



Quality assessment of radiomics models in carotid plaque: a systematic review

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Background: Although imaging techniques provide information about the morphology and stability of carotid plaque, they are operator dependent and may miss certain subtleties. A variety of radiomics models for carotid plaque have recently been proposed for identifying vulnerable plaques and predicting cardiovascular and cerebrovascular diseases. The purpose of this review was to assess the risk of bias, reporting, and methodological quality of radiomics models for carotid atherosclerosis plaques.

Methods: A systematic search was carried out to identify available literature published in PubMed, Web of Science, and the Cochrane Library up to March 2023. Studies that developed and/or validated machine learning models based on radiomics data to identify and/or predict unfavorable cerebral and cardiovascular events in carotid plaque were included. The basic information of each piece of included literature was identified, and the reporting quality, risk of bias, and radiomics methodology quality were assessed according to the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) checklist, the Prediction Model Risk of Bias Assessment Tool (PROBAST), and the radiomics quality score (RQS), respectively.

Results: A total of 2,738 patients from 19 studies were included. The mean overall TRIPOD adherence rate was 66.1% (standard deviation 12.8%), with a range of 45–87%. All studies had a high overall risk of bias, with the analysis domain being the most common source of bias. The mean RQS was 9.89 (standard deviation 5.70), accounting for 27.4% of the possible maximum value of 36. The mean area under the curve for diagnostic or predictive properties of these included radiomics models was 0.876 ± 0.09 , with a range of 0.741–0.989.

Conclusions: Radiomics models may have value in the assessment of carotid plaque, the overall scientific validity and reporting quality of current carotid plaque radiomics reports are still lacking, and many barriers must be overcome before these models can be applied in clinical practice.

Keywords: Machine learning; carotid artery; atherosclerosis (AS); quality improvement

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Introduction

Stroke is one of the most serious diseases threatening human health and is the second leading cause of death around the world after ischemic heart disease (1). In China, it is the most common cause of death and disability, with a standardized prevalence ranging from 7.2% to 4.25% (2,3); meanwhile, in the United States, the mortality rate among Americans 35 to 64 years of age has increased over the past two decades (4,5). Stroke is thus a massive health and economic burden for global society. Carotid atherosclerosis (CAS) is a chronic, progressive disease characterized by focal fibrosis, lipid accumulation, and plaque formation. It causes about 7–18% of ischemic strokes (6) and affects about one-quarter of the population (7). Unfortunately, therapy options for individuals with severe CAS remain unsatisfactory (8–10); hence, risk stratification and individualized treatment of these patients are critical. For high-risk patients, combining strict best medical therapy (BMT) with aggressive revascularization therapy can prevent the occurrence of ischemic events. In contrast, BMT alone may be a preferable option for low-risk patients, as the danger of perioperative stroke and death can also be avoided. As a result, the 2017 European Society of Vascular Surgery Clinical Practice Guidelines stated that there is a need for the development of clinical and imaging algorithms to identify patients with high-risk CAS who require revascularization therapy (11).

Radiomics is an emerging multidisciplinary intersectional research field that integrates digital image information, statistics, artificial intelligence, machine learning, and deep learning methods to transform traditional radiological image information into comprehensive features for quantitative research. It has exhibited exciting potential for oncological diagnosis, differential diagnosis, and prognostic prediction (12) and has opened new possibilities in atherosclerosis (AS) research (13,14). An increasing number of studies have implemented radiomics algorithms preoperatively for AS risk stratification and prognostic assessment, indicating that radiomics-based features have greater potential and lower heterogeneity than do traditional radiological methods (15), especially in coronary artery diseases (16,17). Since radiomics models are predictive, focusing solely on statistical metrics such as the area under the receiver operating characteristic curve (AUC) when evaluating a model seems arbitrary. That is to say, the risk of bias in radiomics models should be assessed before applying the promising results of these earlier studies into actual clinical practice. A model, even if it has a high AUC, is not reliable

if it has a high risk of bias in the development and validation processes. A rigorous and transparent study process accompanied by standardized reporting can improve the reproducibility and reliability of radiomics models. Several recent studies have attempted to evaluate the prediction power and the methodological quality of radiomics models based on the radiomics quality score (RQS) tool (18,19), assessing the risk of bias using the Prediction Model Risk of Bias Assessment Tool (PROBAST) (20) and investigating the report quality of the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Diagnosis) checklist (21). In our previous study, radiomics models for CAS had low RQS scores (19); however, there are no published results concerning the use of PROBAST or TRIPOD for CAS. Therefore, in this review, we aimed to analyze the current status of radiomics research related to diagnosing and/or predicting CAS by combining these three above-mentioned tools (TRIPOD, PROBAST, and RQS) to evaluate their scientific reporting quality, risk of bias, and radiomics methodological quality. We present this article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-23-712/rc>).

Methods

Search strategy

We systematically searched PubMed, Web of Science, and the Cochrane Library for articles published in English up to March 2023. We searched the titles, abstracts, and keywords of literature using the following search phrases: “radiomics/radiomic/texture/textural”, “carotid arteries”, and “atherosclerosis/atherosclerotic plaque/carotid stenosis”. Keywords in different groups were linked together by “AND”, whereas those in the same group were combined using “OR”. [Table S1](#) provides the search details for each database. The protocol of this systematic review has been registered in PROSPERO (International Prospective Register of Systematic Reviews; registration No. CRD42023407441).

