The exact place of PCR and chest CT in screening, staging, and diagnosis of Covid-19: A meta-analysis

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Abstract

Introduction: Nowadays there is an ongoing acute respiratory outbreak causing by the novel highly contagious coronavirus (nCoV). There are two diagnostic protocol based on chest CT scan and quantitative reverse-transcription polymerase chain reaction (RT-PCR) which their diagnostic accuracy is under the debate. We designed this meta-analysis study to determine the diagnostic value of initial chest CT scan in patients with nCoV infection in comparison with RT- PCR.

Search strategy and statistical analysis: Three main databases the PubMed (MEDLINE), Scopus, and EMBASE was systematically searched for all published literatures from January 1st, 2019, to the 27th march 2020 with key grouping of "COVID19 virus", "2019 novel coronavirus", "Wuhan coronavirus", "2019-nCoV", "X-Ray Computed Tomography", "Polymerase Chain Reaction", "Reverse Transcriptase PCR", and "PCR Reverse Transcriptase". All relevant case- series, cross-sectional, and cohort studies were selected. Data extraction was done in Excel 2007 (Microsoft Corporation, Redmond, CA) and their analysis was performed using STATA v.14.0SE (College Station, TX, USA) and RevMan 5.

Result: From first recruited 668 articles we end up to the final 47 studies, which comprised a total sample size of 4238 patients. In compare to RT-PCR, the overall sensitivity, specificity, positive predictive value, and negative predictive value of chest CT scan were 86% (95% CI: 83% -90%), 43 % (95% CI: 26% -60%), 67% (95% CI: 57% -78%), and 84% (95% CI: 74% -

95%) respectively. However the RT-PCR should be repeated for three times in order to give the 99% accuracy especially in negative samples.

Conclusion: According to the acceptable sensitivity of chest CT scan, it can be employed complement to RT-PCR to diagnosis patients who are clinically suspicious for nCoV.

Introduction

In late December of 2019, a cluster of unknown viral pneumonia patients, who later turned out to be infected with novel coronavirus (nCoV) (the disease named COVID-19), has been reported in Wuhan City, Hubei Province, China(1). Until 11 March, over 100 countries and 120000 cases have been involved with this beta coronavirus of whom over 4000 died and its incidence is at increasing pace worldwide. Officially, World Health Organization has declared the pandemic of nCoV, therefore, it has attracted an international interest (2).

Currently, due to non-existence of therapeutic vaccine or certain antiviral drugs, both detecting patient at an early stage and immediate patient isolation play mandatory role in fighting against nCoV(3). Although chest computed tomography (CT) scan has shown promising results regarding early diagnosis of COVID-19, reverse transcription polymerase chain reaction (RT- PCR) remain to be the mainstay of this viral disease's diagnosis given the sixth version of diagnosis and treatment of COVID-19 (3, 4); however, RT-PCR poses several limitations that reduce the sensitivity of this method and cause some patients to be

missed (5). Actually CT and PCR are not comparable in the diagnosis of COVID–19 because CT is valuable tool in staging of disease and checking the treatment efficacy but repeating PCR test is the diagnostic tool. Recent studies have focused on chest CT of patients with COVID–19 features and they claim that initial chest CT may enable to detect the disease with higher sensitivity in comparison to RT-PCR (6). Therefore, this systematic review and meta-analysis was performed to determine diagnostic accuracy of initial chest CT scan compare to RT-PCR in patients who are infected with nCoV.

Materials And Methods

Inclusion criteria

All stages of the study followed the PRISMA guideline. Inclusion criteria were having an observational epidemiological study design, clear report of the number of positive cases by PCR and chest CT, and ability to calculate accuracy indicators.. Articles that did not meet one or more of the study entry criteria were also excluded. All relevant English, Chinese and other language case-series, cross-sectional, and cohort studies were selected. Case reports were excluded and for the remaining literatures scientific validity was performed.

