



Risk factors and predictors associated with the severity of COVID-19 in China: a systematic review, meta-analysis, and meta-regression

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Abstract: Since December 2019, the pneumonia cases infected with 2019 novel coronavirus have appeared, posing a critical threat to global health. In this study, we performed a meta-analysis to discover the different clinical characteristics between severe and non-severe patients with COVID-19 to find the potential risk factors and predictors of this disease's severity, as well as to serve as a guidance for subsequent epidemic prevention and control work. PubMed, Cochrane Library, Medline, Embase and other databases were searched to collect studies on the difference of clinical characteristics of severe and non-severe patients. Meta-analysis was performed using RevMan 5.3 software, and the funnel plots could be made to evaluate the publication bias. $P > 0.05$ means no statistical significance. Furthermore, a meta-regression analysis was performed by using Stata 15.0 to find the potential factors of the high degree of heterogeneity ($I^2 > 50\%$). Sixteen studies have been included, with 1,172 severe patients and 2,803 non-severe patients. Compared with non-severe patients, severe patients were more likely to have the symptoms of dyspnea, hemoptysis, and the complications of ARDS, shock, secondary infection, acute kidney injury, and acute cardiac injury. Interestingly, the former smokers were more prevalent in severe cases as compared to non-severe cases, but there was no difference between the two groups of 'current smokers'. Except for chronic liver disease and chronic kidney disease, the underlying comorbidities of hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease (COPD), malignancy, cerebrovascular disease, and HIV can make the disease worse. In terms of laboratory indicators, the decreased lymphocyte and platelet count, and the increased levels of white blood cell (WBC), D-dimer, creatine kinase, lactate dehydrogenase, procalcitonin, alanine aminotransferase, aspartate aminotransferase, and C-reactive protein were more prevalent in severe patients. Meta-regression analysis showed that patient age, gender, and proportion of severe cases did not significantly impact on the outcomes of any clinical indexes that showed high degree of heterogeneity in the meta-analysis. In conclusion, the severity of COVID-19 could be evaluated by, radiologic finding, some symptoms like dyspnea and hemoptysis, some laboratory indicators, and smoking history, especially the ex-smokers. Compared with non-severe patients, severe patients were more likely to have complications and

comorbidities including hypertension, cardiovascular disease etc., which were the risk factors for the disease to be severer, but the chronic liver disease and chronic kidney disease were not associated the severity of COVID-19 in China.

Keywords: COVID-19; clinical characteristics; clinical features; meta-analysis; meta-regression

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Introduction

Since December 2019, the pneumonia cases infected with 2019 novel coronavirus have appeared, posing a critical threat to global health. As of April 15, 2020, in China, the cumulative number of laboratory confirmed patients reached 83,745, including existing confirmed 2,004 cases (1,500 cases from abroad), 78,389 cured cases, and 3,352 deaths, etc. Fortunately, the recent decrease in the number of new cases means that the spread of the epidemic in China has been effectively controlled and the rate of patient treatment has increased significantly.

Recently, the basic, clinical and epidemiological research on 2019 novel coronavirus pneumonia (COVID-19) has been emerging, but there is a lack of a systematic review and meta-analysis to combine them comprehensively. In order to find the potential risk factors, predictors and prognosis of this disease's severity and better distinguish the severe patients from the non-severe patients based on the basic clinical characteristics at early stages so that reduce the mortality, we systematically summarize the existing main research related to discover the different clinical characteristics between severe and non-severe patients in the outbreak of COVID-19, with a view to serve as a guidance for subsequent epidemic prevention and control work.

We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-1743>).

Methods

Literature search strategy

The databases of PubMed, Embase and the Cochrane Library were searched to collect relevant studies about discovering the difference of clinical characteristics between severe and non-severe patients in the outbreak of COVID-19 in China. The search period was from January 1,

2020 to April 10, 2020. The search terms “clinical features” or “clinical characteristics” AND “2019 novel coronavirus” or “2019-nCoV” or “novel coronavirus” or “SARS-CoV-2” or “COVID-19” were used. To identify missing studies, we had checked the reference list for each selected paper.

