META-ANALYSIS

Chest computed tomography as a primary tool in COVID-19 detection: an update meta-analysis

Caishuang Pang[1] · Qingtao Hou[2] · Zhaowei Yang[1] · Liwei Ren[1]

Abstract

Purpose A growing number of publications have paid close attention to the chest computed tomography (CT) detection of COVID-19 with inconsistent diagnostic accuracy, the present meta-analysis assessed the available evidence regarding the overall performance of chest CT for COVID-19.

Methods 2×2 diagnostic table was extracted from each of the included studies. Data on specificity (SPE), sensitivity (SEN), negative likelihood ratio (LR−), positive likelihood ratio (LR+), and diagnostic odds ratio (DOR) were calculated purposefully.

Results Fifteen COVID-19 related publications met our inclusion criteria and were judged qualified for the meta-analysis. The following were summary estimates for diagnostic parameters of chest CT for COVID-19: SPE, 0.49 (95% CI 46–52%); SEN, 0.94 (95% CI 93–95%); LR−, 0.15 (95% CI 11–20%); LR+, 1.93 (95% CI 145–256%); DOR, 17.14 (95% CI 918–3199%); and the area under the receiver operating characteristic curve (AUC), 0.93.

Conclusion Chest CT has high SEN, but the SPE is not ideal. It is highly recommended to use a combination of different diagnostic tools to achieve sufficient SEN and SPE. It should be taken into account as a diagnostic tool for current COVID-19 detection, especially for patients with symptoms.

Introduction

In December 2019, cases of pneumonia called COVID-19 caused by Severe Acute Respiratory Syndrome coronavirus type 2 (SARS-CoV-2) occurred in Wuhan, China, and, since then, has become a global epidemic disease [1–3]. The symptoms of COVID-19 are nonspecific, ranging from asymptomatic to respiratory failure and even death. The dominant clinical manifestations are fever and dry cough. Pathological diagnosis is established by nucleic acid assay testing, gene sequencing, and serological examination (IgM and IgG) of throat swabs or blood samples. Based on what we know about COVID-19 epidemic, updated clinical protocols are regularly provided to guide screening strategies for COVID-19 in affected areas by the Chinese government [4]. According to reports, in all patients, the crude case-fatality rate of COVID-19 is 2.3% [5], and it is even higher in critically ill patients, 61.5% [6]. Therefore, early diagnosis of COVID-19 remains a significant challenge. In this outbreak, rapid and accurate diagnosis is essential for isolating and treating patients.

To date, real-time reverse transcriptase-polymerase chain reaction (RT-PCR) testing has been considered as the reference standard for the diagnosis of COVID-19 [4, 7–10].

Nonetheless, considering the latent period of the infection (estimated as 2–14 days), an initial negative RT-PCR result does not exclude the possibility of SARS-CoV-2 infection [11]. RT-PCR can also give potential false negatives if the amount of viral loads is insufficient or if the correct time-window of viral replication is missed [12]. Besides, false-negative results may due to improper sample collection or laboratory mistake [13]. Hence the test should be repeated in patients who are persistently suspected by clinical findings but with negative RT-PCR results [14, 15]. Besides, RT-PCR comes with disadvantages, relatively long waiting

✉ Caishuang Pang
  pangcaishuang@126.com

[1] Chongqing Medical University, NO.1, Yi Xue Yuan Road, Yuzhong District, Chongqing 400016, China

[2] Department of Geriatrics, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

time, invasive sampling procedure to process and generate results, and needs for specialized operators and certified laboratories.

Radiology plays an essential role in the early detection as well as in the management of COVID-19 patients. Among various imaging methods, chest computed tomography (CT) occupies a large share due to its higher sensitivity (SEN) and specificity (SPE) rates [16–18]. 67.4–88.0% of COVID-19 infection is detected by chest CT, showing that pneumonia is the most common presentation [13–15]. Typical diagnostic methods include chest CT, RT-PCR test, or both. The number of RT-PCR testing capacity is insufficient, and CT can be conveniently performed for COVID-19 screening according to the situation [19, 20]. Hence CT image is widely used for early diagnosis of this disease. Several recent studies have suggested that chest CT is conductive to detect COVID-19. [13, 17, 18, 21–23] The main CT finding of COVID-19 was bilateral distribution of ground-glass opacities (GGOs) with or without consolidation. With further analysis of increasing cases, multiple CT imaging features were found, which may elucidate the possible mechanism of lung injury in COVID-19 [13]. However, individual studies may be subjected to small sample sizes, applicability to demographics, wrong methodology, or a combination of all the above-mentioned disadvantages. The potential danger is to make critically clinical decisions based on flawed information. When chest CT is used as a diagnostic tool in clinical practice, a critical evaluation of the literature is necessary. A previous meta-analysis drew a conclusion that chest CT had a high SEN but poor SPE in COVID-19 detection [24]. However, more and more studies are dedicated to expand the application of chest CT in COVID-19 detection. Now the present meta-analysis was undertaken to comprehensively assess the diagnostic value of chest CT for COVID-19.

Methods

This meta-analysis was done according to the guidelines about diagnostic research before data collection commenced, as well as the preferred reporting items for systematic reviews and meta-analyses were followed for reporting this meta-analysis [25–27]. This retrospective meta-analysis waived the approval of the institutional review board.

Literature search

We did the literature retrieval systematically in PubMed, Wanfang, and CNKI to find potentially eligible studies published up to September 6, 2020, using the following keywords as search terms: "coronavirus disease 2019" OR "novel coronavirus" OR "SARS-CoV-2" OR "COVID-19" AND "computed tomography" OR "CT" AND "RT-PCR".

Additionally, we also searched the aforementioned terms using different combinations.

Study selection

Two reviewers independently examined the titles and abstracts first, then downloaded the full text of all the possibly eligible studies for further review. Any conflicts between the two reviewers (CSP and QTH) were resolved by a third author (ZWY). We brought into studies which met the following eligibility criteria: (1) original research papers; (2) either in English or Chinese language; (3) investigated the diagnostic value of chest CT for COVID-19; (4) the reference standard is RT-PCR; (5) enough raw data to construct the 2×2 table.