Study selection

Literature was screened according to the inclusion and exclusion criteria of this review ([Table 1](#)). Two reviewers (S.L. and S.Z.) independently screened the titles and abstracts

Table 1 Inclusion and exclusion criteria according to the PICO model

Items	Inclusion criteria	Exclusion criteria
Population	Human participants (adults, age ≥ 18 years) with carotid plaque or carotid atherosclerosis	Nonhuman participants (animals or modeling data generated algorithmically)
Intervention	Assess application of radiomics or texture analysis to patient data; develop a diagnostic or prognostic model by using radiomics features with or without other features	Deep-learning research without any texture feature in the model; assess the predictive value of a single feature without any prediction model
Comparison	Human clinicians or previously validated models	NA
Outcome	Model performance	NA
Study design	Published peer-reviewed scientific reports (prospective or retrospective) published in English until the search date	Letters, reviews, case reports, abstracts, editorial, or other informal publication types

PICO, patient/population, intervention, comparison and outcomes; NA, not applicable.

for initial selection and then performed a full-text review of each paper to identify the studies eligible for final analysis. Any disagreements were resolved via mediation by a senior reviewer (L.P.L.). Reference lists of the eligible studies and pre-existing systematic reviews/meta-analyses were also searched manually to identify any potentially eligible studies.

Data extraction

For each study, information including first author, year of publication, country, study type, population size, mean age, history, imaging modality, number of candidate and final predictors, modeling method, predictive performance, and validation methods was extracted from the full text. If there were multiple prediction models in a study, the one that performed best in the test or training group was selected.

TRIPOD, consisting of 22 main criteria with 37 items, is a guideline specifically devised for reporting studies that developed or validated multivariate predictive models and was used in our review to assess the reporting quality of the included studies (22). Although both the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) and PROBAST assess the risk of bias and applicability, the former tends to focus on diagnostic performance rather than predictive value, whereas the latter focuses on primary studies that developed and/or validated multivariable prediction models for diagnosis or prognosis. Since radiomics models have predictive values, we used PROBAST (23) to assess the concerns regarding the applicability and risk of bias of these included studies. Finally, the methodological quality of the included studies was evaluated with the RQS tool, which comprises 16

different criteria within six categories. Each item has a score range from -5 to 7 , giving a total score of 36 points (100%) (24). Extraction and assessment were completed by two reviewers (S.L. and S.Z.), and any discrepancies were resolved via discussion. The details and description of these 3 evaluation methods are table available at <https://cdn.amegroups.com/static/public/qims-23-712-1.xls>.

Statistical analysis

The extracted information of each study was entered into Microsoft Excel and computed with internal Excel tools. Descriptive statistics were calculated as the mean and SD for continuous variables and as frequencies and rates for categorical data. The overall TRIPOD adherence rate was statistically and numerically explained (adherence rate $\leq 33.3\%$, poor; $33.3\% < \text{adherence rate} \leq 66.7\%$, moderate; adherence rate $> 66.7\%$, good) (20). We did not undertake meta-analysis due to the high heterogeneity of the multiple variables and classifiers used in the final modeling. SPSS 25 (IBM Corp.) was used to perform statistical analyses.

Results

Literature selection

After implementation of the search strategy, 406 studies were initially identified. Following removal of 229 duplicates, 174 studies were screened for titles and abstracts; of these, 24 inappropriate types of publication and 89 studies that were irrelevant to the purpose of this review were excluded through more detailed assessment. Finally, a full-text screening identified 19 studies that met the

