Original Article

Pulmonary vascular enlargement on thoracic CT for diagnosis and differential diagnosis of COVID-19: a systematic review and meta-analysis

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Background: The 2019 coronavirus disease (COVID-19) has become a global pandemic. To date, although many studies have reported on the computed tomography (CT) manifestations of COVID-19, the vascular enlargement sign (VES) of COVID-19 has not been deeply examined, with the few available studies reporting an inconsistent prevalence. We thus performed a systematic review and meta-analysis based on the best available studies to estimate the prevalence and identify the underlying differential diagnostic value of VES.

Methods: We searched nine English and Chinese language databases up to April 23, 2020. Studies that evaluated CT features of COVID-19 patients and reported VES, with or without comparison with other pneumonia were included. The methodologic quality was assessed using Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). Meta-analyses with random effects models were performed to calculate the aggregate prevalence and pooled odds ratios (ORs) of VES. We also conducted meta-regression and subgroup analyses to analyze heterogeneity.

Results: VES findings from a total of 1969 patients were summarized and pooled across 22 studies. Our analysis demonstrated that the prevalence of VES among COVID-19 patients was 69.37% [95% confidence interval (CI): 57.40–79.20%]. Compared with non-COVID-19 patients, VES manifestation was more frequently observed in confirmed COVID-19 patients (OR =6.43, 95% CI: 3.39–12.22). Studies that explicitly defined distribution of VES in the lesion area demonstrated a significantly higher prevalence (P=0.03). Subgroup analyses also revealed a relatively higher VES rate in studies with a sample size larger than 50, but the difference was not statistically significant. No significant difference in VES rates was found between different countries (China/Italy), regions (Hubei/outside Hubei), average age groups (over/less than 50-year-old), or slice thicknesses of CT scan. Extensive heterogeneity was identified across most estimates (I^2>80%). Some of the variations (R^2=19.73%) could be explained by VES distribution, and sample size. No significant publication bias was seen (P=0.29).

Conclusions: VES on thoracic CT was found in almost two-thirds of COVID-19 patients, and was more prevalent compared with that of the non-COVID-19 patients, supporting a promising role for VES in identifying pneumonia caused by coronavirus.

Keywords: 2019 coronavirus disease (COVID-19); computed tomography (CT); pulmonary vascular enlargement sign (VES); meta-analysis; systematic review

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Introduction

Over the past 20 years, the world has witnessed three large-scale coronavirus outbreaks, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and now the 2019 novel coronavirus disease (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2020, COVID-19, a viral disorder characterized by fever, dry cough, fatigue, dyspnea, and myalgia, was first identified and officially reported in Wuhan, Hubei Province, China. With strong measures taken by Chinese government and efforts of medical staff, the China's outbreak centered by Hubei Province has gradually improved (1). But as virus sees no national boundaries, currently, COVID-19 has become a global pandemic, leading to over 9 million confirmed cases and over 400 thousand deaths. According to the World Health Organization (WHO) reports in June, 2020, Americas are the worst-hit places, followed by Europe, Eastern Mediterranean, South-East Asia, Africa and Western Pacific (2). Recently, it was declared a public health emergency of international concern (PHEIC) by the chief of the World Health Organization (WHO), thus ascending to the highest level of global alarm (3). To combat this disease, a united effort is needed now more than ever.

As computed tomography (CT) has features of noninvasiveness, quick speed, high resolution, and easy access, it is recommended by experts for THE first-line screening of suspected COVID-19 patients (4,5). Recently, many descriptive studies, case series, and literature reviews have reported and summarized typical CT manifestations of COVID-19. The common CT features already identified for COVID-19 include multifocal or unifocal patchy and round-shaped ground glass opacity (GGO) or consolidation lesion, along with reticulation or interlobular septal thickening, usually with a bilateral, peripheral, subpleural, lower, and posterior distribution (4,6). Special classic CT signs, including "crazy paving", "vascular thickening", "air-bronchogram", "bronchiectasis or bronchus distortion", "fibrosis", "halo" or "reversed halo", may also be typical, while cavitation, nodules, "tree-in-bud", pleural effusions, and lymphadenopathy are rare (7). Among these CT signs, "vascular enlargement" sign (VES) (8) is found promising to be a typical early CT feature of COVID-19 as reported by Zhao *et al.* (9) and Hu *et al.* (10).

VES, also known as "vascular thickening" (11), "vascular enhancement" (12), "micro-vascular dilation" sign (13,14), "bronchovascular enlarged" (15), or "dandelion fruit" sign (16), is often described as the dilatation of pulmonary vessels around and within the lesions in an unnatural way on CT images (17). The vascular issue is also of great concern for COVID-19 patients from clinical perspective. Elevated D-dimer levels and blood hypercoagulability were found to be common among hospitalized COVID-19 patients (18,19). And some acute exacerbation of COVID-19 was revealed to be related to acute pulmonary embolism (20). Besides, Spagnolo *et al.* (21) have reported that COVID-19 patients with adverse outcome (death) had higher pulmonary artery diameter. In addition, previous work have examined vascular changes on CT in pulmonary neoplasms (22), vascular malformation (23), pulmonary artery hypertension (24,25), smoke-related diseases (26), or hemorrhagic fever (27) for disease diagnosis, evaluation of disease severity, and even prediction of malignancy, suggesting a possible unique diagnostic role for VES. However, to our knowledge, few studies have reported its connection to SARS or MERS, or other coronavirus pneumonia.

If CT manifestation correlates of actual pathologic findings such as vasculitis (28) can be identified, radiologists may be able to diagnose COVID-19 more accurately. With more attention being paid to pulmonary circulation conditions of COVID-19 patients, some causes of death like acute pulmonary embolism may therefore be reduced. Recently, studies on CT features of COVID-19 have been thriving, but only some of them have examined VES proportions, and the results have been varied among those studies. So far, although several systematic reviews and meta-analyses have been published on CT features of COVID-19, none of the studies systematically reported on VES. Therefore, the purpose of this study was to systematically review the literature and to perform a meta-analysis regarding the CT findings on VES of confirmed COVID-19 patients and corresponding suspected or non-COVID-19 patients. We present the following article in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting checklist (29) (available at http://dx.doi.org/10.21037/atm-20-4955).

Methods

This meta-analysis was carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (30). We formulated a research question that was based on a modification of the patient, index test, comparator, outcome, and study design

(PICOS) criteria as follows: (I) with respect to thoracic CT manifestations, is the VES associated with COVID-19 patients? (II) To what extent is it associated with COVID-19 patients compared to corresponding suspected cases or other non-COVID-19 patients?

Protocol

We conducted a systematic literature search in March 2020 as a protocol to evaluate whether there was an appropriate amount of studies with reliable quality for pooling a convincing result.

Literature search

We systematically searched five English-language databases, including PubMed, Ovid, Embase, Scopus, and Web of Science, and four Chinese-language databases, including WanFang Data, CQVIP Database, SinoMed Database, and China National Knowledge Infrastructure (CNKI) up to March 20, 2020, and continued updating the literature search until April 23, 2020. We also screened the references of included studies to find other eligible studies. We set the following retrieval terms according to the basic patient, index test, comparator, outcome, and study design (PICOS) principle elements: P: "COVID-19", "2019 novel coronavirus", "SARS-CoV-2"; I: "comput* AND tomogra*", "CT", "imaging", "radiolog*"; O: "pulmonary vessel enlarge*", "vascular enlarge*", "enlarge* subsegmental vessel", "vascular thicken*", "vascular changes". Within each principle element, the logical connector "OR" was used, and "AND" was used between different elements for logical connection. As there is no unified or standard definition of VES, some studies reporting VES might not have identified it as such in the keyword section. Thus, we conducted two rounds of literature search in each database: the first round only included "PI" elements to ensure an overall reliable recall level, and the second round included "PIO" elements to ensure the accuracy and to find any possible omission after the first round literature search. We only use "in the last 1 year" or "year=2019-2020" limit to focus on most recent studies published on COVID-19. No other limits or filters were set.

Inclusion criteria

Qualified studies were included if they satisfied the following patient, index test, comparator, outcome, and study criteria: patients had confirmed diagnosis or exclusion of COVID-19; COVID-19 infection was determined or excluded by real-time reverse transcription polymerase chain reaction (RT-PCR) test, high-throughput nucleic acid gene sequencing, IgM or IgG antibodies detection kit, or some combination of these techniques; the study reported patients' CT findings including VES or compared CT features between COVID-19 and non-COVID-19 patients including VES; and the publication was an original research article written in English or Chinese.

Exclusion criteria

Studies were excluded for the following reasons: the study did not report VES manifestation; the study population included fewer than 10 patients; the publication was not an original research article; researchers only reported other non-COVID-19 coronavirus-related illnesses, such as MERS, SARS; imaging modalities other than CT were used; or the patient population overlapped with that of other studies. If multiple publications had a considerable overlap of study populations, we only included the study that enrolled the highest number of patients.

Data extraction and quality assessment

Two independent investigators (H Lv and T Chen) screened titles, abstracts or full-texts according to the inclusion and exclusion criteria. If there was any disagreement in the process, the final decision was made by a third investigator (H Wang). For the included studies, data were extracted regarding characteristics of study, patient, CT scan, and VES. Study characteristics included origin of study (first author, country, and institution), journal name, year of publication, date of acceptance, total number of enrolled patients, duration of patient recruitment, study design (prospective or retrospective, cross-sectional or case series, multicenter or single center, consecutive or non-consecutive enrollment), and the Joanna Briggs Institute (JBI) quality assessment result. Patient characteristics consisted of number of patients (sorted by SARS-COV-2 confirmation, sex, disease severity, and abnormal CT manifestations), method of pathogen confirmation, source of patients, average age and age range of study population, and comparison characteristics for those studies that included non-COVID-19 patients. CT scan characteristics were image acquisition time, CT scanner model, slice thickness, interval thickness, CT parameters (tube voltage

and tube current modulation), use of contrast enhancement, and number of CT readers and their working experience. Imaging characteristics mainly included description of VES and main findings of VES in each of the included studies.

As a greater degree of bias is likely to occur in observational studies, we decided to use both the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional studies (31) and the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (32) for detailed methodologic quality assessment. To promote consistent assessments in the usage of QUADAS-2 tool, we developed a rating guideline with operational criteria for each domain (see supplementary QUADAS-2 Quality Assessment Rating Guideline). The JBI evaluation results are listed in tables. The QUADAS-2 evaluation items were interpreted in detail using Review Manager (version 5.3) software, and the results were further exported as graphs from the software. The assessment process was also performed independently by two reviewers (Y Pan and H Wang). Consensus was achieved with the combined use of JBI and QUADAS-2 and through discussion between the two reviewers.

