Exploration of severe Covid-19 associated risk factor in China: meta-analysis of current evidence

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Abstract

Methods: We systemically and comprehensively retrieved the eligible study evaluating clinical difference between severe versus non-severe Covid-19. Main effect sizes were demography characteristics, comorbidities, signs and symptoms, laboratory findings as well as radiological features in chest CT. Results: 14 studies with a total of 2,566 individuals (771 in Severe group and 1,795 in Non-severe group) were eligible for this meta-analysis. It was demonstrated that older and male person was more susceptible to severe Covid-19. Patients with underlying comorbidity, such as hypertension, diabetes, heart disease and COPD were associated with significantly increased susceptibility of severe Covid-19. Patients with dyspnea were more likely to be severe illness. Depressed total lymphocytes were observed in this article. Meanwhile, although reticulation (30.8%), intrathoracic lymph node enlargement (56.4%) and pleural effusions (30.8%) were relatively rarely seen, meta-analysis revealed that patients with these presentations in chest CT were associated with increased risks of severe Covid-19. Conclusions: There are significant differences in clinical characteristic between the severe and non-severe Covid-19 patients. Many factors are related to the severity of the disease, which can help clinicians to differentiate severe patient from non-severe patient.

Statistical analysis

Meta-analysis was performed on crude data extracted from the text. We calculated the weighted mean difference (WMD) for continuous outcomes and the odds ratio (OR) for the dichotomous data, along with the 95% confidence intervals (CIs). In instances in which a standard error was not reported, we calculated the standard error of mean differences according to the methods described in Cochrane Handbook[13].

Prior to analyzing the data, heterogeneity was assessed by the Cochran Q test along with visual inspection of the forest plot. Then, it was quantified by I^2 test. A fixed-effect model was used when the effects were assumed to be homogenous (P>0.05 or I^2 <50 %)[13]. However, given that the clinical settings differed across studies, we assumed the presence of heterogeneity and used random-effects model in all subsequent analyses, for the outcome of which were more conservative as they consider differences both within and among studies in calculating the error term used in the analysis[13].

Funnel plots were employed for detection of publication bias, in which the effect sizes (e.g., OR or WMD) are plotted on the horizontal axis and its variance (e.g., the standard error of the log effect) on the vertical axis. Bias was revealed if the plots were asymmetrical about the pooled value.

All statistical analyses were done with Review Manager 5.3.5 (Cochrane Collaboration, Oxford, UK). Results were regarded as statistically significant if P<0.05.

Result

Trial flow

The search strategy generated a total of 6,821 citations (3,516 from Pubmed and 3,205 from ISI web of science). All the documents were selected strictly according to the criteria described above. Subsequent scrutiny of the title and abstracts led to the exclusion of 6,777 of these articles either for they were irrelevant to the aim of this meta-analysis or for duplication. 21 articles were further excluded for un-relation to our aim. The full publications were obtained for the remaining 23 articles.

According to inclusion criteria, 9 articles were further excluded, leaving 14 studies eligible for this article[14-27]. Specially, two articles were excluded either for overlapping patients with included studies[3], or for they defined the degree of severity of Covid-19 with the different criteria[3, 28]. One article reporting outcome regarding 55 2019-nCoV was also excluded from this meta-analysis, since it did not reported origin of patients[29]. For three articles reporting outcome in Wuhan Tongji hoptital[17, 30, 31], three articles reporting outcome in Jiangsu Province[27, 32, 33] and three article reporting outcome in Zhejiang province[33-35], only the study with larger simple volume was in included in this article[17, 27, 33]. No additional articles were retrieved from the citation list of included studies. The details of study selection flow were explicitly described in Figure 1.

Study characteristics

Finally, 14 retrospective cross-sectional studies regarding different population which can be concluded from patients' origin were suitable for this meta-analysis[14-27]: four multi-center studies[19-21, 27] and ten single-center studies[14-18, 22-26]. All the eligible studies were from China and published in 2020. Due to the instinct design of this meta-analysis, no randomized or non-randomized controlled trial was eligible for this meta-analysis. Characteristics of eligible studies were shown in Table 1.