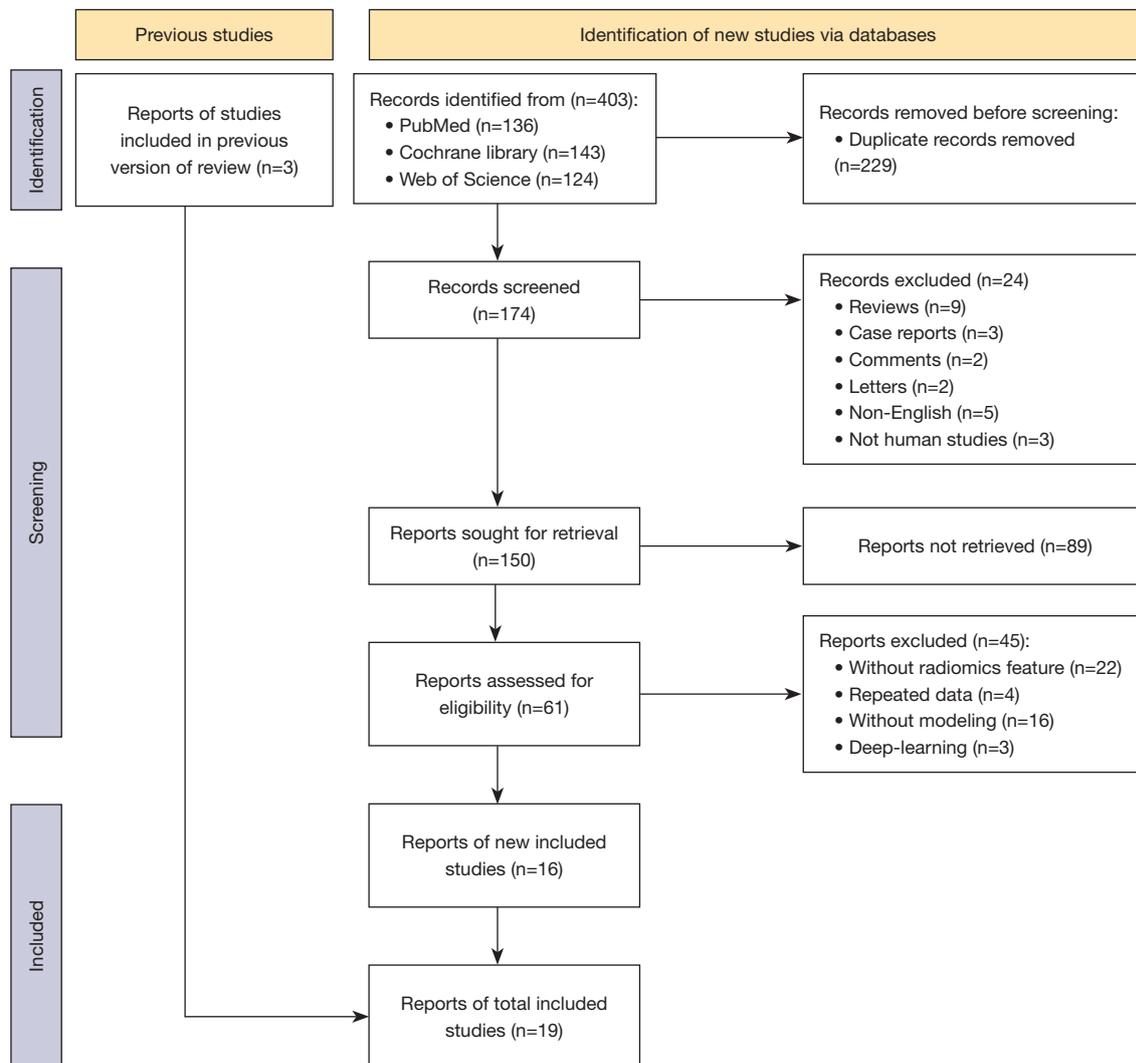


Figure 1 Flowchart of study selection under the Preferred Items for Systematic Reviews and Meta-Analyses checklist.

inclusion criteria for this review (25-43) (*Figure 1*).

General characteristics

Almost all studies (18/19, 94.7%) were single-center research published between July 2014 and January 2023, of which 84.2% (16/19) were published within the past 3 years. Only 1 study was prospectively designed (32). The majority of study participants were Chinese (12/19, 63.1%), followed by Italian (3/19, 15.8%) and British (2/19, 10.5%). Overall, 2,738 patients (1,706 males) were enrolled, with population sizes ranging from 21 to 548 (mean 144), and the mean age was 66.02 ± 9.52 years. Among the included studies, 7 (36.8%) had fewer than

100 participants. Computed tomography angiography (CTA) was the most prevalent imaging modality ($n=7$, 36.8%), followed by ultrasonography (US) ($n=6$, 31.5%); computed tomography (CT), high resolution magnetic resonance imaging (HRMRI), 3D HRMRI, MRI, 3D US, and positron emission tomography CT (PET/CT) were the other modalities used ($n=1$, 5%). Three kinds of features, including radiomics, conventional radiologic, and clinical variables, were used as candidate predictors for further selection and modeling, with the number of candidate features ranging from 2 to 4,198 (mean 768). Least absolute shrinkage and selection operator regression, logistic regression, and support vector machine were common classifiers for the final model. For predictive power, the

mean AUC of the final models in training group was 0.876 ± 0.09 , ranging from 0.741 to 0.989. Internal validation was performed in 14 studies (25-27,29,32-38,40,41,43), and 1 study employed external validation (42), but only 12 studies (25,26,29,32-34,36-38,40,41,43) reported the AUCs of the validation groups, ranging from 0.73 to 0.986. Model calibration was investigated in 7 studies (36.8%) and demonstrated good calibration performance (25,30,32,37,40,42,43).

Through radiomics or texture analysis, 10 studies tended to classify unstable or risk plaques (25,27,29,32,33,39-43). Moreover, 5 studies focused on predicting unfavorable cerebral and cardiovascular events (28,35-38), 2 on evaluating stenosis or in-stent restenosis (26,30), 1 on assessing the robustness of radiomics features (34), and 1 on evaluating the relationship between glycated hemoglobin and ultrasound plaque textures (31). The details are shown in *Table 2*.

Quality of reporting

The quality of reporting for included studies from the TRIPOD checklist is shown in *Figure 2*. The mean overall TRIPOD adherence rate was 66.1% (SD 12.8%), with a range of 45% to 87%. Of the 19 studies, 18 were model development studies, and only 1 aimed to develop and externally validate the same model (42). Of the 31 TRIPOD items, 8 (3a, 3b, 4a, 6a, 7a, 14a, 18, 19b) were completely described in all studies, 11 (4b, 5b, 5c, 8, 10a, 10b, 11, 14, 20, 21, 22) were specified in more than 60% of the studies, the remaining 9 (5a, 6b, 7b, 9, 10d, 13a, 15a, 15b, 16) were described in fewer than 50% of the studies. Notably, 3 items (1, 2, 13b) were poorly represented in all studies.

