

# Systematic review and meta-analysis of the CT imaging characteristics of infectious pneumonia

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**Background:** Since December 2019, there have been cases of infectious pneumonia of unknown cause in Wuhan, Hubei Province, China. On January 12, 2020, the World Health Organization (WHO) named it COVID-19. There are few studies on the clinical characteristics of patients with COVID-19, and results vary widely in sample sizes.

**Methods:** Chinese and English databases were searched with "Infectious pneumonia", "COVID-19", "CT", "SARS-COV-2", and "Diagnose" as keywords. Rev Man 5.3 software provided by the Cochrane system was used to assess the quality of the included literature.

**Results:** Of the 18 included studies, ground-glass shadow was the most common computed tomography (CT) sign [95% confidence interval (CI): 0.79–0.97], followed by thickening of the blood vessels (95% CI: 0.63–0.78), and pleural thickening (95% CI: 0.02–0.15). Of the 18 studies, 12 reported that the lesions were externally subpleural (95% CI: 0.132–0.173), and 6 reported that the lesions were distributed in a single lobe (95% CI: 0.598–0.841). The heterogeneity test results showed that the morphology of the lesions was cord-like (95% CI: 0.092–0.172), grid-like (95% CI: 0.152–0.193), patchy (95% CI: 0.192–0.313), and nodular (95% CI: 0.591–0.745).

**Discussion:** Ground-glass opacity was a typical CT manifestation for patients with infectious pneumonia, and CT signs were instrumental in diagnosing this disease.

Keywords: Computed tomography (CT); infectious pneumonia; imaging

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# Introduction

Pneumonia refers to inflammation in the terminal airways, alveoli, and interstitium of the lungs (1). Pathogenic microorganisms such as bacteria, viruses, fungi and parasites, and physical and chemical factors such as radiation and inhaled foreign bodies may all lead to pneumonia (2). Clinically, it manifests as fever, cough, expectoration, blood in sputum, chest pain, or difficulty breathing. Commonly, pneumonia is not infectious, whereas pneumonia caused by a virus is infectious, such as severe acute respiratory syndrome (SARS), anthrax, and pneumonic plague (3). These different types of pneumonia have different pathogenic mechanisms, causes, and treatment methods.

At present, the COVID-19 pandemic is still spreading around the world. Statistics from the World Health Organization (WHO) reveal that as of January 15, 2020, there were a total of 150 million confirmed cases worldwide and a total of 3.2 million deaths (4). When it comes to a new infectious disease, early detection and early isolation

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is a prerequisite for early treatment (5). A positive virus nucleic acid test result is the gold standard for diagnosing COVID-19. However, as the number of cases gradually increases, asymptomatic infections have appeared. To prevent asymptomatic infections from becoming the source of infection, computed tomography (CT) examination is performed for early diagnosis (6).

CT involves tomographic scanning around a certain part of the human body using X-rays,  $\gamma$ -rays together with a highly sensitive detector. It is characterized by short scanning time and high resolution (7). CT findings of patients with infectious pneumonia were as follows. Eighty percent of the disease in both lungs was visible; most of them were located in the next lateral band of the pleura in the middle and lower fields of both lungs, but the pleura was often transparent band, less involved in the leaf or intersegmental fissure, not in a clear leaf or segment distribution; the early CT findings were characteristic: observed from the lung window, the pulmonary vascular texture was significantly enhanced, and generally exudate was found in the lobule area, mainly interstitial exudate, so the density was light and often showed ground glass density (8). Nowadays, CT imaging has been widely used in clinical diagnosis to determine disease conditions, and is indispensable for diagnosing infectious pneumonia (9).

Despite a large number of CT-imaging reports on COVID-19 worldwide, they have distinct research results and limited samples (10). In China, an evidencebased foundation to evaluate the CT images of patients with COVID-19 is lacking. The innovation of this study lies in the meta-analysis, which is mainly based on the literature on CT imaging features of infectious pneumonia published since the establishment of the database, and it comprehensively analyzes the imaging features of infectious pneumonia, so as to provide a reliable reference basis for further guiding the clinical treatment of infectious pneumonia. We present the following article in accordance with the PRISMA reporting checklist (available at https:// dx.doi.org/10.21037/apm-21-2101).

#### Methods

#### Literature retrieval

Relevant literature from CMCI, MEDLINE, EMbase, PubMed, CNKI, China Biomedical Resources Database, Wanfang Database, VIP Database, Baidu Academic Database were retrieved from the establishment date of the database to February 21th, 2020. Relevant studies were analyzed with the Boolean logic retrieval method. The Chinese and English databases were used for a combination search using "Infectious pneumonia", "COVID-19", "CT", "SARS-COV-2", and "Diagnose".