Search strategy

The study was run by searching all relevant literature from three main databases: MEDLINE (PubMed), Scopus, and EMBASE from January 1st , 2019, to the 27th march 2020 with words the key grouping of “COVID19 virus”, “2019 novel coronavirus”, “Wuhan coronavirus”, “2019- nCoV”, “X-Ray Computed Tomography”, “Polymerase Chain Reaction”, “Reverse Transcriptase PCR”, and “PCR Reverse Transcriptase” (Supplementary file 1). In order to obtain more articles and to ensure that the appropriate search is performed in the databases, the list of selected articles was also reviewed. The variables extracted from each targeted article in included the name of the first author, the year of publication of the article, the country and city of the study, the average age of the subjects, the gender, the study design, total sample size, positive tst result, negative test result, false positive, and false negative.

Data Extraction and Statistical Analysis

To reduce the selection bias, two researchers (SZA and SSTZ) screened articles separately through checking titles and abstracts. Unlikeness and disagreement were removed by the idea of the third ones (FKH). The full text of whole candidate related articles were studied in order to grouping into the included one or excluded one. Actually, included ones had data of confirmed COVID–19 patients by chest CT scan or quantitative real time polymerase chain reaction (RT- PCR). The quality assessment was performed by the Newcastle–Ottawa Scale (NOS) assessment tool. The papers that receive score more than 6 were reflected as the “high quality” one and go to the additional meta-analysis step.

The outcomes of interest, including the diagnostic operation of CT-scan to identify covid–19 by the random effect model, were summary receiver operating characteristic (SROC) curve sensitivity and specificity. Sensitivity, indicating the capacity of index test to identify patients, considered by “Sensitivity = TP/ (TP + FN)”. Specificity as the examination to remove disease- free, calculated by “Specificity = TN/ (FP + TN)”. Positive Predictive Value (PPV) is probability of disease if the test is positive calculated by “Positive predictive Value = TP/ (FP + TP)”. Negative Predictive Value (NPV) is probability of disease-free if the test is negative calculated by “negative predictive value = TN/ (FN + TN)” The Cochran’s Q-test of heterogeneity at an importance amount of 5% was used to evaluate statistical heterogeneity of the researches and I2 was practical for quantitative evaluation of heterogeneity between outcomes based on the Higgins classification in which an I2 value more than 75% is pinpointing of heterogeneity. Deeks’ funnel plot was used to evaluate publication bias by the “Metafunnel”. Briefly, to create the funnel plot, the odds ratio was first calculated using the equations of (TP / FN)/(FP / TN) and after estimating the odds ratio logarithm, the standard error of odds ratio was calculated. Extracted data were collected in Excel 2007 (Microsoft Corporation, Redmond, CA) and analysis was done by using STATA v.14.0SE (College Station, TX, USA) and RevMan 5.

Results

In the present study, at first 668 (667+1) articles were identified through the search of three data bases of Pubmed, Embase, and Scopus. After deleting 188 duplicate articles, the screening was done based on the titles and abstracts which lead to the 89 articles were candidate as the related ones (figure 1). After that scoring of the articles were done based on NOS screening tool and the number of article were limited to the 47.

Finally, 47 articles with the total sample size of 4283 recruited for the final analysis. All studies were published in the first quarter of 2020. A summary of the information in these articles is shown in Table 1. With the exception of one article from the United States, all articles were from China. According to the articles, the types of studies were 23 case-series, 14 cohorts and 10 cross sectional. The forest plot result is shown in figure 2 and the quantity of False Positives (FP), False Negative (FN) and True Positives (TP), and True Negative (TN) is shown more than sensitivity, specificity, and 95% confidence Intervals (CI) of each study. Sensitivity ranged from 25% to 100% and the specificity was estimated to vary from 19% to 70%. One of the important assumptions in calculating sensitivity and specificity using the Metaprop command is to extract studies that have reported 100% sensitivity or specificity.

Table 1: Data of 47 included file in the data extraction step.