For domain “Title and abstract”, there was no study that reported the type of study (development or validation of a model) in item 1 or the information regarding the data sources, study settings, and model calibration results in item 2. Moreover, 9 studies reported blind outcome assessments, whereas blind predictors assessment (item 7b) was presented in another 9 studies. Only 1 study described the details for managing data (item 9) (38). No study reported the number of participants with missing data for predictors (item 13b). For model performance, 18 studies calculated the concordance index or AUC and other performance parameters such as sensitivity and specificity. Only 1 study described the full prediction model (36), and 8 studies used a nomogram to explain how the models generated personalized predictions (item 15b). Finally, 2 studies failed

to discuss the implications for further research (33,36), and appendix information was not available in 7 studies (26,27,30,31,35,37,39).

Risk of bias

Generally, the overall risk of bias was high for all studies, especially in “Analysis” category (*Figure 3A*). The major source of bias stemmed from signaling question 4.1, with no study having reasonable number of participants. All studies exhibited a low events per variable (EPV) value due to the large amount of candidate features and the limited carotid plaque samples. Regarding missing data, 12 studies conducted complete-case analysis and manually eliminated individuals without satisfactory images or clinical data or those who were lost to follow-up (25,26,28-30,32,36-41). In contrast, 7 studies did not describe how missing data were handled or the analytical procedures used to assess missing data (27,31,33-35,42,43), 4 studies lacked validation (28,30,31,39), and 2 studies had a high risk of bias in domain 1 for the stated inappropriate inclusion or exclusion criteria (33,39). The time interval between predictor assessment and outcome determination was unclear in 6 studies (25,30,31,35,40,42). Of note, the overall risk of applicability was low: only 2 studies (33,39) had a high risk in the participant domain, and 6 studies (25,27,30,31,35,42) had an unclear risk in the outcome domain (*Figure 3B*).

RQS results

The lowest RQS score was -2 points while the highest score was 22 points, with an average RQS score of 9.89 (± 5.70), which is equal to 27.4% of the total possible points achievable. Approximately 63.1% (12/19) of studies received 10 to 20 points, accounting for 27.8% to 55.6% of the maximum score. Among the 16 RQS components, 4 were underutilized in all studies: phantom study, imaging at multiple time points, cost-effectiveness analysis, and open science and data. Image protocols in all studies were well-documented without any public sources, and discrimination statistics were well reported with no resample method; therefore, each study was scored 1 point in item 1, and 9. A proportion of 68.4% (13/19) of the studies mentioned 2 physicians who segmented the regions of interest to evaluate the stability and repeatability of texture features. Two studies did not take any measurements to reduce the number of retrieved features (28,39), while another two studies only used radiomics features in their candidate

