



RESEARCH ARTICLE

CT imaging features of 4121 patients with COVID-19: A meta-analysis

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Abstract

Objective: We systematically reviewed the computed tomography (CT) imaging features of coronavirus disease 2019 (COVID-19) to provide reference for clinical practice.

Methods: Our article comprehensively searched PubMed, FMRS, EMBASE, CNKI, WanFang databases, and VIP databases to collect literatures about the CT imaging features of COVID-19 from 1 January to 16 March 2020. Three reviewers independently screened literature, extracted data, and assessed the risk of bias of included studies, and then, this meta-analysis was performed by using Stata12.0 software.

Results: A total of 34 retrospective studies involving a total of 4121 patients with COVID-19 were included. The results of the meta-analysis showed that most patients presented bilateral lung involvement (73.8%, 95% confidence interval [CI]: 65.9%-81.1%) or multilobar involvement (67.3%, 95% CI: 54.8%-78.7%) and just little patients showed normal CT findings (8.4%). We found that the most common changes in lesion density were ground-glass opacities (68.1%, 95% CI: 56.9%-78.2%). Other changes in density included air bronchogram sign (44.7%), crazy-paving pattern (35.6%), and consolidation (32.0%). Patchy (40.3%), spider web sign (39.5%), cord-like (36.8%), and nodular (20.5%) were common lesion shapes in patients with COVID-19. Pleural thickening (27.1%) was found in some patients. Lymphadenopathy (5.4%) and pleural effusion (5.3%) were rare.

Conclusion: The lung lesions of patients with COVID-19 were mostly bilateral lungs or multilobar involved. The most common chest CT findings were patchy and ground-glass opacities. Some patients had air bronchogram, spider web sign, and cord-like. Lymphadenopathy and pleural effusion were rare.

KEYWORDS

computed tomography, coronavirus disease 2019, imaging features, meta-analysis, pneumonia, systematical review

1 | INTRODUCTION

Wuhan, China, became the center of an outbreak of the coronavirus disease 2019 (COVID-19) in late December 2019. The epidemic of COVID-19 has spread to the whole world within a short time. According to reports from the World Health Organization (WHO), up to 24:00 on 16 March 2020, a total of 80 881 confirmed cases and 3226 deaths were reported in China.¹ In addition, COVID-19 has affected 150 countries, with 86 438 confirmed cases and 3388 deaths outside China.² With the further spread of COVID-19, the confirmed cases of COVID-19 in Korea, Japan, Spain, Italy, Iran, and other countries increased rapidly. The number of new confirmed cases, the cumulative number of confirmed cases, and deaths reported in the world outside China have surpassed that in China. COVID-19 has become a serious threat to global health and a significant challenge to health-care systems worldwide.

As a new infectious disease, there is no effective drugs and the vaccine is under development. Early detection, isolation, and treatment can maximize the control the spread of the disease among population. The current gold standard for COVID-19 diagnosis is positive results of the nucleic acid amplification test (NAAT). However, there were many cases of positive results be confirmed after repeated NAAT negative,³ and there were asymptomatic infections in patients with COVID-19.^{4,5} Asymptomatic infections may also become a new source of infection. Therefore, quickly and effectively diagnosing infections play a key role in preventing and controlling the epidemic. The guideline for the diagnosis and treatment of COVID-19 (Trial edition Fifth), issued on 4 February, added clinical diagnostic criteria, that was, the suspected cases with typical imaging features in Hubei were clinically diagnosed cases.⁶ Integrating the first to seventh edition of the guideline, imaging has been playing a pivotal role in the diagnosis and treatment of this disease. Especially in hospitals that cannot perform NAAT, imaging can be a powerful tool for admission screening. Therefore, grasping the imaging features of patients with COVID-19 is of great significance for early screening and diagnosis, curbing the occurrence and development of the disease, and suppressing the speed of transmission.

Although many studies have been published on CT imaging of patients with COVID-19, most of them were single-center, and in the same hospital or region. Due to the different design and insufficient sample size, the imaging features of the published studies were different. Moreover, there is still lack evidence-based medical evidence on the CT imaging features in patients with COVID-19 to guide clinical practice. Therefore, we carried out this study to summarize the CT imaging features of COVID-19, to provide reference for further clinical practice.

2 | MATERIALS AND METHODS

2.1 | Search databases and search strategies

This meta-analysis was carried out according to Preferred Reporting Items for Meta-Analyses of Observational Studies in Epidemiology

(MOOSE) Statement.⁷ PubMed, FMRS, EMBASE, CNKI, WanFang databases, and VIP databases were electronically searched to collect studies about the CT imaging features of COVID-19 from 1 January 2020 to 16 March 2020. We also manually searched the lists of included studies to avoid missing any eligible study. When duplicate studies describing the same population, the most detailed or recent study was included. There was no language restriction placed on the searches, but only literatures published online were included. The search used a combination of subject words and free words, and adjusted according to different database characteristics. The search terms included: "Coronavirus" OR "2019-nCoV" OR "COVID-19" OR "SARS-CoV-2."

2.2 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (a) cohort studies, case-control studies, and case series studies; (b) the study population was patients diagnosed with COVID-19; and (c) the observation indicators were the imaging findings of chest CT or HRCT.

The exclusion criteria were as follows: (a) overlapping or duplicate studies; (b) had no clinical indicators or lacking necessary data which cannot be obtained even by contacting the author; and (c) case reports and studies with a sample size less than 30.

