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A meta-analysis of the diagnostic test accuracy of CT-based radiomics for the prediction of COVID-19 severity

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Abstract

Introduction According to the Chinese Health Commission guidelines, coronavirus disease 2019 (COVID-19) severity is classified as mild, moderate, severe, or critical. The mortality rate of COVID-19 is higher among patients with severe and critical diseases; therefore, early identification of COVID-19 prevents disease progression and improves patient survival. Computed tomography (CT) radiomics, as a machine learning method, provides an objective and mathematical evaluation of COVID-19 pneumonia. As CT-based radiomics research has recently focused on COVID-19 diagnosis and severity analysis, this meta-analysis aimed to investigate the predictive power of a CT-based radiomics model in determining COVID-19 severity.

Materials and methods This study followed the diagnostic version of PRISMA guidelines. PubMed, Embase databases and the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched to identify relevant articles in the meta-analysis from inception until July 16, 2021. The sensitivity and specificity were analyzed using forest plots. The overall predictive power was calculated using the summary receiver operating characteristic curve. The bias was evaluated using a funnel plot. The quality of the included literature was assessed using the radiomics quality score and quality assessment of diagnostic accuracy studies tool.

Results The radiomics quality scores ranged from 7 to 16 (achievable score: 22128 to 36). The pooled sensitivity and specificity were 0.800 (95% confidence interval [CI] 0.662–0.891) and 0.874 (95% CI 0.773–0.934), respectively. The pooled area under the receiver operating characteristic curve was 0.908. The quality assessment tool showed favorable results.

Conclusion This meta-analysis demonstrated that CT-based radiomics models might be helpful for predicting the severity of COVID-19 pneumonia.

Keywords COVID-19 · Radiomics · Computed tomography · Textural · Meta-analysis

Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic [1]. COVID-19 has spread worldwide and has led to millions of deaths. According to the Chinese Health Commission (CHC) guidelines, COVID-19 severity is classified as mild, moderate, severe, or critical [2]. The Chinese Center for Disease Control and Prevention reported that 81% of COVID-19 cases were non-severe, and the remaining 19% were severe

or critical [3]. Existing epidemiological studies suggest that the mortality rate of patients with severe COVID-19 is more than ten times higher than that of patients with non-severe COVID-19 [4]. To treat patients with COVID-19, early identification of severe cases directly influences treatment and prevents clinical deterioration. Similarly, early identification and management of patients with severe COVID-19 prevent disease progression and improve survival [5].

According to recent experience, abnormal findings on lung imaging appear before clinical symptoms develop, which highlights the importance of lung imaging in screening for COVID-19 pneumonia [6]. Computed tomography (CT) is helpful for COVID-19 diagnosis and in assessing COVID-19 pneumonia progression [7, 8]. The typical findings on chest CT imagery for patients with COVID-19 are ground-glass opacities and bilateral lung consolidations with

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peripheral involvement [9]. However, the evaluation of these conventional textures varies among radiologists and is often subjective.

Computed tomography radiomics, a non-invasive developing machine learning technology, can extract histograms, shapes, or textural features from images. In addition, artificial intelligence can further quantify textural information using mathematical analysis; therefore, abnormal lesions on CT images can be evaluated precisely and objectively using radiomics. Recently, CT-based radiomics has been widely used for tumor diagnosis, cancer treatment, and prognosis assessment [10, 11].

In previous studies on COVID-19, machine learning CT-based radiomics has been shown to help diagnose and differentiate COVID-19 pneumonia from pneumonia caused by other pathogens [12–14]. Additionally, CT-based radiomics reportedly predicts the severity and outcome of COVID-19 pulmonary opacities [15]. However, the mechanism between COVID-19 pneumonia severity, pulmonary opacities, and clinical manifestations has not been well addressed, and a detailed meta-analysis using CT-based radiomics has not been performed. Therefore, this study aimed to investigate whether CT-based radiomics models can predict COVID-19 pneumonia severity.

Materials and methods

Study protocol and literature search

This study followed the diagnostic version of PRISMA guidelines [16]. Two investigators searched PubMed, Embase, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews for articles published between the inception of the databases until July 16, 2021. The keywords used were as follows: ("COVID-19" OR "severe acute respiratory coronavirus-2[SARS-CoV-2]") AND ("radiomics" OR "textural") AND ("computed tomography" OR "CT").