The demography

A total of 2,566 individuals were identified (771 in Severe group and 1,795 in Non-severe group) [14-27]. Specially, there were 12 studies reporting 409 males in 747 patients in Severe group (54.8%) and 843 males in 1,724 in Non-severe group (48.9%) [14-17, 19-25, 27]. With the pooled OR of 1.30 (95 % CI: 1.07 to 1.57), it was demonstrated that males were associated with significantly increased susceptibility of severe Covid-19. Consistently, of 14 studies reporting age of patients[15-27], it was revealed that older individuals were more susceptible to severe Covid-19 (WMD: 11.12, 95 % CI: 6.70 to 15.55). The outcome was explicitly expressed in Table 2.

Comorbidity

In 7 eligible trials[15-17, 19, 22-24], hypertension was noted in 166 of 497 patients in Severe group (33.4%) and 151 of 973 in Non-severe group (15.5 %). With pooled OR of 2.30 (95 % CI: 1.35 to 3.92), it was demonstrated that patients with hypertension were associated with significantly increased risk of severe Covid-19 (P=0.002). Consistently, with pooled OR of 2.62 for diabetes (95%CI: 1.27 to 5.44, P=0.009), 4.02 for heart disease (95%CI: 2.08 to 7.77, P<0.0001) and 4.20 for chronic obstructive pulmonary disease (95%CI: 1.61 to 10.95, P=0.003), it was revealed that patients with diabetes[15-17, 19, 22-24], heart disease[15-17, 19, 22-24] and chronic obstructive pulmonary disease[15, 17, 22, 24, 27] were more susceptible to severe Covid-19. Conversely, with pooled OR of 1.81 for cerebrovascular disease (95%CI: 0.56 to 5.84, P=0.32), 1.28 for chronic live disease (95%CI: 0.60 to 2.71, P=0.53), 2.12 for chronic kidney disease (95%CI: 0.80 to 5.61, P=0.13) and 2.69 for tuberculosis (95%CI: 0.66 to 10.97, P=0.17), it was demonstrated that patients with cerebrovascular disease[17, 25], chronic live disease[17, 19, 24, 27], chronic kidney disease[17, 19, 24, 27] and tuberculosis[17, 25] were not associated with increased risk of severe Covid-19. What's more, smoke[17, 19, 22, 24] did not statistically increased risk of severe Covid-19 (OR: 1.07, 95%CI: 0.40 to 2.85, P=0.90).

Overall, 4 trials reported any comorbidity[17, 21, 22, 24] with 226 of 398 patients in Severe group (56.8%) and 137 of 430 in Non-severe group (31.9%). With pooled OR of 3.61 (95% CI: 1.62 to 8.01), it was revealed that individuals with comorbidity were more susceptible to severe Covid-19 (P=0.002). The outcome was explicitly expressed in Table 2.

Signs and symptoms

Among 9 studies[15, 17, 20, 22, 23, 25-27] reporting the clinical characteristics of fever in Covid-19, the incidence was 93.1% (552 in 593) in Severe group and 83.1% (795 in 957) in Non-severe group. With pooled OR of 1.93 (95%CI: 0.94 to 3.96), it was demonstrated severe Covid-19 patient was associated with slightly increased risk of fever. But meta-analysis did not reveal any statistical difference (P=0.07). Consistently, with pooled OR of 1.79 for expectoration (95%CI: 0.79 to 4.05, P=0.17), 1.43 for headache (95%CI: 0.91 to 2.26, P=0.12), 1.75 for fatigue (95%CI: 0.89 to 3.44, P=0.11) and 2.22 for myalgia (95%CI: 0.65 to 7.52, P=0.20), it was demonstrated that patients with expectoration[15, 17, 22, 23], headache[15, 17, 20, 22], fatigue[16, 17, 20, 25] and myalgia[15, 17, 27] were unrelated to severity of Covid-19.