2.3 | Data extraction and quality assessment

Three researchers independently searched and screened the studies, collected data, and cross-checked. If there was a dispute, it was resolved through discussion or consultation with another researcher. The content of the data extraction included: the first author's surname, the date of publication of the article, study region/country, study design, sample size, age, and CT imaging features; relevant elements of bias risk assessment.

The included studies of this meta-analyses were observational studies, so the British National Institute for Clinical Excellence (NICE)⁸ was used to evaluate the study quality by two independent reviewers. This evaluation was conducted based on a set of eight criteria, and studies with a score greater than 4 were considered to be of high quality (total score = 8).

2.4 | Statistical analysis

Meta-analysis was performed using STATA 12 (StataCorp, College Station, TX). Original incidence rates r were transformed by the double arcsine method to make them conformed to normal distribution, and the resulting transformed rate tr was used in meta-analysis. The heterogeneity between studies was analyzed using a χ^2 test ($P < .10$) and quantified using the I^2 statistic. When no statistical heterogeneity was observed, a fixed effects model was utilized. Otherwise, potential sources of clinical heterogeneity were identified using subgroup analysis and sensitivity analyses, these sources were

eliminated and the meta-analysis was repeated using a random effects model. Pooled incidence rates R were back-calculated from transformed rates tr using the $R = [\sin(tr/2)]^2$. A two-tailed $P < .05$ was considered statistically significant. Publication bias was evaluated using a funnel plot along with Egger's regression test and Begg's test.

3 | RESULTS

3.1 | Literature retrieval

A total of 4532 related articles were obtained in the initial retrieval. After a detailed assessment based on the inclusion and exclusion criteria, 34 retrospective studies including 4121 patients with COVID-19 were included⁹⁻⁴² (Figure 1).

3.2 | Basic characteristics of included studies and quality evaluation

A total of 34 retrospective studies⁹⁻⁴² that published from 6 February 2020 to 12 March 2020 were included. All studies were

conducted in China, 16 of the studies included patients in Hubei Province, and the remaining 18 studies included patients in other provinces. All studies received quality scores of 5 to 8, indicating high quality (Table 1).

3.3 | Meta-analysis results

3.3.1 | Lesion distribution

There were 73.8% of the COVID-19 patients presented bilateral lung involvement (95% CI: 65.9%-81.1%) and multilobar involvement 67.3% (95% CI: 54.8%-78.7%) (Figures 2 and 3). Single lung involvement (18.7%) and single lobe involvement (14.9%) were rare. A few patients showed normal CT manifestations(8.4%) (Figure 4 and Table 2).

3.3.2 | Lesion shapes

The lesion shapes included patchy (40.3%, 95%CI: 29.8%-51.4%), cord-like (36.8%, 95% CI: 21.7%-53.4%), nodular(20.5%, 95% CI: 6.8%-39.1%), and spider web sign (39.5%, 95% CI: 27.2%-52.6%) (Table 2).