Data extraction and quality assessment

Data were extracted using Microsoft Excel from eligible studies by two reviewers independently, including name of first author, year of publication, country, number of patients, inclusion criteria, age, sex, reference standard, specimen type or location, type of CT, diagnostic CT criteria, true positive (TP), false positive (FP), false negative (FN), and true negative (TN). Disagreements between two reviewers were resolved through negotiation. When different diagnostic CT criteria were used, TP, FP, FN, and TN were reconstructed separately.

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist was used to assess the methodological quality in each study [28]. QUADAS-2 assesses the methodological quality in two parameters: the risk of bias and applicability concerns. Two reviewers independently assessed these in each eligible study based on predefined key factors. Conflicts were resolved by discussion.

Statistical analysis

Standard methods recommended for diagnostic accuracy meta-analysis were followed. We extracted the accuracy data (TP, FP, FN, and TN) from each eligible study and calculated the following diagnostic estimates: pooled SEN, specificity SPE, positive likelihood ratio (LR+), negative likelihood ratio (LR−), diagnostic odds ratio (DOR), and their corresponding 95% confidence intervals (CIs). We also plotted summary receiver operating characteristic (SROC) curve to obtain the value of area under the curve (AUC). Based on the estimates of the heterogeneity tests, a random effects model or a fixed effects model was used to calculate correlation index across studies.

Heterogeneity across the studies was evaluated using chi-squared and Fisher's exact tests. Meta-regression analysis was conducted to determine potential covariates of the

heterogeneity. Deeks funnel plot was conducted to evaluate the potential publication bias [29]. Forest plot was performed using Meta-DiSc 1.4 (XI. Cochrane Colloquium, Barcelona, Spain). Quality assessment was performed using RevMan 5.2 (Cochrane Collaboration, Oxford, UK), and publication bias using STATA 12.0 (Stata Corp., College Station, TX) software. A two-tailed *P* value smaller than 0.05 was judged statistically significant.

Results

Study selection

We initially screened on title and abstract levels, and then reviewed on full-text level. Finally, 15 publications were deemed eligible for inclusion. [17, 18, 21–23, 30–39]. Studies were eliminated mainly because of unpaired chest CT and RT-PCR, as well as incomplete data. Figure 1 shows the selection process of potentially qualified studies. Considering that there were more than one criteria used for CT diagnosis (high-risk vs moderate and low-risk cases, moderate- and high-risk vs low-risk cases) [39]. The publication was perceived as two independent research studies, which offered up 16 studies in our meta-analysis in the aggregate.

Study characteristics

Twelve studies were conducted in China, two in Italy, one in Japan, and one in Netherland. The average sample size was 187 (varied from 21 to 1014), with a total of 2992 patients. Most studies enrolled patients consecutively and retrospectively, except two studies were prospectively [33, 37]. The inclusion criteria in these studies were patients clinically suspected COVID-19 infection, and who underwent both chest CT and RT-PCR. The CT images were read by at least two radiologists independently and reached a consensus in 13 included studies [17, 21–23, 30, 32–35, 37–39], and others unknown. In these 13 studies, radiologists were blind to the RT-PCR results, except two unknown [33, 38]. A standardized method for CT report was reported by Stanzione et al. [40], however, none of the included studies mentioned about the standardized method. Nasopharyngeal and oropharyngeal swab was the most common specimen type for RT-PCR in eligible studies [21–23, 33, 36, 37]. Three studies had sampled lower respiratory tract specimen for RT-PCR [18, 23, 32]. Four studies did not mention about the specimen type or location [34, 38, 39]. Details of pivotal characteristics of included studies are indicated in Table 1.

QUADAS-2 appraised methodology of selected studies in the following four fields: patient selection, index test, reference standard, and flow and timing with the utility of RevMan [25, 41]. The quality of studies included in
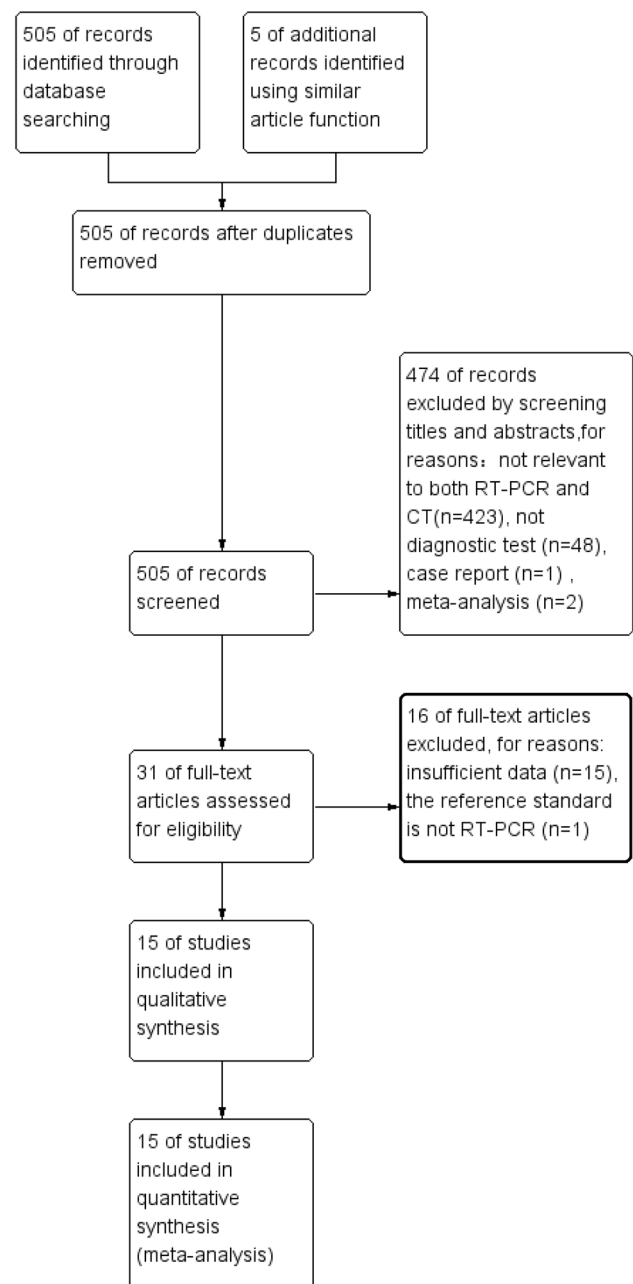

