagnosis of PD -CI. We present the following article in accordance with the PRISMA-DTA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1396/rc) (17).

Highlight box

Key findings

- Machine learning performed potential value for diagnosing PD patients with early cognitive impairment.

What is known and what is new?

- Machine learning for predicting PD with cognitive impairment (PD-CI) exists some debates.
- Although there is certain heterogeneity, machine learning still could be used as a potential diagnostic tool for PD patients with early cognitive impairment (PD-CI).

What is the implication, and what should change now?

- This study provides a theoretical basis for scoring systems of PD-CI with machine learning in the future. More large-scale, multicenter, and multi-ethnic studies need to be conducted in the future for diagnosing PD-CI with machine learning.

Methods

The research scheme for the current research was registered with PROSPERO (registration No. CRD42022353619).

Literature retrieval

A search was performed of the PubMed, Cochrane, Embase, and Web of Science databases. Original articles, published from the inception of the databases to 6 August 2022, on the performance of machine learning in diagnosing PD-CI were retrieved. We searched for the relevant articles using keywords plus subject headings. Details of our search strategies are available online in the supplementary materials (Table S1).

Inclusion criteria

Studies were included in the meta-analysis if they met the following inclusion criteria: (I) included PD patients; (II) related to a case-control, cohort, nest case-control, or case-cohort study; (III) included a fully constructed machine-learning prediction model; (IV) did or did not have external validation; and (V) examined different machine-learning studies published with the same data set.

Exclusion criteria

Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) related to a meta-analysis, review, guideline, or expert opinion; (II) only analyzed predictive factors, and did not construct a complete machine-learning model; (III) lacked certain outcome indicators for the predictive accuracy of the risk model [i.e., the receiver operating receiver operating characteristic (ROC) curve, concordance-index (c-index), sensitivity, specificity, accuracy, recovery, precision, confusion matrix, diagnosis 4-grid table, F1 score, and calibration curve]; (IV) had small sample sizes (<50 cases); and (V) only validated mature neuropsychological assessment..

Literature screening and data extraction

We imported the retrieved literature into Endnote. After Endnote's duplicate identification strategies had been employed, any duplicate articles were manually deleted. Some additional articles were excluded in the title and abstract screening. Next, the full text of the articles deemed to be preliminarily eligible were downloaded and reviewed, and the original studies that met the above-mentioned criteria were selected for inclusion in the systematic analysis.

Information of the included articles were analyzed using a spreadsheet, including the title, first author, study design, geographical location, year of publication (prospective *vs.* retrospective), patient source (single center *vs.* multicenter), diagnostic criteria for cognitive impairment, patient numbers in data sets (total, training, and testing sets), internal and external validation (random split *vs.* n-folds cross validation if internal validation), overfitting method, procedures adopted for missing data, methods of feature screening, model names, predictor types, predictive performance measures [accuracy, specificity, sensitivity, positive and negative predictive accuracy, and c-statistic or area under (the ROC) curve and relevant 95% confidence intervals (CIs)]. Two researchers (i.e., RL, and XZ) independently extracted the described information from the selected articles and performed the cross-validation. If there were discrepancies, a 3rd investigator (i.e., TY) made the determination.

Assessment of risk of bias

The risk of bias in each of the prognostic models developed by the studies was assessed by researchers (i.e., MS and JJ) using PROBAST. A prevalence bias tool was used to systematically evaluate the prognostic or diagnostic predictive models (18,19). This tool examined 4 aspects (i.e., participants, predictors, outcomes, and analysis), and each aspect was examined and marked "yes", "unclear", or "no" on the basis of the features of the included study. A classification of "no", indicated a high risk of bias, while a classification of "yes" indicated a low risk of bias. The overall risk of bias was considered low when all the aspects were marked low risk. The overall risk of bias was considered high if only 1 of the given aspects was marked high risk. The evaluation was visually displayed using Excel 2019.

Outcome index

Our systematic review employed the C-index as the outcome measure to determine the overall accuracy of the response model. The C-index cannot be used to determine the prediction accuracy of a machine-learning model for PD-CI patients if the sample proportion is too small (e.g., <10%). Our systematic review of the outcome measures also examined the sensitivity and specificity of the machine-learning models.

Data synthesis and statistical analysis

We conducted a meta-analysis of the metrics (C-index and accuracy) to evaluate the machine-learning models. If the C-index did not include the 95% CIs and standard errors, we used Debray *et al.*'s approach to estimate the standard errors (20). In addition, a bivariate mixed-effects model (21) was used for the meta-analysis of sensitivity and specificity. If there was a lack of accuracy in the original study, we calculated accuracy by combining the number of samples of each molecular subtype and the number of modeling samples according to the sensitivity and specificity. Given the differences in the variables included in the learning