In 5 trials reporting data on dyspnea[15, 20, 22, 23, 25], 82 of 192 patients in Severe group (42.7%) and 52 of 477 in Non-severe group (10.9%) were found to have dyspnea. With pooled OR of 7.83 (95 % CI: 1.75 to 34.99), it was demonstrated that patients with dyspnea were more likely to progress into severe Covid-19 too (P=0.007). The outcome was explicitly expressed in Table 2.

Laboratory findings

Of 7 studies reporting data on blood tests, lymphocyte count was revealed in all 7 studies[15, 17, 18, 22, 23, 26, 27]. With pooled WMD of -0.42 (95 % CI: -0.64 to -0.20), it was revealed that severe Covid-19 case was more likely to have decreased lymphocyte count when compared with non-severe case (P=0.0002). However, no significant difference was found in leucocytes[15, 17, 22, 23, 27], neutrophils[15, 17, 22, 23, 26, 27] and monocyte count[15, 17, 27]. The outcome was explicitly expressed in Table 2.

Imaging features

Among 5 studies reporting data on chest CT[15, 21, 22, 25, 27], the incidence of bilateral pneumonia was 95.8% (162 in 219) in Severe group and 73.4% (378 in 515) in Non-severe group. With pooled OR of 1.48 (95%CI: 0.50 to 4.35), it was demonstrate severe Covid-19 patient was associated with slightly increased risk of bilateral pneumonia. But meta-analysis did not reveal any statistical difference (P=0.48). Consistently, with pooled OR of 0.98 for unilateral pneumonia (95%CI: 0.40 to 2.42, P=0.97), 3.71 for ground-glass opacities (95%CI: 0.45 to 30.23, P=0.22), 3.32 for consolidation (95%CI: 1.00 to 11.03, P=0.05) and 8.23 for bronchial wall thickening (95%CI: 0.59 to 115.05, P=0.12), it was demonstrated that unilateral pneumonia[21, 25], ground-glass opacities [15, 21], consolidation[15, 21] and bronchial wall thickening [15, 21] were unrelated to the severity of Covid-19.

However, in 2 trials reporting data on reticulation in CT [15, 21], 12 of 39 patients in Severe group (30.8%) and 40 of 145 in Non-severe group (27.9%) were found to have reticulation in chest CT. With pooled OR of 2.86 (95%CI: 1.01 to 8.14, P<0.05), it was demonstrated that patients with reticulation in CT were more likely to progress into severe Covid-19.

In 2 trials reporting data on intrathoracic lymph node enlargement [15, 21], 8 of 39 patients in Severe group (20.5%) and 0 of 145 in Non-severe group (0%) were found to have intrathoracic lymph node enlargement. With pooled OR of 31.90 (95%CI: 3.65 to 278.98, P=0.002) it was demonstrated that patients with intrathoracic lymph node enlargement were more likely to progress into severe Covid-19.

In 2 trials reporting data on pleural effusions [15, 21], 12 of 39 patients in Severe group (30.8%) and 9 of 145 in Non-severe group (6.2%) were found to have pleural effusions. With pooled OR of 10.84 (95%CI: 1.07 to 109.80, P=0.04) it was demonstrated that patients with pleural effusions were more likely to progress into severe Covid-19. The outcome was explicitly expressed in Table 2.

Publication bias

Publication bias statistics were determined by funnel plot. The plot demonstrated asymmetry about the pooled effect which publication bias might exist (Figure 2).

Discussion

Up to now, this is the first meta-analysis to explore severe Covid-19 associated clinical, laboratory and imaging factor when compared with non-severe Covid-19. By systemically and comprehensively reviewed the current evidence published, 14 studies with a total of 2,566 individuals (771 in Severe group and 1,795 in Non-severe group) were eligible for this meta-analysis[14-27], which retrieved the largest sample size when compared with studies on the same topic. Overlapping patient was checked by examining the first author of article and the origin of patients, since we recognized that different articles might report of the same patients.