Data synthesis and analysis

For studies that only included COVID-19 patients, data were constructed in a "study, event, n" table. The "event" referred to the number of patients or lesions that had presented with VES in each study. The "n" referred to the total number of patients who had both positive SARS-COV-2 test result and abnormal thoracic CT, or the total number of lesions on thoracic CT of those patients in each study. For studies that included both COVID-19 patients and non-COVID-19 patents, data were reconstructed into a 2×2 contingency table showing the presence or absence of VES in patients with or without COVID-19 infection.

The following statistical processes were all conducted using the 'meta' and 'metafor' packages of R software (version 3.6.3, R Foundation for Statistical Computing) in R Studio (version 1.2.5042). The random effects model with restricted maximum-likelihood (REML) estimator was used for pooling.

To calculate the pooled VES prevalence and 95% confidence intervals (CIs), logit transformation of the raw proportions was performed in advance to make them conform to a normal distribution. A normal approximation interval based on summary measure (NAsm) method was then used in R software for calculating 95% CIs. The association between the VES and COVID-19 infection was assessed and pooled in the form of an odds ratio (OR) with 95% CIs, also using the random effects model.

For pooled data, statistical heterogeneity between studies was examined with Cochrane's Q test and the inconsistency index (I^2) statistic. For the Q statistic, a P value <0.10 was considered statistically significant for heterogeneity; for I^2, a value >50% was considered to show significant heterogeneity (33). Publication bias was evaluated using funnel plot and Egger's test (34). Asymmetry of the funnel shaped distribution by visual inspection and a P value <0.10 in Egger's test was considered to indicate statistically significant publication bias.

Potential sources of heterogeneity were first analyzed through leave-one-out analysis i.e., leave one study out at a time, and get the pooling results from the remaining studies to see if there are huge variations after each leave-one-out. Sensitivity analysis, which mainly focused on the variations of the total heterogeneity after leave-one-out, was also conducted. Another adopted method was the influence diagnostic test provided by the 'metafor' package, which included calculation of externally standardized residual, DFFITS value, Cook's distance, covariance ratio, the leave-one-out amount of (residual) heterogeneity, the leave-one-out test statistic for the test of (residual) heterogeneity, and DFBETAS value. A study may be considered to be statistically influential if at least one of the following is true: the absolute DFFITS value is larger than $3\sqrt{(p/[k-p])}$, where p is the number of model coefficients and k the number of studies; the lower tail area of a Chi-square distribution with p degrees of freedom cut off by the Cook's distance is larger than 50%; the hat value is larger than 3(p/k); any DFBETAS value is larger than one (35,36).

Heterogeneity was further investigated using visual inspection and meta-regression analysis. The covariates selected through visual inspection included average age (over or less than 50-year-old), country (China or Italy), region [Hubei (epicenter) or the rest of the world], sample size ("n" smaller or larger than 50), VES distribution (clearly defined as inside the lesion area or not clearly defined), and slice thickness [no thicker than 1 mm (0–1 mm); greater than 1 mm but no thicker than 3 mm, (1–3 mm); greater than 3 mm; or slice thickness varying within the range of 0.625–5 mm]. Univariate meta-regression analyses were performed to test the individual association of selected covariates with the pooled estimates and to calculate the amount of heterogeneity each covariate accounts for (R^2 statistic) (37).

Based on univariate analyses, subgroup analyses were then performed. A multivariate meta-regression model was also developed based on sample size and VES distribution to determine the amount of heterogeneity these two covariates accounted for. Subgroups with no fewer than five studies that provided useful data were considered appropriate for calculating an accurate tau square; otherwise, a common tau square was estimated across subgroups.

Results

Literature search

The search initially identified a total of 3,773 articles, of which 1,934 were duplicates. The remaining 1,839 articles were screened based on title and abstract, and 147 of them eventually underwent full-text review after three main steps were conducted (*Figure 1*). No additional eligible studies from an extended search of references of included studies were identified for our meta-analysis. There were no disagreements between the two reviewers. Ultimately, a total of 22 studies evaluating 1,638 COVID-19 patients and 331 non-COVID-19 patients (8,9,11,13-15,38-53) were included. Among them, four studies (50-53) had comparisons of VES proportions between COVID-19 and non-COVID-19 patients.

Characteristics of included studies

Study characteristics are shown in *Table 1*. Overall, 21 studies were retrospective in design, and 1 study was prospective. The sample size of included studies ranged from 10 to 459. Additionally, seven studies were performed at multiple centers. Patient recruitment was consecutive in three studies.

Patient characteristics are described in *Table 2*. Patient enrollment took place from January to March in 2020. The source of COVID-19 patients included 11 provinces or municipalities in China and 2 different cities in Italy. Age at diagnosis ranged from 1 to 98 years old. CT acquisition parameters and scanner characteristics are shown in *Table 3*. Descriptions and main findings on VES of each study are also summarized in *Table 4*.

Quality assessment

Before conducting the quality assessment, a QUADAS-2 quality assessment rating guideline was made according to our study condition and with the consensus of all authors (for more details, readers can read the supplementary online). The quality assessment results according to the JBI checklist are listed in *Table 1*. All studies met the overall appraisal for inclusion criteria. Quality assessment details using JBI Critical Appraisal Checklist were listed in *Table S1*. Results of the QUADAS-2 study quality assessment are summarized in *Figure 2*. There was a certain amount of risk of bias in this meta-analysis, mainly arising from the patient selection and index test domains, as most studies were retrospective and did not clarify a consecutive or random enrollment of patients, or did not describe a blinding method during CT evaluation. Regarding the flow and timing domain, all studies had a low risk of bias.

Publication bias was investigated using a funnel plot. A symmetrical distribution of the funnel plot (*Figure 3*), and the P value >0.10 in Egger's test (P=0.29) indicated the unlikelihood of publication bias.

Prevalence and OR estimate of VES

VES rates were first calculated for each included study. The results are shown in *Table 4*. Pooled estimates of VES prevalence were then calculated for all 22 selected studies (8,9,11,13-15,38-53) comprising 1,638 COVID-19 patients. Because the prevalence extracted from those studies ranged from 19.2 to 94.7, logit transformation was performed on the raw prevalence data in advance. The results of the Shapiro–Wilk normality test (W=0.95533, P=0.401) confirmed the normal distribution of the transformed sample data. The overall pooled prevalence of VES in COVID-19 patients was 69.37% (95% CI: 57.40–79.20%) according to the random effects model. The I^2 statistic (94%, P<0.01) indicated substantial heterogeneity (*Figure 4*).

Further meta-analysis of three studies (51-53) after removing an identified outlier (50) showed patients with confirmed COVID-19 infection were more frequently to have VES manifestation on thoracic CT compared with those without COVID-19 infection (OR =6.43, 95% CI: 3.39–12.22, P<0.0001). The I^2 statistic (I^2=61%, P=0.08) indicated statistically significant heterogeneity (*Figure 5*).

Source of heterogeneity analysis: leave-one-out analysis, influence diagnostic test, and meta-regression

In influential analysis, the leave-one-out results of VES rates were relatively stable (67.04–71.41%) after removing each study (*Figure S1*), and no statistically significant influence

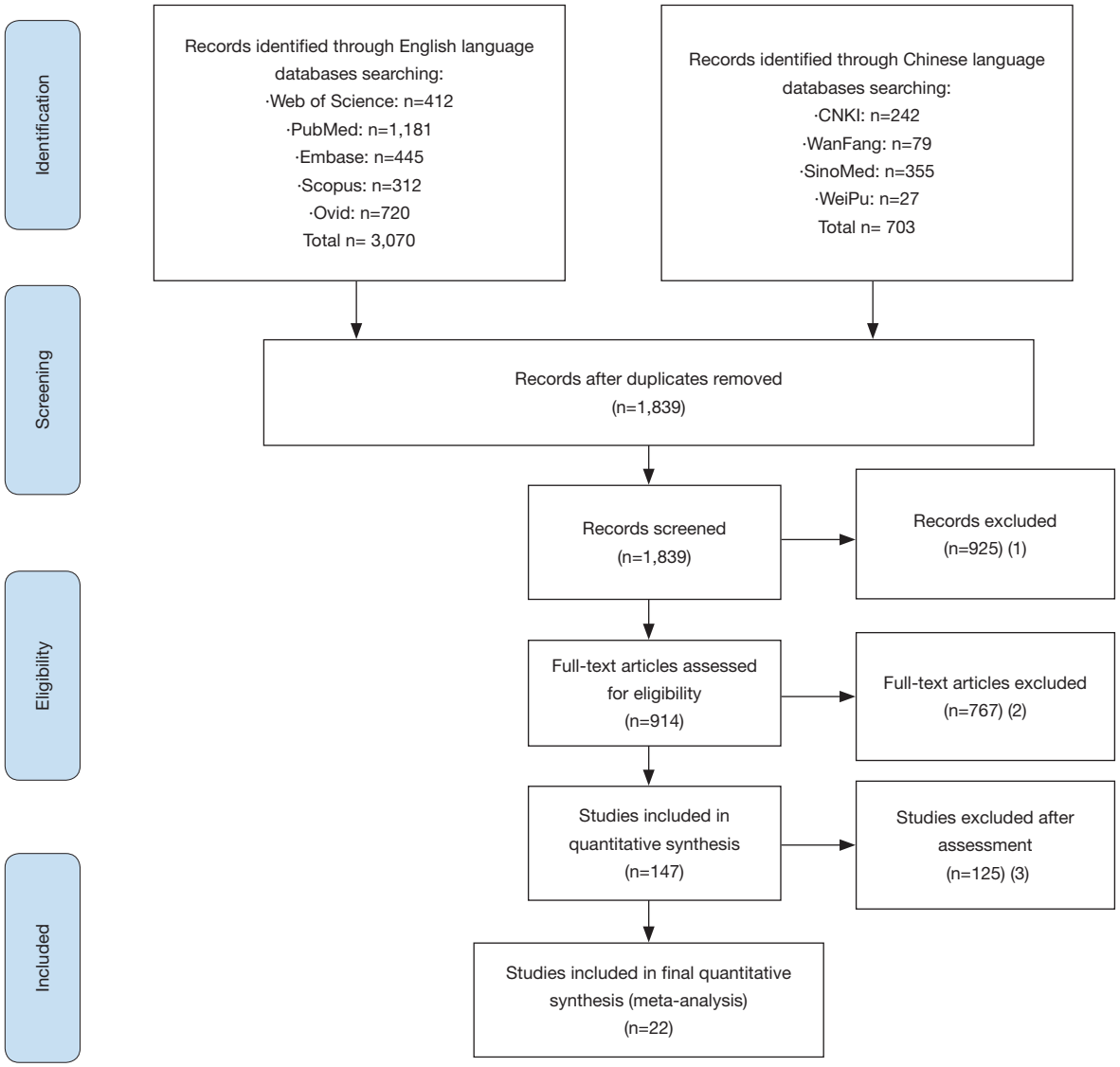

Figure 1 A flow diagram illustrating the study selection process for this meta-analysis. Step (1): language different from English or Chinese, non-original research, did not match the purpose of this study. Step (2): did not match the inclusion criteria, presence of exclusion criteria, irrelevant titles or abstracts. Step (3): lack of information, with incomplete result data on VES, did not reach a sufficient score in the quality assessment.

was identified through influence diagnostics among all the 22 included studies for prevalence pooling (*Figure S2*). However, one significant outlier (50) was identified when only the four studies that compared VESs in COVID-19 and non-COVID-19 patients were involved for pooling ORs (*Figure S3*); this study was then excluded in the OR calculating process.