A combined search strategy of free text and subject headings was used for every database. Once confirmed, using a search engine, references were tracked, and after contacting experts and researchers, the latest research progress was acquired.

#### Literature inclusion and exclusion criteria

Inclusion criteria: (I) studies on infectious pneumonia; (II) randomized controlled trials (RCTs); (III) compared with clinical anatomy and pathology, the index has high reliability in 95% confidence interval (CI); (IV) the experimental group underwent CT examination; (V) the diagnosis of infectious pneumonia met the standards of the American Society of Infectious Diseases and the American Thoracic Society.

Exclusion criteria: (I) the research object was special population, restricted by age and gender; (II) studies that were replicated in different journals; (III) literature reviews, abstracts, case reports, or animal experiments; (IV) studies with unavailable complete data; (V) research literature on noninfectious pneumonia patients and animals.

Two senior experts screened the topic, abstract and full text, and if there is any disagreement, they can obtain a consistent conclusion through discussion.

## **Observation** indicators

CT imaging for patients with infectious pneumonia was evaluated based on lesion positioning, lesion morphology, lesion density, and accompanying signs.

#### Data extraction

With a unified Microsoft Excel table, two experts independently extracted the relevant data. Disagreements between experts could be resolved through discussion and consensus, or a third expert could be asked to arbitrate. The extracted data were as follows: (I) research title; (II) published first author and years; (III) study design type; (IV) general information of subjects: gender, age, sample size, country; (V) extraction evaluation index: CT image features.

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No	lteme	Evaluation results		
NO.	Trens	Risk assessment	Score	
1	The cases were from different levels of medical institutions and it	High	0	
	was a multicenter study	Low	1	
		Unclear	-	
2	The research objective was clearly delivered	High	0	
		Low	1	
		Unclear	-	
3	In accordance with the inclusion and exclusion criteria	High	0	
		Low	1	
		Unclear	-	
4	There were clear evaluation criteria	High	0	
		Low	1	
		Unclear	-	
5	The data collected reached the expected standards	High	0	
		Low	1	
		Unclear	-	
6	The research subjects were recruited continuously	High	0	
		Low	1	
		Unclear	-	
7	The findings were presented in detail	High	0	
		Low	1	
		Unclear	-	
8	The outcome indicators were analyzed hierarchically	High	0	
		Low	1	
		Unclear	-	

Table 1 Evaluation items proposed by the NICE

NICE, National Institute of Clinical Excellence.

# Risk of bias assessment and quality evaluation

The risk of bias and quality assessment should be carried out by two researchers at the same time. If the two researchers were disagreed, the results would be determined through discussion. As for quality evaluation, the items proposed by the National Institute of Clinical Excellence (NICE) were adopted, as shown in *Table 1*. Each item was 1 point, and the total score ranged from 0–8. The score of each item was 1 point, and the score range was 0–8 points: 6–8 points were defined as high-quality research, 3–6 points were defined as medium-quality research, and 0-2 points were defined as low-quality research. Two experts independently carried out quality assessment, and when the opinions were inconsistent, they could obtain consistent conclusions through discussion.

# Statistical analysis

Stata SE 12.0 software (College Station, USA) was used for statistical analysis. The Rev Man 5.3 software provided by Cochrane collaboration network is used to draw the biased risk assessment chart, evaluate the risk bias included in the



Figure 1 Literature search flowchart.

reference documents, and input the sorted and screened data into the software to draw the corresponding chart. The heterogeneity of each study was explored by  $I^2$  test. When P>0.01 and  $I^2$ <50%, the fixed effect model was used for meta-analysis, which indicated that the heterogeneity included in the study was small. When P<0.01 and  $I^2$ >50%, the random effect model was used for meta-analysis, which indicated that the included research was heterogeneous.

# **Results**

#### The basic information of the included literature

One hundred and forty-eight articles were included in this study through the database and 137 through the registry. Eleven literatures published repeatedly were excluded, 8 literatures unqualified were excluded, and 3 literatures for other reasons were excluded, leaving 263 literatures remaining. Read the full text and eliminate 135 articles, leaving 128 articles. Eighty-two cases reports, reviews and conferences were excluded, and 46 qualified articles remained. Fifteen literatures that were not included in the randomized controlled analysis, 9 literatures that were not included in the study of benign and malignant thyroid nodules, and 4 literatures whose relevant information could not be extracted were excluded. Finally, 18 literatures were obtained and entered into the meta-analysis (*Figure 1*).