N.	1st author	Country(city)	Gender% male	Age mean, range(yr.)	Type of study	Sample size
1	Adam Bernheim(1)	United States (New York)	50%	45, 18-80	Case-series	121
2	Chun Shuang Guan(7)	China (Beijing)	47%	42, 1-86	Case-series	53
3	Chunbao Xie(8)	China (Chengdu)	58%	33, 8-62	Cross-sectional	19
4	Dahai Zhao(9)	China (Anhui)	50%	42, 27-56	cohort	34
5	Dehan Liu(10)	China (Wuhan)	%0	32, 23-40	Case-series	51
6	Fang ZHENG(11)	China (Wuhan)	56%	3, 2-9	Case-series	25
7	Fengxiang Song(12)	China (shanghai)	49%	49, 33-65	Case-series	51
8	Fneg Pang(13)	China (Wuhan)	29%	40, 25-63	Case-series	21
9	Feng Kai(14)	China (Shenzhen)	33%	8, 4-14	Case-series	15
10	Jasper Fuk-Woo Chan(15)	China (Hong Kong)	50%	46, 33-66	Case-series	6
11	Guangming Ye(16)	China (Wuhan)	40%	32, 27-42	Case-series	5
12	Guo-Qing Qian(17)	China (Ningbo)	41%	50, 5-96	Case-series	91
13	Harrison X. Bai(18)	China (Changsha)	NS*	NS	cohort	256
14	Heshui Shi(19)	China (Wuhan)	52%	49.5, 39-61	Case-series	81
15	Huanhuan Liu(20)	China (Shanghai)	14%	20(2month-58 yr)	Case-series	51
16	Huijun Chen(21)	China (Wuhan)	0%	30, 26-40	Case-series	9
17	Jian Wu(22)	China (Yuncheng)	49%	46, 4->65	Case-series	80
18	Jianhua Xia MM(23)	China (Zhejiang)	70%	54.5, 13-74	Cross-sectional	30
19	KC Liu(24)	China (Hefei)	51%	42, 5-86	Cohort	73
20	Li Guo(25)	China (Beijing)	50%	35, 2-64	Cross-sectional	6
21	Li Yuanyuan(26)	China (Wuhan)	46%	52, 25-82	Cross-sectional	54
22	Lia Na Ji(27)	China (Beijing)	NS	NS	Case-series	7
23	Lisi Deng(28)	china (Zhuhai)	NS	≥18year	Cohort	56
24	Michael Chung(29)	United States (New York)	61%	51, 29-77	Case-series	21
25	Mingzhi Li(30)	China (Nanchang)	55.5%	43, 31-68	Case-series	9
26	Nanshan Chen(31)	China (Wuhan)	68%	, 21-821151	Case-series	99
27	Rui Han(32)	China (Wuhan)	35%	45, 21-95	Case-series	108
28	Shuchang Zhou(33)	China (Wuhan)	63%	53, 30-77	Case-series	118
29	Soon Ho Yoon(34)	Korea (Seoul)	44%	54	Case-series	9
30	Suxin Wan(35)	China (Chongqing)	53%	47, 36-55	Cross-sectional	135
31	Tao Ai(36)	China (Wuhan)	46%	51, 2-95	Cross-sectional	1014
32	Tao Lu(37)	China (Sichuan)	20%	52, 41-62	Case-series	5

33	Tianmin Xu(38)	China (Changzhou)	49%	42, 24-65	Cohort	51
34	Wanbo Zhu(39)	China (Hefei)	48%	40, 27-53	Case-series	116
35	Wang XF(40)	China (Shenzhen)	41%	9	Case-series	34
36	Wei Li(41)	China (Zhuhai)	80%	3(10month-6yr)	Case-series	5
37	Wenjie Yang(42)	China (Shanghai)	54%	45	Case-series	149
38	Wu Jing(43)	China (Nanjing)	40%	52, 25-80	Case-series	130
39	Xi Xu(44)	China (Guangzhou)	43%	50, 18-86	Case-series	90
40	Xiang Dong(45)	China (Wuhan)	45%	37(2-69)	Case-series	11
41	Xiaoli Zhang(46)	China (Zhejiang)	51%	46	Cross-sectional	645
42	Xingzhi Xie(47)	China (Changsha)	NS	NS	Cross-sectional	167
43	Xiong Zeng(48)	China (Changsha)	NS	NS	Cross-sectional	47
44	Yicheng Fang(4)	China (Shanghai)	57%	45, 39-55	Case-series	51
45	Yueying Pan(49)	China (Wuhan)	52%	45	Case-series	63
46	Zenghui Cheng(50)	China (Shanghi)	NS	NS	Cross-sectional	38
47	Zhang MQ(51)	China (Beijing)	56%	36, 15-49	Case-series	9

*NS: not stated.