Currently, the National Health Commission (NHC) issued the China Guidelines for the Diagnosis and Treatment Plan of Novel Coronavirus (COVID-19), which defined the degree of severity of Covid-19 (i.e., mild, common, severe and critical). As we all know, treatment algorithm of Covid-19 depended on illness severity. Most severe and critical patients required oxygen therapy and a minority of the patients needed invasive ventilation or even extracorporeal membrane oxygenation. Moreover, there were some patient who developed worsening respiratory failure and acute respiratory distress syndrome (ARDS) rapidly that required intubation[36]. According to epidemiological investigation, severe illness occurred in 15.7% of the Covid-19 patients after admission to a hospital. As the clinical spectrum of COVID-19 ranges widely from mild illness to ARDS with a high risk of mortality, there is an urgent need for research to identify early markers of disease severity, which is of great value for clinician to diagnosis of the severity of Covid-19 rapidly and exactly.

Though statistical analysis, it was demonstrated that patients in Severe Covid-19 group were older and had a greater number of comorbid conditions (e.g., hypertension, diabetes and heart disease) than Non-severe group. Compromised respiratory status on admission (e.g., COPD) was also associated with severe illness. This suggests that age and comorbidity may be risk factors for poor outcome. Meanwhile, severe 2019-nCoV infection is more likely to affect males. These data was consistent with the recent report that showed 2019-nCoV infection is more likely to affect males [37]. What's more, our outcome did not support that smoking was associated with severity of COVID-19 illness. Consistently, Lippi et al conducted a meta-analysis of current evidence and concluded that active smoking does not apparently seem to be significantly associated with enhanced risk of progressing towards severe disease in Covid-19, which further confirmed our outcome[38].

Common symptoms of Covid-19 at onset of illness were fever, dry cough, expectoration, myalgia, fatigue, and dyspnea [1]. However, some patients presented initially with atypical symptoms, such as diarrhea and nausea [39, 40]. By statistical synthesis the data on common sign and symptoms, the incidence of fever, expectoration, headache, fatigue, myalgia and dyspnea were more common in Severe group than in Non-severe group. However, only the incidence of dyspnea was statistically different across groups. Thus, patient presented with dyspnea should gain more caution for which might be severe Covid-19. And this outcome was consistent with outcome found in ICU patient[41].

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 might have a cytokine storm syndrome[42]. In our study, compared with non-severe patients, severe Covid-19 patients had numerous laboratory abnormalities. By meta-analysis of current evidence, depressed total lymphocytes were observed in this article. These abnormalities suggest that 2019-nCoV infection may be associated with cellular immune deficiency. And these laboratory abnormalities are similar to those previously observed in patients with MERS-CoV and SARS-CoV infection[43].

Individuals with severe Covid-19 might present with bilateral (95.8%) or unilateral (30.5%) lung pathological changes, ground-glass opacities (100%), consolidation (76.9%) and bronchial wall thickening (56.4%) in chest CT. However, no statistical difference was revealed when compared with Non-severe group. Although reticulation (30.8%), intrathoracic lymph node enlargement (20.5%) and pleural effusions (30.8%) were relatively rarely seen, meta-analysis revealed that patients with reticulation, intrathoracic lymph node enlargement and pleural effusions in chest CT were associated with more likelihood to be a severe Covid-19. The outcome was further confirmed in a study carried by Yuan eta al which investigated the association of radiologic findings with mortality of patients infected with Covid-19[16].

The results should be viewed with recognition of limitations inherent in this study. Firstly, although a broad review scope provides us with a larger sample size and finally adequate statistical power to detect a risk factor, three articles reporting data comparing clinical characteristic between severe Covid-19 and non-severe Covid-19 was excluded for overlapping patients [3, 35, 44]. One article that did not reported the origin of patient was also excluded from this meta-analysis [29], which resulted in relative small sample size. However, their outcome further confirmed our conclusion.