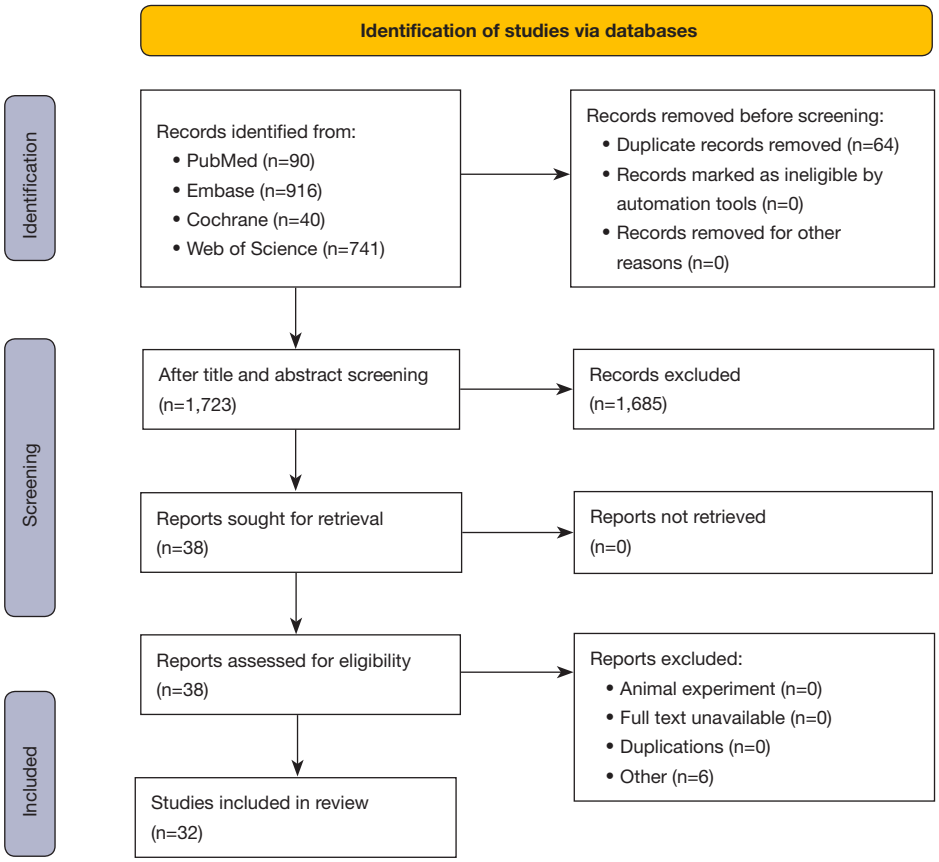

Figure 1 Flow diagram of literature search.

models of the different original studies and the inconsistent parameters, we prioritized the use of the random-effects model in the meta-analysis. The meta-analysis in this study was implemented in R4.2.0 (R Development Core Team, Vienna, http://www.R-project.org).

Results

Study selection

A systematic literature search was carried out, and 1,787 articles from the above-mentioned databases were initially retrieved. Next, 64 duplicate articles were removed, and after a screening of the titles and abstracts, 38 articles remained. A review of the bibliographies revealed no additional relevant articles. The full texts of the 38 screened articles were then reviewed, and 6 more articles were removed because they fell outside the area of research interest. For further details of our inclusion strategies, see *Figure 1*. Following a thorough and careful review of the full texts of the remaining articles, 32 studies were ultimately included in the meta-analysis.

Characteristics of the included literature

There was a total of 10,778 participants in the included studies of whom, 2,270 had cognitive defects. Most of the countries that applied prognostic models were in the United States, United Kingdom, and China, and had been published from 2016 to 2022 (Table S2). The diagnostic criteria and the grouping of different studies also differed (https://cdn.amegroups.cn/static/public/apm-22-1396-1.xlsx).

Characteristics of the included prediction models

The most commonly used predictors were neuroimaging, Minimum Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), age, sex, disease duration, and composite scores (Table S2). The modeling variables were mainly derived from the clinical features combined

with brain magnetic resonance imaging (MRI), which showed that radiomics had significant application value in the diagnosis of PD-CI.

Risk of bias assessment

The supplementary table (available online: https://cdn.amegroups.cn/static/public/apm-22-1396-2.xlsx) shows the risk of bias and assessment results for each research model based on the 4 aspects of PROBAST, and also provides an overall summary of the aspect assessment for the included articles. Collectively, almost all of the results for the models had a high risk of bias. Of the 51 prognostic models, 11 were validated. However, only 2 models had undergone external validation with an independent team. Given the defects caused by the original research, only 2 studies applied prognostic models for which external validation had been performed (*Figure 2*).

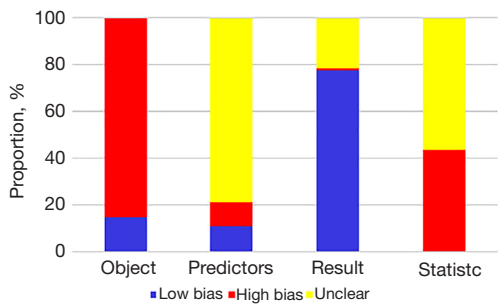

Figure 2 Bias risk assessment results for each machine-learning model.

Meta-analysis of prognostic models

Subsequently, 19 meta-analyses of the C-statistics were performed for the 51 prognostic models, and the total C-index values in the training and testing sets were 0.857 (0.842–0.873) and 0.845 (0.804–0.886), respectively. We conducted a subgroup analysis according to the type of machine learning (for further details, see *Table 1* and *Figure 3*). We also summarized the sensitivity and specificity of machine learning in PD-CI diagnosis. The meta-analysis results revealed that the sensitivity of the training set was 0.77 (95% CI: 0.72–0.81) and that of the testing sets was 0.85 (95% CI: 0.82–0.88), and the specificity of the training set was 0.83 (95% CI: 0.80–0.85), and that of the testing sets was 0.74 (95%

Table 1 C-statistics for 51 prognostic models and the total C-index in the training and testing sets

Model	Training sets		Testing sets	
	n	C-index (95% CI)	n	C-index (95% CI)
ANN	4	0.872 (0.810–0.934)	1	0.911 (0.839–0.983)
Boosting	4	0.840 (0.744–0.937)	2	0.770 (0.684–0.856)
Cox	3	0.783 (0.693–0.872)	3	0.819 (0.776–0.862)
DT	6	0.788 (0.713–0.863)	–	–
KNN	1	0.958 (0.929–0.987)	–	–
LDA	2	0.803 (0.773–0.834)	–	–
LR	9	0.907 (0.887–0.927)	2	0.926 (0.910–0.942)
NB	10	0.856 (0.819–0.892)	–	–
RF	7	0.865 (0.833–0.897)	3	0.809 (0.742–0.877)
SVM	13	0.882 (0.845–0.918)	3	0.850 (0.755–0.946)
Overall	51	0.857 (0.842–0.873)	14	0.845 (0.804–0.886)

ANN, artificial neural networks; Cox, Cox proportional-hazards model; DT, Decision Tree; KNN, K-Nearest Neighbor; LDA, Linear Discriminant Analysis; LR, logistic regression; NB, Naïve Bayes; RF, Random Forest; SVM, support vector machines.