Study selection and data extraction

The articles involving the comparison of clinical characteristics between severe and non-severe patients (ICU/non-ICU data as the second choice if severe/non-severe data was not provided) such as etiology, epidemiology, symptoms, imaging characteristics, blood indicators, comorbidities, complications and treatment methods were eligible for the present meta-analysis.

Non-severe patients included: (I) patients with mild to moderate disease; (II) non-ICU patients. Severe patients included: (I) patients with severe to critically severe disease; (II) patients entering ICU for treatment. The severity of disease was classified as follows according to the 5th edition of the guidelines for the diagnosis and treatment of COVID-19 (1): (I) mild type: patients with mild clinical symptoms and without abnormal CT findings; (II) moderate type: patients with symptoms of fever, cough, etc., and having abnormal changes on CT image; (III) severe type: patients presenting with any one of following criteria: (i) respiratory distress, respiratory rate ≥ 30 per min; (ii) in resting condition, oxygen saturation of finger $\leq 93\%$; (iii) partial pressure of oxygen in arterial blood/fraction of inspired oxygen ≤ 300 mmHg; (IV) critical type: any one of the following conditions has to be met: (i) respiratory failure occurs and mechanical ventilation is required; (ii) shock; (iii) patients with multiple organ failure needing ICU monitoring treatment.

Studies were excluded as follows: (I) duplicate publications; (II) reviews, editorials; case reports, letters, and comments; (III) only on the cases of children, pregnant women, older patients, infants, and some special groups

with special disease like HIV, etc.; (IV) no full-text; etc.

The clinical characteristics of severe and non-severe patients in this meta-analysis were compared, and the extracted information included: (I) basic information of the research, including the title, first author, the time and the journal of publication; (II) clinical characteristics of patients with COVID-19, including the number of patients in each group, the age, gender, and symptoms, complications, comorbidities etc. of this disease.

Article quality assessment

All articles were evaluated and compared independently by two evaluators. If there are any inconsistencies, a discussion should be taken or an independent expert was further consulted. The NRCT was scored according to Newcastle-Ottawa Scale (NOS) quality criteria (2), and the highest quality of the literature was 9 stars and the lowest 0 stars.

Statistical method

Meta-analysis was performed by using RevMan 5.3 software. The odds ratio [OR, 95% confidence intervals (CI)] was used to describe the ratio of the probability of the Coronavirus occurring in severe patients versus non-severe patients. Before the meta-analysis, the heterogeneity test was performed, if $I^2 < 50\%$, $P > 0.1$, suggesting that the degree of heterogeneity was low, and the meta-analysis was performed using the fixed effect model (FE); otherwise, the random effects model (RE) was used. If necessary, we should perform subgroup analysis. The funnel plots could be made to evaluate the publication bias. $P > 0.05$ means no statistical significance.

Furthermore, a meta-regression analysis was performed to assess the potential effect of demographic and clinical variables (patient age, male gender, proportion of severe cases) on the outcomes of some clinical indexes that showed high degree of Heterogeneity ($I^2 > 50\%$) in the meta-analysis.

Results

Literature search results and document characteristics

In order to find the possible risk factors and predictors of the severity in COVID-19 to better distinguish the severe patients from the non-severe patients based on the basic clinical characteristics in the future epidemic prevention and control work, we use meta-analysis to combine some results

of demographic and clinical characteristics of each study, including gender, smoking status, symptoms, complications, comorbidities, laboratory indicators, and the prognosis to observe the difference of them between the severe and non-severe cases.

A total of 1,911 related publications were obtained in the initial examination. After layer-by-layer screening, 16 retrospective studies (3-18) including totally 3,975 patients met the inclusion criteria, of which 1,172 were in the group of severe patients and 2,803 were in the group of non-severe patients. The literature screening process and results were shown in *Figure 1*, and the basic characteristics and information of the 16 studies were shown in *Table 1*.