After careful consideration of baseline features of included studies, six categorical covariates were identified as potential sources of heterogeneity. Univariate meta-regression against average age (P=0.665), country (P=0.711), region (P=0.755), VES distribution (P=0.031), sample size (P=0.183), and slice thickness (P=0.963) was conducted. Among them, only the VES distribution was found to have statistically significant effects to the overall pooled result. The R^2 (amount of heterogeneity accounted for) for the VES distribution was R^2_{VES}=15.33%. Together, the VES, and sample size accounted for 19.73% ($R^2_{VES+ sample}$

Table 1 Characteristics of the included studies

Study (No. reference)	Journal	Year of publication	Date (MM/DD)	Country	Institution	Total No. enrolled patients	Duration of patient recruitment	Consecutive enrollment	Multicenter study	Research type	Study type	JBI quality tool
Zhou SC *et al*. (14)	*American Journal of Roentgenology*	2020	02/19	China	Department of Radiology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, Hubei province, China	62	2020/01/16–2020/01/30	NR	No	Retrospective study	Cross-sectional	Include
Wu J *et al*. (38)	*European Radiology*	2020	04/23	China	Department of Radiology, Nanjing First Hospital, Nanjing Medical University, Nanjing, Jiangsu province, China	130	2020/01/24–2020/02/17	NR	Yes	Retrospective study	Cross-sectional	Include
Shi BB *et al*. (39)	*Shi Yong Lin Chuang Yi Yao Za Zhi (Journal of Clinical Medicine in Practice)*	2020	02/26	China	Department of Medical Imaging, Subei People's Hospital of Yangzhou University, Yangzhou, Jiangsu province, China	23	2020/01/21–2020/02/20	NR	No	Retrospective study	Cross-sectional	Include
Dai H *et al*. (8)	*International Journal of Infectious Diseases*	2020	04/01	China	Department of Radiology, the First Affiliated Hospital of Soochow University, Suzhou city, Jiangsu province, China	234	2020/01/10–2020/02/07	NR	Yes	Retrospective study	Cross-sectional	Include
Damiano C *et al*. (40)	*Radiology*	2020	04/03	Italy	Department of Surgical and Medical Sciences and Translational Medicine, Sapienza University of Rome-Sant'Andrea University Hospital, Via di Grottarossa, Rome, Italy	158	2020/03/04–2020/03/19	Yes	No	Prospective study	Cross-sectional	Include
Han R *et al*. (11)	*American Journal of Roentgenology*	2020	02/15	China	Department of Radiology, Wuhan No. 1 Hospital, Wuhan, Hubei province, China	108	2020/01/04–2020/02/03	No	No	Retrospective study	Cross-sectional	Include
Zhao W *et al*. (9)	*American Journal of Roentgenology*	2020	02/19	China	Department of Radiology, The Second Xiangya Hospital, Central South University, Changsha, Hunan province, China	101	NR	NR	Yes	Retrospective study	Cross-sectional	Include
Lu XF *et al*. (41)	*Zhong Hua Fang She Xue Za Zhi (Chinese Journal of Radiology)*	2020	02/04	China	Department of Radiology, Renmin Hospital of Wuhan University, Wuhan, Hubei province, China	141	2020/01/20–2020/01/28	No	No	Retrospective study	Cross-sectional	Include
Zhu ZX *et al*. (42)	*Xi Nan Da Xue Xue Bao (Zi Ran Ke Xue Ban) [Journal of Southwest University (Natural Science Edition)]*	2020	03/18	China	Puren Hospital of Wuhan University of Science and Technology, Wuhan, Hubei province, China	82	2020/01/30–2020/02/29	NR	No	Retrospective study	Cross-sectional	Include
Cheng SP *et al*. (13)	*Shandong Da Xue Xue Bao (Yi Xue Ban) [Journal of Shandong University (Health Sciences)]*	2020	04/08	China	Shandong Medical Imaging Research Institute Affiliated to Shandong University, Jinan, Shandong, China; Department of Radiology, Linyi People's Hospital, Lin Yi, Shandong, China; Department of Radiology, Yantai Qishan Hospital, Yantai, Shandong, China; Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University; Department of Radiology, Zaozhuang Municipal Hospital, Zaozhuang, Shandong, China	105	2020/01–2020/03	NR	Yes	Retrospective study	Cross-sectional	Include
Li M *et al*. (43)	*Zhong Nan Da Xue Xue Bao (Yi Xue Ban) (Journal of Central South Univercity (Medical Science))*	2020	02/26	China	Department of Radiology, Zhuzhou Central Hospital, Zhuzhou, Hunan province, China	57	2019/12/28–2020/02/20	NR	Yes	Retrospective study	Cross-sectional	Include
Lei PG *et al*. (15)	*Journal of X-Ray Science and Technology*	2020	03/09	China	Department of Radiology, the Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou province, China	14	2020/01/16–2020/02/22	Yes	No	Retrospective study	Cross-sectional	Include
Jie BK *et al*. (44)	*Canadian Association of Radiologists' Journal*	2020	04/20	China	Department of Radiology, Dezhou People's Hospital, Dezhou, Shandong province, China	24	2020/01/22–2020/02/05	NR	No	Retrospective study	Cross-sectional	Include
Zhao SQ *et al*. (45)	*Fen Zi Ying Xiang Xue Za Zhi (Journal of Molecular Imaging)*	2020	02/24	China	Department of Radiology, Baoan People's Hospital, Shenzhen, Guangdong province, China	13	NR	NR	No	Retrospective study	Cross-sectional	Include
Pascal L. *et al*. (46)	*European Journal of Radiology Open*	2020	04/01	Italy	Radiology Department, Valduce Hospital, Como, Italy	58	2020/02/15–2020/03/15	Yes	No	Retrospective study	Cross-sectional	Include
Meng C *et al*. (47)	*Guangdong Yi Xue (Guangdong Medical Journal)*	2020	03/02	China	Department of Respiratory and Critical Medicine, the People's Hospital of Hainan province, Haikou, Hainan province, China	20	2020/01–2020/02	NR	No	Retrospective study	Cross-sectional	Include
Li XH *et al*. (48)	*Shou Du Yi Ke Da Xue Xue Bao (Journal of Capital Medical University)*	2020	02/28	China	Department of Radiology, the First Affiliated Hospital of Anhui Medical University, Anhui province Clinical Image Quality Control Center; Department of Radiology, The People's Hospital of Bozhou, Hefei, Anhui province, China	26	2020/01–2020/02	NR	Yes	Retrospective study	Cross-sectional	Include
Li L *et al*. (49)	*Shou Du Yi Ke Da Xue Xue Bao (Journal of Capital Medical University)*	2020	02/28	China	Department of Radiology, Beijing Youan Hospital, Capital Medical University, Beijing, China; Department of Postgraduate, Jiangxi University of Traditional Chinese Medicine, Nanchang, Jiangxi province, China	25	2020/01/23–2020/02/06	NR	No	Retrospective study	Cross-sectional	Include
Zhang Y *et al*. (50)	*Lin Chuang Hui Cui (Clinical Focus)*	2020	02/28	China	Department of Medical Imaging, the Second Hospital of Hebei Medical University, Shijiazhuang, Hebei province, China	40	2020/01/26–2020/02/12	NR	Yes	Retrospective study	Cross-sectional	Include
Xiao HJ *et al*. (51)	*Zhengzhou Da Xue Xue Bao (Yi Xue Ban) [Journal of Zhengzhou University (Medical Sciences)]*	2020	03/03	China	Department of Radiology, the First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan province, China	54	2020/01/20–2020/02/25	NR	No	Retrospective study	Cross-sectional	Include
Hu R *et al*. (52)	*Zhong Hua Fang She Xue Za Zhi (Chinese Journal of Radiology)*	2020	03/05	China	Department of Imaging, Shi Yan Tai He Hospital Affiliated of Hubei University of Medicine, Shiyan, Hubei province, China	202	2020/01/21–2020/02/10	NR	No	Retrospective study	Cross-sectional	Include
Bai HX *et al*. (53)	*Radiology*	2020	03/10	China and USA	Department of Diagnostic Imaging, Rhode Island (RI) Hospital, Providence, RI, USA	424	COVID-19 patients: 2020/01/06–2020/02/20 Patients with other viral pneumonia: 2017-2019	NR	Yes	Retrospective study	Cross-sectional	Include

JBI, Joanna Briggs Institute; MM/DD, month/date; NR, not reported.