Table 2 The general characteristics of the included studies

Study	Country	Study design	No. of patients	Age, mean ± SD, years	Males	Participant type	Modality	Candidate features (RF/TRF/CF)	Modeling method	No. of features in the final model	AUC in training set (95% CI)	Validation and method	Validation performance (95% CI)
Chen et al., 2022 (24)	China	R	115	51.38±13.32	91	≥30% stenosis	HRMRI	1,130 (1,121/2/7)	LASSO, LR	8	0.93 (0.88–0.98)	Internal, 10-FCV	0.91 (0.81–1.00)
Cheng et al., 2022 (25)	China	R	221	66.89±8.07	186	Carotid endarterectomy	CTA	2,134 (2,107/10/17)	Cox, LASSO	6	0.88 (0.82–0.95)	Internal, 5-FCV	0.83 (0.74–0.91)
Cilla et al., 2022 (26)	Italy	R	30	72.96	19	>70% stenosis	CTA	230 (230/0/0)	LR, SVM, CART	2	0.99 (NA)	Internal, 5-FCV	NA
Colombi et al., 2021 (27)	Italy	R	172	77	112	Underwent carotid artery stenting	CTA	20 (2/9/9)	LR	3	0.79 (0.73–0.85)	NA	NA
Dong et al., 2022 (28)	China	R	120	66.68±7.75	100	≥50% stenosis	CTA	2,129 (2,107/8/14)	LR, SVM, SGBBOOST	20	0.86 (0.78–0.93)	Internal, 5-FCV	0.85 (NA)
Ebrahimian et al., 2022 (29)	USA	R	85	73±10	56	Suspected or known stenosis	US	78 (74/0/4)	LR	10	0.94 (NA)	NA	NA
Huang et al., 2016 (30)	China	R	136	68.6±8.86	NA	Carotid plaques	US	318 (300/2/16)	Linear regression	12	0.83 (NA)	NA	NA
Huang et al., 2022 (31)	China	P	548	62±10	373	Carotid plaque	US	124 (107/17/10)	LASSO, LR	4	0.93 (0.90–0.96)	Internal, randomly	0.912 (0.87–0.96)
Kafouris et al., 2021 (32)	France	R	21	70.43±7	18	High-grade stenosis	¹⁸ F-FDG PET	67 (67/0/0)	LR	1	0.97 (NA)	Internal, 200 bootstrap	0.87 (NA)
Le et al., 2021 (33)	UK	R	41	63.47±8.89	32	Carotid artery-related stroke or TIA	CTA	96 (93/3/0)	LASSO, SVM, decision tree, random forest	3	NA	Internal, 5-FCV	0.73±0.09
Lo et al., 2022 (34)	China	R	177	61.5	89	Stroke	CCD	49 (49/0/0)	LR, SVM,	11	0.94 (NA)	Internal, LOOCV	NA
van Engelen et al., 2014 (35)	Netherlands	R	298	70.45	110	Plaque area between 40–600 mm ²	3D US	402 (376/3/23)	Cox	8	0.78 (NA)	Internal, 10-FCV	0.94 (0.86–1.00)
Wang et al., 2022 (36)	China	Cohort	105	63.4	73	CAD	US	883 (851/11/21)	LASSO, LR	11	0.741 (0.65–0.84)	Internal, 10-FCV	0.94 (0.86–1.00)
Xia et al., 2023 (37)	China	R	179	65.4	119	30–50% stenosis	CTA	142 (129/0/13)	XGBoost, KNN, SVM, LR	11	0.98 (0.98–0.99)	Internal, 5-FCV	0.88 (0.79–0.98)
Zaccagna et al., 2021 (38)	UK	R	24	63±10	14	Carotid atherosclerosis	CT	25 (6/6/13)	NA	6	0.81 (NA)	NA	NA
Zhang et al., 2022 (39)	China	Case-control	150	61.7±10	120	Atherosclerotic plaque	US	331 (303/4/24)	LASSO, LR	8	0.88 (NA)	Internal, 10-FCV	0.87
Zhang et al., 2021 (40)	China	R	162	66.8±7.35	148	>30% stenosis	MRI	802 (788/8/6)	LASSO, LR	33	0.99 (NA)	Internal, 1000 Bootstrap	0.99
Zhang et al., 2022 (41)	China	R	64	60.9±10.3	46	Carotid atherosclerosis	CTA	1,414 (1,409/4/11)	LASSO, LR	9	0.743 (0.65–0.84)	External, 5-FCV	0.81 (0.66–0.96)
Zhang et al., 2023 (42)	China	R	90	/	NA	50% stenosis	3D-HRMRI	4,188 (4,170/4/24)	LASSO, LR	17	0.96 (0.92–0.99)	Internal, 5-FCV	0.86 (0.72–1.00)

RF/TRF/CF, radiomics feature/traditional radiological feature/clinical feature; AUC, area under the curve; CI, confidence interval; R, retrospective study; HRMRI, high-resolution magnetic resonance; LASSO, least absolute shrinkage and selection operator; LR, logistic regression; FCV, folds cross-validation; CTA, computed tomography angiography; SVM, support vector machine; CART, classification and regression trees; US, ultrasonography; NA, not available; P, prospective study; TIA, transient ischemic attack; ¹⁸F-FDG PET, fluorine-18 fluorodeoxyglucose positron emission tomography; UK, United Kingdom; CCD, carotid color doppler; LOOCV, leave-one-out cross-validation; KNN, k-nearest neighbor; CAD, coronary artery disease.

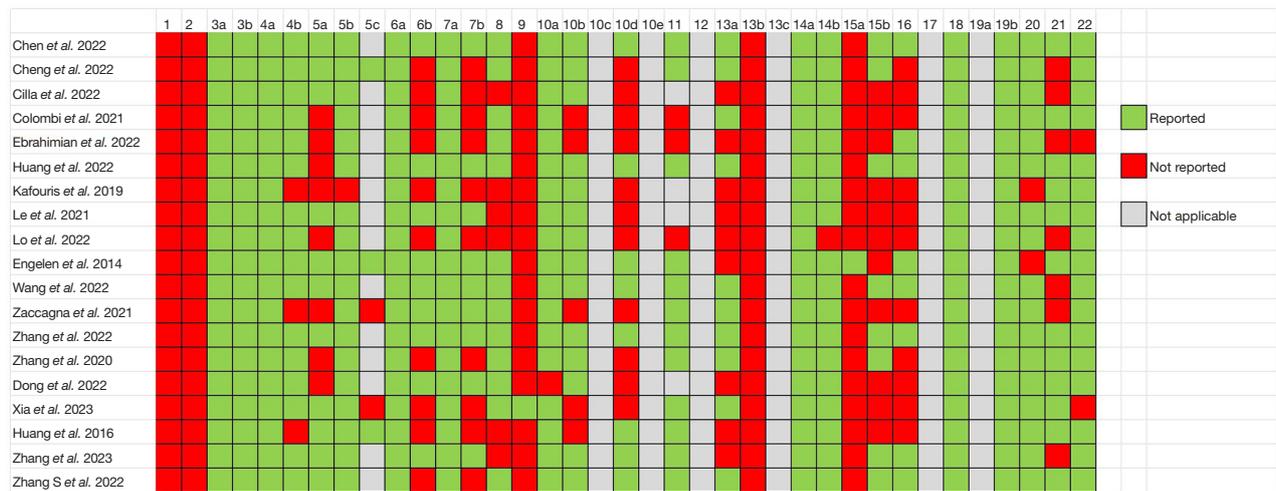


Figure 2 The quality of reporting evaluated with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Diagnosis checklist.