Demographics and clinical characteristics of patients with COVID-19

Through subgroup analysis, we found that males were more prevalent in severe group (OR =1.34, $P=0.0001$). Interestingly, the previous smoking history (ex-smoking) in the two groups of patients was statistically different (OR =3.29, $P=0.003$), but the difference in current smoking had no statistical significance ($P=0.17$). The most common symptoms at onset of illness in many studies (3-18) were fever, cough, myalgia, dyspnea and fatigue; less common symptoms were nausea, vomiting, headache, diarrhea, sputum production, hemoptysis and abdominal pain etc. Compared with non-severe patients, severe patients were more likely to have the symptoms of dyspnea (OR =5.52, $P<0.00001$), hemoptysis (OR =3.76, $P=0.0003$), nausea and vomiting (OR =1.73, $P=0.02$), muscle ache (OR =1.67, $P=0.04$), and dizziness (OR =1.91, $P=0.008$) (especially dyspnea and hemoptysis), but the difference of symptoms such as cough ($P=0.42$), fever ($P=0.06$), highest temperature ($P=0.88$), diarrhea ($P=0.07$), anorexia ($P=0.18$), fatigue ($P=0.27$), headache ($P=0.05$), sputum production ($P=0.13$), pharyngalgia ($P=0.58$), rhinorrhea ($P=0.16$), chest pain ($P=0.09$), and abdominal pain ($P=0.11$) between the two groups had no statistical significance.

Compared with non-severe patients, severe patients had significantly higher risk to have the complications of ARDS (OR =34.45, $P<0.00001$), AKI (OR =7.70, $P=0.002$), acute cardiac injury (OR =6.35, $P=0.03$), secondary infection (OR =9.21, $P=0.04$), and shock (OR =33.18, $P<0.00001$), and more likely to have the underlying comorbidities (OR =2.77, $P<0.00001$), like hypertension (OR =2.50, $P<0.00001$), diabetes (OR =2.06, $P<0.0001$), cardiovascular