Secondly, all eligible studies came from China, since first Covid-19 was identified in Wuhan, China. Data in other country was not acceptable right now. Thus, the outcome of our study could not be considered conclusive on this topic. An update of this article is necessary when needed.

Thirdly, more and more articles on Covid-19 were published every day. There might be lots of article evaluating the clinical difference across severe and non-severe Covid-19 unpublished. And funnel plot of this meta-analysis revealed that publication bias might exist. Thus, it is necessary for clinicians to interpret our outcome carefully.

In conclusion, it was demonstrated that older males manifested with dyspnea whose blood routine test revealed lymphopenia should gain more caution for which might be severe Covid-19. Patients with comorbidity, such as hypertension, diabetes and heart disease were more susceptible to severe Covid-19. Compromised respiratory status on admission (e.g., COPD) was also associated with severe illness. Specially, although reticulation, intrathoracic lymph node enlargement and pleural effusions were relatively rarely seen, meta-analysis revealed that patients with such presentations in chest CT were associated with more likelihood to be a severe Covid-19.

Although lots of risk factors were filtrated in this article, exploration of predicted value of these factors in severe Covid-19 patients was impossible with aggregated data extracted from published studies. Further diagnostic article evaluating how to differentiate severe from non-severe Covid-19 with the manifestation in chest CT and study evaluating the relation across clinical characteristic and severity of Covid-19 with the help of logistic regression analysis is needed.

Author Contributions

Conceptualization, YJ Zhang and SL Han; methodology, YJ Zhang and SL Han; software, YJ Zhang and SL Han; validation, XF Sun and B Xie.; formal analysis, YJ Zhang and SL Han; investigation, YJ Zhang and SL Han; resources, YJ Zhang and SL Han; data curation, YJ Zhang and SL Han; writing—original draft preparation, YJ Zhang and SL Han; writing—review and editing, YJ Zhang and SL Han; visualization, YJ Zhang and SL Han; supervision, WJ Feng; project administration, YJ Zhang and SL Han. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest:

The intent of this statement is to display our idea on severe Covid-19. There are no financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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Table 1. Characteristic of eligible studies.

Study ID	Location	Hospital	Date (month, day)	Study type	Sample size	Severe group	Non-severe group
Tian et al	Beijing, China	Designated hospitals in Beijing	Jan 20 to Feb 10	Multi-center	262	Severe: 46	Common: 216
Li et al	Chongqing, China	Second Affiliated Hospital of Chongqing Medical University	Jan to Feb	Single-center	83	Severe/critical: 25	Common: 58
Qin et al	Wuhan, Hubei province	Tongji Hospital	Jan 10 to Feb 12	Single-center	452	Severe: 286	Non-severe:166
Qu et al	Huizhou, Guang-dong Province	Huizhou municipal central hospital	Jan to Feb	Single-center	30	Severe: 3	Non-severe: 27
Shi et al	Zhejiang Province	Designated hospitals in Zhejiang Province	Up to Feb 17	Multi-center	487	Severe:49	Mild: 438
Zhao et al	Hunan Province	Designated hospitals in Hunan Province	NR	Multi-center	101	Severe/critical: 14	Common/Mild 87
Zhang et al	Wuhan, Hubei Province	No.7 hospital of Wuhan	Jan 16 to Feb 3	Single-center	140	Severe: 58	Non-severe: 82