Therefore, based on this approach and by analyzing 26 articles that reported less than 100% sensitivity, summary sensitivity of CT compared to PCR 86% (95% CI: 83%–90%) and summary specificity of CT based on six articles 43 % (95% CI: 26% –60%). sensitivity is ranging from 25% to 97% and specificity is 25% to 70% in included articles (figure 3–4). The PPV of CT was 67% (95% CI: 57% –78%) and the negative predictive value was 84% (95% CI: 74% –95%). Variation of estimated numbers is 33% to 97% and 33% to 95% for PPV and NPV respectively (figures 5,6). The symmetry between the two sides of the

funnel plot regression line indicates that the publication is not biased in these articles. However, due to the large number of zeros in the FP and TN cells, it was possible to calculate the odds ratio for six studies, and the interpretation of this plot in our study should be done with caution (figure 7).

The table 2 set out 15 articles which the information of the first test was available (subsequent RT-PCR data were included if available). Moreover, the swabs should have been taken from sputum, nasopharyngeal, oropharyngeal, nose or throat (if a combination used, nasopharyngeal swab (if not available, throat swab) considered as the primary). The result of the first, second, third and fourth positive RT-PCR test and also information of patients who had negative result until the fourth test but considered as confirmed or most likely ill later according to more RT-PCR tests or examining other swabs, clinical manifestations, typical chest CT scan's features or developmental changes in the series of CT scans or mixture of prior methods.

Table 2: The number of positive test result in RT-PCR testing and the number of confirmed ones (ordered by total number of cases)

N.	First author	N. of total cases	Number of total confirmed patients	N. of patients confirmed with the first RT-PCR test (perc. 1)	N. of patients confirmed with the second RT-PCR test (perc. 2)	N. of patients confirmed with the third RT-PCR test (perc. 3)	N. of patients confirmed with the fourth RT-PCR test (perc. 4)	N. of Patients confirmed later (perc. 5)
1	Tao Ai(36)	1014	909	343 (37.7%)	205 (22.6%)	45 (5%)	8 (0.9%)	308 (33.9%)
2	Xingzhi Xie(47)	167	167	162 (97%)	2 (1.2%)	2 (1.2%)	0 (0%)	1 (0.6%)
3	Jian Wu(22)	80	80	41 (51.2%)	30 (37.5%)	9 (11.3%)	0 (0%)	0(0%)
4	Li Yuanyuan(52)	54	54	31 (57%)	_6	_	_	23 (42.6%)
5	Yicheng	51	51	36 (70.6%)	12 (23.6%)	2 (7.8%)	1 (2%)	0 (0%)

	Fang(4)						
6	Qing Chen(53)	9	9 (100%)	_	_	_	0 (0%)
7	Li-Na Ji(54)	7	4 (80%)	_	_	_	1 (20%)
8	Jasper Fuk-Woo Chan (15)	6	4 (80%)	_	_	_	1 (20%)
9	Wei Li(41)	15	(80%)4	0 (0%)	0 (0%)	0 (0%)	1 (20%)
10	Li Ni(55)	3	1 (33.3%)	0 (0%)	0 (0%)	_	2 (66.7%)
11	Yuanzhe Li(56)	2	1 (50%)	1 (50%)	_	_	0 (0%)
12	Wendong Hao(57)	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
13	Peikai Huang(58)	1	0 (0%)	0 (0%)	1 (100%)	_	100%
14	Jinrong Qu(59)	1	1 (100%)	_	_	_	0 (0%)
15	Xavier Marchand-Sénécal(60)	1	1 (100%)	_	_	_	0 (0%)

1 number of primarily confirmed patients divided total confirmed patients.