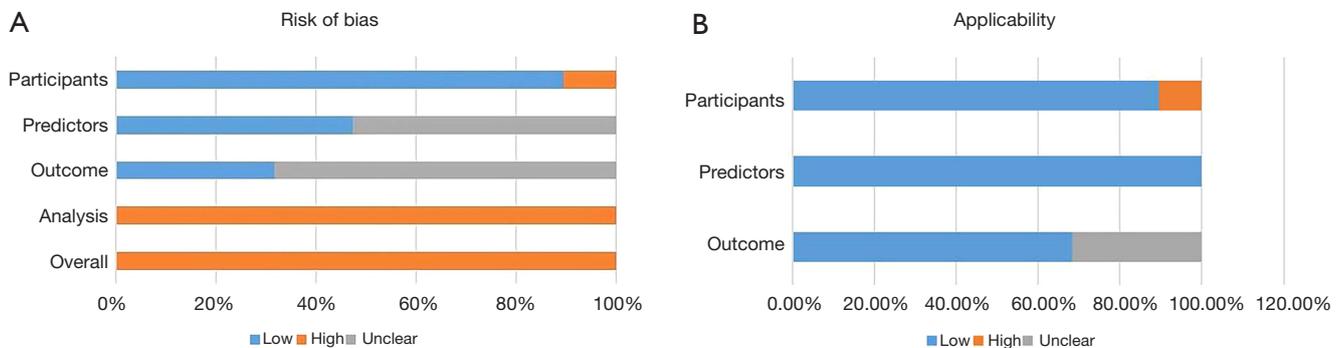


Figure 3 The risk of bias (A) and concerns of applicability (B) of the Prediction Model Risk of Bias Assessment Tool.

predictors (27,35). A biological correlate was analyzed in 1 study (33), and 5 studies calculated cutoff values to delineate risk groups (30,32,33,39,41). Seven studies reported calibration statistics using calibration plots or the Hosmer-Lemeshow test (17,30,32,37,40,42,43), and 73.7% (14/19) of the studies had internal validation, with only one study using external validation (42). Two studies did not include a comparison with a gold standard (30,34). Five studies conducted decision curve analysis to determine the current and potential application of the models (32,37,42,43,44). The details of RQS results are shown in *Table 3*.

Discussion

Even with the growing number of radiomics studies,

there have been relatively few cases of radiomics models being successfully translated into clinically useful tools or receiving Food and Drug Administration approval. This can partially be attributed to the limited repeatability and reproducibility of the developed models. Therefore, reliable radiomics model with a standardized modeling process, high-quality reporting, and a lower risk of bias are necessary. In this systematic review, TRIPOD, PROBAST, and RQS were used to assess various aspects of radiomics models for carotid plaques. These models had adequate AUCs to show their predictive or diagnostic power for CAS, and adherence to TRIPOD was generally relatively good throughout these studies; however, some key aspects of the assessment methods were lacking, and studies with low RQS values and a high risk of bias were also common.

Table 3 Results of radiomics quality score assessment

Study	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	Total points (N=36), n (%)
Chen <i>et al.</i> , 2022 (24)	1	1	0	0	3	1	0	0	1	1	0	2	2	2	0	0	14 (38.89)
Cheng <i>et al.</i> , 2022 (25)	1	1	0	0	3	1	0	0	1	0	0	2	2	0	0	0	11 (30.56)
Cilla <i>et al.</i> , 2022 (26)	1	1	0	0	3	0	0	0	1	0	0	2	2	0	0	0	10 (27.78)
Colombi <i>et al.</i> , 2021 (27)	1	1	0	0	-3	1	0	0	1	0	0	-5	2	0	0	0	-2 (-5.56)
Dong <i>et al.</i> , 2022 (28)	1	1	0	0	3	1	0	1	1	1	0	-5	0	0	0	0	4 (11.11)
Ebrahimian <i>et al.</i> , 2022 (29)	1	1	0	0	3	1	0	1	1	1	7	2	2	2	0	0	22 (61.11)
Huang <i>et al.</i> , 2016 (30)	1	0	0	0	3	0	0	0	1	0	0	2	2	0	0	0	9 (25.00)
Huang <i>et al.</i> , 2022 (31)	1	1	0	0	3	1	0	0	1	0	0	2	0	0	0	0	9 (25.00)
Kafouris <i>et al.</i> , 2021 (32)	1	0	0	0	3	1	0	0	1	0	0	2	2	0	0	0	10 (27.78)
Le <i>et al.</i> , 2021 (33)	1	0	0	0	3	1	0	0	1	1	0	2	2	2	0	0	13 (36.11)
Lo <i>et al.</i> , 2022 (34)	1	0	0	0	-3	1	0	1	1	0	0	-5	2	0	0	0	-2 (-5.56)
Engelen <i>et al.</i> , 2014 (35)	1	0	0	0	3	1	1	1	1	0	0	2	2	0	0	0	12 (33.33)
Wang <i>et al.</i> , 2022 (36)	1	1	0	0	3	1	0	0	1	1	0	2	2	0	0	0	12 (33.33)
Xia <i>et al.</i> , 2023 (37)	1	1	0	0	3	1	0	1	1	0	0	2	2	0	0	0	12 (33.33)
Zaccagna <i>et al.</i> , 2021 (38)	1	1	0	0	3	1	0	0	1	0	0	2	2	0	0	0	11 (30.56)
Zhang <i>et al.</i> , 2022 (39)	1	1	0	0	3	1	0	0	1	0	0	-5	2	0	0	0	4 (11.11)
Zhang <i>et al.</i> , 2021(40)	1	0	0	0	3	1	0	0	1	0	0	2	2	0	0	0	10 (27.78)
Zhang <i>et al.</i> , 2022 (41)	1	1	0	0	3	1	0	0	1	1	0	3	2	2	0	0	15 (41.67)
Zhang <i>et al.</i> , 2023 (42)	1	1	0	0	3	1	0	0	1	1	0	2	2	2	0	0	14 (38.89)