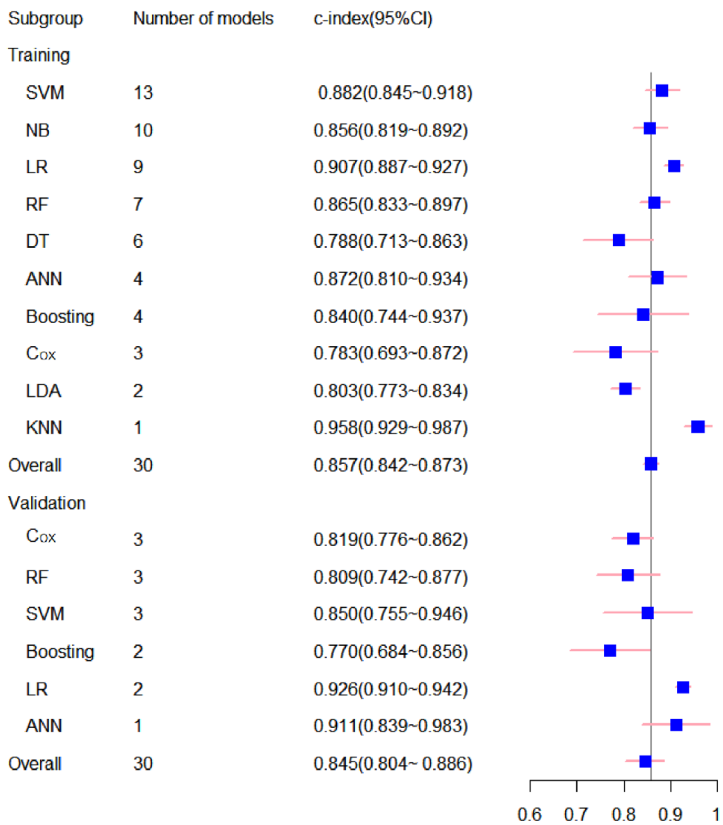

Figure 3 Forest plot of the c-index values. SVM, support vector machines; NB, Naïve Bayes; LR, logistic regression; RF, Random Forest; DT, Decision Tree; ANN, artificial neural networks; Cox, Cox proportional-hazards model; LDA, Linear Discriminant Analysis; KNN, K-Nearest Neighbor.

Table 2 The sensitivity and specificity of machine learning in PD-CI diagnosis (training sets)

Model	Training sets		Training sets	
	n	Sensitivity (95% CI)	n	Specificity (95% CI)
ANN	4	0.77 (0.68–0.84)	4	0.93 (0.89–0.95)
Boosting	9	0.66 (0.61–0.70)	9	0.79 (0.71–0.85)
RF	8	0.74 (0.68–0.79)	8	0.79 (0.74–0.84)
SVM	10	0.83 (0.72–0.90)	10	0.85 (0.81–0.89)
Overall	41	0.77 (0.72–0.81)	–	0.83 (0.80–0.85)

PD-CI, Parkinson's Disease-Cognitive Impairment; ANN, artificial neural networks; RF, Random Forest; SVM, support vector machines.

CI: 0.70–0.78). For further details, see *Tables 2,3* and *Figure 4*.

Discussion

This meta-analysis of 32 original studies indicated that machine learning could potentially be an ideal tool for predicting PD-CI, and the total C-index of all models was 0.857 (0.842–0.873). For PD patients with and without cognitive impairment, the overall models in this study had an ideal accuracy with a sensitivity and specificity >70%.

Table 3 The sensitivity and specificity of machine learning in PD-CI diagnosis (testing sets)

Model	Testing sets		Testing sets	
	n	Sensitivity (95% CI)	n	Specificity (95% CI)
RF	4	0.85 (0.79–0.89)	4	0.74 (0.70–0.78)
SVM	3	0.83 (0.71–0.90)	3	0.77 (0.65–0.86)
Boosting	2	0.82 (0.73–0.89)	2	0.76 (0.53–0.92)
ANN	1	1	1	0.6
Cox	1	0.87	1	0.72
Overall	11	0.85 (0.82–0.88)	–	0.74 (0.70–0.78)

PD-CI, Parkinson's Disease-Cognitive Impairment; RF, Random Forest; SVM, support vector machines; ANN, artificial neural networks; Cox, Cox proportional-hazards model.