Literature selection criteria

The inclusion criteria were as follows:

1. Studies using shape- and texture-based radiomics to predict COVID-19 severity.
2. Studies wherein COVID-19 severity was defined according to the CHC guidelines.
3. Studies with full text available.
4. Studies published in the English language.

In contrast, the exclusion criteria were as follows:

1. Studies wherein radiomics was not used to predict the severity of COVID-19.
2. Conference posters or papers for which only the abstract was available.

COVID-19 pneumonia severity classification

According to the CHC guidelines, COVID-19 illness is classified according to disease severity [4]. Patients with COVID-19 pneumonia included in this study were classified into those with non-severe disease (non-SVD) and those with severe disease (SVD). Patients who met any of the following criteria were included in the SVD group: (1) respiratory rate ≥ 30 times per minute, (2) oxygen saturation $\leq 93\%$ by finger oximetry at resting status, (3) partial pressure of oxygen in arterial blood (PaO$_2$)/fraction of inspired oxygen (FiO$_2$) ≤ 300 mmHg, (4) patients with $> 50\%$ lesion progression on chest imaging over 1–2 days, (5) respiratory failure and assisted ventilation requirement; (6) shock, or (7) organ failure that required admission to the intensive care unit (ICU).

Data collection

We extracted the true-positive, false-positive, false-negative, and true-negative rates from the literature. The radiomics model with the highest area under the receiver operating characteristic curve (AUC) within the articles was used for extraction. Some studies used bootstrapping or cross-validation; therefore, the resulting values were not integers that could be used for extraction. For simplicity, we rounded the figures used in the calculations. Additionally, we extracted other information from the literature, including the author details, publication year, nation, number of patients, and further information.

Statistical analysis

The pooled sensitivity and specificity of the included radiomics studies were determined using statistical analysis. The pooled results are presented as forest plots. The overall predictive power was calculated by creating a summary receiver operating characteristic (SROC) curve. We evaluated the heterogeneity of the included literature by visually investigating the SROC curve [17]. The analysis was conducted using the R language [18], R package (Mada [19] and Meta [20]), and R studio [21].

Bias and study quality assessment

The publication bias was evaluated using a funnel plot. The quality of the included studies was assessed using the radiomics quality score (RQS) [22] and quality assessment of

diagnostic accuracy studies (QUADAS-2) tool [23]. The RQS assessment investigated 16 components, which resulted in a score ranging from − 8 to 36, defined as 0% and 100%, respectively. The QUADAS-2 tool, which assesses seven components, was used to evaluate the risk of bias and applicability concerns. Two authors independently scored the RQS and QUADAS-2 tools. If a discrepancy was observed, the final score was discussed by the two authors to reach consensus.

Results

We retrieved a total of 682 articles. After removing duplicates, 118 articles were selected for evaluation. After screening for eligibility based on titles and abstracts, 12 articles were retrieved for complete evaluation. Four studies were excluded from the analysis as follows: one observational study [24], which used a repetitive patient population, one observational study [15], which used pulmonary opacities on chest images to predict disease severity, and two observational studies [25, 26], which used other severity assessment protocols to predict disease outcome. Finally, eight articles were used for qualitative analysis [27–34]. Only seven reports were included in the meta-analysis as a study by Li et al. [34] was excluded because only patients with severe COVID-19 were included in the report. A flowchart of the literature review is shown in Fig. 1. The details of the selected studies are presented in Table 1.

Pooled analysis of the included studies

Seven studies comprising 1460 patients with COVID-19 were included in this meta-analysis. The forest plot of pooled sensitivity was 0.800 (95% confidence interval [CI] = 0.662–0.891), as shown in Fig. 2. The forest plot of pooled specificity was 0.874 (95% CI = 0.773–0.934), as shown in Fig. 3. The pooled AUC was 0.908, and the SROC curve is shown in Fig. 4. We identified the heterogeneity within the included studies by visually investigating the SROC curve.

SROC, summary receiver operating characteristic curve; conf. region, 95% confidence region for the SROC curve.

Radiomics quality score of the included studies

The radiomics quality scores of the included studies are presented in Table 2. The radiomics quality scores ranged from 7 to 16. After a detailed evaluation of each RQS component by two authors, all included studies presented their image protocols, feature reduction performance, discrimination statistics reports, a comparison of the results to the gold standard, and potential clinical utility.

Qualities assessment of the selected literature

The QUADAS-2 tool was used to evaluate the literature. All studies had at least five out of seven low-risk bias assessment points. The results are presented in Fig. 5.