I, image protocol quality; II, multiple segmentation; III, phantom study; IV, imaging at multiple time points; V, feature reduction; VI, multivariable analysis with non-radiomics features; VII, biological correlates; VIII, cutoff analysis; IX, discrimination statistics; X, calibration statistics; XI, prospective study; XII, validation; XIII, comparison to gold standard; XIV, potential clinical utility; XV, cost-effectiveness analysis; XVI, open science and data.

These findings illustrate that current radiomics models may not yet be applicable for carotid atherosclerotic plaque evaluation in actual clinical practice and there is still room for the improvement of radiomics methods.

TRIPOD is a guideline specifically designed to assess the development or validation of multivariate prediction models for diagnostic or prognostic purposes and enables the scientific or medical community to objectively examine the strengths and shortcomings of prediction model-based research. RQS is a tool for standardizing and improving the methodological quality of radiomics reports. Finally, PROBAST functions to assess the risk of bias and applicability of diagnostic and prognostic prediction model studies. Study design, predictor selection, and model performance are three intersecting items within these checklists. First, for study design, both TRIPOD

and PROBAST encourage authors to enroll acceptable data sources with suitable inclusion and exclusion criteria; however, in our review, this was poorly reported in 68.4% (13/19) of the included articles. Notably, a prospective study earned 7 points in the RQS tool, although this was the only prospective trial, accounting for only 5.2% (1/19) of the included literature. Overall, radiomics studies with prospective designs are lacking, both in the oncologic and cardiovascular fields (45,46). Prospective studies have many desirable properties, but they can be time-consuming and costly, and a prospective-retrospective hybrid study with a well-designed protocol may serve as a suitable compromise (47). Second, predictors play key role in model development. Region of interest segmentation and feature selection are the two prerequisite steps before final model implementation. TRIPOD requires authors to

report predictors included in the final model in the abstract and results sections, and predictor definition is needed in TRIPOD and PROBAST. The approach employed for feature reduction and selection to limit the risk of overfitting is necessary in RQS and TRIPOD; fortunately, most of included studies in our review satisfied these requirements. Additionally, radiomics models included multivariable analysis with non-radiomics features in modeling, and detecting the correlation between radiomics features and biological factors is expected to deepen the understanding of radiomics and biology but appears to have better prospects in the oncologic field (48,49) than in the cardiovascular field (45). However, according to the consensus of the European Society of Radiology, biological relevance can be established after clinical validation. Third, model performance is typically evaluated in terms of discrimination and calibration: the former was achieved in all included studies, but the latter in less than half of them. In addition to ROC curve and AUC or concordance index, sensitivity, specificity, predictive values, and decision curve analysis are also excellent indicators of model power. Using appropriate model validation techniques to show the sufficiently robust ability of a developed model to predict an end point of interest is required before the model can be translated into clinical use (47). An externally validated model is considered to be more credible than is an internally validated one, as the former obtains more individualized data (e.g., varying temporally or geographically), which reinforces the validation and decreases model overfitting risk (50). In a comprehensive review of the internal validation approach, data from simulation studies showed that inadequate internal validation methods can still result in AUC estimates of 0.7–0.8 even when variables are not relevant to the outcome (51). Even though the external validation based on 3 or more datasets scored 5 points in RQS, the study by Zhang *et al.* was the only study in our review that applied a single external data source for validation (42). External validation was better performed in oncology studies; for instance, in Park *et al.*'s systematic review, which enrolled 77 radiomics studies (including 70 in the field of oncology), 18.2% (14/77) of the studies were externally validated (21).