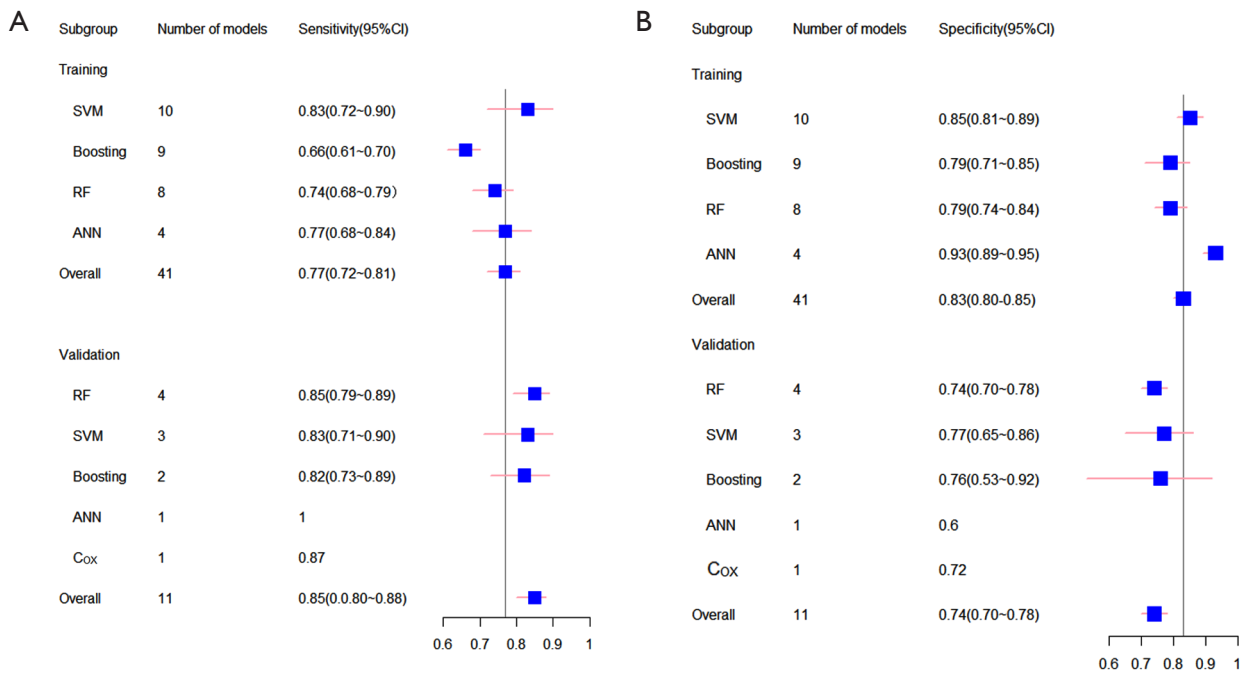

Figure 4 Forest plot of the sensitivity and specificity. (A) Forest plot of sensitivity; (B) Forest plot of specificity. SVM, support vector machines; RF, Random Forest; ANN, artificial neural networks; Cox, Cox proportional-hazards model.

In addition, the present study suggested that the accuracy of the testing sets was not significantly lower than that of the training set, which indicated that the machine-learning models had an ideal value in real world. Thus, machine learning may be applied as a potential tool for the identification of PD-CI.

At present, in the systematic review of machine learning for predicting PD, the applied fields, such as motor symptoms, pathology, and pathogenesis, have achieved good results (22,23). A similar investigation was conducted on the use of machine learning in the diagnosis of Alzheimer's disease (24,25). Inspired by this previous research, we examined the value of machine learning in predicting PD-CI.

In the included original studies, the main variables in the models were generally clinical features and neuroimaging.

In recent years, the PD patterns of cognitive neural substrates have been identified using MRI techniques, which can be applied as prediction tools in PD-CI detection; however, few studies have applied such techniques to validate the exact sensitivity and specificity of MRI techniques in predicting PD-CI (12). A previous review and meta-analysis noted that further investigations of potential predictors are needed using multi-modal MRI technology, targeted biomarkers for different cognitive domains, and predictive algorithms (26). The current research used machine learning to build a pre-diagnostic model that contained MRI and some other predictable elements, such as representative biomarkers, and cognitive domain tests (as necessary). This type of model should achieve more accurate results than using the above predictors without machine learning.

Currently, there are several cut-offs for PD-CI in neuropsychological examinations, and a few global scales for cognitive screening (15). Overall, the sensitivity and specificity of pre-diagnostic values using these diverse testing techniques are inadequate. Importantly, changes in PD-CI patients in terms of cognitive performance are largely restricted to certain relevant domains associated with human cognition, but may also include function alteration after long-term follow-up progression. Some researchers have indicated that speech issues appear during the transition to dementia in PD patients, especially in the presentation of problems in the comprehension and production of speech (27). However, these aspects have not been fully and intelligently characterized in PD, and current tests have only been designed to test the sentence comprehension and oral fluency of the subjects (28).

Many investigators have reported that the underlying neuropathology of certain speech problems associated with the temporal lobe and executive-frontal disorders explain speech problems (29). As such, the primary cause leading to disorders may be dopaminergic or cholinergic dysfunction in the described areas (30). Consequently, a combination of radiomics and other different types of markers (e.g., related biomarkers) may perform well, as they use multi-dimensional information. Further, several investigations have explored the combination of machine learning with the above indicators for the diagnosis of Alzheimer's disease, and reported an increase in the sensitivity and specificity of diagnosing Alzheimer's disease (25,31). Regrettably, almost no qualified studies that combine the above indicators based on machine learning for the pre-diagnosis of PD-CI have been conducted, but several recent studies have confirmed that neuroimaging and other sensitive predictors, such as quantitative electroencephalograms (qEEG), based on machine learning improve prognostic accuracy (32,33).

In summary, the diagnosis of PD-CI based on brain MRI and cognitive scale assessment tools has certain defects. We encourage and advocate for the application of machine learning. We undertook the first comprehensive and systematic analysis of the application of machine learning in PD-CI. Our findings may lead to advances in digital therapy in this field, and also provide theoretical evidence for the subsequent development of machine-learning models for the diagnosis of this disease.

However, the study also had some limitations. First, it included a variety of models, each of which had a different diagnostic performance. According to previous studies and analyses, PD-CI can be affected by education level and environment, which causes certain heterogeneity. Second, some of the models were only tested with small sample sizes. Third, due to the particularity of this disease, some the original studies were not multicenter studies. Fourth, there is no international consensus on the diagnosis of PD-CI, which also caused certain selective biases. Finally, since the progression of PD-CI is slow and heterogenic, we may need to establish a longitudinal multi-model to enhance the diagnosis accuracy.