2 number of secondary confirmed patients divided total confirmed patients.

- 3 number of thirdly confirmed patients divided total confirmed patients.
- 4 number of fourthly confirmed patients divided total confirmed patients.
- 5 number of patients who were confirmed later divided total confirmed patients.
- 6 This means the test has not been conducted or reported.

The mean percentage of primarily confirmed patients divided total confirmed patients in the articles with more than 10 total confirmed patients (the first 5 articles included), is 62.7%. This means among these 5 articles, RT-PCR test could diagnose 62.7% of the COVID–19 infected patients in the first test, among all confirmed patients a nd about 37.3% of infected patients couldn’t be recognized in the first place by RT-PCR test. Among these 5 articles, 4 included the exact information of further tests (number 1,2,3 and 5). In these for articles the mean percentage of secondary, thirdly and fourthly confirmed patients divided total confirmed patients is 21.2%, 6.3%, 0.7% retrospectively. Moreover, the percentage of the patients who were not diagnosed after 4 times of repeating test was 8.6% (in the previous 4 articles). The number and sequence of primers and probes could be influential on PCR sensitivity and specificity which were surveyed in table 3.

Table 3: Based on the the information illustrated in table 2, the primer and probe ‘s data is presented (ordered by total number of cases)

N.	First author	Total N. of cases	N. of patients confirmed with the first RT-PCR test	N. patients confirmed later	primarily confirmed patients divided total confirmed patients (%)	Target genes
1	Jian Wu(22)	80	41	39	51.2%	N and ORF1ab
2	Qing Chen(53)	9	9	0	100%	RdRP, E and N

3	Jasper Fuk-Woo Chan (15)	64	1	80%	RdRP and S
4	Wendong Hao(57)	10	1	0%	ORF1ab
5	Xavier Marchand-Senécal(60)	11	0	100%	RdRP

As we can see in table 3, in the case report by Wendong Hao (57), consuming one pair of primer and probe did not indicate positive result at first but in the fourth time. On the other hand, Xavier Marchand-Senécal et al. reported a case that was diagnosed initially with one pair primer and probe PCR test. By using 2 pairs of primer and probe, the mean of initially detecting patients divided total confirmed patients, was 65.5%. In addition, Qing Chen (53) findings implied utilization of 3 pair of primer and probe caused 100% of initially discovering COVID–19 patients (53). Based on limited data that has been found, totally, it seems that the more number of primer and probe have been used, the more initially detected patients have been achieved. Although more specific information is needed and demanded from future researchers to determine the exact desired conclusion.

Discussion

Considering the outcomes of RT-PCR as reference, in our meta-analysis, the sensitivity and specificity of initial chest CT scan for detecting patients, who were highly suspicious for nCoV, were 86% and 43% respectively. The positive predictive value and negative predictive value of CT scan were 67% and 84% respectively. In a broader sense, 67% of individuals with positive chest CT scan had positive RT-PCR and 84% of individuals with negative chest CT scan had negative RT-PCR. Despite numerous studies have been conducted on various subjects of nCoV, the early diagnosis of patients who were infected with nCoV and also, suitable quarantine of them are under the debate. In accordance with previous studies, chest CT scan when it compares to RT-PCR, may have a variety of beneficial features including, but not limited to, less time-consuming and more availability, that makes doctors to take it into consideration as an adjuvant diagnostic tool (61, 62).

Tao Ai and his colleagues performed a study on 1014 patients and 888 (88%) of them had positive chest CT scan and 601 patients had positive RT-PCR for nCoV, and the sensitivity, specificity, PPV, and NPV of CT scan were about 97%, 25%, 65%, and 83% respectively that compare to our result sensitivity and specificity were much different. The possible reason behind relatively high sensitivity and low specificity in this study is the odds ratio of positive RT-PCR was low, which was considered as the reference (61).