Table 2 Patient characteristics

Study (No. reference)	No. patients		Method for pathogen confirmation	Source of patients	Average age (y-old)	Age range (y-old)	Sex	Patient disease severity	Comparison	CT abnormal
	SARS-CoV-2 tested positive	SARS-CoV-2 tested negative								
Zhou SC *et al*. (14)	62	_	RT-PCR	Wuhan, Hubei province, China	52.8±12.2	30–77	Male: 39, female: 23	NR	_	62
Wu J *et al.* (38)	130	_	Nucleic acid test	Jiangsu province, Shandong province, Guangxi province, Guangdong province, Henan province, Jiangxi province, China	42.9±15.0	25–80	Male: 78, female: 52	NR	_	130
Shi BB *et al.* (39)	23	_	Nucleic acid test	Yangzhou, Jiangsu province, China	50.2±13.0	22–72	Male: 10, female: 13	NR	_	23
Dai H *et al.* (8)	234	_	RT-PCR; genetic sequencing analysis	Jiangsu province, China	44.6±14.8	7–82	Male: 136, female: 98	Mild: 9, moderate: 210, severe: 13, critical: 2	_	219
Damiano C *et al.* (40)	62	96	RT-PCR	Rome, Italy	57±17	18–89	Male: 83, female: 75	NR	_	102
Han R *et al.* (11)	108	_	RT-PCR	Wuhan, Hubei province, China	45	21–90	Male: 38, female: 70	Mild: 108	_	108
Zhao W *et al. (9)*	101	_	Isolation of SARS-COV-2 or RT-PCR assay	Four cities in Hunan province,, China,	44.44±12.32, median: 43	17–75	Male: 56, female: 45	Mild and moderate: 87, severe and critical: 14	_	All: 93, mild & moderate: 79, severe & critical: 14
Lu XF *et al*. (41)	141	_	RT-PCR	Wuhan, Hubei province, China	Median: 49	9–87	Male: 77, female: 64	NR	_	141
Zhu ZX *et al.* (42)	82	_	RT-PCR	Wuhan, Hubei province, China	Male: 45.13±14.28 female: 48.33±15.24	NR	Male: 38, female: 44	Mild: 10, moderate: 60, severe &, critical: 12	_	76
Cheng SP *et al.* (13)	105	_	RT-PCR	Shandong province, China	48±14	21–88	Male: 58, female: 47	Mild: 0, moderate: 92, severe &, critical: 13	_	NR
Li M *et al.* (43)	57	_	RT-PCR	Zhuzhou, Hunan province, China	Median: 47	18–82	Male: 30, female: 27	NR	_	Initial CT: 54, follow-up CT: 57
Lei PG *et al*. (15)	14	_	RT-PCR	Guiyang, Guizhou province, China	47±19	12–83	Male: 8, female: 6	NR	_	10
Jie BK *et al.* (44)	24	_	RT-PCR	Dezhou, Shandong province, China	48.80±17.41	18–83	Male: 16, female: 8	Mild: 17, severe: 7	_	24
Zhao SQ *et al*. (45)	13	_	RT-PCR	Shenzhen, Guangdong province, China	49±12	31–67	Male: 9, female: 4	Mild: 1, moderate: 11, severe: 1	_	12
Pascal L. *et al.* (46)	58	_	RT-PCR	Como, Italy	66.3±16.6	18–98	Male: 36, female: 22	NR	_	40
Meng C *et al.* (47)	20	_	RT-PCR	Haikou, Hainan province, China	51±14	27–73	Male: 13, female: 7	Mild: 1, moderate: 18, severe: 1, critical: 0	_	19
Li XH *et al.* (48)	26	_	RT-PCR	Anhui province, China	Median: 40.5	8–60	Male: 16, female: 10	NR	_	26
Li L *et al.* (49)	25	_	RT-PCR; genetic sequencing analysis	Beijing, China	49.72±20.69	1–89	Male: 10, female: 15	NR	_	25
Zhang Y *et al*. (50)	40	20	RT-PCR; genetic sequencing analysis	Hebei province, China	COVID-19: 49.33±14.19	COVID-19: 25–79	COVID-19: male: 20, female: 20	NR	Patients with other pneumonia	COVID-19: 40 (No. patients), 459 (No. lesions)
					Non-COVID-19: 48.90±21.96	Non-COVID-19:7–81	Non-COVID-19: male: 9, female: 11			Non-COVID-19: 20 (No. patients), 258 (No. lesions)
Xiao HJ *et al.* (51)	25	29	Pathogen nucleic acid tests	Zhengzhou, Henan province, China	COVID-19: ≤50 16 cases, >50 9 cases	COVID-19: 3–94	Male: 29, female: 25	NR	BP: 9 (streptococcus: 6, Klebsiella: 3); MP: 10; P Ed: 2; Can.: 1; AP: 2; EI: 1; PCP: 1; Flu P.: 2; CMV P.: 1	COVID-19: 25
					Non-COVID-19: NR	Non-COVID-19: NR				Non-COVID-19: 29
Hu R *et al*. (52)	105	97 (5 cases turned positive during follow-up)	Nucleic acid test	Shiyan, Hubei province, China	COVID-19: 44.38±15.69	NR	COVID-19: male: 55, female: 50	NR	Suspected COVID-19 (>2 times negative RT-PCR results)	COVID-19: 104
					Non-COVID-19: 37.00±25.43		Non-COVID-19: male: 59 female: 38			Suspected-COVID-19: 97
Bai HX *et al*. (53)	219	205	RT-PCR for COVID-19	COVID-19 patients: Hunan province, China;	COVID-19: 44.8±14.5	COVID-19: 4–76	COVID-19: male: 119, female: 100	COVID-19: mild: 6, moderate: 190, severe: 14, critical: 7	Patients with other viral pneumonia	COVID-19: 219
			Respiratory Pathogen Panel (RPP) test for other viral pneumonia	Other viral pneumonia patients: Rhode Island, USA	Non-COVID-19: 64.7±18.6	Non-COVID-19: 3–96	Non-COVID-19: male: 103, female: 102	NR		Non-COVID-19: 205

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19,coronavirus disease 2019; Non-COVID-19: non-coronavirus disease 2019; RT-PCR: reverse transcription-polymerase chain reaction; NR, not reported; y-old, year old; BP, bacterial pneumonia; MP, mycoplasmal pneumonia; P Ed, pulmonary edema; Can., lung cancer; AP, aspiration pneumonia; EI, eosinophilic infiltration of lung; PCP, pneumocystis pneumonia; Flu P., influenza virus pneumonia; CMV P., cytomegalovirus pneumonia.

Table 3 CT acquisition parameters and scanner characteristics

Study (No. reference)	Image acquisition time	CT scanner	Slice thickness (mm)	Slice interval (mm)	Tube voltage (kv)	Tube current modulation (mAs)	Contrast enhancement	No. CT readers	CT reader experience (year)
Zhou SC *et al*. (14)	Initial CT and follow-up CT	the 16-MDCT LightSpeed scanner (GE Healthcare) or the uCT 760 scanner (United Imaging)	1.25	NR	100–120	200–300	No	2	13, 9 respectively
Wu J *et al.* (38)	All patients' initial CT and 35 last follow-up CT	Siemens SOMATOM Definition AS 128-slice spiral CT, US; NeuViz 128-slice CT, China; GE LightSpeed V spiral CT, US	5	NR	NR	NR	No	10	>5
Shi BB *et al.* (39)	Unclear	Cannon Aquilion Prime 160 16-slice CT	5	5	120	NR	No	2	NR
Dai H *et al.* (8)	On admission, within 24 h after admission	GE Bright Speed Elite 16, Neusoft 16, SOMATOM Emotion, SOMATOM definition AS, PHLIPS MX-16, Philips 64-row spiral Ingenuity and the UNITED IMAGING Elite 16	5	NR	120	110	No	5	>10
Damiano C *et al.* (40)	After the RT-PCR swabs	128-slice CT (GE Revolution EVO 64 Slice CT Scanner)	0.625	NR	120	100–250	No	2	15, 25 respectively
Han R *et al.* (11)	On admission, initial CT	BrightSpeed (GE Healthcare) or Somatom, Definition Flash (Siemens Healthineers) scanner	10	NR	120	50–350	No	2	>5
Zhao W *et al*. (9)	On admission, mean interval between first CT scan and admission: 1d	Anatom 16HD (Anke Medical Solutions), HiSpeed-Dual (GE Healthcare), 64-MDCT LightSpeed VCT (GE Healthcare), and Somatom Emotion (Siemens Healthcare)	0.625-5	NR	120	100–200	No	2	5, 15 respectively
Lu XF *et al.* (41)	On admission, initial CT	GE HealthOptima 680 and Brightspeed CT	0.625	5	120	200	No	2	NR
Zhu ZX *et al.* (42)	On admission, initial CT	GE Optima 660	0.625	5	120	50–400	No	2	NR
Cheng SP *et al*. (13)	Initial CT: within 1w after positive RT-PCR test; follow-up CT: during hospitalization	Siemens: 16-slice spiral CT; GE: 64-slice spiral CT; Philips: 128-slice spiral CT	5	5	100–120	100–200	No	2	NR
Li M *et al.* (43)	Initial CT: on admission; follow-up CT: during hospitalization	GE/Siemens: 64-slice spiral CT	2.5	NR	120	100	No	3	>10
Lei PG *et al*. (15)	On admission, initial CT	128-slice MSCT (SOMATOM Definition AS+, Siemens, Germany); 16-slice MSCT (Aquilion16, Toshiba Medical, Nasu, Japan)"	1 or 5	NR	120	150	No	2	6, 20 respectively
Jie BK *et al*. (44)	Initial CT: on admission; follow-up CT: during hospitalization	128-slice spiral CT system (LianYing, Shanghai, China)	5	NR	80–120	NR	No	2	NR
Zhao SQ *et al.* (45)	On admission, initial CT	GE Optimal 680 64-channel 128-slice spiral CT	0.625	NR	120	120–150	No	2	NR
Pascal L. *et al.* (46)	On admission, initial CT	MDCT scanner with 64 channels	1	1	120	60–120	No	2	12, 32 respectively
Meng C *et al.* (47)	Initial CT	Neusoft 128-slice spiral CT	1	1	NR	NR	No	2	>5
Li XH *et al.* (48)	On admission, initial CT	Toshiba Aquilion 64-slice CT, GE Light Speed CT, GE Optima CT540 16-slice CT	5	2	120	120–200	No	2	NR
Li L *et al.* (49)	0–5 d from symptom onset	Philips Brilliance iCT 256	5	NR	120	NR	No	2	NR
Zhang Y *et al*. (50)	Initial CT	GE Lightspeed 16-slice CT	5	2	NR	NR	No	NR	NR
Xiao HJ *et al.* (51)	Initial CT: on admission; follow-up CT: 3–6 d after first CT scan	GE Revolution; SOMATOM Force, Siemens	1	0.5–1.0	120	50–200	No	2	>8
Hu R *et al*. (52)	Unclear	GE OPTIMA 540 16-slice CT scanner	5	5	120	200	No	3	NR
Bai HX *et al*. (53)	Unclear	SIEMENS: SOMATOM Definition; Emotion 16; SOMATOM go.Now; SOMATOM Definition AS20; SOMATOM Definition AS+ GE: BrightSpeed; LightSpeed Ultra; LightSpeed VCT/Resolution; Lightspeed 16/Optima CT580 Philips: Access CT; Hitachi ECLOS	0.6–2.5	NR	100–130	30–450	No	2	>5

CT, computed tomography; MDCT, multidetector computed tomography; MSCT, multislice computed tomography/multisection computed tomography; GE, General Electric Company; NR, not reported.