Study ID	Location	Hospital	Date (month, day)	Study type	Sample size	Severe group	Non-severe group
Wu et al	Yancheng and Wuxi, Jiangsu province; Fuyang, Anhui Province	First People's Hospital of Yancheng; Second People's Hospital of Fuyang; Second People's Hospital of Yancheng; Fifth People's Hospital of Wuxi	Jan 20 to Feb 19	Muti-center	280	Severe/critical: 83	Common/Mild 197
Zhang et al	Wuhan, Hubei Province	Xinzhou District People's Hospita	Up to Mar 2	Single-center	95	Severe:32	Non-severe: 63
Zheng et al	Wuhan, Hubei Province	Wuhan Union Hospital	Up to Feb 15	Single-center	55	Severe:21	Common: 34
Wan et al	Chongqing, China	Three Gorges Central Hospital	Jan 23 to Feb 8	Single-center	135	Severe:40	Mild: 95
Yuan et al	Shenzhen, China	Shenzhen Third People's Hospital	Jan 11 to Feb 13	Single-center	94	Severe: 11	Common/Mild 83
Han et al	Wuhan, Hubei province	Renmin Hospital of Wuhan University	Jan 1 to Feb 18	Single-center	273	Severe/critical: 75	Mild: 198
Xie et al	Wuhan, Hubei province	Wuhan Jinyintan hospital	Feb 2 to Feb 23	Single-center	79	Severe: 28	Common: 51

Table 2. The pooled outcome for the association between demography characteristic, comorbidity, signs and symptoms, laboratory test, image feature in chest CT and severity of Covid-19.

Outcome	No. of study	Sample size	Sample size	OR or WMD (95%CI)	Heterogeneity	Difference
		Severe Group	Non-Severe Group			

Outcome	No. of study	Sample size	Sample size	OR or WMD (95%CI)	Heterogeneity	Difference
Demography characteristic	Demography characteristic	Demography characteristic	Demography characteristic	Demography characteristic	Demography characteristic	Demography characteristic
Age	14	771	1795	11.12 [6.70, 15.55]	P<0.0001; I^2 =92%	P<0.00001
Sex (male, year)	12	409 in 747 (54.8%)	843 in 1724 (48.9%)	1.30 [1.07, 1.57]	P= 0.62; I^2 = 0%	P=0.007
Comorbidity	Comorbidity	Comorbidity	Comorbidity	Comorbidity	Comorbidity	Comorbidity
Hypertension	7	166 in 497(33.4%)	151 in 973(15.5 %)	2.30 [1.35, 3.92]	P=0.03; I^2= 57%	P=0.002
Diabetes	7	88 in 497(17.7%)	65 in 973(6.7%)	2.62 [1.27, 5.44]	P=0.02; I^2= 61%	P=0.009
Heart Disease	7	46 in 497 (9.3%)	29 in 973 (3.0%)	4.02 [2.08, 7.77]	P=0.29; I^2 = 18%	P<0.0001
Cerebrovascular Disease	2	10 in 344(2.9%)	4 in 248(1.6%)	1.81 [0.56, 5.84]	P=0.66; I^2 = 0%	P=0.32
COPD	5	20 in 492(4.1%)	4 in 598(0.7%)	4.20 [1.61, 10.95]	P=0.42; I^2 = 0%	P=0.003
Chconic live disease	4	13 in 476(2.7%)	30 in 883(3.4%)	1.28 [0.60, 2.71]	P=0.45; I^2 = 0%	P=0.53
Chronic kidney disease	4	12 in 476(2.5%)	10 in 883(1.1%)	2.12 [0.80, 5.61]	P=0.34; I^2= 11%	P=0.13
Tuberculosis	2	9 in 344(2.6%)	2 in 248(0.8%)	2.69 [0.66, 10.97]	P=0.47; I^2 = 0%	P=0.17
Smoke	4	16 in 433(3.7%)	49 in 781(6.3%)	1.07 [0.40, 2.85]	P=0.12; I^2= 48%	P=0.90
Any	4	226 in 398(56.8%)	137 in 430(31.9%)	3.61 [1.62, 8.01]	P=0.003; I^2 = 78%	P=0.002
Signs and Symptoms	Signs and Symptoms	Signs and Symptoms	Signs and Symptoms	Signs and Symptoms	Signs and Symptoms	Signs and Symptoms
Fever	9	552 in 593(93.1%)	795 in 957(83.1%)	1.93 [0.94, 3.96]	P=0.007; I^2 = 62%	P=0.07
Expectoration	4	144 in 379(38.0%)	94 in 370(25.4%)	1.79 [0.79, 4.05]	P=0.02; I^2= 69%	P=0.17
Headache	4	56 in 397(14.1%)	56 in 525(10.7%)	1.43 [0.91, 2.26]	P=0.74; I^2 = 0%	P=0.12
Fatigue	4	210 in 396(53.0%)	189 in 522(36.2%)	1.75 [0.89, 3.44]	P=0.02; I^2 = 69%	P=0.11
Myalgia	3	114 in 394(28.9%)	70 in 421(16.6%)	2.22 [0.65, 7.52]	P<0.0001; I^2 = 90%	P=0.20
Dyspnea	5	82 in 192(42.7%)	52 in 477(10.9%)	7.83 [1.75, 34.99]	P<0.0001; I^2=86%	P=0.007
Laboratory test(x109 per L)	Laboratory test(x109 per L)	Laboratory test(x109 per L)	Laboratory test(x109 per L)	Laboratory test(x109 per L)	Laboratory test(x109 per L)	Laboratory test(x109 per L)
Leucocytes count	6	518	649	0.65 [-1.02, 2.32]	P<0.0001;I^2=94%	P=0.44
Neutrophils count	6	483	601	0.33 [-0.66, 1.33]	P<0.0001;I^2=94%	P=0.51