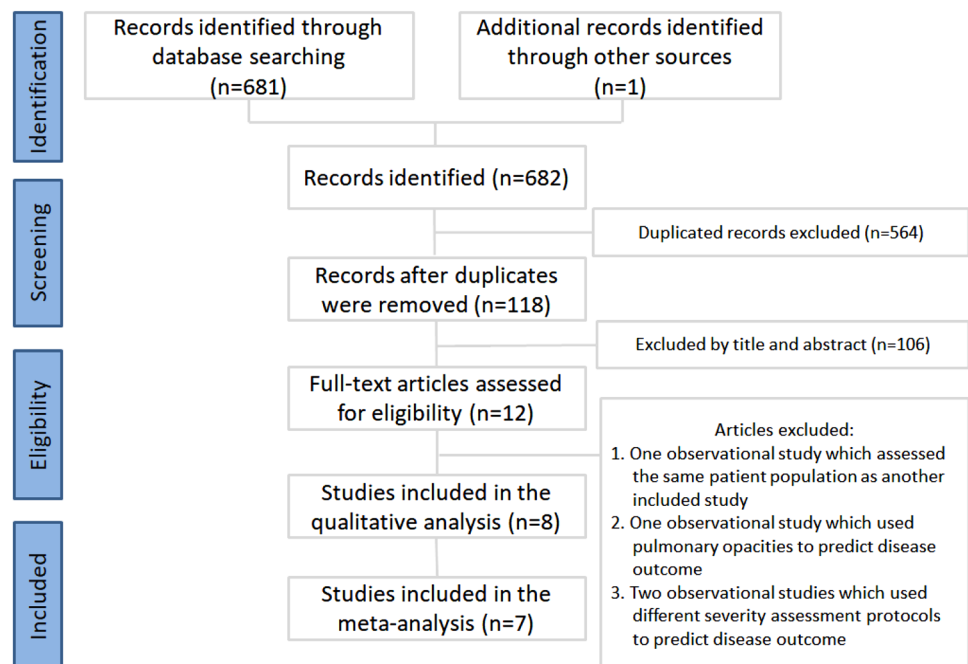Fig. 1 A flowchart illustrating the inclusion process used to identify studies

Table 1 Characteristics of the selected studies

Author Nation, year	Study type	Patient selection, ROI	Patient number of disease severity by CHC guidelines		Patient number of radiomics training model			Highest AUC (95% CI)
			Non-SVD	SVD	Training set	Internal validation	Test cohort	
Xie et al. China, 2021[27]	Retrospective Observational	Hospital admission, PN	110	40	105	Tenfold cross-validation	45	0.98
Liang Li et al. China, 2021[28]	Retrospective Observational	Hospital admission, PN	246	70	159	70	87	0842 (0.761–0.922)
Wang et al. China, 2020[29]	Retrospective Observational	Hospital admission, PN	216	44	156	Tenfold cross-validation	104	0.978
Xiong et al. China, 2021 [30]	Retrospective Observational	Hospital admission, PN	136	83	175	Fivefold cross-validation	44	0.97
Wei et al. China, 2020 [31]	Retrospective Observational	Hospital admission, PN	60	21	81	100-fold cross-validation	Nil	0.93 (0.86–1.00)
Cai et al. China, 2020 [32]	Retrospective Observational	Hospital admission, PN	25	74	99	Tenfold cross-validation	Nil	0.927 (0.92–0.931)
Tang et al. China, 2021 [33]	Retrospective Observational	Hospital admission, PN	76	42	55	24	39	0.98
Cong Li et al. China, 2020 [34]	Retrospective Observational	Hospital admission, PN	Nil	217	174	Tenfold cross-validation	43	0.861 (0.753–0.968)