Table 4 Summary of descriptions and main findings on VES of included studies

Study (No. reference)	No. patients with VES (VES rate)[†]	VES description	Main findings on VES
Zhou SC *et al.* (14)	28 (45.2)	Microvascular dilation sign (dilated small vessels in the lesion)	28 (45.2%) patients had microvascular dilation sign; The microvascular dilation sign probably indicated increased blood supply to the inflammatory area
Wu J *et al.* (38)	100 (76.9)	Vascular thickening, accompanying sign	Vascular sign: On thoracic CT, vascular thickening within lesion areas were found in 76.9% of COVID-19 patients, which was conformed to the general vascular changes during inflammation. We considered that the inflammatory stimuli could increase vascular permeability and consequently gave rise to the dilation of capillaries and thickening of the corresponding pulmonary artery
Shi BB *et al.* (39)	10 (43.5)	Vascular augmentation	10 cases (43.5%) had vascular augmentation, which indicated the congestion and edema of pulmonary interstitial around vessels
Dai H *et al.* (8)	207 (94.5)	Vascular enhancement sign (VES, vascular enlargement inside the lesion resulted from congestion and dilation of small vessels)	The frequency of VES was the highest (94.5) among all CT signs, and no significant difference among the four stage groups of CT performance (stage I: early stage, stage II: progressive stage, stage III: recovery stage, stage IV: severe stage)
Damiano C *et al.* (40)	52 (89.0) (mean vessel diameter: 3.9±0.6 mm)	Vessel enlargement; enlarged subsegmental pulmonary vessel; subsegmental vascular enlargement (more than 3 mm diameter)	An enlarged subsegmental vessel, defined as vessel diameter >3 mm, was observed in 52/58 patients (89%) with mean vessel diameter of 3.9±0.6 mm., On CT, subsegmental vascular enlargement (more than 3 mm diameter) in areas of lung opacity was observed in 89% of patients with confirmed COVID-19 pneumonia
Han R *et al.* (11)	86 (80)	Vascular thickening	Eighty-six (80%) patients had vascular thickening
Zhao W *et al.* (9)	All: 72 (77.4), moderate & mild: 59 (74.7), severe & critical: (92.9)	Vascular enlargement in the lesion	We found that most patients had vascular enlargement of the lesion (71.3%) that might have been caused by an acute inflammatory response
Lu XF *et al.* (41)	48 (34.04)	Bronchovascular bundle thickening and vascular perforator sign	48 (34.04%) had bronchovascular bundle thickening and vascular perforator sign, which was relevant to pulmonary interstitial changes, such as edema and thickening of bronchial walls and interstitial around vessels
Zhu ZX *et al.* (42)	68 (89.47)	GGO lesions with vascular bundle thickening	GGO lesions with vascular bundle thickening were found in 64 (64/70, 91.43%) COVID-19 patients, while absence of this manifestation were only found in 6 (6/70, 8.57%) patients
Cheng SP *et al.* (13)	42 (40.0)	Microvascular dilation sign (MVDS), defining as the abnormal tortuous and enlarged shape of tiny blood vessels.	Our study adopted reconstruction method of chest HRCT to pay special attention on specific interstitial changes in the extrapulmonary zone. We found that the microvascular dilation sign (MVDS) was presented in 40% of our patients. The pathology mechanism might be associated with vascular proliferation, thickening of tiny blood vessels and congestion of alveolar walls
Li M *et al.* (43)	46 (80.70)	Thick vascular shadows in the lesions; thickened small blood vessels	46 cases (80.70%) had thick vascular shadows in the lesions. The congestion and dilation of pulmonary vessels caused by inflammatory stimuli might explain the underlying mechanism
Lei PG *et al.* (15)	9 (90.0)	Bronchovascular enlarged	Presence of bronchovascular enlarged was up to (9/10, 90%)
Jie BK *et al.* (44)	8 (33.33)	Vascular thickening; vasodilatation sign; thickening of adjacent vessels; widening of pulmonary-vessel diameters in the lesion area	Computed tomography also showed widening of pulmonary-vessel diameters in the lesion area, which was considered to be due to the increased oxygen exchange in blood caused by virus damage to the stroma and parenchyma of the lung
Zhao SQ *et al.* (45)	9 (75.0)	Thickening of the adjacent bronchial bundle	Accompanying sign: thickening of the adjacent bronchial bundle was observed in 9 cases (9/12)
Pascal L. *et al.* (46)	10 (25.0)	Vascular thickening, vascular enlargement	We noted the presence of perilesional vascular thickening in ten patients (23.8%), representing a peculiar CT manifestation of COVID-19
Meng C *et al.* (47)	18 (94.7)	Enlarged vascular lumens and blood vessel penetration sign	Enlarged vascular lumens and blood vessel penetration sign were found common in our study (18 patients, 94.7%)
Li XH *et al.* (48)	5 (19.2)	Bronchovascular bundle thickening and vascular perforator sign; GGO with internal bronchovascular bundle thickening	Bronchovascular bundle thickening and vascular perforator sign were seen in 5 patients (19.2%)
Li L *et al.* (49)	19 (76.0)	Ground glass opacity with thickened blood vessels and dilated bronchioles	The early chest CT manifestations of COVID-19 were most commonly ground glass opacity, with thickened blood vessels and dilated bronchioles, which might be caused by the inflammatory stimulation
Zhang Y *et al.* (50)	COVID-19 No. lesions: 416 (90.63), Non-COVID-19 No. lesions: 3 (1.16)	Vascular thickening	In NCP group, the number of lesions with vascular thickening was 416 (90.63%), while in non-NCP group, the number was only 3 (1.16%). Significant difference (P<0.01) was found between the two groups. The CT signs of NCP are characteristic, and they may be more likely to invade blood vessels and cause vasculitis, which may lead to pulmonary edema and cardio-pulmonary circulation disorder
Xiao HJ *et al.* (51)	COVID-19: 17 (68.0), Non-COVID-19: 10 (34.4)	Ground glass density and thickening of the interval inside flocculus, accompanying vessels enlargement	Stimulation of inflammatory cytokines can increase the vascular permeability of alveolar septal capillaries. The transudate, therefore, can enter the extravascular space, which can manifest as the vessel enlargement under the GGO background
Hu R *et al.* (52)	COVID-19: 73 (70.2), Non-COVID-19: 16 (16.5)	Vascular thickening	73 cases in our study had vascular thickening manifestation. Because most lesions were of ground glass density, the vessels could be clearly observed, and many of them were enlarged. This phenomenon might be related to abnormalities of pulmonary interstitial around vessels and the congestion and dilation of vessels due to inflammation
Bai HX *et al.* (53)	COVID-19: 129 (59.0), Non-COVID-19: 46 (22.0)	Vascular thickening	The most discriminating features for COVID-19 pneumonia included a peripheral distribution (80% *vs.* 57%, P<0.001), ground-glass opacity (91% *vs.* 68%, P<0.001) and vascular thickening (58% *vs.* 22%, P<0.001)

[†], VES rates were revised and recalculated using the original figures, as we redefined the dominator to be the total number of patients who had both positive SARS-COV-2 test result and abnormal thoracic CT, or the total number of lesions on thoracic CT of those patients in each study. VES, vascular enlargement sign; COVID-19, coronavirus disease 2019; Non-COVID-19, non-coronavirus disease 2019; CT, computed tomography; HRCT, high resolution computed tomography; GGO, ground glass opacity; NCP, novel coronavirus pneumonia; non-NCP, non-novel coronavirus pneumonia; *vs*, versus.

Figure 2 QUADAS-2 quality assessment of included studies. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2.

$_{size}$=19.73%) of the total amount of heterogeneity.

Variations in VES prevalence: subgroup analysis

Subgroup analyses of all 22 studies according to average age, country, region, VES distribution, sample size, and slice thickness were also conducted. The results are shown in *Figures 6*,*S4-S8*.

Studies with a sample size larger than 50 reported a higher VES prevalence of 74.61% (95% CI: 62.68–83.72%), while a rate of 57.24% (95% CI: 32.68–78.68%) was found in studies with sample sizes smaller than 50, but the differences were not statistically significant (P=0.183). When prevalence was stratified by VES distribution,

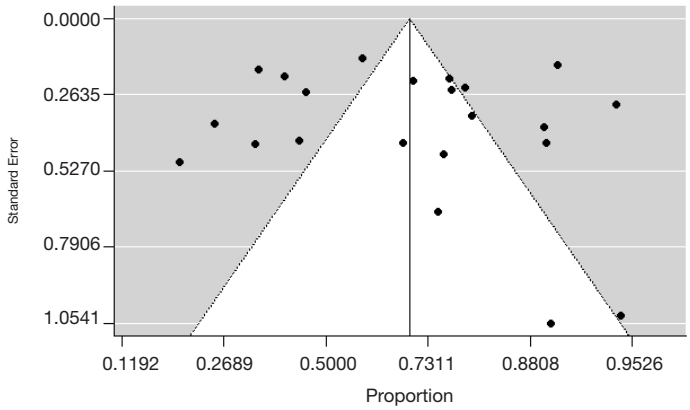

Figure 3 Funnel plot with 95% confidence interval (CI) to assess publication bias.

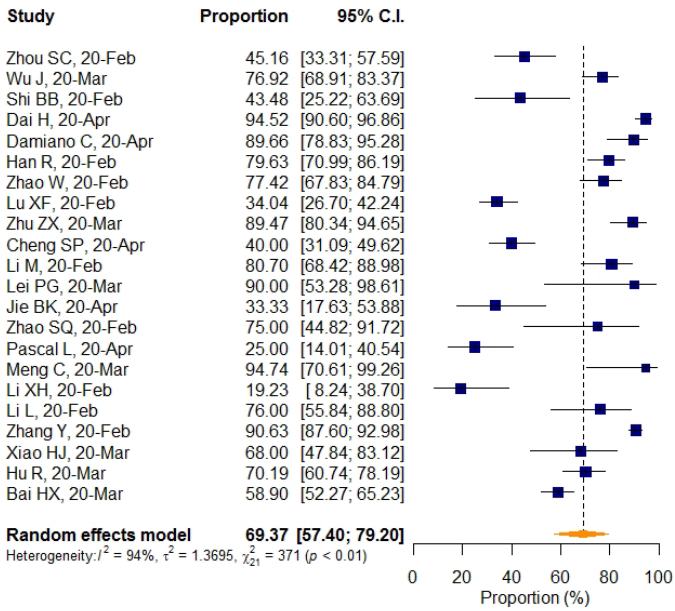

Figure 4 Forest plot of VES prevalence. VES, vascular enlargement sign.

VESs that were explicitly defined as inside the lesion area were shown to have relatively higher prevalence (80.33%; 95% CI: 68.79–88.32%), than VESs that were distributed either inside or outside of the lesion area (59.51%; 95% CI: 42.33–74.64%). The meta-regression (P=0.031) as mentioned before, indicated that this difference was statistically significant, even though a small portion of the two 95%CIs overlapped (*Table 5*).

No significant difference in VES rates was found between patients from different countries (China/Italy), regions (Hubei/outside Hubei), average age groups (over/less than 50-year-old), or among CT images acquired at different slice thicknesses.