Fig. 1 Studies selection process for the meta-analysis

the present meta-analysis was not that good. Most studies that were included did not mention whether the reference standard results and the CT results were blinded to each other, and whether an appropriate interval was applied between CT and RT-PCR [31, 33, 36–39]. Thus, there were unclear risk and/or unclear concern with respect to the index text, reference standard, and flow and timing. However, most studies included in the present meta-analysis did well in patient selection. Except for one of which was concluded unclear risk of bias [36]. Because it did not

Table 1 Characteristics of eligible studies

First author	Country	Number of patients	Age, mean(range)/median(range)	Sex, male/female	Reference standard	Specimen type	CT interpreters, NO./Type/experience amount(y)	CT type
Tao Ai	China	1014	51/NA	467/547	RT-PCR	Throat swab	2/radiologist/12, 3	Chest CT
Xingzhi Xie	China	167	NA	NA	RT-PCR	Mouth swab	2/radiologist/NA	Chest CT
Yuanyuan Li	China	54	NA/51.5 (25–82)	22/32	RT-PCR	Throat swab	NA	Chest CT
Yicheng Fang	China	51	NA/45 (39–55)	29/22	RT-PCR	Throat swab or sputum	NA	Chest CT
Zeying Wen	China	103	46 (12–98)/NA	48/55	RT-PCR	Throat-swab, sputum, or alveolar lavage fluid	3/radiologist/8–15	Chest CT
Damiano Caruso	Italy	158	57 (18–89)/NA	83/75	RT-PCR	Naso- and oropharyngeal swabs	2/radiologist/15, 25	Chest CT
Yuki Himoto	Japan	21	NA	12/9	RT-PCR	NA	2/senior radiology residents/3	Chest CT
Wanbo Zhu	China	116	NA/40 (27–53)	56/65	RT-PCR	Swab	2/chest radiologist/NA	Chest CT
Chunbao Xie	China	19	NA/33	8/11	RT-PCR	Oropharyngeal swab, blood, urine and stool	NA	CT scan
Dandan Chen	China	21	49.7 (26–90)/NA	9/12	RT-PCR	Nasopharyngeal or oropharyngeal swab	2/thoracic radiologist/5	Chest CT
Zeno Falaschi	Italy	773	62.4 (16–100)/NA	423/350	RT-PCR	Nasopharyngeal swab	2/radiologist/> 10	Chest CT
Hester A. Gietema	Netherland	193	NA/66 (55–76)	113/80	RT-PCR	Nasopharyngeal and/or oropharyngeal swab	2/a senior resident, an experienced chest radiologist/NA	Chest CT
Chunqin Long	China	36	44.8/NA	20/16	RT-PCR	NA	2/radiologist/10, 15	Chest CT
Jianlong He	China	82	NA	49/33	RT-PCR	Nasopharyngeal swab, oropharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage	2/radiologist/17, 14	Chest CT
Zicong Li	China	92	NA	51/41	RT-PCR	NA	2/radiologist/3, 10	Chest CT
Zicong Li	China	92	NA	51/41	RT-PCR	NA	2/radiologist/3, 10	Chest CT

RT-PCR real-time reverse transcriptase-polymerase chain reaction, NA not available, CT computed tomography

mention the patients enrolled consecutively or randomly. The overall quality is shown in Fig. 2.

Diagnostic accuracy

Figure 3 summarizes the results of diagnostic accuracy. SEN of CT for COVID-19 varied from 0.76 to 1.00, SPE varied from 0 to 0.96. With RT-PCR as the reference standard, there was a pooled SEN for COVID-19 of 0.94 (95% CI 0.93–0.95) and a pooled SPE of 0.49 (95% CI 0.46–0.52). The LR+ was 1.93 (95% CI 1.45–2.56) and the LR− was 0.15 (95% CI 0.11–0.20). We found DOR was 17.14 (95% CI 9.18–31.99). Considerable heterogeneity among studies was noted by chi-squared values for the following parameters (Table 2): SEN, 43.26 ($P < 0.001$); SPE, 341.54 ($P < 0.001$); LR+, 405.87 ($P < 0.001$); LR−, 17.80 ($P = 0.22$); and DOR, 44.91 ($P < 0.001$). We calculated SROC curves to evaluate the overall diagnostic performance. Figure 4 provides the SROC curve with AUC of 0.93 (SEM = 0.02), and Q value for SEN and SPE was 0.87 (SEM = 0.02), indicating that CT has a high ability to distinguish COVID-19.

Sub-group analysis and publication bias

Sub-group analyses were performed to assess the impact of countries, study design, patient number, test interval between CT and RT-PCR, and experience of radiologists. We compared studies from different countries. Studies from Italy seemed to have the optimal SPE 0.73 (95% CI 0.69–0.78), and the highest DOR of 36.34 (95% CI 24.38–54.19), indicating CT for COVID-19 performed better in Italian epidemic than in china. When considering the patient number, small-scale studies had a more excellent SEN than bigger ones (0.98 vs. 0.94). AUC of small-scale studies was higher (0.97 vs 0.93). Studies with experienced radiologists (≥ 10 years' experience in reviewing chest CT images) seemed to have the optimal SPE 0.75 (95% CI 0.71–0.79), and DOR of 35.46 (95% CI 16.75–75.07). Table 2 shows the details.