Outcome	No. of study	Sample size	Sample size	OR or WMD (95%CI)	Heterogeneity	Difference
Lymphocyte count	7	539	683	-0.42 [-0.64, -0.20]	P<0.0001; I^2 = 92%	P=0.0002
Monocyte count	3	384	391	0.01 [-0.06, 0.09]	P = 0.05; I^2 = 66%	P=0.70
Image feature in chest CT	Image feature in chest CT	Image feature in chest CT	Image feature in chest CT	Image feature in chest CT	Image feature in chest CT	Image feature in chest CT
Bilateral pneumonia	5	162 in 219(95.8%)	378 in 515(73.4%)	1.48 [0.50, 4.35]	P=0.09; I^2 = 53%	P=0.48
Unilateral pneumonia	3	47 in 154(30.5%)	99 in 362(27.3%)	0.98 [0.40, 2.42]	P =0.18; I^2 = 42%	P=0.97
Ground-glass opacities	2	39 in 39(100%)	129 in 145(89.0%)	3.71 [0.45, 30.23]	P = 0.66; I^2 = 0%	P=0.22
Consolidation	2	30 in 39(76.9%)	67 in 145(46.2%)	3.32 [1.00, 11.03]	P = 0.17; I^2 = 48%	P=0.05
Reticulation	2	12 in 39(30.8%)	40 in 145(27.9%)	2.86 [1.01, 8.14]	P = 0.34; I^2 = 0%	P<0.05
Bronchial wall thickening	2	22 in 39(56.4%)	25 in 145(16.0%)	8.23 [0.59, 115.05]	P = 0.004; I^2 = 88%	P=0.12
Intrathoracic lymph node enlargement	2	8 in 39(20.5%)	0 in 145(0%)	31.90 [3.65, 278.98]	P = 0.67; I^2 = 0%	P=0.002
Pleural effusions	2	12 in 39(30.8%)	9 in 145(6.2%)	10.84 [1.07, 109.80]	P = 0.13; I^2 = 57%	P=0.04
OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.	OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.	OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.	OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.	OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.	OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.	OR= odds ratio; WMD=weighted mean difference; 95%CIs+95% confidence intervals; COPD= chronic obstructive pulmonary disease.

Figure legend

Figure 1. Trials flow of selecting eligible studies.

Figure 2. Funnel plot for publication bias.