Discussion

Our study presents a comprehensive meta-analysis of pulmonary vascular enlargement manifestations on thoracic CT of COVID-19 patients. To the best of our knowledge, this is the first meta-analysis to focus on vascular changes caused by SARS-Cov-2 on thoracic CT. With the accumulation of clinical experience and the proliferation

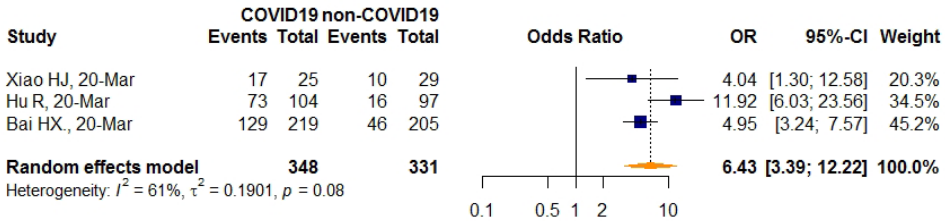

Figure 5 Forest plot comparing VES prevalence in COVID-19 versus non-COVID-19 cases. VES, vascular enlargement sign.

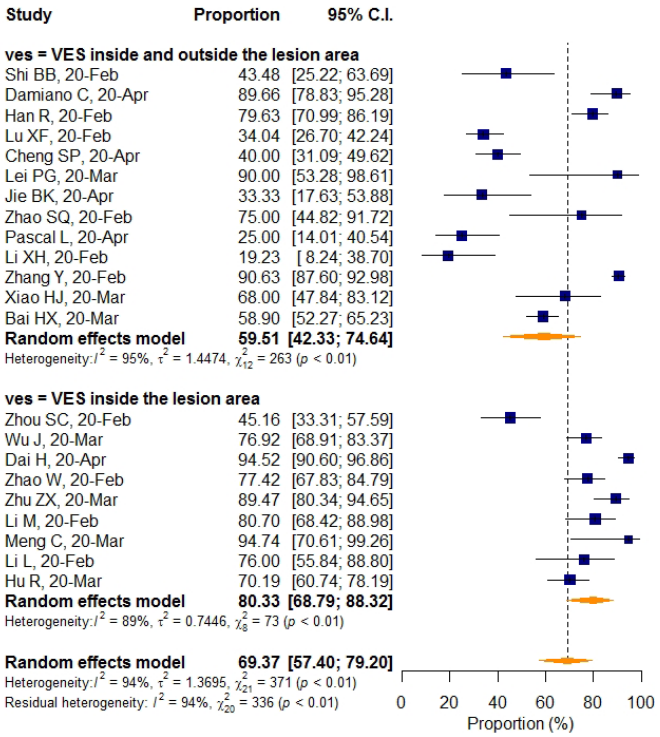

Figure 6 Forest plot of the subgroup analysis by VES distribution. VES, vascular enlargement sign.

of medical studies, the evidence clearly indicates that COVID-19 patients are at a higher risk of pulmonary vascular damage and blood coagulation dysfunction.

Elevated D-dimer levels and blood hypercoagulability were found to be common among hospitalized COVID-19 patients (18,19), and prominent elevation of D-dimmer and comorbidities relating to blood circulation, such as hypertension, could predict poorer prognosis of COVID-19 (54). With regard to pathologic findings, Dr. Menter *et al.* published a 21-case post-mortem multi-organ autopsy study in Switzerland (55), reporting exudative diffuse alveolar damage (DAD) with massive capillary congestion in most of the cases and accompanying microthrombi of alveolar capillaries despite anticoagulation in 45% of all cases. Besides this, pulmonary embolisms, alveolar hemorrhage, vasculitis, and signs of disseminated intravascular coagulation (DIC) with small fibrin thrombi in glomerular capillaries were also found. Yao and colleagues have also reported the presence of congested, edematous and widened blood vessels of the alveolar septum, and hyaline thrombi in microvessels in both the lung and kidney (56). Importantly, another pathology study consisting of five cases from the USA by Magro *et al.* (57) revealed that, apart from DAD with edema, hyaline membranes, inflammation,

Table 5 Subgroup analyses

Subgroups comparison	Studies (N)	Pooled prevalence (%)	95% confidence interval (%)
Average age, P=0.665			
Less than 50 y-old	17	71.15	58.58–81.13
Over 50 y-old	5	63.76	29.79–87.95
Country, P=0.711			
China	20	70.08	57.30–80.34
Italy	2	62.33	22.31–90.51
Region, P=0.755			
Hubei	5	66.35	42.33–84.12
Outside Hubei	17	70.37	55.97–81.61
Sample size, P=0.183			
Larger than 50	14	74.61	62.68–83.72
Smaller than 50	8	57.24	32.68–78.68
VES distribution, P=0.031*			
VES inside the lesion area	9	80.33	68.79–88.32
VES inside and outside the lesion area	13	59.51	42.33–74.64
Slice thickness, P=0.963			
(0,1] mm	7	71.52	47.55–87.43
(1,3] mm	2	64.73	23.02–91.84
Greater than 3 mm	10	67.33	47.67–82.34
Varied within [0.625, 5] mm	3	75.37	39.00–93.61

P values denoted the comparison between subgroups sorted by each moderator. *, indicates a significant P value. VES, vascular enlargement sign; y-old, year old.

and type II pneumocyte hyperplasia, which were reported by preliminary studies as features characteristic of typical ARDS, the pulmonary abnormalities in their patients appeared largely restricted to the alveolar capillaries, which is more characteristic of a thrombotic microvascular injury with few signs of viral cytopathic or fibroproliferative changes. Cases of pulmonary embolism and symmetric cutaneous vasculitis in COVID-19 patients were also reported by Dr. Rotzinger (20) and Dr. Castelnovo (58), respectively.

On thoracic CT, VES was usually defined as blood vessels seen thickening and passing through or passing by the ground glass opacity (GGO), the probable pathological basis of which might be congestion of alveolar septal capillaries (59). Our meta-analysis across 22 studies included a total of 1,969 patients from China, the United States (U.S.), and Italy in regions inside or outside of Hubei (the epicenter) who had undergone non-contrast thoracic CT scans. Herein, we paid special attention to vascular features in those studies in order to ascertain the vascular changes observed by CT and to explore their role in diagnosis. Before synthesis, we strictly followed the QUADAS-2 critical appraisal tool and JBI checklist to define the methodologic quality of each study. We strictly applied inclusion and exclusion criteria and up-to-date estimates using a random effects model with logit transformed values. We found that the overall pooled prevalence of VES among COVID-19 patients was 69.37% (95% CI: 57.40–79.20%). Because the number (four) of studies that reported VES proportions in non-COVID-19 patients was considered small and the enrolled non-COVID-19 patient characteristics of each study varied, the VES prevalence was

not pooled in the non-COVID-19 group. After exclusion of one outlier, which had a different, yet much larger sample size (No. of lesions) and reported a much greater VES rate than the other three, the OR pooling results showed that VES manifestation was more frequently observed in COVID-19 patients than in non-COVID-19 patients, (OR =6.43, 95% CI: 3.39–12.22). The main descriptions and findings of VES are systematically summarized in *Table 4*.

After pooling, heterogeneity was detected and analyzed using a meta-regression model and subgroup analysis. Interestingly, VES distribution was found as a source of heterogeneity (R^2=15.33%). Studies that explicitly defined VES in the lesion area pooled a significantly higher prevalence (80.33%, 95% CI: 68.79–88.32%) than studies without a clear definition of VES distribution (59.51%, 95% CI: 42.33–74.64%) (P=0.03), which might indicate a possible underestimation of VES prevalence when lacking an established standard.

Subgroup analyses also revealed a relatively higher VES rate in studies with a sample size larger than 50, but the difference was not statistically significant. No significant difference in VES rates was found between patients from different countries (China/Italy), regions (Hubei/outside Hubei), average age groups (over/less than 50-year-old), or among images acquired at different CT slice thicknesses. The above non-significant moderators also suggested that VES prevalence was relatively stable regardless of patient age, sample size, country, region, CT scan slice thicknesses.

VES findings in COVID-19 patients with different clinical severities or at different disease stages were not analyzed due to limited study materials. However, as reported by Zhou *et al.* (14) and Zhao *et al.* (9) no significant differences of VES rates were found among patients at the early phase (no more than 7 days after symptom onset) or advanced phase (8–14 days after symptom onset) of COVID-19, or among non-emergency groups (mild and common clinical types) and emergency groups (severe and fatal clinical types) of COVID-19.

Although the specific physiopathologic mechanisms of VES remain unclear, previous evidence has shown that SARS-CoV-2 had a much stronger ability to combine with angiotensin-converting enzyme 2 (ACE2) receptor compared with SARS-CoV-1 (60), which indicates a higher chance of immunoreaction in the vessels. Reduced expression of ACE2 in the vasculature may also promote endothelial dysfunction and inflammation and exacerbate existing atherosclerosis and diabetes (61-65). As reported by Magro *et al.*, extensive deposition of complement components within the lung septal microvasculature might result in membrane attack complex-mediated microvascular endothelial cell injury and subsequent activation of the clotting pathway (57). Although the term "vascular enlargement" for chest CT might be non-specific and was interchangeably reported by different studies, as mentioned by Salehi *et al.* (66), our results suggest that considering VES along with other specific CT manifestations of COVID-19 would be very helpful for the diagnosis and differential diagnosis of COVID-19.

Some limitations were identified in this meta-analysis. First, a great degree of heterogeneity was identified across most estimates (I^2>80%), with only about 20% of the heterogeneity being attributable to VES distribution, and sample size. This leaves the other factors that contributed to large remaining portion of heterogeneity unidentified, making it difficult to obtain valid and stable meta-analysis results despite the use of a standardized analysis process. Second, quality assessment showed that many involved studies were retrospective. Thus, a consecutive enrollment of patients or a blind method in CT evaluation during the study period was not always applied. Third, we did not compare VES findings in patients with different clinical severities or at different disease stages of COVID-19 infection due to the insufficient figures found in the studies. Fourth, even though we tried our best to search for all eligible studies available online without any nationality restriction, we only got study populations coming from China, U.S., or Italy. With COVID-19 becoming a global pandemic, future studies are encouraged to involve patient population from more different countries. Furthermore, to our knowledge, vascular enlargement sign (VES) has not been uniformly described in the widely read glossaries of thoracic imaging (67), and thus requires a standard definition in the near future. Future meta-analysis should include more prospective cohort studies to control the possible bias during evaluation and lower the heterogeneity across studies.

Conclusions

Pulmonary VES on thoracic CT was found in almost two-thirds of the COVID-19 patients and was more prevalent in COVID-19 patients than in non-COVID-19 patients. While the physiopathologic mechanisms remain unclear, the current findings suggest a promising role of VES for identifying pneumonia caused by coronavirus and indicate that more attention should be paid to pulmonary vascular

changes in thoracic CT–based diagnosis.