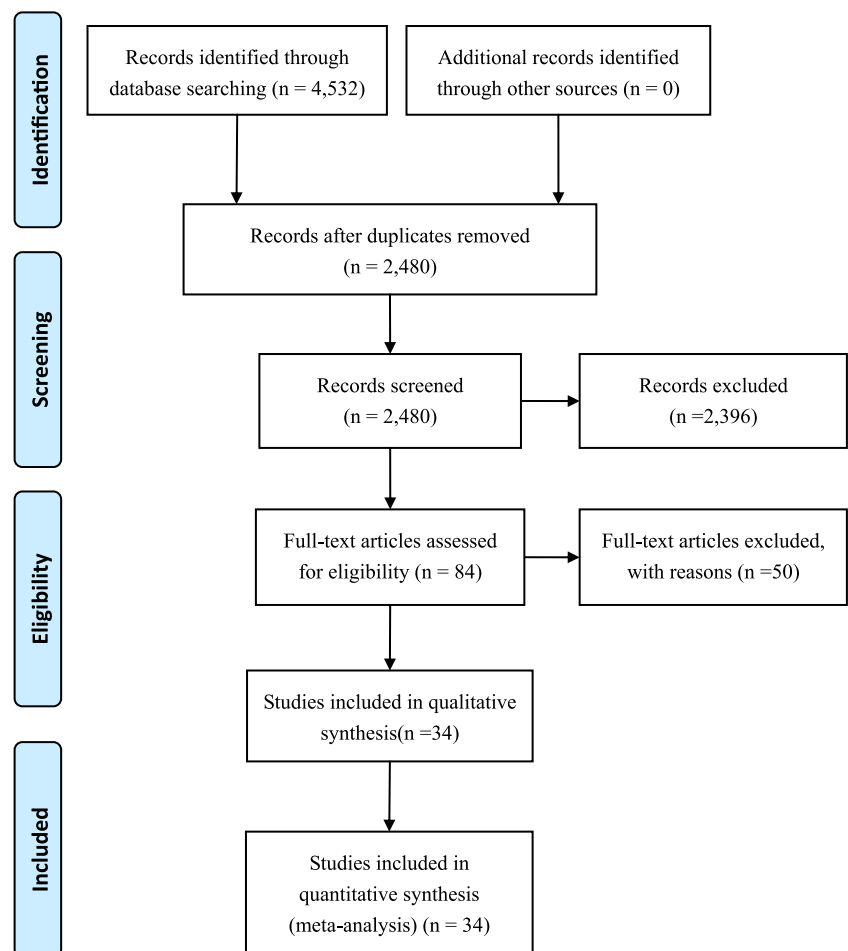


FIGURE 1 Flow chart of literature screening

TABLE 1 Basic characteristics of included studies

Study	Publication date	Region (China)	Sample size (n)	Study population	Age, y	Male (n)	Outcomes	Quality score
Guan et al ⁹	Feb 28	31 Provinces	1099	COVID-19 patients in 552 hospitals in 31 provinces/province-level municipalities	47.0	640	0000	6
Cheng et al ¹⁰	Mar 12	Hubei	463	COVID-19 patients in wuhan Jinyintan Hospital	15-90	244	0000	6
Gong et al ¹¹	Mar 9	Chongqing	225	COVID-19 patients in Chongqing University Three Gorges Hospital	46.35 ± 16.1	125	0000	6
Yuan et al ¹²	Mar 6	Chongqing	223	COVID-19 patients in Chongqing Public Health Medical Center	46.5 ± 16.1	105	00	6
Zhou et al ¹³	Mar 9	Wuhan	191	COVID-19 patients in Jinyintan Hospital and Wuhan Pulmonary Hospital	18-87	119	0000	7
Yang et al ¹⁴	Feb 26	Wenzhou	149	COVID-19 patients in three tertiary hospitals of Wenzhou	45.1 ± 13.4	81	0000	7
Wu et al ¹⁵	Mar 3	Provinces	130	COVID-19 patients in seven hospitals of China	25-80	78	0000	7
Bernheim et al ¹⁶	Feb 20	4 Provinces	121	COVID-19 patients in four centers in China	45(18-80)	61	0000	8
Zhao et al ¹⁷	Feb 19	Hubei	101	COVID-19 patients in four cities in Hunan, China	17-75	56	0000	6
Chen et al ¹⁸	Feb 15	Wuhan	99	COVID-19 patients in Wuhan Jinyintan Hospital	55.5 ± 13.1	67	00	6
Xu et al ¹⁹	Feb 28	Guangzhou	90	COVID-19 patients in Guangzhou Eighth People's Hospital	18-86	39	0000	6
Li et al ²⁰	Feb 29	Chongqing/Jinan	83	COVID-19 patients in Chongqing/Jinan provinces	45.5	44	0000	8
Shi et al ²¹	Feb 24	Wuhan	81	COVID-19 patients in Wuhan Jinyintan hospital or Union Hospital of Tongji Medical College	49.5	42	0000	7
Wu et al ²²	Feb 21	Chongqing	80	COVID-19 patients in Chongqing province	44 ± 11	42	0000	7
Wu et al ²³	Feb 29	Jiangsu	80	COVID-19 patients in the First and Second People's Hospital of Yancheng City, the Fifth People's Hospital of Wuxi	46.1	39	0	8
Fang et al ²⁴	Feb 25	Anhui	79	COVID-19 patients in Infection Hospital of Anhui Provincial Hospital	45.1 ± 16.1	45	0	5
Chen et al ²⁵	Mar 10	Wuhan	76	COVID-19 patients in Wuhan Puren Hospital	28-86	40	0000	6
Ma et al ²⁶	Mar 10	Anhui	75	COVID-19 patients in 4 hospitals in Fuyang city, Anhui province	43.9 ± 15.1	46	0000	7
Pan et al ²⁷	Feb 6	Wuhan	63	COVID-19 patients in Tongji hospital	44.9 ± 15.2	33	0000	6
Zhou et al ²⁸	Feb 19	Wuhan	62	COVID-19 patients in Tongji hospital	52.8 ± 12.2	39	0000	6
Wang et al ²⁹	Feb 25	Zhejiang	52	COVID-19 patients in the First Affiliated Hospital, Zhejiang University School of Medicine	13-73	29	0000	6
Xu et al ³⁰	Feb 25	Beijing/Hebei	50	COVID-19 patients in 4 hospitals in Beijing/Hebei provinces	43.9 ± 16.8	29	0000	6
Liao et al ³¹	Feb 26	Wuhan	42	COVID-19 patients in Zhongnan Hospital of Wuhan University	51.6	29	0000	6
Xiong et al ³²	Mar 3	Wuhan	42	COVID-19 patients in Tongji Hospital	49.5 ± 14.1	25	0000	5
Liu et al ³³	Feb 18	Hubei	41	COVID-19 patients in Xiao chang First People's Hospital	48.45	32	0000	6

TABLE 1 (Continued)

Study	Publication date	Region (China)	Sample size (n)	Study population	Age, ^a y	Male (n)	Outcomes	Quality score
Huang et al ³⁴	Jan 24	Wuhan	41	COVID-19 patients in the designated hospital in Wuhan	41-58	30	①	6
Yu et al ³⁵	Feb 26	Zhejiang	40	COVID-19 patients in Wenzhou Sixth People's Hospital	45.9	22	①②③	6
Yu et al ³⁶	Feb 17	Beijing	40	COVID-19 patients in the 5th Medical Centre of Chinese PLA General Hospital	39.9 ± 18.2	26	①	6
Zhang et al ³⁷	Mar 6	Hebei	40	COVID-19 patients in Hebei provinces	49.33 ± 14.19	20	①④	5
Cao et al ³⁸	Feb 28	Wuhan	36	COVID-19 patients in Zhongnan Hospital of Wuhan University	72.45 ± 6.82	20	①②③④	6
Huang et al ³⁹	Feb 28	Guangdong	35	COVID-19 patients in Guangdong Second People's Hospital	44.0 ± 15.2	19	①②③	6
Wang et al ⁴⁰	Feb 19	Wuhan	32	COVID-19 patients in The Central Hospital of Xiaogan	27-78	16	①②③	6
Zhong et al ⁴¹	Feb 13	Wuhan	30	COVID-19 patients in Zhongnan Hospital of Wuhan University	50.17 ± 17.6	18	①②③④	5
Liu et al ⁴²	Feb 17	Wuhan	30	COVID-19 patients in the Affiliated Hospital of Jiangnan University	21-59	10	①②③	6

Note: ① lesion distribution; ② lesion shapes; ③ lesion density; ④ accompanying signs.