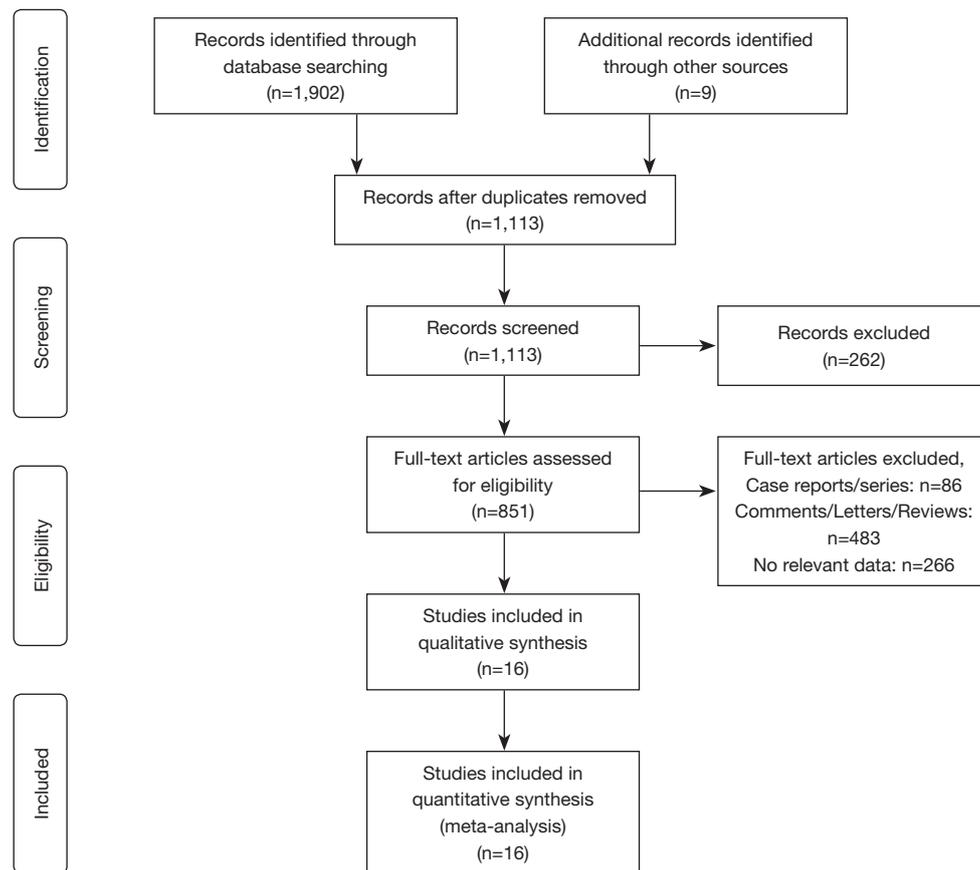


Figure 1 Literature screening flow diagram.

disease (OR =3.53, $P<0.00001$), cerebrovascular disease (OR =2.88, $P=0.0003$), malignancy (OR =1.66, $P=0.03$), chronic obstructive pulmonary disease (COPD) (OR =4.67, $P<0.00001$), and HIV or other immunodeficiency disease (OR =3.28, $P=0.02$) (Table 2).

In Figure 2, the funnel plots demonstrated symmetrical distributions of the effect size of cardiovascular disease, malignancy, chronic liver disease, and chronic kidney disease on either side of the pooled estimate, which indicated that the publication bias was not significant.

Radiologic and laboratory findings

In Table 2, we could find that severe patients have lower Lymphocyte count (OR =3.65, $P<0.00001$) and platelet count (OR =2.48, $P<0.00001$), as well as higher levels of D-dimer (OR =4.90, $P=0.006$), Lactate dehydrogenase (LDH) (OR =5.57, $P<0.00001$), C-reactive protein (CRP) (OR =4.33, $P=0.0001$), creatine kinase (OR =2.50,

$P<0.00001$), white blood cell (WBC) count (OR =3.57, $P=0.0004$), procalcitonin (PCT) (OR =3.09, $P<0.00001$), alanine aminotransferase (ALT) (OR =1.89, $P=0.0003$), and aspartate aminotransferase (AST) (OR =3.09, $P<0.00001$) as compared to non-severe patients. In terms of chest CT, we found that severe patients were more likely to yield more prominent radiologic abnormalities like bilateral lung involvement (OR =4.84, $P<0.00001$).

The treatments and prognosis between severe patients and non-severe patients

The most commonly used treatments in these studies included antiviral therapy, corticosteroid, invasive mechanical ventilation (IMV), noninvasive ventilation (NIV), and continuous kidney replacement therapy (CKRT), etc., in which we found that except for use of traditional Chinese medicine ($P=0.68$) and antiviral therapy ($P<0.0001$), these therapies showed above were used much more

Table 1 Basic information of included studies

Study	Year	Country	No. patients (severe/non-severe)	Follow-up (days)	Sex	Age, median [IQR] or mean \pm SD	Research type	Literature quality
Wan <i>et al.</i> (3)	2020	China	135 (40/95)	17	Male: 72; female: 63	47 [36–55]	Retrospective study	8
Qin <i>et al.</i> (4)	2020	China	452 (286/166)	33	Male: 235; female: 217	58 [47–67]	Retrospective study	6
Guan <i>et al.</i> (5)	2020	China	1,099 (173/926)	28	Male: 640; female: 459	47.0 [35.0–58.0]	Retrospective study	9
Zhang <i>et al.</i> (6)	2020	China	140 (58/82)	18	Male: 71; female: 69	57 [25–87]	Retrospective study	8
Tian <i>et al.</i> (7)	2020	China	262 (46/216)	21	Male: 127; female: 135	47.5 [1–94]	Retrospective study	7
Zhang <i>et al.</i> (8)	2020	China	95 (32/63)	N/A	Male: 53; female: 42	49.0 [39.0–58]	Retrospective study	9
Chu <i>et al.</i> (9)	2020	China	54 (43/11)	35	Male: 36; female: 18	39 [26–73]	Retrospective study	8
Wu <i>et al.</i> (10)	2020	China	280 (83/197)	30	Male: 151; female: 129	43.12 \pm 19.02	Retrospective study	7
Wang <i>et al.</i> (11)	2020	China	138 (36/102)	34	Male: 75; female: 63	56 [42–68]	Retrospective study	7
Huang <i>et al.</i> (12)	2020	China	41 (13/28)	17	Male: 30; female: 11	49.0 [41.0–58.0]	Retrospective study	7
Zheng <i>et al.</i> (13)	2020	China	161 (30/131)	21	Male: 80; female: 81	45 [33.5–57]	Retrospective study	8
Mao <i>et al.</i> (14)	2020	China	214 (88/126)	34	Male: 87; female: 127	52.7 \pm 15.5	Retrospective study	7
Du <i>et al.</i> (15)	2020	China	109 (51/58)	N/A	Male: 74; female: 35	70.7 \pm 10.9	Retrospective study	7
Feng <i>et al.</i> (16)	2020	China	476 (124/352)	35	Male: 271; female: 205	53 [40–64]	Retrospective study	9
Chen <i>et al.</i> (17)	2020	China	21 (11/10)	N/A	Male: 17; female: 4	56.0 [50.0–65.0]	Retrospective study	8
Cai <i>et al.</i> (18)	2020	China	298 (58/240)	26	Male: 145; female: 153	47.5 [33–61]	Retrospective study	7