Conclusions

Our systematic review showed that machine learning could be used as a prospective diagnostic tool for PD patients with early cognitive impairment, and our findings provide a theoretical basis for the development and update of relevant scoring systems in the future. However, given the high risk of bias in the modeling process, more large-scale, multicenter, and multi-ethnic studies need to be conducted in the future with more effective predictors, especially non-invasive or minimally invasive predictors, to enable the early identification and prediction of this disease.

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Footnote

Reporting Checklist: The authors have completed the

PRISMA-DTA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1396/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1396/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Literature search strategy

1.Pubmed

Search number	Query
#1	parkinson disease[MeSH Terms]
#2	"Parkinson Disease"[Title/Abstract] OR "Parkinson's Disease"[Title/Abstract] OR "Primary Parkinsonism"[Title/Abstract] OR "Parkinsonism, Primary"[Title/Abstract] OR "Paralysis Agitans"[Title/Abstract] OR "idiopathic parkinsonism"[Title/Abstract] OR "paralysis agitans"[Title/Abstract] OR "Parkinson dementia complex"[Title/Abstract] OR "Parkinsons disease"[Title/Abstract] OR "primary parkinsonism"[Title/Abstract]
#3	#1 OR #2
#4	machine learning[MeSH Terms]
#5	"machine learning"[Title/Abstract] OR "Transfer Learning"[Title/Abstract] OR "Deep learning"[Title/Abstract] OR "Learning, Transfer"[Title/Abstract] OR "Ensemble Learning"[Title/Abstract] OR "artificial intelligence"[Title/Abstract] OR "Prediction model"[Title/Abstract] OR "random forest"[Title/Abstract] OR "artificial neural network"[Title/Abstract] OR "ANN"[Title/Abstract] OR "Support vector machine"[Title/Abstract] OR "SVM"[Title/Abstract] OR "Gradient Boosting Machine"[Title/Abstract] OR "GBM"[Title/Abstract] OR "Nomogram"[Title/Abstract] OR "XGboost"[Title/Abstract] OR "Decision tree"[Title/Abstract] OR "Development and validation"[Title/Abstract] OR "Risk Prediction"[Title/Abstract] OR "Risk-Prediction"[Title/Abstract]
#6	#4 OR #5
#7	Cognitive Dysfunction[MeSH Terms]
#8	"Cognitive Dysfunction"[Title/Abstract] OR "Cognitive Dysfunctions"[Title/Abstract] OR "Dysfunction, Cognitive"[Title/Abstract] OR "Dysfunctions, Cognitive"[Title/Abstract] OR "Cognitive Impairments"[Title/Abstract] OR "Cognitive Impairment"[Title/Abstract] OR "Impairment, Cognitive"[Title/Abstract] OR "Impairments, Cognitive"[Title/Abstract] OR "Mild Cognitive Impairment"[Title/Abstract] OR "Cognitive Impairment, Mild"[Title/Abstract] OR "Cognitive Impairments, Mild"[Title/Abstract] OR "Impairment, Mild Cognitive"[Title/Abstract] OR "Impairments, Mild Cognitive"[Title/Abstract] OR "Mild Cognitive Impairments"[Title/Abstract] OR "Mild Neurocognitive Disorder"[Title/Abstract] OR "Disorder, Mild Neurocognitive"[Title/Abstract] OR "Disorders, Mild Neurocognitive"[Title/Abstract] OR "Mild Neurocognitive Disorders"[Title/Abstract] OR "Neurocognitive Disorder, Mild"[Title/Abstract] OR "Neurocognitive Disorders, Mild"[Title/Abstract] OR "Cognitive Decline"[Title/Abstract] OR "Cognitive Declines"[Title/Abstract] OR "Decline, Cognitive"[Title/Abstract] OR "Declines, Cognitive"[Title/Abstract] OR "Mental Deterioration"[Title/Abstract] OR "Deterioration, Mental"[Title/Abstract] OR "Deteriorations, Mental"[Title/Abstract] OR "Mental Deteriorations"[Title/Abstract] OR "cognitive defect"[Title/Abstract] OR "cognition disorder"[Title/Abstract] OR "cognition disorders"[Title/Abstract] OR "cognitive defects"[Title/Abstract] OR "cognitive deficit"[Title/Abstract] OR "cognitive disability"[Title/Abstract] OR "cognitive disorder"[Title/Abstract] OR "cognitive disorders"[Title/Abstract] OR "cognitive dysfunction"[Title/Abstract] OR "cognitive impairment"[Title/Abstract] OR "overinclusion"[Title/Abstract] OR "response interference"[Title/Abstract]
#9	#7 OR #8
#10	#3 AND #6 AND #9

2.Cochrane

Search number	Query
#1	MeSH descriptor: [Parkinson Disease] explode all trees
#2	('Parkinson Disease' OR 'Primary Parkinsonism' OR 'Parkinsonism, Primary' OR 'Paralysis Agitans' OR 'idiopathic parkinsonism' OR 'paralysis agitans' OR 'Parkinson dementia complex' OR 'Parkinsons disease' OR 'primary parkinsonism'):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Machine Learning] explode all trees