Acknowledgments

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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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QUADAS-2 Quality Assessment Rating Guideline (32,68)

Domain 1: patient selection

Signaling questions and answering guidelines

Was a consecutive or a random sample of persons enrolled?

Since CT examination is usually taken as a recommendation rather than a must-do test for all/consecutive COVID-19 patients, it is acceptable that original studies focusing on CT manifestations will not have to enroll all/consecutive COVID-19 patients, but patients with a CT scan. Therefore, it will not be considered a high risk of bias when the study excludes patients without available CT results.

Answer 'yes' if one of the following conditions is met.

(I) It is explicitly stated in the study report that enrolment was consecutive (or random).

(II) It is reported that all eligible, screened, or potential study participants with a CT scan were included, and that enrollment took place at all hours on any day during the enrolment period.

Answer 'no' if neither of the conditions is met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Was a case-control design avoided?

This question is irrelevant because studies with case-control design are excluded from the review.

Did the study avoid inappropriate exclusions?

Answer 'yes' if both of the following conditions are met.

(I) The appropriate exclusion criteria are explicitly explained in the study.

(II) No exclusions that are unrelated to execution of the index test (e.g. fear of radiation exposure, inability to be positioned, sex or age restriction).

Answer 'no' if neither of the conditions is met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Guidelines for assessing risk of bias

Risk of bias from patient selection will be assessed as 'low' when signaling question 1 and 3 are answered 'yes'.

Risk will be assessed as 'high' when signaling question 1 or 3 is answered 'no'.

Risk will be assessed as 'unclear' when insufficient information is reported to answer signaling question 1 or 3.

Guidelines for assessing concern regarding applicability

Is there concern that the included patients do not match the review question?

Concern regarding applicability in relation to patient selection will be assessed as 'low' when the study population represents an unselected sample of patients with suspected COVID-19. Because the study question concerns the CT manifestation for diagnosing COVID-19 in the general population, exclusion of children or persons with diabetes etc. will be considered inappropriate. By contrast, we do not consider it inappropriate if persons with extreme a priori probabilities of COVID-19 or non-COVID-19 are excluded. As stated in the background section, it is probably in persons with intermediate a priori probability that CT has the greatest role in guiding decisions on management. Finally, exclusion of severely or acutely ill persons and persons with mental incapacities is not considered inappropriate. If inappropriate exclusions account for 5% or less of the number of included persons, the potential impact of inappropriate exclusions will be considered negligible.

Concern will be assessed as 'high' when the study population does not represent an unselected sample of adults with suspected COVID-19.

Concern will be assessed as 'unclear' when insufficient information is available.

Domain 2: index test

Signaling questions and answering guidelines

Were the index test results interpreted without knowledge of the results of the reference standard?

For practical reasons, COVID-19 is highly contagious and a CT-scan must take place with communication and good

cooperation between doctors and patients. Hence, it is often necessary for doctors to be aware of the potential infectious status of the patients before CT scan. However, a third person who is involved only in the evaluation scenario and not in the diagnosis procedure is considered to have low risk of bias.

Answer 'yes' if one of the following conditions is met.

(I) The CT evaluations used in the analyses were performed before the patient had laboratory confirmation of certain pathogens.

(II) The CT evaluations used in the analyses were postponed evaluations or reevaluations, and the radiologists were kept unaware of laboratory findings and of whether persons had a certain lung infection.

Answer 'no' if neither of the conditions is met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

If a threshold was used, was it pre-specified?

Answer 'yes' if the following two conditions are met.

(I) The components (e.g., distribution, size, shape of lung lesion; characteristics of lung lesion, esp. the VES sign) included in the evaluation of the CT-scan are explicitly reported in the study report.

(II) The hierarchy and logical combination of components are explicitly reported in the study report.

Answer 'no' if one or more of the conditions above are not met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Guidelines for assessing risk of bias

Risk of bias from index test execution will be assessed as 'low' when signaling questions 1 and 2 are answered 'yes'.

Risk will be assessed as 'high' when signaling question 1 or 2 is answered 'no'.

Risk will be assessed as 'unclear' when insufficient information is reported to answer signaling questions 1 or 2.

Guidelines for assessing concern regarding applicability

Two issues will influence our assessment concerning applicability in relation to execution of the index test.

Is the index test described in sufficient detail to permit its replication?

Answer 'yes' when the following details are reported.

(I) Number of slices of the CT device.

(II) Use of multi-planar reformations (assumed not used if the number of slices of the CT device is lower than 16, unless stated otherwise).

(III) Taken in the supine position and at full-inhalation.

(IV) Region included in the scan (involve entire lung, from the inlet of thoracic to costophrenic angles).

(V) Slice thickness, slice interval, tube voltage (kilovolt, kv), and tube current modulation (milliampere second, mAs).

Answer 'no' if one or more of the details listed above (I to V) are not described.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Was the report of CT signs (e.g., VES sign) accurate?

Answer 'yes' if following two conditions are met.

(I) CT signs are clearly defined and explicitly illustrated in the study.

(II) CT readers have no fewer than 5 years of experience.

Answer 'no' if the analysis is based on a reassessment of the CT-scan by a senior radiologist or a consensus panel.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Concern regarding applicability in relation to index test execution will be assessed as 'low' when questions 1 and 2 are answered 'yes'.

Concern will be assessed as 'high' when question 1 or 2 is answered 'no'.

Concern will be assessed as 'unclear' when insufficient information is reported to answer questions 1 and 2.

Domain 3: reference standard

Signaling questions and answering guidelines

Is the reference standard likely to correctly classify the target condition?

Answer 'yes' if the following conditions are met.

(I) The diagnosis of COVID-19 infection is based on the pathogen gene sequencing or RT-PCR test. Also classify as 'yes' if the diagnosis of COVID-19 is based on IgG or IgM kit for SARS-COV-2 specific antibody examination.

(II) The diagnosis of COVID-19 in patients who did not prove initially positive for the above tests is based on clinical follow-up and repeated lab pathogen tests.

Answer 'no' if the diagnosis of COVID-19 (or its absence; i.e., non-COVID-19) is not based on the conditions stated above.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Were the reference standard results interpreted without knowledge of the results of the index test?

Answer 'yes' if the laboratory technicians performing the RT-PCR or the pathogen gene sequencing work in different departments from the radiologists and are kept unaware of the results of the CT-scan.

Answer 'no' if one of the relevant conditions stated above is not met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Guidelines for assessing risk of bias

Risk of bias related to the reference standard will be assessed as 'low' when signaling questions 1 or 2 is answered 'yes'.

Risk will be assessed as 'high' when both signaling question 1 and 2 are answered 'no'.

Risk will be assessed as 'unclear' when insufficient information is reported to answer signaling questions 1 and 2.

Guidelines for assessing concern regarding applicability

Is there concern that the target condition as defined by the reference standard does not match the review question?

Sometimes, due to the quick spread of the pandemic, there may be a shortage of lab diagnostic kits, and the quality control of kits may be lax.

Concern regarding applicability in relation to patient selection will be assessed as 'low' when the lab diagnostic procedure or the production of diagnostic kit is clearly reported.

Concern will be assessed as 'unclear' when insufficient information is available.

Concern will be assessed as 'high' when neither the lab diagnostic procedure nor the production of diagnostic kit is reported in the study.

Domain 4: flow and timing

Signaling questions and answering guidelines

Did all persons receive a reference standard?

Answer 'yes' if at least 95% of included persons had pathogen gene sequencing, RT-PCR test, IgG or IgM kit for SARS-COV-2 specific antibody examination, or clinical follow-up.

Answer 'no' if fewer than 95% of included persons had pathogen gene sequencing, RT-PCR test, IgG or IgM kit for SARS-COV-2 specific antibody examination, or clinical follow-up.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Did all persons receive the same reference standard?

Answer 'yes' if one of the following conditions is met.

(I) 90% of included persons had pathogen gene sequencing, RT-PCR test, or IgG or IgM kit examination.

(II) 90% of included persons were managed by clinical follow-up.

Answer 'no' if neither of the conditions is met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Was there an appropriate interval between the index test and reference standard?

The appropriate time interval between the CT-scan and laboratory tests is unclear. To our knowledge, CT is usually more sensitive to detecting signs of infection than laboratory tests. Even though CT is not considered as the golden standard of

COVID-19, it is advised that a CT scan should be performed in timely fashion. After careful consideration, we generally consider both the CT scan conducted on admission and in follow-up as acceptable regardless of the time period from symptom onset to admission.

Were all patients included in the analysis?

Answer 'yes' if the analyses encompassed all included persons. Also, answer 'yes' if 5% or fewer were excluded from the analysis because no reference standard assessment was available (to accommodate signaling question 1).

Answer 'no' if the requirement stated above is not met.

Answer 'unclear' if insufficient information is available to answer 'yes' or 'no'.

Guidelines for assessing risk of bias

Risk of bias related to patient flow and timing will be assessed as 'low' when three of above signaling questions are answered 'yes'.

Risk will be assessed as 'high' when signaling question 1, 2, or 4 is answered 'no'.

Risk will be assessed as 'unclear' when insufficient information is reported to answer signaling questions 1, 2, or 4.

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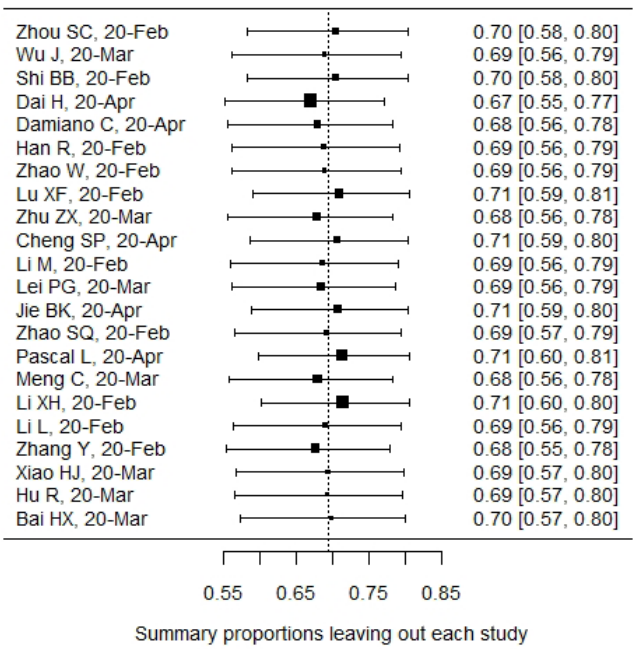

Figure S1 Sensitivity (leave-one-out) analysis plot.