There have been a number of patients with typical chest CT scan findings and symptoms for nCoV that their initial RT-PCR results were negative according to previous literatures (4, 18, 61). For instance, following Y Fang [et.al.](#), study that showed that the result of initial RT-PCR in 15 out of 51 patients were negative while their chest CT scan were positive (4, 47, 61). Hence, negative result of RT-PCR is not able to roll out nCoV and it is very important to pay attention to chest CT scan, epidemiologic features, and clinical symptoms. Diagnostic approach with favorably sensitivity and specificity is needed to control the rapid distribution of this disease. Therefore RT-PCR is suggested as a method for diagnosis of SARS-CoV-2 by World Health Organization (WHO) (63). The swabs are commonly taken from sputum, nasopharyngeal, pharyngeal and throat which were included in our meta-analysis. Although WHO recommends examining stool specimens, together with nasopharyngeal swabs (63). Furthermore, combination of humoral and cellular immunity, for instance IgG-IgM antibody, alongside RT-PCR could possibly refine the detection of COVID-19 (25, 68).

According to Chen W., and his colleagues research, positive results based on blood samples, represent deterioration of the disease. Additionally, positive results of anal swabs are related to the severe phase of the disease and the RNA load was higher in anal swabs indicates that the virus may replicate in the digestive system (53). Stool swabs were positive in 8 out of 9 confirmed patients but urine and blood samples were negative in all (8). Also, plasma and urine samples caused negative result in the study by Jasper Chan et al, as well (15). A prospective case series including 30 confirmed COVID-19 patients (21 common type, 9 severe type and one of them had conjunctivitis) underwent RT-PCR test for both tear and conjunctival secretions specimens. Surprisingly, the results of the two specimens were positive the only conjunctivitis patient and the other 58 samples were negative. Therefore, tear and conjunctival secretions

samples could possibly yield result for RT-PCR test in COVID-19 infected patients with conjunctivitis(23). Based on distinctly targeted genomes, the sensitivity of RT-PCR would be various. The results of Chan et al indicated that among 273 specimens from 15 positive COVID-19 patients, RdRp-P2 test showed 77 positive specimens and RdRp/Hel test showed 42 positives, more and revealed RdRp/Hel assay has higher sensitivity. Moreover, RdRp/Hel analysis did not cross reacted with any human coronaviruses or other respiratory pathogens while RdRp-P2 analysis reacted to SARS-CoV, either (64). Another study expressed that the sensitivity of N gene assay in finding the positive samples, is 10 times more than ORF-1b gene assay(65).

In February, 280 suspected patients with clinical manifestations were enrolled in a hospital in Marseille, RT-PCR assay was conducted. About 51% of the patients were negative for all the common viruses, additionally none of the patients were positive for SARS-CoV-2 (66). As reported by Guo-Qing Qian et al. 88 out of 91 suspected patients, were confirmed at least one time by RT-PCR assay in 2 sequential tests with 24 hour interval, and 3 patients with negative outcome reported as confirmed due to clinical manifestation (17). In the study by Tao Ai et al (N.1 in the table), from total 1014 patients, 601 patients were confirmed by Positive RT-PCR test and 308 patients with negative results were strongly perceived infected by clinical manifestations and CT scans approval. From total 909 patients, the percent of positive first, second, third and fourth test were 37.7%, 22.6%, 5%, and 0.9%, retrospectively. Additionally, about 33.9% of the patients could not be diagnosed with four repeating tests. Whereas CT scans were positive in 580 of 601(97%) confirmed RT-PCR test and 308 in 413(74.6%) patients with negative RT-PCR assay, as well(36). On the report of Xingzhi Xie (N.2), from total 167 patients, 162 patients were confirmed by the first test (7 of them had normal CT), while 4 patients turned positive after the second and third test and the other patients became positive after multiple tests. Whereas all these patients had clinical symptoms in addition to GGO pattern on their CT scans(47). In the third study, more than two-thirds of the patients had abnormal CT scans(22). In a retrospective analysis(N.5), in the group of 51 patients, 98% (50/51) had abnormal CT, besides 70.6% (36/51) had positive PCR assay, initially, about 30% of the tests became positive after second, third and fourth scanning(4). from the report of a family cluster (N.7), 4 patients were confirmed by RT-PCR, one patients with negative PCR had GGO patterns in her CT and the other two with the same test result, had mild cough and fever for few days(54). On the report of 5 children (N.9), 4 of them had positive PCR outcome within first assay but one with CT findings turned positive after six times of examining (41). As specified by Li Ni (N.10), from 3 suspected patients, 2 patients showed negative PCR result after 3 repeated tests in 11 days and finally affirmed to be infected by typical CT features and clinical manifestations (55). On a report of 2 children, one of them had positive and the other had negative RT-PCR result which became positive in the day after, and at the same time, both had CT symptoms (56). In a case report represented a 56 years old man (N.12), RT-PCR assay was negative for 3 times and the fourth time became positive while CT demonstrated typical features such as ground-glass opacification (GGO) (57). Another case report(N.13) presented a patient with negative PCR result but typical features of COVID-19 in CT. finally RT-PCR result became positive in the third examination (58).