A high level of significant heterogeneity was noted by chi-squared values for SEN ($P < 0.001$), SPE ($P < 0.001$), LR+ ($P < 0.001$), DOR ($P < 0.001$), and AUC ($P = 0.02$). To distinguish possible sources of heterogeneity, meta-regression was conducted.
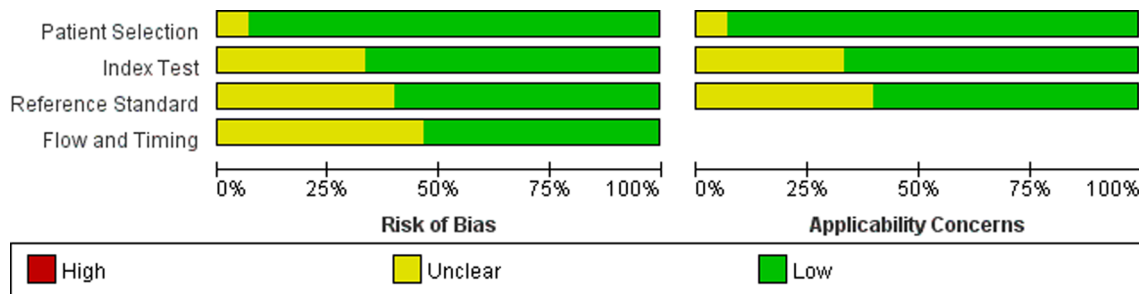

Fig. 2 Summary of QUADAS-2 assessments of included studies. QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2
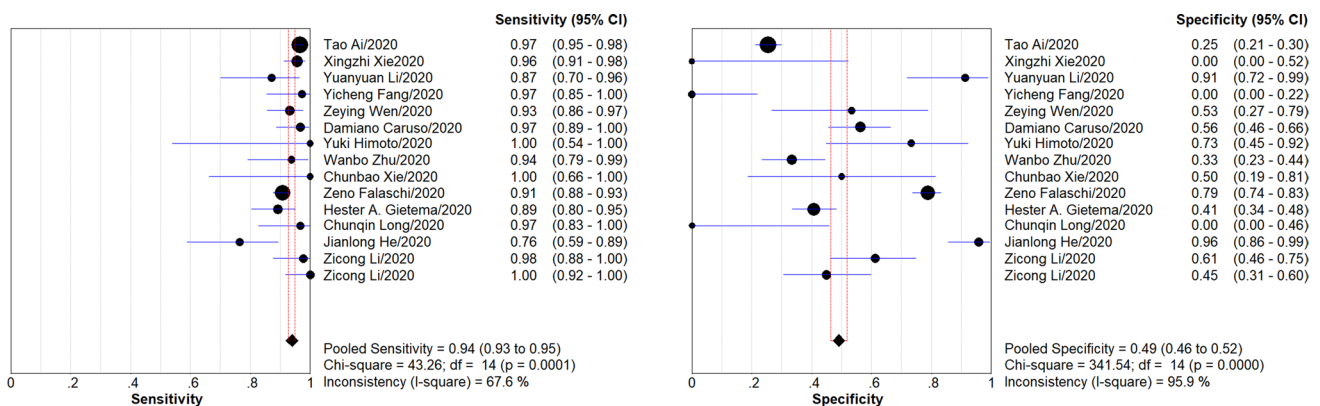

Fig. 3 Forest plot of the summary sensitivity and specificity of pleural effusion. The sensitivity/specificity of individual study is represented by a circle, through which runs a horizontal line (95% CI). The diamond at the bottom represents the pooled sensitivity/specificity from the studies. *df* degrees of freedom

Table 2 Meta-analyses results

	Number of study	Sensitivity (95% CI)	Heterogeneity (P)	Specificity (95% CI)	Heterogeneity (P)	LR+ (95% CI)	Heterogeneity (P)	LR− (95% CI)	Heterogeneity (P)	DOR (95% CI)	Heterogeneity (P)	AUC (SEM)
Overall	16	0.94 (0.93–0.95)	43.26 (<0.001)	0.49 (0.46–0.52)	341.54 (<0.001)	1.93 (1.45–2.56)	405.87 (<0.001)	0.15 (0.11–0.20)	17.80 (0.22)	17.14 (9.18–31.99)	44.91 (<0.001)	0.93 (0.02)
Country												
China	12	0.95 (0.94–0.97)	26.79 (0.003)	0.37 (0.33–0.41)	171.74 (<0.001)	1.57 (1.25–1.96)	118.25 (<0.001)	0.16 (0.12–0.22)	10.49 (0.40)	15.75 (7.33–33.88)	20.21 (0.03)	0.94 (0.02)
Italy	2	0.91 (0.89–0.94)	3.22 (0.07)	0.73 (0.69–0.78)	17.89 (<0.001)	3.08 (1.51–6.28)	20.26 (<0.001)	0.11 (0.08–0.16)	1.08 (0.30)	36.34 (24.38–54.19)	0.01 (0.93)	NA
Design												
Retrospective	14	0.94 (0.93–0.95)	39.45 (<0.001)	0.50 (0.47–0.53)	334.11 (<0.001)	1.99 (1.41–2.81)	407.30 (<0.001)	0.14 (0.11–0.17)	12.19 (0.43)	18.63 (9.42–36.84)	33.99 (0.001)	0.94 (0.01)
Prospective	2	0.92 (0.87–0.96)	3.23 (0.07)	0.46 (0.40–0.52)	6.09 (0.01)	1.80 (1.23–2.66)	8.14 (0.004)	0.14 (0.03–0.66)	4.36 (0.04)	13.32 (1.98–89.52)	5.41 (0.02)	NA
Number												
<50	4	0.9 (0.88–1.00)	0.82 (0.66)	0.52 (0.33–0.70)	11.68 (0.003)	1.78 (0.69–4.59)	19.36 (<0.001)	0.17 (0.03–0.87)	1.14 (0.57)	10.76 (1.73–67.05)	2.02 (0.36)	0.97 (0.04)
≥50	12	0.94 (0.93–0.95)	40.86 (<0.001)	0.49 (0.46–0.52)	329.78 (<0.001)	1.99 (1.45–2.73)	381.11 (<0.001)	0.15 (0.11–0.20)	16.65 (0.12)	18.01 (9.24–35.11)	42.62 (<0.001)	0.93 (0.02)
Testing interval between CT and RT-PCR												
NA	9	0.94 (0.91–0.97)	14.70 (0.07)	0.48 (0.43–0.52)	49.23 (<0.001)	1.84 (1.42–2.37)	58.38 (<0.001)	0.14 (0.08–0.24)	10.61 (0.22)	19.03 (7.66–47.28)	16.87 (0.03)	0.93 (0.04)
≤7 days	7	0.94 (0.92–0.95)	28.38 (<0.001)	0.50 (0.47–0.54)	291.59 (<0.001)	2.02 (1.13–3.59)	345.66 (<0.001)	0.15 (0.11–0.21)	7.51 (0.19)	15.28 (5.92–39.48)	26.06 (<0.001)	0.94 (0.01)
Experience (year)												
≥10	4	0.91 (0.88–0.93)	11.16 (0.01)	0.75 (0.71–0.79)	50.41 (<0.001)	3.16 (1.16–8.59)	152.27 (<0.001)	0.15 (0.08–0.28)	7.22 (0.07)	35.46 (16.75–75.07)	4.31 (0.23)	0.94 (0.01)
<10	6	0.96 (0.95–0.98)	5.94 (0.20)	0.33 (0.29–0.37)	43.27 (<0.001)	1.92 (1.36–2.73)	27.86 (<0.001)	0.12 (0.08–0.18)	3.34 (0.50)	16.81 (7.52–37.57)	5.86 (0.21)	0.94 (0.05)
NA	6	0.93 (0.90–0.96)	7.50 (0.19)	0.40 (0.35–0.46)	49.41 (<0.001)	1.44 (1.02–2.04)	77.05 (<0.001)	0.22 (0.14–0.36)	3.24 (0.66)	8.17 (2.83–23.57)	9.65 (0.09)	0.92 (0.03)