Other questionable items with TRIPOD and PROBAST were related to participants, handling of missing data, and blinding of the assessment of predictors and outcomes. The average population size in the 19 included studies was 144, with a mean number of candidate features of 768. Almost all studies had missing data, but only that by Xia *et al.* imputed

mean values with missing values (38). Moreover, 52.6% of studies did not mention any information concerning blindness assessment. In theory, the larger the sample size is, the smaller the standard error and the narrower the confidence intervals are, leading to more accurate results and less risk of overfitting and underfitting. Currently, an EPV value of at least 10 is the baseline criterion for radiomics models; for validation models, an EPV larger than 100 is preferable (52). Although different opinions on these criteria are inevitable (53–55), a well-planned prospective longitudinal cohort study, in practice, will allow researchers to predetermine sample size based on statistical grounds and generate plausible records. Missing data are unavoidable in research, and most studies eliminate patient data from analysis if an outcome or predictor is lacking to perform complete-case analysis. Not only is it inefficient to include only participants with complete data, but the remaining participants without missing data are not representative of the entire original study sample (i.e., they are selective participants). Missing data are consistently inadequately reported and managed, as shown by systematic reviews of methodological practices and research reports on predictive model development and evaluation (56–58). There are already several imputation approaches that may be used to estimate missing cases from multiple imputation datasets in statistical packages (such as Stata, R, SAS, and Python) (59). Blinded assessment of predictor and outcome is important not only in prognostic trails but also in diagnostic model studies to reduce the risk of bias (60,61). Knowledge of predictor results may affect how outcomes are determined; in other words, lacking blinding of predictor assessors to outcome information increases their association and inflates model performance estimates (62,63).

For RQS, no study in our review reported on the cost-effectiveness or open science and data. Given the status of radiomics in methodological and clinical validation, the evaluation of cost-effectiveness may be perceived to be less urgent (18,45). However, cost-effectiveness analysis can assess the value of radiomics predictive models in health economics when applied clinically (19,64). New models with comparable prediction power should not be more expensive than pre-existing ones. In addition, adopting open access to scientific data ensures better clinical applicability and academic transparency, as researchers will be able to use the database for external validation, reproduction, or replication if there is available publication of code and partial disclosure of raw data (24,65). It is worth mentioning that “phantom study” and “test-retest analysis” were two more items in

which the reviewed studies showed poor performance, and these were intended to detect any uncertainties associated with organ movement or contraction, and a phantom study in particular can recognize potential differences in characteristics between suppliers. The reliability of radiomics features depends on the choice of feature calculation platforms and software version, and failure to harmonize calculation settings results in poor reliability, even on platforms compliant with the Image Biomarker Standardization Initiative (66).

This review has some inherent limitations. First, we did not search literature through Embase or Scopus, which might have led to some key data being missed. Second, direct comparisons of AUCs between individual studies suggested the potential of radiomics in assessing carotid plaque, but we were unable to evaluate the pooled predictive power via meta-analysis due to different research objectives, high heterogeneity, and wide variations in predictor variables. Furthermore, future prospective studies designed with a reasonable EPV and external validation are recommended, as there was a lack of sufficient evidence from prospective studies and independent external validation cohorts. Finally, the results of RQS, PROBAST, and TRIPOD were not always consistent. RQS can help assess the methodological quality of radiomics studies but does not evaluate sources of bias; moreover, obtaining a perfect RQS score is extremely difficult due to complex computation and subtractive factors (45). The PROBAST primarily deals with regression-based clinical prognostic models instead of radiomics models, whereas TRIPOD is a benchmark for traditional predictive model development studies and is less suitable for radiomics research of image analysis and large feature libraries. Thus, comprehensive checklists for studies based on artificial intelligence, such as TRIPOD-AI and PROBAST-AI, will be more viable in the future (67).

Conclusions

Our review suggests that radiomics models have potential value in assessing carotid plaque, but the overall methodology and reporting quality of radiomics studies on carotid plaque remain inadequate, and many obstacles must be overcome before these models can be translated into clinical practice. We anticipate that reliable and reproducible imaging predictions will be achieved under rigorously designed prospective study with sufficiently large sample sizes and external validation. Greater attention

should be paid to the correlations among radiomics features and gene expressions, the handling of missing data, analysis methods, and open-access code and data.

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Footnote

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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 Search strategy

Database	Terms
PubMed	(("radiomics" [Title/abstract] OR "radiomic" [Title/abstract] OR "texture" [Title/abstract] OR "textural" [Title/abstract]) AND ("carotid arteries" [MeSH]) AND ("atherosclerotic plaque" [MeSH] OR "atherosclerosis" [MeSH] OR "carotid stenosis" [MeSH]))
Cochrane library	<ol style="list-style-type: none"> 1. MeSH descriptor: [carotid arteries] explode all tree 2. MeSH descriptor: [atherosclerotic plaque] explode all tree 3. MeSH descriptor: [atherosclerosis] explode all tree 4. MeSH descriptor: [atherosclerotic plaque] explode all tree 5. "radiomics": ti,ab,kw (Word variations have been searched) 6. "radiomic": ti,ab,kw (Word variations have been searched) 7. "texture": ti,ab,kw (Word variations have been searched) 8. "textural": ti,ab,kw (Word variations have been searched) 9. 3 or 4 or 5 10. 6 or 7 or 8 11. 1 and 9 and 10
Web of Science	<ol style="list-style-type: none"> 1. TS= (plaque, atherosclerotic OR plaque, stenosis OR atherosclerosis) 2. TS= (carotid OR carotid artery OR carotid arteries OR artery carotid OR arteries carotid) 3. TS= (radiomics OR radiomic OR texture OR textural) 4. 1 AND 2 AND 3