Table 2 The difference between severe and non-severe patients in demographics and clinical characteristics

Clinical characteristics	Included studies	No. (events/total)		Heterogeneity*	OR	95% CI	P value ^a
		Severe	Non-severe				
Sex							
Female	16	484/1,172	1,326/2,803	P=0.36; I ² =8%	0.75	0.64–0.86	0.0001
Male	16	688/1,172	1,477/2,803	P=0.36; I ² =8%	1.34	1.16–1.56	0.0001
Subgroup analysis	16	1,172/2,344	2,803/5,606	P=0.0008; I ² =50%	1.00	0.90–1.11	1.00
Smoking							
Ex-smokers	2	13/230	15/995	P=0.40; I ² =0%	3.29	1.51–7.18	0.003
Current smokers	4	32/283	119/1,118	P=0.20; I ² =36%	1.34	0.88–2.03	0.17
Symptoms							
Fever	14	994/1,117	2,250/2,700	P<0.00001; I ² =80%	1.89	0.96–3.70	0.06
Highest temperature (°C)							
<37.3	4	52/150	95/397	P=0.96; I ² =0%	1.00	0.60–1.69	0.99
37.3–38.0	4	53/150	152/397	P=0.08; I ² =56%	1.15	0.56–2.33	0.71
38.1–39.0	5	37/159	132/407	P=0.009; I ² =70%	0.73	0.25–2.12	0.56
>39.0	5	12/159	28/407	P=0.37; I ² =6%	0.83	0.33–2.07	0.68
Subgroup analysis	5	154/618	407/1,608	P=0.11; I ² =31%	0.97	0.69–1.38	0.88
Cough	15	622/1,127	1,588/2,709	P<0.00001; I ² =79%	1.19	0.78–1.79	0.42
Nausea and vomiting	4	47/572	60/1,420	P=0.37; I ² =4%	1.73	1.09–2.73	0.02
Headache	12	138/914	225/2,292	P=0.001; I ² =64%	1.67	1.00–2.80	0.05
Dyspnea	13	546/977	516/2,341	P<0.00001; I ² =85%	5.52	2.87–10.60	<0.00001
Fatigue	11	361/799	704/1,955	P=0.05; I ² =45%	1.20	0.87–1.65	0.27
Diarrhea	13	159/968	165/2,169	P=0.003; I ² =60%	1.58	0.96–2.59	0.07
Sputum production	9	289/769	543/1,730	P=0.02; I ² =57%	1.33	0.91–1.94	0.13
Hemoptysis	6	27/666	14/1,603	P=0.98; I ² =0%	3.76	1.83–7.71	0.0003
Anorexia	6	128/550	117/582	P=0.0003; I ² =78%	1.77	0.76–4.10	0.18
Pharyngalgia	9	92/910	231/2,193	P<0.00001; I ² =81%	1.25	0.56–2.79	0.58
Abdominal pain	4	93/467	50/476	P=0.06; I ² =60%	2.35	0.83–6.65	0.11
Muscle ache	9	191/817	292/1,934	P=0.0006; I ² =71%	1.67	1.03–2.72	0.04
Rhinorrhea	3	18/412	18/374	P=0.91; I ² =0%	1.67	0.82–3.42	0.16
Dizziness	3	53/410	33/394	P=0.14; I ² =49%	1.91	1.19–3.09	0.008
Chest pain	2	17/188	15/532	P=0.05; I ² =73%	4.39	0.78–24.64	0.09
Complications							
ARDS	4	80/226	17/1,151	P=0.32; I ² =14%	34.45	19.41–61.13	<0.00001
AKI	5	25/320	11/1,391	P=0.06; I ² =55%	7.70	2.08–28.47	0.002
Acute cardiac injury	4	29/147	16/465	P=0.004; I ² =77%	6.35	1.22–33.14	0.03