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#5	('machine learning' OR 'Transfer Learning' OR 'Deep learning' OR 'Learning, Transfer' OR 'Ensemble Learning' OR 'artificial intelligence' OR 'Prediction model' OR 'random forest' OR 'artificial neural network' OR 'ANN' OR 'Support vector machine' OR 'SVM' OR 'Gradient Boosting Machine' OR 'GBM' OR 'Nomogram' OR 'XGboost' OR 'Decision tree' OR 'Development and validation' OR 'Risk Prediction' OR 'Risk-Prediction'):ti,ab,kw
#6	#4 OR #5
#7	MeSH descriptor: [Cognitive Dysfunction] explode all trees
#8	'Cognitive Dysfunction' OR 'Cognitive Dysfunctions' OR 'Dysfunction, Cognitive' OR 'Dysfunctions, Cognitive' OR 'Cognitive Impairments' OR 'Cognitive Impairment' OR 'Impairment, Cognitive' OR 'Impairments, Cognitive' OR 'Mild Cognitive Impairment' OR 'Cognitive Impairment, Mild' OR 'Cognitive Impairments, Mild' OR 'Impairment, Mild Cognitive' OR 'Impairments, Mild Cognitive' OR 'Mild Cognitive Impairments' OR 'Mild Neurocognitive Disorder' OR 'Disorder, Mild Neurocognitive' OR 'Disorders, Mild Neurocognitive' OR 'Mild Neurocognitive Disorders' OR 'Neurocognitive Disorder, Mild' OR 'Neurocognitive Disorders, Mild' OR 'Cognitive Decline' OR 'Cognitive Declines' OR 'Decline, Cognitive' OR 'Declines, Cognitive' OR 'Mental Deterioration' OR 'Deterioration, Mental' OR 'Deteriorations, Mental' OR 'Mental Deteriorations' OR 'cognitive defect' OR 'cognition disorder' OR 'cognition disorders' OR 'cognitive defects' OR 'cognitive deficit' OR 'cognitive disability' OR 'cognitive disorder' OR 'cognitive disorders' OR 'cognitive dysfunction' OR 'cognitive impairment' OR 'overinclusion' OR 'response interference'):ti,ab,kw
#9	#7 OR #8
#10	#3 AND #6 AND #9

3.Embase

Search number	Query
#1	'parkinson disease'/exp
#2	'parkinson disease':ti,ab,kw OR 'parkinsonism, primary':ti,ab,kw OR 'idiopathic parkinsonism':ti,ab,kw OR 'paralysis agitans':ti,ab,kw OR 'parkinson dementia complex':ti,ab,kw OR 'parkinsons disease':ti,ab,kw OR 'primary parkinsonism':ti,ab,kw
#3	#1 OR #2
#4	'machine learning'/exp
#5	'machine learning':ti,ab,kw OR 'transfer learning':ti,ab,kw OR 'deep learning':ti,ab,kw OR 'learning, transfer':ti,ab,kw OR 'ensemble learning':ti,ab,kw OR 'artificial intelligence':ti,ab,kw OR 'prediction model':ti,ab,kw OR 'random forest':ti,ab,kw OR 'artificial neural network':ti,ab,kw OR 'ann':ti,ab,kw OR 'support vector machine':ti,ab,kw OR 'svm':ti,ab,kw OR 'gradient boosting machine':ti,ab,kw OR 'gbm':ti,ab,kw OR 'nomogram':ti,ab,kw OR 'xgboost':ti,ab,kw OR 'decision tree':ti,ab,kw OR 'development and validation':ti,ab,kw OR 'risk prediction':ti,ab,kw OR 'risk-prediction':ti,ab,kw
#6	#4 OR #5
#7	'cognitive defect'/exp
#8	'cognitive dysfunctions':ti,ab,kw OR 'dysfunction, cognitive':ti,ab,kw OR 'dysfunctions, cognitive':ti,ab,kw OR 'cognitive impairments':ti,ab,kw OR 'impairment, cognitive':ti,ab,kw OR 'impairments, cognitive':ti,ab,kw OR 'mild cognitive impairment':ti,ab,kw OR 'cognitive impairment, mild':ti,ab,kw OR 'cognitive impairments, mild':ti,ab,kw OR 'impairment, mild cognitive':ti,ab,kw OR 'impairments, mild cognitive':ti,ab,kw OR 'mild cognitive impairments':ti,ab,kw OR 'mild neurocognitive disorder':ti,ab,kw OR 'disorder, mild neurocognitive':ti,ab,kw OR 'disorders, mild neurocognitive':ti,ab,kw OR 'mild neurocognitive disorders':ti,ab,kw OR 'neurocognitive disorder, mild':ti,ab,kw OR 'neurocognitive disorders, mild':ti,ab,kw OR 'cognitive decline':ti,ab,kw OR 'cognitive declines':ti,ab,kw OR 'decline, cognitive':ti,ab,kw OR 'declines, cognitive':ti,ab,kw OR 'mental deterioration':ti,ab,kw OR 'deterioration, mental':ti,ab,kw OR 'deteriorations, mental':ti,ab,kw OR 'mental deteriorations':ti,ab,kw OR 'cognitive defect':ti,ab,kw OR 'cognition disorder':ti,ab,kw OR 'cognition disorders':ti,ab,kw OR 'cognitive defects':ti,ab,kw OR 'cognitive deficit':ti,ab,kw OR 'cognitive disability':ti,ab,kw OR 'cognitive disorder':ti,ab,kw OR 'cognitive disorders':ti,ab,kw OR 'cognitive dysfunction':ti,ab,kw OR 'cognitive impairment':ti,ab,kw OR 'overinclusion':ti,ab,kw OR 'response interference':ti,ab,kw
#9	#7 OR #8
#10	#3 AND #6 AND #9