*Figure 2* shows the results of quality classification. Seven studies scored 6–8 (38.89%), 10 studies scored 3–6 (55.56%), and 1 scored between 0–2 (5.55%).

Eighteen studies met the inclusion criteria, involving a total of 1,586 cases. Of the 18 studies, there were 11 with a small sample size ranging from 35-154. The research subjects were all above 20 years old, as shown in *Table 2*.

#### Risk of bias evaluation

Figures 3,4 show that of the 18 included RCTs, 5 had the

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Figure 2 Literature quality classification results.

# Table 2 General information of the included studies

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correct random allocation method (11-15), accounting for 27.78%, and only 2 (16,17) had detailed allocation concealment, accounting for 16.67%. One study (18) was evaluated using the blinding method, accounting for 5.55%, which was not adopted in the other studies.

# CT signs

*Figure* 5 shows the forest plot of the CT signs of infectious pneumonia. Of the 18 studies, the heterogeneity test results showed that among the CT signs, lung ground-glass shadow, lung consolidation shadow, and lung ground-glass shadow combined with consolidation exhibited high heterogeneity, with  $I^2$ =96.4%>50%. Ground-glass shadow

Author	Year of publication	Sample size (case)	Sample resources	Sex (male/female)	Age (year)	Outcome indicator
Wu X	2016 (1)	35	China	18/17	32.26±12.34	Lesion distribution; lesion morphology; changed lesion density
Li X	2020 (2)	72	China	32/40	43.26±15.67	Lesion morphology
Umapathi T	2004 (3)	94	Italy	45/49	28.45±15.49	Lesion distribution
Burhan E	2020 (4)	154	America	70/84	34.67±18.52	Lesion morphology; accompanying signs
Shi F	2020 (5)	136	Italy	71/65	42.58±16.54	Lesion distribution; changed lesion density
Ooi GC	2004 (6)	68	UK	30/38	25.69±8.52	Lesion morphology
Chaimayo C	2020 (7)	152	America	81/71	45.67±18.52	Lesion morphology
Chang YC	2005 (8)	84	China	35/49	48.52±13.54	Lesion morphology; changed lesion density; accompanying signs
Xie L	2005 (9)	86	China	48/38	35.69±17.84	Lesion distribution
Chen D	2021 (10)	74	China	42/32	38.52±12.64	Lesion morphology
Antonio GE	2003 (11)	68	America	38/30	52.36±12.21	Lesion distribution; changed lesion density
Xia T	2020 (12)	45	China	24/21	49.62±10.25	Lesion morphology; accompanying signs
Kawamura K	2018 (13)	96	Italy	52/44	56.39±18.52	Lesion morphology; changed lesion density
Das JP	2021 (14)	72	UK	33/39	46.98±11.34	Lesion distribution
Assaad S	2020 (15)	62	France	35/27	35.26±11.64	Lesion morphology
Hon KL	2003 (16)	54	German	25/29	48.59±12.84	Lesion distribution; changed lesion density
Wong KT	2004 (17)	106	Italy	55/51	29.63±15.98	Lesion morphology; accompanying signs
Ng CK	2004 (18)	128	UK	63/65	32.98±11.82	Lesion distribution



Figure 3 The risk of bias evaluation results.

was the most common (95% CI: 0.79–0.97), followed by thickening of the blood vessels (95% CI: 0.63–0.78), and pleural thickening (95% CI: 0.02–0.15).

# Lesion distribution

*Figure 6* shows the meta-analysis results of lesion distribution. The heterogeneity test results found that external subpleural distribution, external semicenter distribution, double lung distribution, and single lung distribution all exhibited high heterogeneity ( $I^2$ =98.8%>50%, P<0.01). Of the 18 studies, 12 reported that the lesions were externally subpleural (95% CI: 0.132–0.173), and 6 reported that the lesions were distributed in a single lobe (95% CI: 0.598–0.841).

# Lesion morphology changes

*Figure* 7 shows the results of the meta-analysis on lesion morphology changes. The heterogeneity test results showed that the morphology of the lesions was cord-like (95% CI: 0.092–0.172), grid-like (95% CI: 0.152–0.193), patchy (95% CI: 0.192–0.313), and nodular (95% CI: 0.591–0.745).