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation.

^aReported variously as range or mean ± SD or median, and interquartile range (IQR) values.

3.3.3 | Lesion density

The most common lesion density change was ground-glass opacities (68.1%, 95% CI: 56.9%-78.2%) (Figure 5). Other changes included air bronchogram sign (44.7%, 95% CI: 32.9%-56.8%), crazy-paving pattern (35.6%, 95% CI: 11.3%-64.8%), and consolidation (32.0%, 95% CI: 21.5%-43.4%) (Table 2).

3.3.4 | Accompanying signs

Pleural thickening (27.1%, 95% CI: 15.6%-40.5%) was found in some patients. Lymphadenopathy (5.4%, 95% CI: 0.022-0.098), and pleural effusion (5.3%, 95% CI: 3.7%-7.3%) were rare (Figure 6 and Table 2).

3.3.5 | Subgroup analysis

This study showed significant heterogeneity. To explore the source of heterogeneity, subgroup analysis was performed. The results showed that the analysis results of the subgroups were basically consistent with the overall results, and there was no significant difference between the heterogeneity of the subgroups and the overall heterogeneity, which indicated that the study subject's location and sample size were not the main sources of heterogeneity (Table 3).

3.3.6 | Sensitivity analysis

Sensitivity analysis was performed for the observation indicators of bilateral lung involvement, and statistics were recombined after excluding each study in turn. The results did not change substantially, suggesting that the results were stable (Figure 7).

3.4 | Publication bias

The *P* values derived using Egger's and Begg's tests for all the observation indicators showed no obvious publication bias (Table 4). A funnel plot regarding the observation indicators of bilateral lung involvement showed the *P* values of Egger's and Begg's tests were .859 and .277, respectively, suggesting that the publication bias was not existed (Figure 8).

4 | DISCUSSION

2019-nCoV is one type of β -coronavirus with a positive-stranded single-stranded RNA.⁴³ In the past two decades, humans have experienced three fatal coronavirus infections, including severe acute respiratory syndrome (SARS) in 2002, Middle East respiratory syndrome (MERS) in 2012, and COVID-19.⁴⁴ The fatality rate of

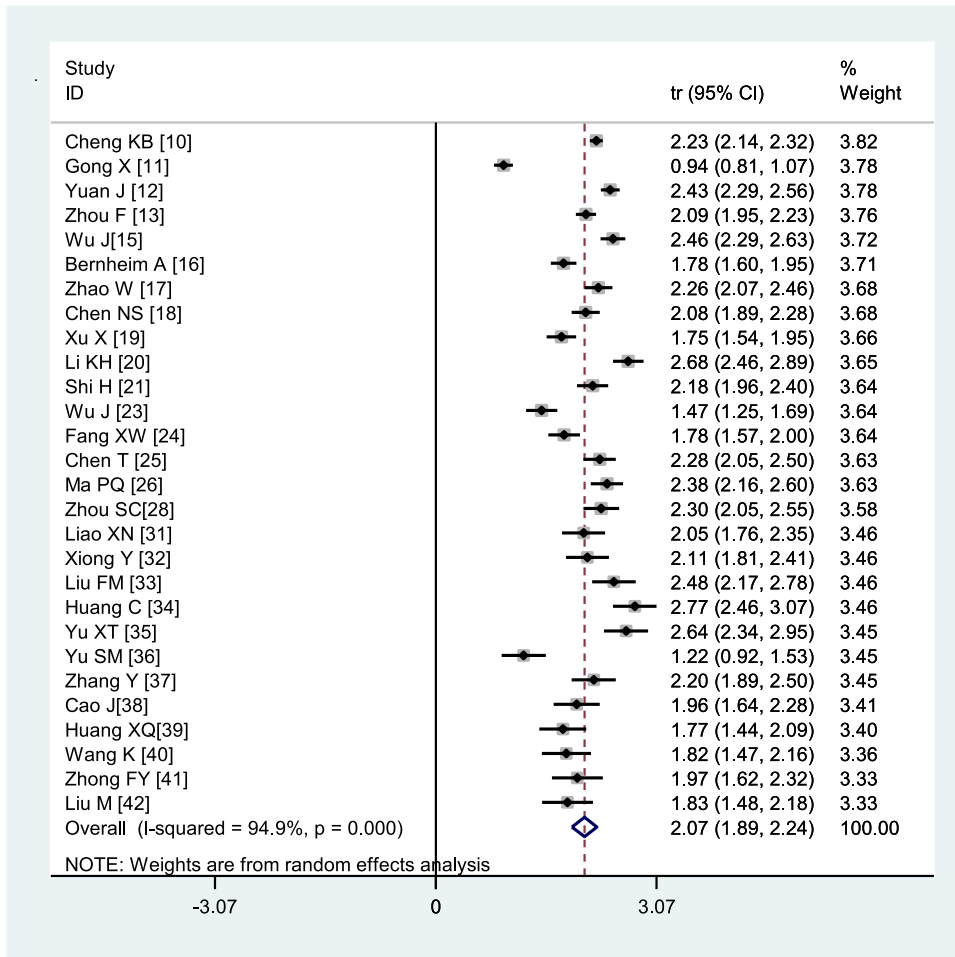


FIGURE 2 Transformed incidence rate of the indicator of bilateral lung involvement in patients with COVID-19. COVID-19, coronavirus disease 2019