What stands out from table 2 is that, 62.7% of the infected COVID-19 patients could be recognized in the first test and about 21.2%, 6.3%, 0.7% could be diagnosed in the further second, third and fourth tests, retrospectively. Actually, about 9% of the infected patients have not been detected, even after the fourth test. According to the results and due to the PCR's cost and time consumption, it seems repeating the test for 3 times is reasonable in patients with initially negative results (with 24hrs to 3 days' time interval based on literatures).

In fact about forth/ fifth of infected patients with COVID-19 virus have mostly mild and just about 15% of them may have severe ones. Usually patients who have the worse clinical symptoms like fever, dry cough, and low saturation are candidate for RT-PCR testing. Positive RT-PCR results usually have high positive predictive value, but negative RT-PCR should be repeated for three times in order to increase the negative predictive value equal to 98% (57% first test, 34% second one, and 7% third times). If the patient's death is due to Covid-19 but their PCR indicated to the negative presence of virus and their chest CT is positive no death as the result of Covid-19 is reported. In fact, some patient with negative PCR result dies, but based on our results, 86% of them are covid positive and their disease should be confirmed by repeating PCR for three times. So the exact place of chest CT is staging the COVID-19 disease as the mild, moderate, and severe, but not screening and diagnosis of the disease. Serological tests can complement the PCR results because the negative value of chest CT can be due to the early stages of the disease. So PCR does not compete with chest CT but is used as a supplementary test.

We acknowledge that our study had some limitations: 1. the specificity of CT scan was not as reliable as the sensitivity of that as a result of the majority of studies' nature, which were case- series and the number of true negative patients in those studies were zero. 2 it has been postulated in A Bernheim et al's study that chance of detecting lung involvement in chest CT scan will be increased if the duration between symptom onset and initial chest CT scan rises and this duration was different among 47 studies. So, the different outcomes would have emerged if the duration between studies were equal.

Declarations

Availability of data and material: Information, data, and photos will be provided if they requested.

Competing interests: All authors claim that there is not any potential competing or conflict of interest

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Authors' contributions: SMK. A. was the principal investigator and supervisor of the project. M. S. was the epidemiologist who runs the statistical analysis of data and provides figures. SS.TZ and SZ. A. individually screened the data and make the data extraction sheet and tables of the article. F. KH had design the search strategy and wrote the manuscript. AN.SH edited the manuscript and co-supervised the project.

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Figures

PRISMA 2009 Flow Diagram

Figure 1

The number of article during several steps based on the PRISMA flow diagram (2009)

Figure 2

Sensitivity and specificity of 47 included studies

Figure 3

Summary of sensitivity and 95% CI of 26 study, generated by the STATA procedure metaprop

Figure 4

Summary of specificity and 95% CI of 6 study, generated by the STATA procedure metaprop

Figure 5

Summary of positive predictive value and 95% CI of 18 study, generated by the STATA procedure Metaprop

Figure 6

Summary of negative predictive value and 95% CI of 6 study, generated by the STATA procedure Metaprop

Figure 7

The Deeks' funnel plot curve for assessment of publication bias

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