#### Changed lesion density

*Figure 8* shows the results of the meta-analysis on the changed lesion density. The heterogeneity test results showed that the lesion density exhibited consolidation (95% CI: 0.182–0.253), crazy-paving (95% CI: 0.452–0.793), empty-bronchus sign (95% CI: 0.292–0.415), and ground-glass opacity (95% CI: 0.521–0.765).

# Accompanying CT signs

*Figure 9* shows the meta-analysis results of accompanying CT signs. The heterogeneity test results showed that the accompanying CT signs included pleural effusion (95% CI: 0.021–0.045) and pleural thickening (95% CI: 0.252–0.453).

## **Publication bias**

A funnel plot of ground-glass opacity (*Figure 10*) was generated by Rev Man 5.3. Meta-analysis was conducted on the ground glass change indicators of infectious pneumonia patients. The funnel plot showed that the circles in the included studies were distributed near the midline and basically symmetrical, indicating that there was no bias in publication and the conclusions obtained were reliable.

#### Discussion

The progress of COVID-19 has resulted in an increasing number of patients, and its diagnosis and treatment has attracted worldwide attention (18). In this study, 18 studies met the inclusion criteria, involving a total of 1,586 cases. The items proposed by the NICE were adopted for quality evaluation (19). There were 7 studies scoring 6–8 (38.89%), 10 studies scoring 3–6 (55.55%), and 1 scoring 0–2 (5.56%), suggesting that the included literature had good reliability (20).

Early CT findings are usually multiple lesions in both lungs, which are often irregular, fan-shaped, or flaky or almost round, and generally do not involve the whole lung segment. The lesion density is not uniform, often showing small localized patches or large flake ground glass shadow. In the advanced stage, CT shows increased lesion



**Figure 4** The risk of bias evaluation results. "+": low risk; "-": high risk; "?": unclear.

distribution area and increased lesion density, irregular, wedge-shaped or fan-shaped consolidation appeared in the lesions, with unclear boundaries, thickened bronchovascular bundles or multifocal lung consolidation under the pleura. In the critical phase, CT findings shows diffuse lesions in both lungs, with the appearance of "white lung" when

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most of the lungs are involved, and the diaphragmatic surface is elevated. The lesions are of uneven density, with air bronchial signs and bronchiectasis, and patchy ground glass shadows in areas of non-consolidation. The CT findings during the absorption period are density diminishes, lung consolidation disappears gradually, ground glass shadows are fully absorbed, and exudates are absorbed or organized by the body. The CT findings of bacterial pneumonia are mainly patchy consolidation shadows, which often accompanied by pneumonic bronchial signs; the CT findings of viral pneumonia are mainly multilobular peripheral ground glass shadows accompanied by lithotrite signs and interstitial thickening; and the CT findings of mycoplasma pneumonia are mainly interstitial inflammatory reactions, which distributed in double lower lungs, with thickening of bronchiole walls.

Of the 18 studies, the heterogeneity test results showed that among the CT signs, lung ground-glass shadow, lung consolidation shadow, and lung ground-glass shadow combined with consolidation exhibited high heterogeneity, with  $I^2$ =96.4%>50%. Ground-glass shadow was the most common (95% CI: 0.79–0.97), followed by thickening of the blood vessels (95% CI: 0.63–0.78), and pleural thickening (95% CI: 0.02–0.15). Asadollahi-Amin *et al.* [2020] (21) pointed out that diagnosis based on lung imaging is accurate. The CT imaging characteristics change with the disease condition, suggesting that CT images can be used for real-time diagnosis and evaluation (22).

Of the 18 studies, 12 reported that the lesions were externally subpleural (95% CI: 0.132–0.173), and 6 reported that the lesions were distributed in a single lobe (95% CI: 0.598–0.841). The heterogeneity test results showed that the morphology of the lesions was cord-like (95% CI: 0.092–0.172), grid-like (95% CI: 0.152–0.193), patchy (95% CI: 0.192–0.313), and nodular (95% CI: 0.591–0.745). Furthermore, ground-glass opacity was a typical CT manifestation of patients with infectious pneumonia (23). Therefore, it is highly necessary to combine CT characteristics to diagnose and treat infectious pneumonia.

The heterogeneity test results showed that the accompanying CT signs included pleural effusion (95% CI: 0.021–0.045) and pleural thickening (95% CI: 0.252–0.453). Some patients also had lymph node enlargement. If there is pleural effusion combined with lymph node enlargement, it indicates that the patient may have an adverse reaction and the condition will become worse.