RT-PCR real-time reverse transcriptase-polymerase chain reaction, *CT* computed tomography, *LR+* positive likelihood ratio, *LR−* negative likelihood ratio, *DOR* diagnostic odds ratio, *AUC* area under curve, *NA* not available

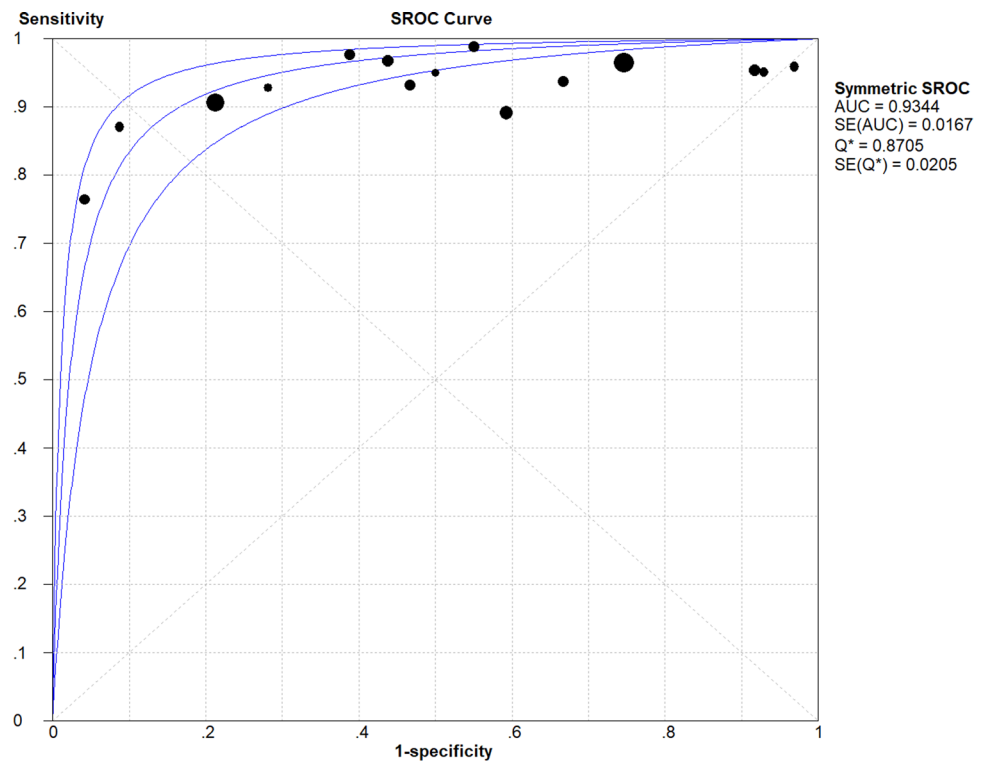**Fig. 4** Summary receiver operating characteristic (SROC) curve of pleural effusion. *AUC* area under the curve

Table 3 Meta-regression of chest CT for COVID-19 detection

Covariate	Number of study	Coefficient	RDOR(95%CI)	*P* value
Country				
China	12	− 0.385	0.68 (0.49–0.94)	0.02
Japan	1			
Italy	2			
Netherland	1			
Design				
Retrospective	14	− 0.783	0.46 (0.20–1.03)	0.06
Prospective	2			
Female				
<50%	9	2.648	14.13 (0.08–2647.19)	0.29
≥50%	6			
Number				
<50	4	0	1 (1.00–1.00)	0.61
≥50	12			
Testing interval between CT and RT-PCR				
NA	9	− 0.054	0.95 (0.34–2.64)	0.91
≤7 days	7			
Experience (year)				
≥ 10	4	0.539	1.72 (1.10–2.67)	0.02
<10	6			
NA	6			

RDOR relative diagnostic odds ratio, *RT-PCR* real-time reverse transcriptase-polymerase chain reaction, *NA* not available, *CT* computed tomography

Meta-regression analyses revealed that country and experience of radiologists ($P = 0.02$) accounted for part of the heterogeneity. While there was no evidence to show that the heterogeneity can be explained by study design and proportion of females. The results of the RDOR analysis are shown in Table 3.

Deeks funnel plot was used to test publication bias. As shown in Fig. 5, there was no evidence suggesting any potential publication bias ($P = 0.79$).

Discussion

According to the 7th edition of the "2019 New Coronavirus Pneumonia Diagnosis and Treatment Program" issued by the National Health Commission of China, it combines the information of contact history, clinical manifestations shown by chest CT, presence of viral genes and virus-specific antibodies to diagnose COVID-19. Patients suspected of having COVID-19 symptoms and/or have a confirmed exposure history will be assessed by CT scan and RT-PCR test first. Patients with positive PCR test results are confirmed infected cases. Patients with a definite history of contact and showing typical CT imaging manifestations of viral pneumonia but negative PCR are reported to support COVID-19 clinical diagnosing [42, 43]. Chest CT has been recommended as a time-saving and reliable auxiliary examination for the detection of COVID-19 [17]. However, its diagnostic value has