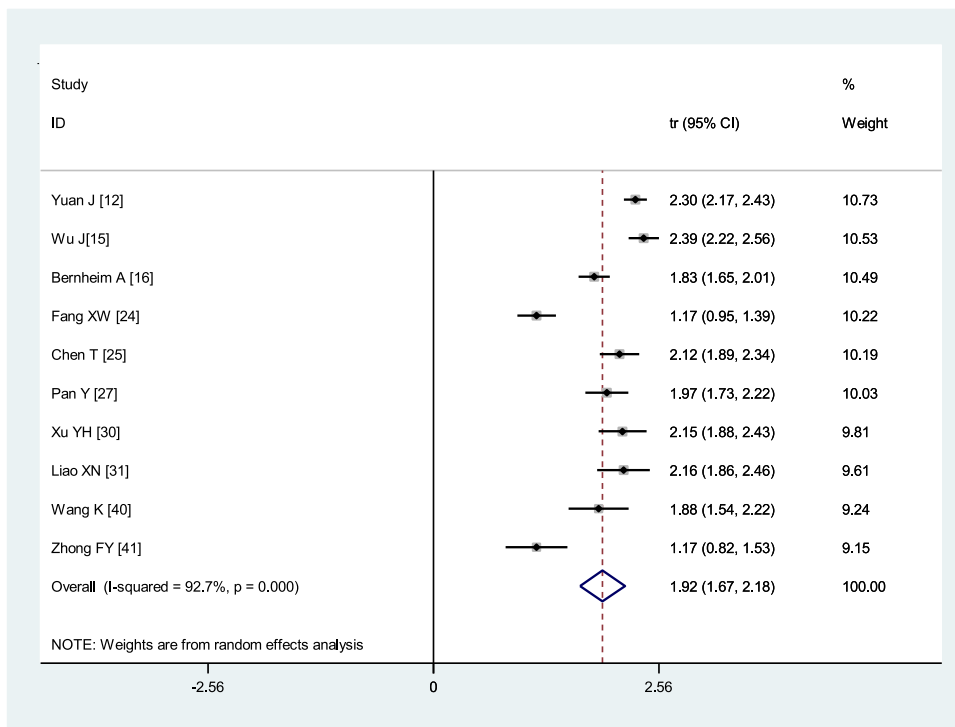


FIGURE 3 Transformed incidence rate of the indicator of multilobar involvement in patients with COVID-19. COVID-19, coronavirus disease 2019

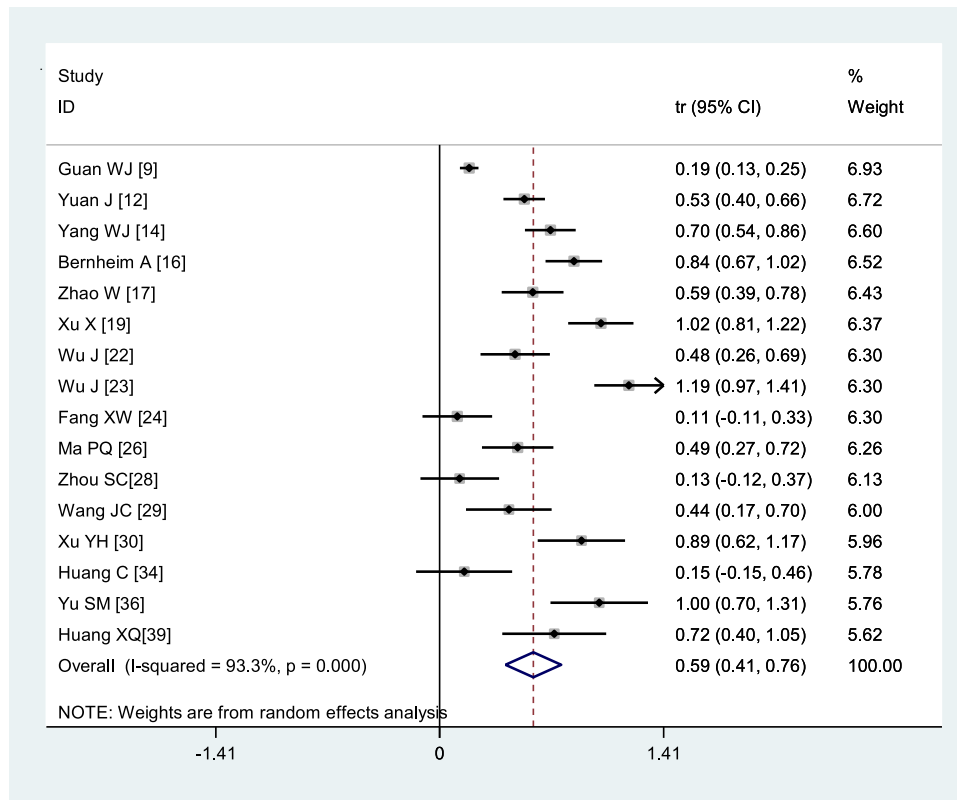


FIGURE 4 Transformed incidence rate of the indicator of normal CT manifestation in patients with COVID-19. COVID-19, coronavirus disease 2019