Patients with common type showed no obvious lesions on lung CT after healing, while patients with severe type showed

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Study ID	ES (95% CI)	% Weight
Wu X (2016)	<b></b> 0.89 (0.80, 0.97)	1.24
Li X (2020)	0.09 (0.04, 0.14)	3.25
Umapathi T (2004)	0.29 (0.17, 0.41)	2.54
Burhan E (2020)	0.03 (0.01, 0.05)	3.48
Shi F (2020)	0.07 (0.02, 0.12)	2.58
Ooi GC (2004)	0.17 (0.10, 0.25)	3.54
Chaimayo C (2020)	<b></b> 0.70 (0.63, 0.78)	1.98
Chang YC (2005)	<b>→</b> 0.26 (0.21, 0.31)	3.87
Xie L (2005) —	<b>♦</b> 0.20 (0.15, 0.24)	2.85
Chen D (2021)	0.88 (0.79, 0.97)	3.67
Antonio GE (2003) —	• 0.76 (0.54, 0.99)	2.85
Xia T (2020)	<b>0.85 (0.80, 0.90)</b>	2.64
Kawamura K (2018) —	●●●●    0.60 (0.43, 0.77)	3.58
Das JP (2021)	<b>──</b> ◆── 0.23 (0.04, 0.43)	3.52
Assaad S (2020)	<b>0.05 (0.02, 0.08)</b>	3.85
Hon KL (2003)	<b>──</b> ◆── 0.32 (0.21, 0.44)	1.67
Wong KT (2004)	<b>0.08 (0.05, 0.11)</b>	2.58
Ng CK (2004)	- <b>-</b> 0.08 (0.02, 0.15)	1.42
Overall (I-squared =96.4%, P=0.001)		
NOTE: weights are form random effects analysis		

Figure 5 Forest plot showing the CT signs of infectious pneumonia. CT, computed tomography; ES, effect size; CI, confidence interval.



Figure 6 Meta-analysis of lesion distribution. ES, effect size; CI, confidence interval.

different degrees of lesion retention on lung CT, which was consistent with the results of Chen *et al.* [2020] (24). Of the 18 RCTs included in this study, 5 had the correct random allocation method, accounting for 27.78%, and only 2 had detailed allocation concealment, accounting for 16.67%. One study was evaluated using the blinding method, accounting for 5.55%, which was not adopted in the other studies. Meta-analysis was conducted on the

ground glass change indicators of infectious pneumonia patients. The funnel plot showed that the circles in the included studies were distributed near the midline and basically symmetrical, indicating that there was no bias in publication and the conclusions obtained were reliable. In the prevention of infectious diseases, laws and regulations should be taken as the guidance, corresponding measures should be taken in time according to the progress of the

Outcome indicator	ES (95% CI)	% Weight
		0
Single lung involvement	0.12 (0.08, 0.15)	11.32
	0 16 (0 13 0 17)	54 43
	0.10 (0.13, 0.17)	54.45
Multiple lobes are involved	0.75 (0.60, 0.84)	34.25
Overall (I-squared = 99.1%, P=0.000)	0.26 (0.24, 0.29)	100.00
0.084 1	11.9	

Figure 7 Meta-analysis on lesion morphology changes. ES, effect size; CI, confidence interval.



Figure 8 Meta-analysis on the changed lesion density. ES, effect size; CI, confidence interval.



Figure 9 Meta-analysis results of accompanying CT signs. CT, computed tomography; ES, effect size; CI, confidence interval.



**Figure 10** Funnel plots of ground-glass opacity included in the literature. SE, standard error; OR, odds ratio.

epidemic, the publicity function of social media should be given full play, information should be kept unblocked, and public opinion should be guided. In an emergency outbreak, public health authorities need to continuously improve their management capacity and efficiency, and make the right response measures in the first time.

# Conclusions

In this meta-analysis, RCTs involving patients with infectious pneumonia were selected to evaluate the diagnostic value of CT imaging. It was found that groundglass opacity was a typical CT manifestation in patients with infectious pneumonia, and some patients also showed thickening of blood vessels. It was concluded that CT signs were instrumental in the diagnosis, evaluation, and prognosis of infectious pneumonia. However, some limitations should be noted. The classification of patients with infectious pneumonia is not accurate enough. The subjects may also have hypertension and cardiovascular and cerebrovascular diseases, among others, which are not taken into consideration, reducing the power of the study. The included subjects were from different countries and regions, and the analysis results may be affected by the subjective factors of the equipment and doctors. In conclusion, CT is instrumental in diagnosing infectious pneumonia, and corresponding treatment plans can be determined based on CT manifestations.

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