ROI Region of interest, *CHC* Chinese health commission, *SVD* severe disease, *AUC* the area under the receiver operating characteristic curve, *CI* confidence interval, *PN* pneumonia
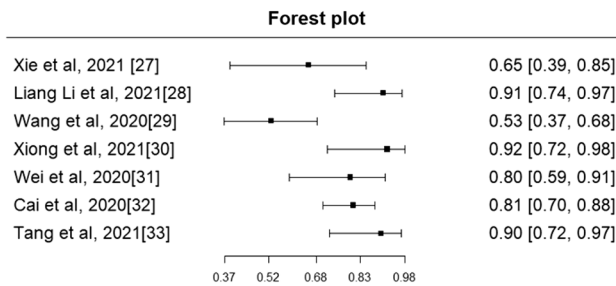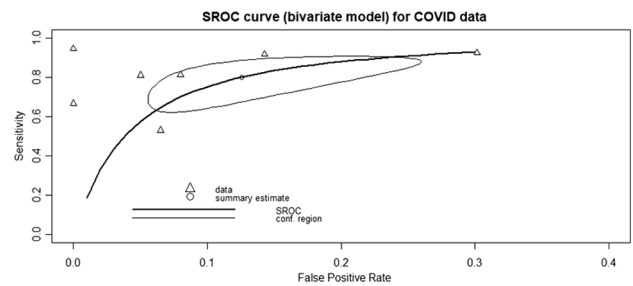

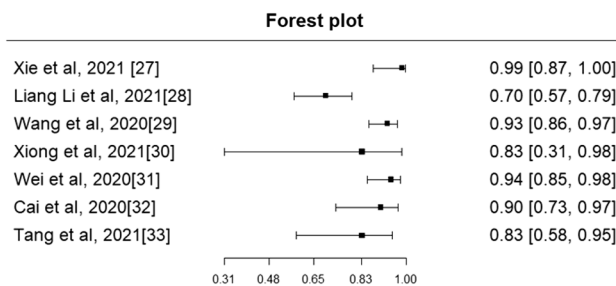**Fig. 2** The forest plot for sensitivity

Fig. 3 The forest plot for specificity

Fig. 4 The SROC curve

Publication bias assessment of the included studies

The funnel plot is shown in Fig. 6. As the number of included studies was less than 10, we cannot conclude whether a publication bias exists.

Review of the radiomics and clinical features used in the included studies

As stated by the IEEE International Symposium on Biomedical Imaging, there are many types of texture features, including first-order texture features, shape-based texture features, gray-level distance-zone matrix texture features, gray-level size-zone matrix texture features,

Table 2 Radiomics quality scores of the selected literature

Study criteria	Xie et al. 2021[27]	Liang Li et al. 2021[28]	Wang et al. 2020[29]	Xiong et al. 2021[30]	Wei et al. 2020[31]	Cai et al. 2020[32]	Tang et al. 2021[33]	Cong Li et al. 2020[34]
Image protocol quality	+1	+1	+1	+1	+1	+1	+1	+1
Multiple contouring	+1	+1	+1	+1	+1	+1	+0	+0
Phantom study	+0	+0	+0	+0	+0	+0	+0	+0
Imaging at additional time points	+0	+0	+0	+0	+0	+0	+0	+0
Feature reduction or multiple testing correction	+3	+3	+3	+3	+3	+3	+3	+3
Multivariate analysis with non-radiomics covariates	+1	+1	+1	+0	+1	+1	+1	+0
Detection and discussion of biological mechanism	+0	+0	+0	+0	+0	+0	+0	+0
Cutoff analyses	+0	+0	+0	+0	+0	+0	+0	+0
Discrimination analyses	+2	+2	+2	+2	+2	+2	+2	+2
Calibration analyses	+1	+1	+1	+0	+0	+0	+0	+0
Prospective study registration in a study database	+0	+0	+0	+0	+0	+0	+0	+0
Validation	+2	+3	+2	+2	-5	-5	+2	+2
Comparison to the "gold standard"	+2	+2	+2	+2	+2	+2	+2	+2
Future application	+2	+2	+2	+2	+2	+2	+2	+2
Cost–benefit analysis	+0	+0	+0	+0	+0	+0	+0	+0
Public science and data	+0	+0	+0	+0	+0	+0	+0	+0
Total score (possible score range −8 (0%) to 36 (100%))	15 (34%)	16 (36%)	15 (34%)	13 (30%)	7 (16%)	7 (16%)	13 (30%)	12 (27%)