TABLE 2 Meta-analysis of different CT Imaging features in COVID-19 patients

Outcomes	No. studies	No. patients	Heterogeneity		Model	Meta-analysis	
			P	I ²		R (95% CI)	P
Lesion distribution							
Single lung lesions	22	1977	<.001	81.6%	Random	.187 (0.147, 0.231)	<.001
Bilateral lung lesions	28	2628	<.001	94.9%	Random	.738 (0.659, 0.811)	<.001
Multilobar lesions	10	846	<.001	92.7%	Random	.673 (0.548, 0.787)	<.001
Single lobe lesions	9	629	<.001	79.6%	Random	.149 (0.092, 0.217)	<.001
Normal CT manifestation	13	2195	<.001	93.3%	Random	.084 (0.042, 0.139)	<.001
Lesion shapes							
Nodular	8	739	<.001	96.8%	Random	.205 (0.068, 0.391)	<.001
Patchy	8	2009	<.001	94.1%	Random	.403 (0.298, 0.514)	<.001
Cord-like	6	267	<.001	87.3%	Random	.368 (0.217, 0.534)	<.001
Spider web sign	11	806	<.001	92.9%	Random	.395 (0.272, 0.526)	<.001
Lesion density							
Ground-glass opacities	26	3574	<.001	97.7%	Random	.681 (0.569, 0.782)	<.001
Consolidation	14	1637	<.001	95.4%	Random	.320 (0.215, 0.434)	<.001
Air bronchogram sign	15	1075	<.001	93.9%	Random	.447 (0.329, 0.568)	<.001
Crazy-paving pattern	4	264	<.001	95.8%	Random	.356 (0.113, 0.648)	<.001
Accompanying signs							
Pleural effusion	17	1627	.024	44.8%	Random	.053 (0.037, 0.073)	<.001
Pleural thickening	9	1077	<.001	95.6%	Random	.271 (0.156, 0.405)	<.001
Lymphadenopathy	8	622	<.001	82.0%	Random	.054 (0.022, 0.098)	<.001

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography.

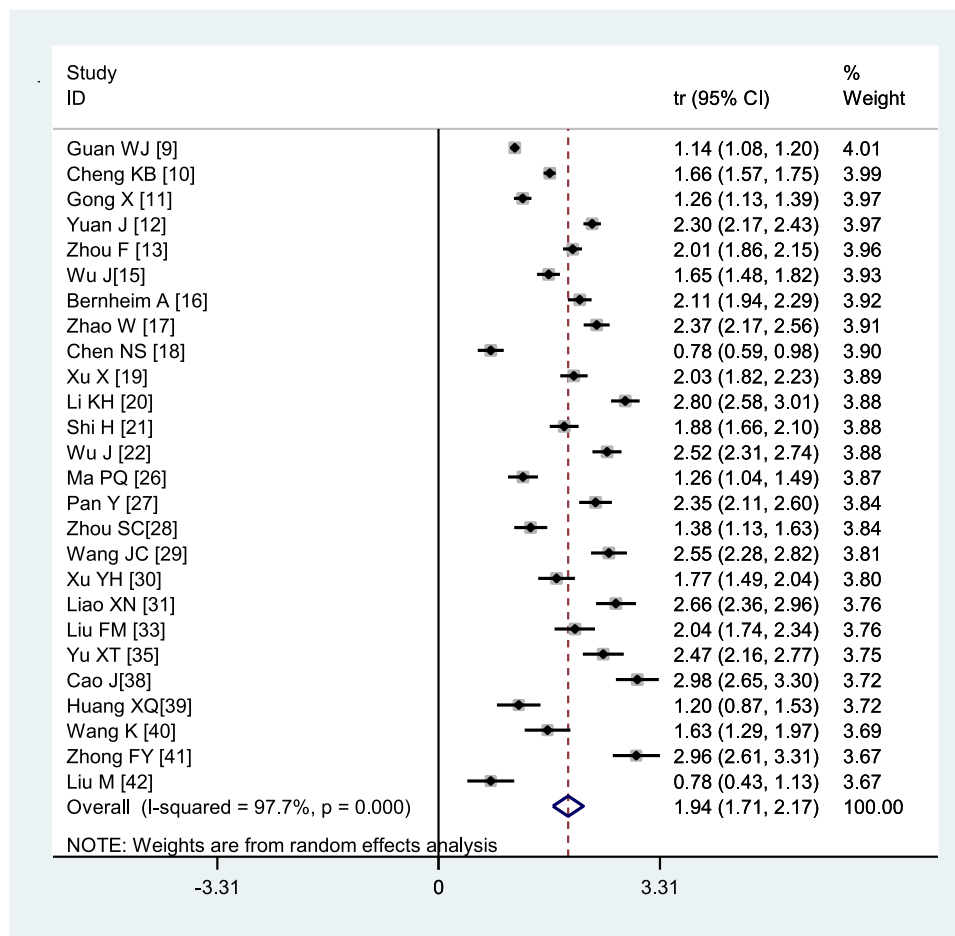


FIGURE 5 Transformed incidence rate of the indicator of ground-glass opacities in patients with COVID-19. COVID-19, coronavirus disease 2019

COVID-19 was lower than SARS (9.6%) and MERS (35%),⁴⁵⁻⁴⁷ but its transmission ability was stronger.⁴⁸ Therefore, early diagnosis, isolation, and treatment of suspected or infected patients are of great significance for the prevention and control of COVID-19. The current gold standard for COVID-19 diagnosis is positive results of NAAT, viral gene sequencing, positive serum novel coronavirus-specific Immunoglobulin M antibodies and Immunoglobulin G antibodies. However, such diagnostic methods also have some limitations, and not all hospitals can implement them. For example, NAAT can only make a positive diagnosis, but cannot judge the severity of the patients; when the viral load is low, it would make a false-negative results; due to the sudden increase of a large number of suspected cases and the shortage of nucleic acid testing reagents, many patients will not be diagnosed in time.⁴⁹ However, compared with various limitations of NAAT, the lung CT examinations is timely, rapid, and has a high positive rate.^{49,50} Most important of all, CT can be carried out in most hospitals. So thin-layer CT scan of the lung is of great significance for the early diagnosis and assessment of COVID-19.