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4.Web of science

Search number	Query
#1	Parkinson Disease (Topic) OR Parkinson's Disease (Topic) OR Primary Parkinsonism (Topic) OR Parkinsonism, Primary (Topic) OR Paralysis Agitans (Topic) OR idiopathic parkinsonism (Topic) OR paralysis agitans (Topic) OR Parkinson dementia complex (Topic) OR Parkinsons disease (Topic) OR primary parkinsonism (Topic)
#2	machine learning (Topic) OR Transfer Learning (Topic) OR Deep learning (Topic) OR Learning, Transfer (Topic) OR Ensemble Learning (Topic) OR artificial intelligence (Topic) OR Prediction model (Topic) OR random forest (Topic) OR artificial neural network (Topic) OR ANN (Topic) OR Support vector machine (Topic) OR SVM (Topic) OR Gradient Boosting Machine (Topic) OR GBM (Topic) OR Nomogram (Topic) OR XGboost (Topic) OR Decision tree (Topic) OR Development and validation (Topic) OR Risk Prediction (Topic) OR Risk-Prediction (Topic)
#3	Cognitive Dysfunction (Topic) OR Cognitive Dysfunctions (Topic) OR Dysfunction, Cognitive (Topic) OR Dysfunctions, Cognitive (Topic) OR Cognitive Impairments (Topic) OR Cognitive Impairment (Topic) OR Impairment, Cognitive (Topic) OR Impairments, Cognitive (Topic) OR Mild Cognitive Impairment (Topic) OR Cognitive Impairment, Mild (Topic) OR Cognitive Impairments, Mild (Topic) OR Impairment, Mild Cognitive (Topic) OR Impairments, Mild Cognitive (Topic) OR Mild Cognitive Impairments (Topic) OR Mild Neurocognitive Disorder (Topic) OR Disorder, Mild Neurocognitive (Topic) OR Disorders, Mild Neurocognitive (Topic) OR Mild Neurocognitive Disorders (Topic) OR Neurocognitive Disorder, Mild (Topic) OR Neurocognitive Disorders, Mild (Topic) OR Cognitive Decline (Topic) OR Cognitive Declines (Topic) OR Decline, Cognitive (Topic) OR Declines, Cognitive (Topic) OR Mental Deterioration (Topic) OR Deterioration, Mental (Topic) OR Deteriorations, Mental (Topic) OR Mental Deteriorations (Topic) OR cognitive defect (Topic) OR cognition disorder (Topic) OR cognition disorders (Topic) OR cognitive defects (Topic) OR cognitive deficit (Topic) OR cognitive disability (Topic) OR cognitive disorder (Topic) OR cognitive disorders (Topic) OR cognitive dysfunction (Topic) OR cognitive impairment (Topic) OR overinclusive (Topic) OR response interference (Topic)
#4	#1 AND #2 AND #3

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Table S2 Characteristics of the included literature