Fig. 5 Deeks funnel plot to assess the likelihood of publication bias
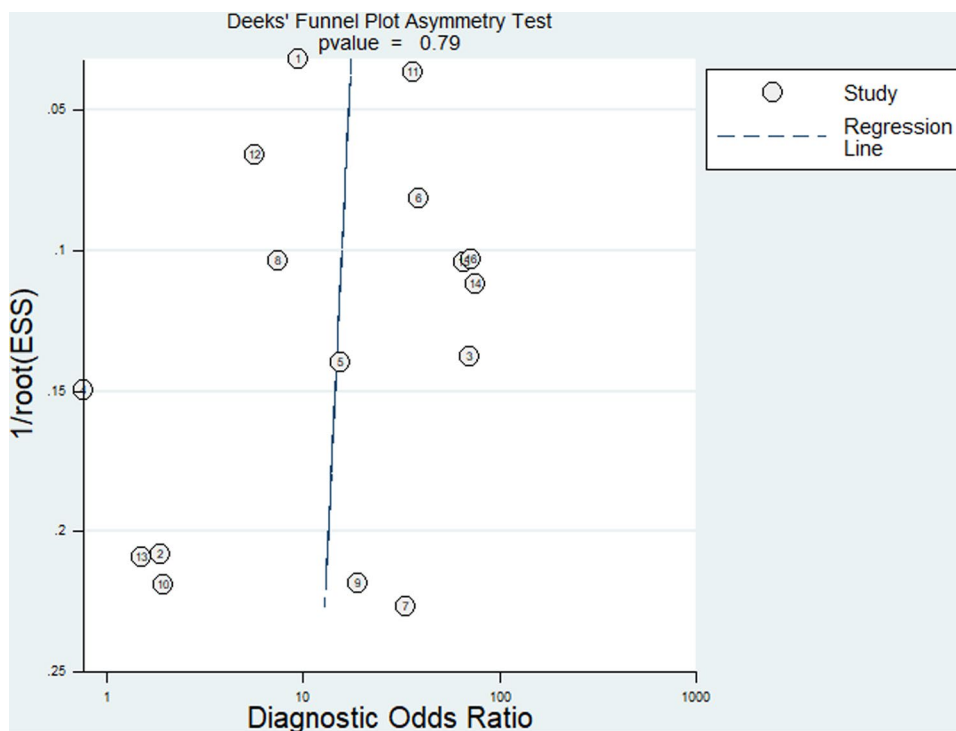
come under debate. In fact, a previous meta-analysis which included four original papers has been launched to analyze the role of chest CT for COVID-19 diagnosis [24]. Since then, several new studies investigating the diagnostic ability of chest CT scanning in COVID-19 identification have been published. We carried out this updated meta-analysis to systematically review the articles with regard to the diagnostic ability of chest CT for COVID-19.

We analyzed the existing evidence and found that chest CT had a combined SEN of 0.94 and SPE of 0.49 when using RT-PCR as the reference standard. The moderate SPE indicates a high rate of misdiagnosis (51%). The relatively high SEN indicates a low missed diagnoses (6%), which is more important than misdiagnosis rate of a primary tool for COVID-19 detection. A normal chest CT scan negates the diagnosis in a majority of patients. A previous meta-analysis which included four eligible studies finds a rather high SEN (0.95) but poor SPE (0.09) of chest CT, using RT-PCR as the reference method [24]. With more original studies included, CT shows a good SEN and a concordantly higher SPE for diagnosing COVID-19 than previous studies. Meanwhile, we obtained an AUC of 0.93 from the SROC curve. On account of an AUC of 1.0 showing us perfect discrimination, our meta-analysis shows that the level of overall diagnostic accuracy is relatively high. The optimal AUC indicates that chest CT might be a suitable diagnostic tool for patients who are clinical suspected cases of COVID-19, especially those with negative initial RT-PCR results. However, in our study, the combined LR+ and LR− were moderate. The larger the

LR+ is the higher the diagnostic accuracy will be, while the smaller the LR− is the higher the diagnostic accuracy will be. The present meta-analysis revealed a combined LR+ of 1.93. This is somewhat frustrating for clinical applications. Similarly, the combined LR− was 0.15, which is not low enough to make an excluded diagnosis in the clinic.

Patients from four countries were enrolled in our included studies. We compared the pooled diagnostic accuracy of studies carried out in China and Italy, and found CT for COVID-19 detecting performed better in Italian epidemic [22, 33]. We found this was in accordance with the experience of radiologists evaluated the images. The veteran chest radiologists would comprehensibly attain better SPE than those inexperienced. Studies with more experienced radiologists have more optimal diagnostic performance [18, 22, 33, 38]. There is good reason to suspect that two Italian studies performed better maybe because they adopted more experienced radiologists (15 and 25 years, > 10 years of experience) to evaluate the chest CT. The experience and skill of radiologist have affected the evaluation of diagnostic performance. The criteria of chest CT for COVID-19 detection are important for diagnostic accuracy. A high level of heterogeneity was found, we attempt to discriminate sources with meta-regression. Countries and experience of radiologists have an effect on diagnostic accuracy ($P = 0.02$).

Typical chest CT findings include peripherally distributed multifocal GGOs with patchy consolidations. CT findings can change as the disease progresses [1, 44]. SARS-CoV-2 first causing pulmonary interstitial damages and subsequent

with parenchymal changes. GGO was believed to be the earliest radiographically visible CT findings in some patients and consolidation was considered as an indication of disease progression. As duration of the disease gets longer, the prevalence of reticulation could increase [44–46]. Varied findings and manifestations of chest CT were evaluated in included studies, for instance, GGO, consolidation, reticulation, thickened interlobular, septa, nodular lesions, traction bronchiectasis, bronchial wall thickening, subpleural bands, vascular enlargement. However, there is a paucity of details permitting corresponding sub‑group analysis to determine their effects on diagnostic performance. Testing interval between CT and RT-PCR in seven studies were no more than a week, especially two within 24 h. [33, 35] Symptomatic patients may have lung abnormalities till the disease develops to a certain extent [47, 48]. And many symptomatic upper respiratory tract infections do not end up with pneumonia [49]. Those all made CT findings of COVID-19 a certain degree of empirical dependence.