In this study, we collected the latest articles up to 16 March 2020, included 34 retrospective studies⁹⁻⁴² involving 4121 patients with

COVID-19 distribution in 31 provincial-level regions in China. The results of meta-analysis showed that most patients presented bilateral lung involvement or multilobar involvement. The most typical manifestations of chest CT were ground-glass opacities, patchy, cord-like, and nodular. Pleural thickening was found in some patients. Lymphadenopathy and pleural effusion were rare. These were basically consistent with the guideline for the diagnosis and treatment of COVID-19.⁶ Lin et al⁵¹ also pointed out that the imaging findings of lungs appeared earlier than clinical symptoms, and the CT findings of lungs changed dynamically as the disease progressed, so CT imaging can reveal disease progression. Therefore, in different stages of the disease, CT can be used to evaluate the severity of the disease and efficacy of the treatment.¹⁷ For patients with an epidemiological history, a CT scan of the lung should be performed even if there are no clinical symptoms or NAAT negative. If patients with epidemiological history are found that the CT of the lung has typical features such as ground-glass opacities of the bilateral lungs or multiple lobes, they should be highly suspected they are with COVID-19. The faster isolation measures should be taken, and further diagnosis and treatment should be performed as soon as possible to avoid the wide-spread of the disease or loss of treatment opportunities.

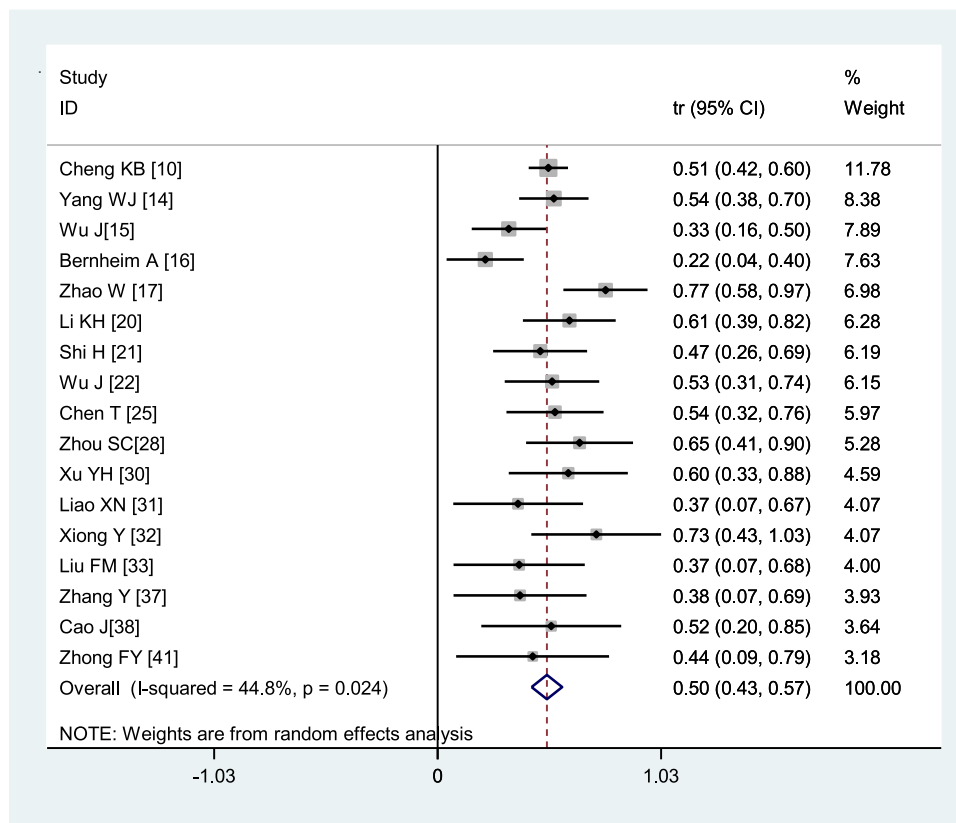


FIGURE 6 Transformed incidence rate of the indicator of pleural effusion in patients with COVID-19. COVID-19, coronavirus disease 2019

This study has several strengths including its large sample size and high quality of included studies. We conducted subgroup analysis according to studies' region and sample size. We also conducted sensitivity analysis by excluding each study one by one. The results did not change significantly, indicating the reliability and stability of our results.