No.	Title	First author	Year	Country	Research type	Patient origin	Total number	Validation	Missing value	Variable selection methods	Model
1	Topologically convergent and divergent morphological gray matter networks in early-stage Parkinson's disease with and without mild cognitive impairment	Xueling Suo (1)	2021	China	case-control	Single center	70	NA	NA		SVM
2	Exploring Parkinson's Disease Predictors based on Basic Intelligence Quotient and Executive Intelligence Quotient	Haewon Byeon (2)	2021	Korea	case-control	Single center	368	5-fold cross-validation	NA		LR/SVM/RF
3	Predicting motor, cognitive & functional impairment in Parkinson's	Christine Lo (3)	2019	UK	case-control	Single center	110	10-fold cross-validation	NA		RF/NB/LDA
4	Predicting early cognitive decline in newly-diagnosed Parkinson's patients:A practical model	Olivia Hogue (4)	2018	USA	case-control	PPMI database	351	NA	NA	Stepwise regression	LR
5	Optimization of cognitive assessment in Parkinsonisms by applying artificial intelligence to a comprehensive screening test	Paola Ortelli (5)	2022	Italy	case-control	Multicenter	500	10-fold cross-validation	NA	Single-factor ROC analysis	LR
6	In vivo cholinergic basal forebrain atrophy predicts cognitive decline in de novo Parkinson's disease	Nicola J. Ray (6)	2018	UK	case-control	Multicenter	61	Random Sampling	NA	The decrease in the GINI coefficients.	RF/NLG/NB
7	Multi-Class Diagnosis of Neurodegenerative Diseases: A Neuroimaging Machine Learning based Approach	Gurpreet Singh, Meet Vadera (7)	2019	USA	case-control	Multicenter	2540	10-fold cross-validation	NA	Fischer Discriminant Ratio scores	LR
8	Machine learning-based prediction of cognitive outcomes in de novo Parkinson's disease	Joshua Harvey, BSc (8)	2022	UK	case-control	PPMI1 database	209	10-fold cross-validation	excluded 175 cases showing missing values or indeterminate diagnoses.	Recursive feature elimination (RFE) /Shapley values	RF/SVM/ElasticNet
9	Machine learning trained with quantitative susceptibility mapping to detect mild cognitive impairment in Parkinson's disease	Haruto Shibata (9)	2022	Japan	case-control	Multicenter	163	10-fold cross-validation	NA		RF/XGBoost
10	Learning Classification Models of Cognitive Conditions from Subtle Behaviors in the Digital Clock Drawing Test	William Souillard-Mandar (10)	2016	USA	case-control	Multicenter	653	5-fold cross-validation	NA		SVM/RF/CART/ C4.5/XGBoost/LR
11	Is the Random Forest Algorithm Suitable for Predicting Parkinson's Disease with Mild Cognitive Impairment out of Parkinson's Disease with Normal Cognition?	Haewon Byeon (11)	2020	Korea	case-control	Registered Database	368	NA	NA		RF/DT
12	Identification of metabolic correlates of mild cognitive impairment in Parkinson's disease using magnetic resonance spectroscopic imaging and machine learning	Sevim Cengiz (12)	2022	Turkey	case-control	Single center	76	NA	NA		XGBoost/SVM
13	Gait-Based Machine Learning for Classifying Patients with Different Types of Mild Cognitive Impairment	Pei-Hao Chen1,2 (13)	2020	China	case-control	Single center	81	NA	The MATLAB package was used to perform SVR to address the missing data;	SVM	SVM
14	Factor analysis-derived cognitive profile predicting early dementia conversion in PD	Seok Jong Chung, (14)	2020	Korea	case-control	Single center	350	5-fold cross-validation	NA	Factor analysis/Cox regression	Cox
15	Electroencephalography-Based Machine Learning for Cognitive Profiling in Parkinson's Disease: Preliminary Results	Nacim Betrouni, (15)	2019	France	case-control	Single center	118	10-fold cross-validation	NA	Analyses of variance	SVM/KNN
16	Discriminating cognitive status in Parkinson's disease through functional connectomics and machine learning	Alexandra Abós (16)	2017	Spain.	case-control	Single center	108	10-fold cross-validation	NA		SVM
17	Cortical Thickness from MRI to Predict Conversion from Mild Cognitive Impairment to Dementia in Parkinson Disease: A Machine Learning–based Model	Na-Young Shin (17)	2021	Korea	case-control	Single center	141	Random Sampling	NA		RF/SVM
18	Cognitive signature of brain FDG PET based on deep learning:domain transfer from Alzheimer's disease to Parkinson's disease	Hongyoon Choi (18)	2020	Korea	case-control	Single center	62	NA	NA		RF/NB/LDA
19	Best early-onset Parkinson dementia predictor using ensemble learning among Parkinson's symptoms, rapid eye movement sleep disorder, and neuropsychological profile	Haewon Byeon (19)	2020	Korea	case-control	Registered Database	368	NA	NA		CNN
20	Application of Machine Learning Technique to Distinguish Parkinson's Disease Dementia and Alzheimer's Dementia: Predictive Power of Parkinson's Disease-Related Non-Motor Symptoms and Neuropsychological Profile	Haewon Byeon (20)	2020	Korea	case-control	Registered Database	368	10-fold cross-validation+Random Sampling	NA	Univariate	RF
21	An SBM-based machine learning model for identifying mild cognitive impairment in patients with Parkinson's disease	Jiahui Zhang (21)	2020	China	case-control	Single center	113	5-fold cross-validation	NA		SVM
22	An individualized prediction of time to cognitive impairment in Parkinson's disease: A combined multi-predictor study	Chunyan Tang (22)	2021	China	case-control	PPMI1 database	108	4-fold cross-validation	NA	LASSO	LR
23	Accuracy of Machine Learning Using the Montreal Cognitive Assessment for the Diagnosis of Cognitive Impairment in Parkinson's Disease	Junbeom Jeon (23)	2022	Korea	case-control	PPMI1 database	397	Random Sampling	exclude：SGDS results missing (n = 4) 3) MDS-UPDRS Score missing (n = 7)	Univariate	SVM/RF/LR
24	A Novel Machine Learning Algorithm Predicts Dementia With Lewy Bodies Versus Parkinson's Disease Dementia Based on Clinical and Neuropsychological Scores	Anastasia Bougea, (24)	2022	Greece	case-control	Multicenter	140	NA	NA		K-NNs/SVM/NB/LR
25	Brain connectivity markers in advanced Parkinson's disease for predicting mild cognitive impairment	Hai Lin (25)	2021	China	case-control	PPMI1 database	179	10-fold cross-validation	NA		RF
26	Distinct manifestation of cognitive deficits associate with different resting-state network disruptions in non-demented patients with Parkinson's disease	Kazuya Kawabata (26)	2018	Japan	case-control	Single center	96	Random Sampling	NA		SVM
27	Clinical variables and biomarkers in prediction of cognitive impairment in patients with newly diagnosed Parkinson's disease: a cohort study	Anette Schrag (27)	2017	London	case-control	PPMI1 database	568	10-fold cross-validation+Random Sampling	We repeated analyses by imputing missing predictor variable data with means. These missing data did not alter the overall results of any analysis (data not shown).		LR
28	Combining quantitative susceptibility mapping to radiomics in diagnosing Parkinson's disease and assessing cognitive impairment	Jin Juan Kang (28)	2022	China	case-control	Single center	149	Random Sampling	NA	LASSO	LR/SVM
29	Development and Validation of a Prognostic Model for Cognitive Impairment in Parkinson's Disease With REM Sleep Behavior Disorder	Fangzheng Chen (29)	2021	China	case-control	Single center	338	Random Sampling	NA		LR
30	Identifying Parkinson's disease with mild cognitive impairment by using combined MR imaging and electroencephalogram	Jiahui Zhang (30)	2021	China	case-control	Single center	113	Random Sampling	NA	Univariate analysis	SVM
31	Plasma extracellular vesicles tau and β - amyloid as biomarkers of cognitive dysfunction of Parkinson's disease	Chen- Chih Chung (31)	2021	China	case-control	Single center	162	4-fold cross-validation+Random Sampling	NA	Univariate analysis	ANN
32	Prediction of cognition in Parkinson's disease with a clinical–genetic score: a longitudinal analysis of nine cohorts	Ganqiang Liu (32)	2017	USA	case-control	Multicenter	1350	NA	NA	The lowest Akaike information criterion	Cox

note: ANN, artificial neural networks; Cox, cox proportional-hazards model; DT, Decision Tree; KNN, K-Nearest Neighbor; LDA, Linear Discriminant Analysis; LR, logistic regression; NB, Naïve Bayes; RF, Random Forest; SVM, support vector machines; NA, not applicable.