neighborhood gray-tone difference matrix texture features, neighboring gray-level dependence matrix texture features, gray-level run-length matrix texture features, and gray-level co-occurrence matrix texture features [35]. The types of textural features used in the included studies are listed in Table 3. Four studies used shape-based radiomics features, six studies used first-order radiomics features, and five studies used second-order radiomics features.
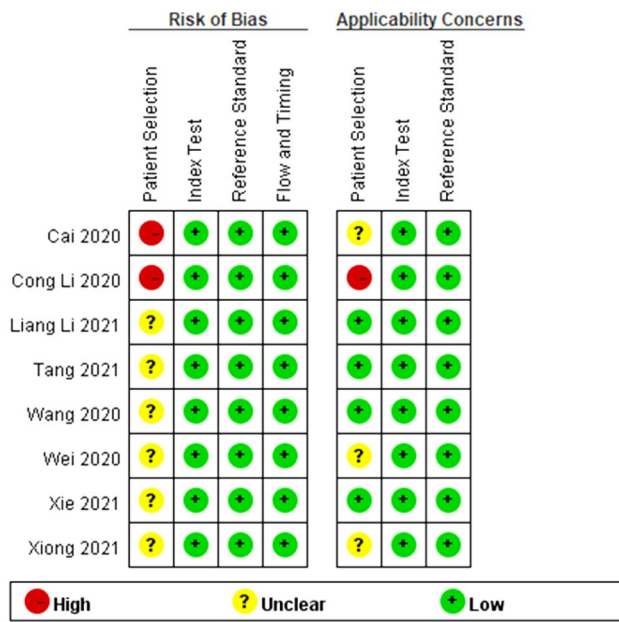
Fig. 5 Quality assessment of diagnostic accuracy studies

Review of the prediction algorithms used in the included studies

Three selected studies used the least absolute shrinkage and selection operator (LASSO). One of the included studies used the XGBclassifier. Two of the studies used the random forest method. The other two studies used logistic regression, and the details of the prediction algorithms are listed in Table 4.

Discussion

Our meta-analysis revealed that CT-based radiomics could be used to predict the severity of COVID-19 pneumonia. In other CT-based radiomics studies, different COVID-19 pneumonia severity protocols could predict the severity

of COVID-19 pneumonia [25, 26]. The management of COVID-19 pneumonia depends on disease severity [38, 39]. Therefore, early prediction of severe COVID-19 pneumonia before clinical deterioration using CT-based radiomics may aid in providing early management for these patients and reduce mortality [5, 40].

Our study included 1460 patients. The pooled sensitivity and specificity were 0.800 (95% CI = 0.662–0.891) and 0.874 (95% CI = 0.773–0.934), respectively. The pooled AUC was quite high at 0.908, indicating that radiomics is a promising tool for predicting the severity of COVID-19 pneumonia. The heterogeneity within the included studies may be attributed to the properties of radiomics features. As a previous study implied, radiomics features could be influenced by the calculation kernel, tumor delineation variability, technical settings of the CT scan, and software used to produce radiomics features [41]. This meta-analysis pooled results from various studies with different settings, thus providing robust results.

The RQS assessment resulted in a score ranging from −8 to 36, defined as 0% and 100%, respectively. The RQS values of the included literature ranged from seven to 16; thus, the highest RQS in the selected studies was only 40%. A previous meta-analysis also found a maximum RQS score of 16 for CT-based texture features used to differentiate between COVID-19 and viral pneumonia [14]. Compared with this study, a low RQS score makes it challenging to conduct a high-quality radiomics study in current research settings.

In contrast, the QUADAS-2 tool showed a favorable quality assessment of the selected studies. The risk of bias was primarily low in the selected studies, except for the patient selection bias. The patient selection bias was unclear or high because the selected studies were retrospective, and the patients were not randomly enrolled. The concern of applicability rating was low because the patient and index test interpretations were suitable for our review of the selected studies.

The types of radiomics features used in the selected studies should be discussed. While six studies assessed
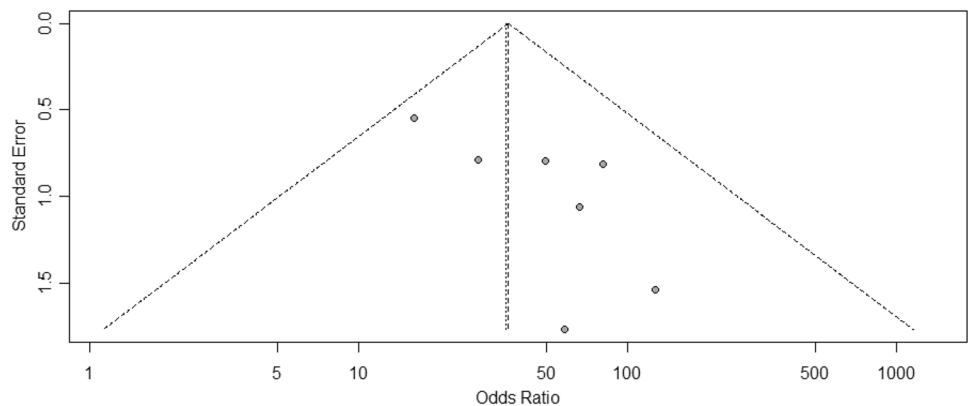