Nevertheless, some limitations should be noted in our meta-analysis. First, most of our included studies are single-center, which may have admission bias and selection bias. Second, most of our included studies did not clarify the inclusion or exclusion criteria, the course and severity of disease were not the same. Third, all the included studies were

TABLE 3 Subgroup analysis of different CT manifestations in COVID-19 patients

Outcomes	No. studies	No. patients	Heterogeneity		Model	Meta-analysis	
			P	I ²		R (95%CI)	P
Normal CT manifestation							
Hebei province	1	101	<.001	94.4%	Random	.103 (0.050, 0.174)	.067
Other provinces	12	094	<.001	80.8%	Random	.022 (0.042, 0.139)	<.001
Bilateral lung lesions							
Hebei province	15	1367	.001	61.5%	Random	.784 (0.743, 0.822)	<.001
Other provinces	13	1261	<.001	97.3%	Random	.690 (0.524, 0.834)	<.001
Ground-glass opacities							
Hebei province	13	1271	<.001	96.5%	Random	.688 (0.536, 0.821)	<.001
Other provinces	13	2303	<.001	98.3%	Random	.674 (0.503, 0.823)	<.001
Pleural effusion							
Hebei province	10	974	.249	21.3%	Random	.036 (0.017, 0.063)	<.001
Other provinces	7	653	.002	66.8%	Random	.073 (0.054, 0.095)	<.001

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography.

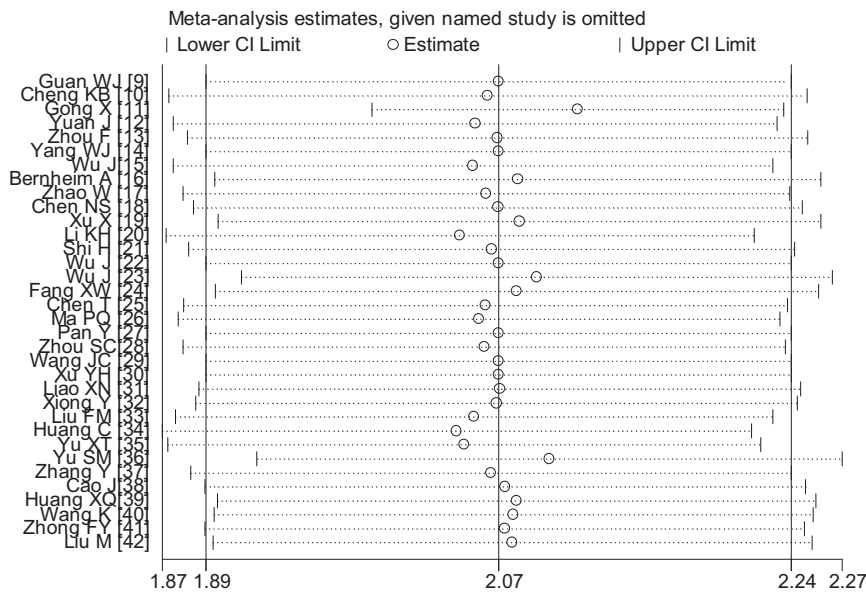


FIGURE 7 Sensitivity analysis of the indicator of bilateral lung involvement in patients with COVID-19. COVID-19, coronavirus disease 2019

TABLE 4 Evaluation of publication bias using Egger's and Begg's tests

Characteristic	P (Egger's)	P (Begg's)	Characteristic	P (Egger's)	P (Begg's)
Single lung lesions	.037	.090	Ground-glass opacities	.003	.552
Bilateral lung lesions	.859	.277	Consolidation	.053	.228
Multilobar lesions	.160	.210	Air bronchogram sign	.616	.960
Single lobe lesions	.952	.754	Crazy-paving pattern	.429	.734
Nodular	.667	.902	Pleural effusion	.854	.869
Patchy	.328	.386	Pleural thickening	.062	.910
Cord-like	.995	.851	Lymphadenopathy	.121	.386
Spider web sign	.049	.138	Normal CT manifestation	.404	.964

Abbreviation: CT, computed tomography.

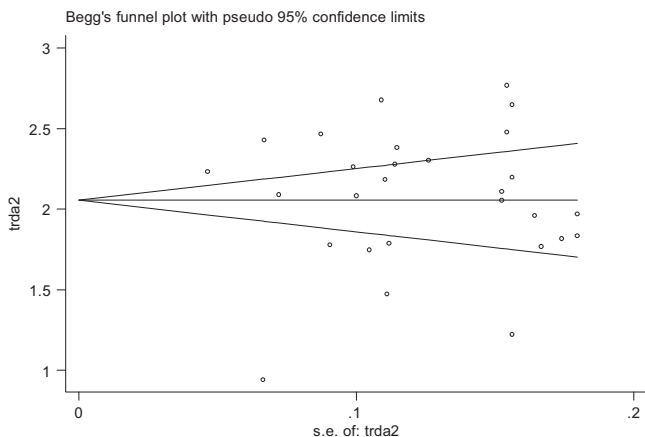


FIGURE 8 Evaluation of publication bias using a funnel plot based on the incidence rate of bilateral lung involvement

retrospective studies, we were unable to control the influence of confounding factors. Lastly, this meta-analysis indicated a significant heterogeneity between the studies. But the subgroup analysis fails to eliminate all sources of heterogeneity, which may affect the accuracy of the results of meta-analysis.

5 | CONCLUSION

To sum up, most patients presented bilateral lung involvement or multilobar involvement. The most common changes were ground-glass opacities and air bronchogram sign. Other common changes included patchy, spider web sign, and so forth. Lymphadenopathy and pleural effusion were rare. But due to the quality and quantity of included studies, the above conclusions need to be confirmed by more high-quality studies.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

Data curation was done by JP, PJ, and HL. JZ contributed to funding acquisition. JZ, ZZ, BL, and JZ contributed to methodology. PJ, HL, and JP provided the software. BL and JZ were involved in supervision. JZ and ZZ wrote the original draft. Reviewing and editing were done by BL and JZ.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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