Specimen type or location used for RT-PCR was different in included studies, including nasopharyngeal and/or oropharyngeal swab, sputum, urine stool. Four studies did not mention about the specimen type or location. A previous study by Abbas Mohammadi et al. suggests sputum sampling as a primary diagnosis and monitoring method of COVID-19 [50]. According to the 7th edition of the Diagnosis and Treatment Program of the 2019 New Coronavirus Pneumonia issued by the National Health Commission of China, multiple samples can be used for RT-PCR, such as nasopharyngeal swab, sputum, blood and urine and stool. Lower respiratory tract specimen is most recommended, sputum and endotracheal aspirate, for example. However, collection of lower respiratory tract samples often involves the production of aerosols and poses a high risk of virus transmission to staff, upper respiratory tract samples are more frequently used in practice. Only three studies [17, 18, 23] have sampled lower respiratory tract specimen for RT-PCR. In addition, it was indistinct whether all COVID-19 suspects with a negative initial RT-PCR test result were tested for repeated RT-PCR in two studies [34, 39]. These potential defects in the reference standard may have led to improper diagnosis of COVID-19 in a part of patients. It is the thing that urgently needs to be improved in the following research.

It is unavoidable to mention the limitations of this meta-analysis. First, after the rigorous literature search and study selection, only 15 publications were finally included. It is difficult to draw a definitive conclusion about the diagnostic capacity of chest CT due to the scant statistical power. The truth is that most studies currently available are impossible to extract SEN and SPE estimates due to insufficient data. Second, based on QUADAS-2 evaluation, the

methodological quality of original studies was not so good. It was mainly because of insufficient data. Lacking of large sample size studies and high-quality studies which compare the chest CT in paired RT-PCR urgently calls for further studies. Third, although publication bias was not detected by statistical methods, it must be pointed out that due to language restrictions, we only take into English and Chinese articles.

Conclusions

Chest CT alone is not accurate enough for the diagnosis of COVID-19 infection. It should be taken into account as a diagnostic tool for the current COVID-19 detection, particularly for patients who show symptoms. The high SEN indicates that CT can be used as a quick tool to divide patients into "probably positive" and "probably negative" cohorts. The poor SPE indicates that it may be necessary to combine epidemiological characteristics, laboratory examinations and chest CT findings to confirm the presence of infection.

Declarations

References

1. Zhu N, Zhang D, Wang W et al (2020) A novel coronavirus from patients with pneumonia in China. N Engl J Med. https://doi.org/10.1056/NEJMoa2001017

2. Li Q, Guan X, Wu P et al (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. https://doi.org/10.1056/NEJMoa2001316

3. Chan JF, Yuan S, Kok KH et al (2020) A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 395:514–523. https://doi.org/10.1016/S0140-6736(20)30154-9

4. China National Health Commission (2020) 7th edition of the Diagnosis and Treatment Program of the 2019 New Coronavirus Pneumonia issued by the National Health Commission of China.

5. Ebrahim SH, Ahmed QA, Gozzer E, Schlangenhauf P, Memish YA (2020) Covid-19 and community mitigation strategies in a pandemic. BMJ. https://doi.org/10.1136/bmj.m1066

6. Yang XB, Yu Y, Xu JQ et al (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30079-5

7. World Health Organization (2020) World Health Organization Coronavirus disease (COVID-19) technical guidance: laboratory testing for 2019-nCoV in humans. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance. Accessed 31 Mar 2020

8. European Centre for Diseases Prevention and Control (ECDC) (2020) An overview of the rapid test situation for COVID-19 diagnosis in the EU/EEA. https://www.ecdc.europa.eu/sites/default/files/documents/Overview-rapid-test-situation-for-COVID-19-diagnosis-EU-EEA.pdf. Accessed 15 Apr 2020

9. Tang YW, Schmitz JE, Persing DH, Stratton CW (2020) The laboratory diagnosis of COVID-19 infection: current issues and challenges. J Clin Microbiol. https://doi.org/10.1128/JCM.00512-20

10. Vashist SK (2020) In vitro diagnostic assays for COVID-19: recent advances and emerging trends. Diagnostics. https://doi.org/10.3390/diagnostics10040202

11. Sharfstein JM, Becker SJ, Mello MM (2020) Diagnostic testing for the novel coronavirus. JAMA. https://doi.org/10.1001/jama.2020.3864

12. Zou L, Ruan F, Huang M et al (2020) SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. https://doi.org/10.1056/NEJMc2001737

13. Shi HS, Han XY, Jiang N et al (2020) Radiological findings from 81 patients with COVID-19 pneumonia in, China: a descriptive study. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(20)30086-4

14. Song FX, Shi NN, Shan FS et al (2020) Emerging 2019 novel coronavirus (2019-nCoV) pneumonia. Radiology. https://doi.org/10.1148/radiol.2020209021

15. World Health Organization website (2020) Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance. https://apps.who.int/iris/bitstream/handle/10665/331329/WHOCOVID-19-laboratory-2020.4-eng.pdf. Accessed 11 May 2020

16. Inui S, Fujikawa A, Jitsu M et al (2020) Chest CT findings in cases from the cruise ship "Diamond princess" with coronavirus disease 2019 (COVID-19). Radiology. https://doi.org/10.1148/ryct.2020200110

17. Ai T, Yang ZL, Hou HY et al (2020) Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. https://doi.org/10.1148/radiol.2020200642

18. Fang Y, Zhang H, Xie J et al (2020) Sensitivity of chest CT for COVID-19: comparison to RT-PCR. Radiology. https://doi.org/10.1148/radiol.2020200432

19. Cheng ZH, Lu Y, Cao QQ et al (2020) Clinical features and chest CT manifestations of coronavirus disease 2019 (COVID-19) in a single-center study in Shanghai, China. AJR Am J Roentgenol. https://doi.org/10.2214/AJR.20.22959

20. Rubin GD, Ryerson CJ, Haramati LB et al (2020) The role of chest imaging in patient management during the COVID-19 pandemic: a multinational consensus statement from the Fleischner Society. Radiology. https://doi.org/10.1148/radiol.2020201365

21. Chen DD, Jiang XQ, Hong Y et al (2020) Can chest CT features distinguish patients with negative from those with positive initial RT-PCR results for coronavirus disease (COVID-19)? AJR Am J Roentgenol. https://doi.org/10.2214/AJR.20.23012