Fig. 6 Funnel plot

Table 3 The type of radiomics and non-radiomics features used in the selected studies

Author, year	Radiomics features	Non-radiomics features
Xie et al. 2021 [27]	Shape-based, first-order, GLCM, GLRM	Age, number of lesions, CT score[※], comorbidity, GGO with consolidation
Liang Li et al. 2021 [28]	First-order, GLCM, GLDZM, GLRM, GLSZM, NGTDM	Age, comorbidities, CTSS*, CTLP[#]
Wang et al. 2020 [29]	Shape-based	Nil
Xiong et al. 2021 [30]	Shape-based, first-order, GLCM, GLRM, GLSZM, NGTDM, GLDZM	Nil
Wei et al. 2020 [31]	GLSZM, GLRM	CT score[※]
Cai et al. 2020 [32]	First-order	PaO_2; eosinophil ratio; blood oxygen saturation; age
Tang et al. 2021 [33]	Shape-based, first order	WBC-DC, blood coagulation function, blood electrolytes, inflammatory markers
Cong Li et al. 2020 [34]	First-order, GLCM, GLDZM	Deep learning features

CT score.[※], the score used to evaluate the severity of ground-glass opacity [36]

GLCM, gray-level co-occurrence matrix; GLRM, gray-level run-length matrix; GGO, ground-glass opacity; GLDRM, gray-level distance-zone matrix; GLSZM, gray-level size-zone matrix; NGTDM, neighborhood gray-tone difference matrix; CTSS*, CT severity score, volume of lesions/volume of the lungs on CT; CTLP.[#], CT lesion percentage of pulmonary involvement [37]; WBC-DC, white blood cell differentiated count

Table 4 The prediction algorithms used in the selected studies

Author, year	Algorithms used in the study
Xie et al. 2021 [27]	LASSO
Liang Li et al. 2021 [28]	LASSO
Wang et al. 2020 [29]	LASSO
Xiong et al. 2021 [30]	XGBClassifier
Wei et al. 2020 [31]	Backward stepwise multivariate logistic regression
Cai et al. 2020 [32]	Random forest
Tang et al. 2021 [33]	Random forest
Cong Li et al. 2020 [34]	Logistic regression

LASSO, least absolute shrinkage and selection operator

first-order features, five studies assessed second-order features, either alone or in combination with other features. Second-order features have been widely used in radiomics models for cancer patients, as they measure the heterogeneity within the region of interest. Hence, future studies investigating the molecular mechanisms associated with second-order radiomics features are warranted to deepen the understanding of COVID-19.

The algorithms used significantly varied between the selected studies. The most frequently used algorithm was the LASSO. The LASSO algorithm is a logistic regression-based algorithm that adds a regularization term to reduce the effect of noise on prediction. Another study used the XGBclassifier, a tree-based prediction algorithm that starts with a weak classifier and subsequently boosts to a stronger classifier [42]. Two of the included studies used the random forest method, another tree-based classifier, which starts with a robust classifier and reaches the final prediction result by voting [43]. The other two studies used traditional logistic regression models.

This meta-analysis had some limitations. First, the articles selected for this meta-analysis were retrospective. Second, the study protocols for each article were conducted in China, which can be attributed to our use of the CHC guidelines for COVID-19 pneumonia severity classification. Third, as this meta-analysis focused on predicting COVID-19 pneumonia severity using a CT-based radiomics learning model, the patients' clinical data and disease course spectrum were not analyzed further. Although CT-based radiomics models were helpful for predicting COVID-19 pneumonia severity, the equivalence of pneumonia severity prediction to the prognosis and mortality prediction was not investigated in this meta-analysis. Therefore, future prospective and multicenter research should be performed to verify the effectiveness of radiomics in predicting COVID-19 pneumonia severity.

Conclusions

Our meta-analysis demonstrated that CT-based radiomics feature models might be powerful tools for predicting the severity of COVID-19 pneumonia.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights The study data were extracted from the included papers. The research was conducted in accordance with the 1964 Helsinki declaration and its amendments.

Informed consent This meta-analysis was performed using data extracted from published papers. Informed consent was obtained from included papers.

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