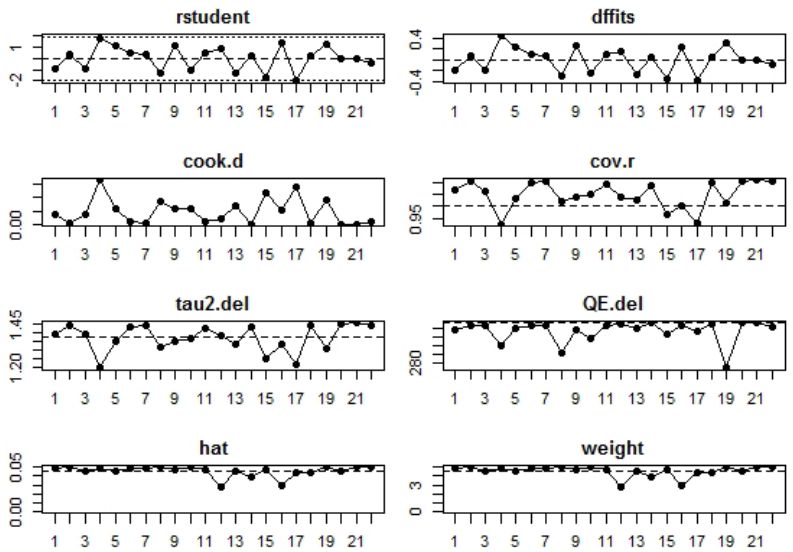

Figure S2 Influence diagnostic tests of the included studies.

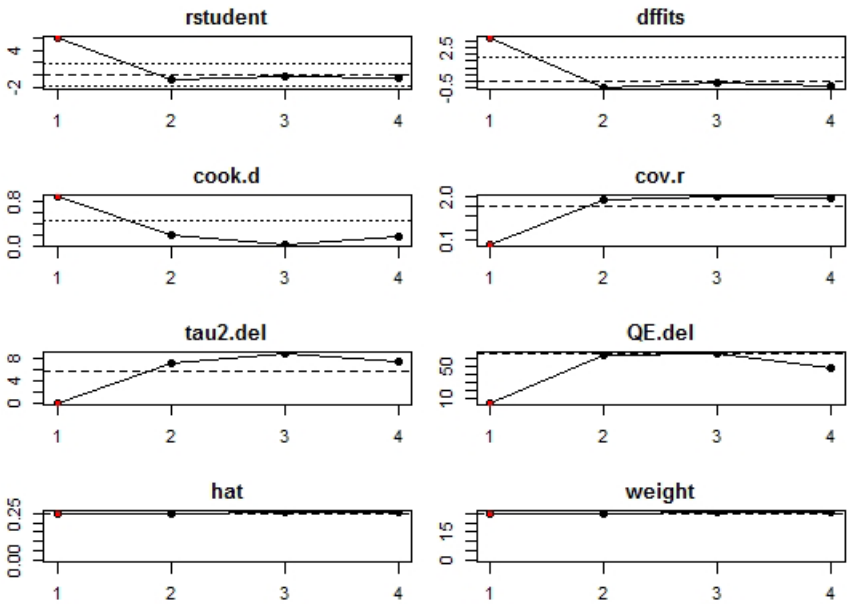

Figure S3 Influence diagnostic tests of the four included studies that had a comparison of VES rates in COVID-19 versus non-COVID-19 patients.

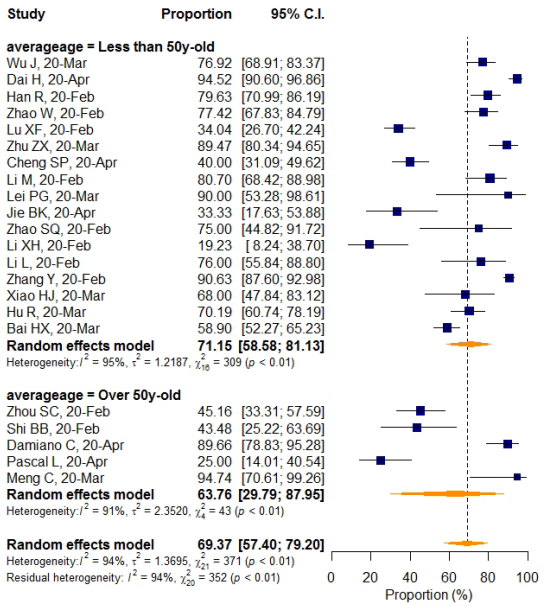

Figure S4 Forest plot of subgroup analysis by average age.

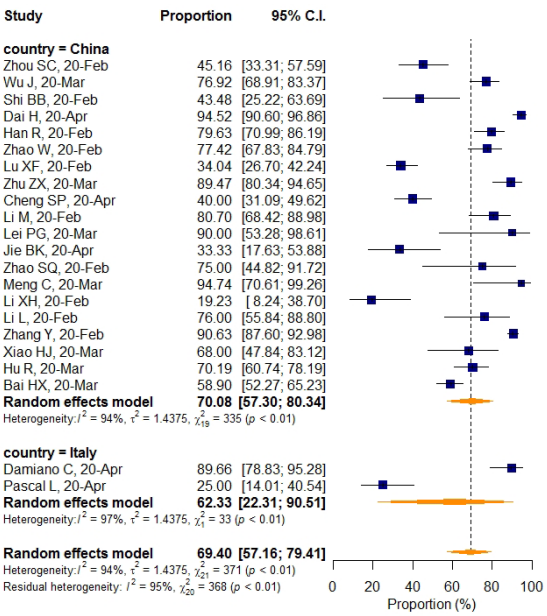

Figure S5 Forest plot of subgroup analysis by country.

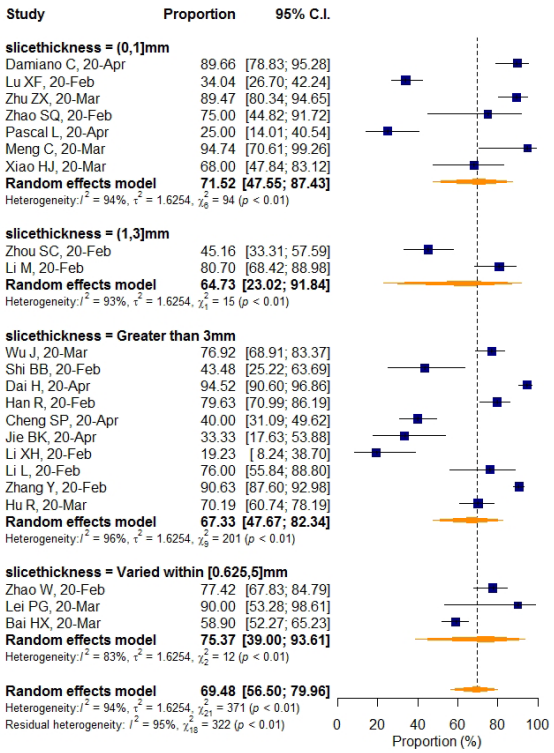

Figure S6 Forest plot of subgroup analysis by slice thickness.

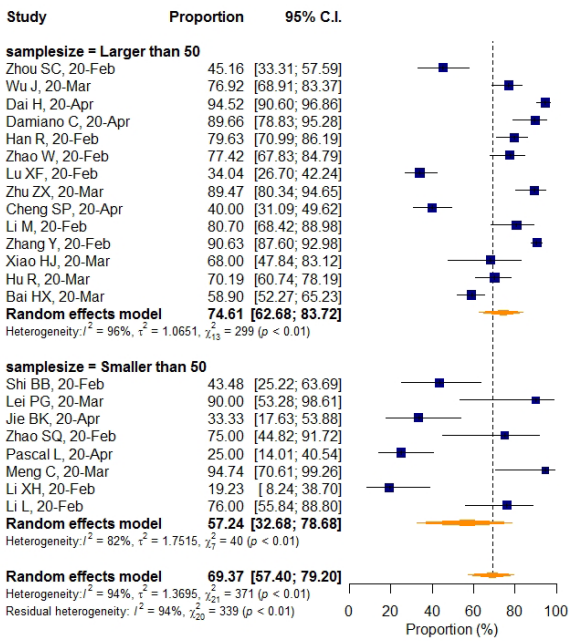

Figure S7 Forest plot of subgroup analysis by sample size.

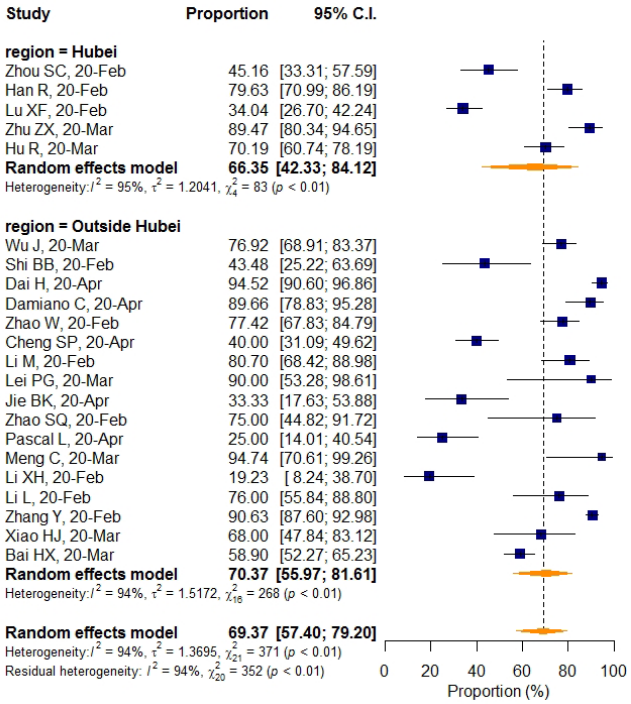

Figure S8 Forest plot of subgroup analysis by region.

Table S1 Quality assessment details using JBI Critical Appraisal Checklist [The Joanna Briggs Institute (JBI) Critical Appraisal Checklist for analytical cross-sectional study (last amended in 2017)]

Study (No. reference)[†]	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Overall appraisal
Zhou SC *et al*. (14)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Wu J *et al*. (38)	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Include
Shi BB *et al*. (39)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Dai H *et al*. (8)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Damiano C *et al*. (40)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Han R *et al*. (11)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Zhao W *et al*. (9)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Lu XF *et al*. (41)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Zhu ZX *et al.* (42)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Cheng SP *et al.* (13)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Li M *et al*. (43)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Lei PG *et al*. (15)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
Jie BK *et al*. (44)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Include
Zhao SQ *et al*. (45)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Pascal L. *et al*. (46)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Meng C *et al.* (47)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Li XH *et al*. (48)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Li L *et al.* (49)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Zhang Y *et al.* (50)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Xiao HJ *et al*. (51)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Hu R *et al.* (52)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Bai HX. *et al*. (53)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include

[†], first author and corresponding number of the reference were listed as study ID. The number of reference is in consistent with that in the formal article. NA, not applicable.