22. Falaschi Z, Danna PSC, Arioli R et al (2020) Chest CT accuracy in diagnosing COVID-19 during the peak of the Italian epidemic: a retrospective correlation with RT-PCR testing and analysis of discordant cases. Eur J Radiol. https://doi.org/10.1016/j.ejrad.2020.109192

23. JL, Luo L, Luo ZD, et al (2020) Diagnostic performance between CT and initial real-time RT-PCR for clinically suspected 2019 coronavirus disease (COVID-19) patients outside Wuhan, China. Respir Med. https://doi.org/10.1016/j.rmed.2020.105980

24. Huang EPC, Sung CW, Chen CH, Fan CY, Lai PC, Huang YT (2020) Can computed tomography be a primary tool for COVID-19 detection? Evidence appraisal through meta-analysis. Crit Care. https://doi.org/10.1186/s13054-020-02908-4

25. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. BMJ. https://doi.org/10.1136/bmj.b2535

26. Leeflang MMG, Deeks JJ, Takwoingi Y, Macaskill PM (2013) Cochrane diagnostic test accuracy reviews. Syst Rev. https://doi.org/10.1186/2046-4053-2-82

27. Leeflang MMG, Deeks JJ, Gatsonis C, Bossuyt PMM (2008) Cochrane diagnostic test accuracy working group, systematic reviews of diagnostic test accuracy. Ann Intern Med. https://doi.org/10.1186/2046-4053-2-82

28. Whiting PF, Rutjes AWS, Westwood ME et al (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

29. Lee CK, Davies L, Wu YL et al (2017) Gefitinib or erlotinib vs chemotherapy for EGFR mutation-positive lung cancer: individual patient data meta-analysis of overall survival. J Natl Cancer Inst. https://doi.org/10.1093/jnci/djw279

30. Xie XZ, Zhong Z, Zhao W, Zheng C, Wang F, Liu J (2020) Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. Radiology. https://doi.org/10.1148/radiol.2020200343

31. Li YY, Wang WN, Lei Y et al (2020) Comparison of the clinical characteristics between RNA positive and negative patients clinically diagnosed with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi. https://doi.org/10.3760/cma.j.cn112147-20200214-00095

32. Wen ZY, Chi YC, Zhang L, Liu H, Wang DQ (2020) Coronavirus disease 2019: initial detection on chest CT in a retrospective multicenter study of 103 chinese subjects. Radiol Cardiothorac Imaging. https://doi.org/10.1148/ryct.2020200092

33. Caruso D, Zerunian M, Polici M et al (2020) Chest CT features of COVID-19 in Rome, Italy. Radiology. https://doi.org/10.1148/radiol.2020201237

34. Himoto Y, Sakata A, Kirita M et al (2020) Diagnostic performance of chest CT to differentiate COVID-19 pneumonia in

non-high-epidemic area in Japan. Jpn J Radiol. https://doi.org/10.1007/s11604-020-00958-w

35. Zhu WB, Xie K, Lu H, Xu L, Zhou S, Fang S (2020) Initial clinical features of suspected coronavirus disease 2019 in two emergency departments outside of Hubei China. J Med Virol. https://doi.org/10.1002/jmv.25763

36. Xie CB, Jiang LX, Huang G et al (2020) Comparison of different samples for 2019 novel coronavirus detection by nucleic acid amplifcation tests. Int J Infect Dis. https://doi.org/10.1016/j.ijid.2020.02.050

37. Gietema HA, Zelis N, Nobel JM et al (2020) CT in relation to RT-PCR in diagnosing COVID-19 in the Netherlands: a prospective study. PLoS ONE. https://doi.org/10.1371/journal.pone.0235844

38. Long CQ, Xu HX, Shen QL et al (2020) Diagnosis of the coronavirus disease (COVID-19): rRT-PCR or CT? Eur J Radiol. https://doi.org/10.1016/j.ejrad.2020.108961

39. Li ZC, Zeng BL, Lei PG et al (2020) Differentiating pneumonia with and without COVID-19 using chest CT images: from qualitative to quantitative. J X-Ray Sci Technol. https://doi.org/10.3233/XST-200689

40. Stanzione A, Ponsiglione A, Cuocolo R et al (2021) Chest CT in COVID-19 patients: structured vs conventional reporting. Eur J Radiol. https://doi.org/10.1016/j.ejrad.2021.109621

41. Review Manager (RevMan) (2012)[Computer program] Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration

42. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020) The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 41:145–151

43. Wu F, Huang WS (2020) COVID-19 diagnostic process in mainland China: the math beyond pneumonia. J Allergy Clin Immunol 146:64–66. https://doi.org/10.1016/j.jaci.2020.04.015

44. Ye Z, Zhang Y, Wang Y, Huang Z, Song B (2020) Chest CT manifestations of new coronavirus disease 2019 (COVID-19): a pictorial review. Eur Radiol. https://doi.org/10.1007/s00330-020-06801-0

45. Razek A, Fouda N, Fahmy D et al (2021) Computed tomography of the chest in patients with COVID-19: what does radiologists want to know? Pol J Radiol. https://doi.org/10.5114/pjr.2021.104049

46. Razek AAKA, El Badrawy MK, Alnaghy E (2020) Interstitial lung fibrosis imaging reporting and data system: what radiologist wants to know? J Comput Assist Tomogr. https://doi.org/10.1097/RCT.0000000000001075

47. Bernheim A, Mei X, Huang M et al (2020) Chest CT findings in coronavirus disease-19 (COVID-19): relationship to duration of infection. Radiology. https://doi.org/10.1148/radiol.2020200463

48. Adams HJA, Kwee TC, Yakar D, Hope MD, Kwee RM (2020) Systematic review and metaanalysis on the value of chest CT in the diagnosis of coronavirus disease (COVID-19): Sol Scientiae. AJR Am J Roentgenol, Illustra Nos. https://doi.org/10.2214/AJR.20.23391

49. Guan WJ, Ni ZY, Hu Y et al (2020) China medical treatment expert group for COVID-19 clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. https://doi.org/10.1056/NEJMoa2002032

50. Mohammadi A, Esmaeilzadeh E, Li Y, Bosch RJ, Li JZ (2020) SARS-CoV-2 detection in different respiratory sites: a systematic review and meta-analysis. EBioMedicine. https://doi.org/10.1016/j.ebiom.2020.102903