Table 2 (continued)

Table 2 (continued)

Clinical characteristics	Included studies	No. (events/total)		Heterogeneity*	OR	95% CI	P value ^a
		Severe	Non-severe				
Shock	5	27/345	1/1,348	P=0.59; I ² =0%	33.18	10.28–107.05	<0.00001
Secondary infection	4	52/214	24/670	P=0.55; I ² =0%	9.21	5.48–15.48	<0.00001
Comorbidities							
Any	9	435/829	526/1,887	P=0.02; I ² =55%	2.77	2.02–3.81	<0.00001
Hypertension	12	334/968	372/2,316	P=0.003; I ² =61%	2.50	1.78–3.51	<0.00001
Diabetes	12	169/968	179/2,316	P=0.07; I ² =40%	2.06	1.46–2.91	<0.0001
Cardiovascular disease	9	88/818	73/2,122	P=0.72; I ² =0%	3.53	2.49–5.01	<0.00001
COPD	9	42/843	22/2,077	P=0.80; I ² =0%	4.67	2.73–7.99	<0.00001
Malignancy	10	38/952	43/2,290	P=0.34; I ² =11%	1.66	1.05–2.61	0.03
Chronic liver disease	10	21/828	64/2,025	P=0.44; I ² =0%	0.99	0.59–1.64	0.96
Chronic kidney disease	8	20/899	25/2,009	P=0.18; I ² =31%	1.26	0.70–2.28	0.45
Cerebrovascular disease	6	30/707	27/1,759	P=0.44; I ² =0%	2.88	1.63–5.07	0.0003
HIV or immunosuppression	5	7/467	6/1,635	P=0.56; I ² =0%	3.28	1.21–8.89	0.02
Laboratory indicators							
Chest CT images: bilateral lung	5	333/386	772/1,472	P=0.32; I ² =15%	4.84	3.52–6.66	<0.00001
White blood cell (×10 ⁹ /L)							
>10	9	112/524	98/1,628	P=0.001; I ² =69%	3.57	1.78–7.18	0.0004
<4	9	160/524	445/1,628	P<0.00001; I ² =89%	0.59	0.25–1.40	0.23
4–10	6	98/177	220/384	P=0.006; I ² =69%	0.89	0.41–1.96	0.78
Decreased lymphocyte count	9	414/511	934/1,555	P=0.01; I ² =60%	3.65	2.25–5.92	<0.00001
Decreased platelet count	7	118/333	261/1,097	P=0.30; I ² =17%	2.48	1.85–3.33	<0.00001
Increased D-dimer	4	158/230	254/615	P<0.00001; I ² =86%	4.90	1.57–15.22	0.006
Increased creatine kinase	6	62/261	100/887	P=0.17; I ² =36%	2.50	1.73–3.61	<0.00001
Increased creatinine	6	22/304	36/989	P=0.04; I ² =58%	1.61	0.61–4.28	0.34
Increased lactate dehydrogenase	6	170/250	317/877	P=0.01; I ² =65%	5.75	2.68–12.34	<0.00001
Increased procalcitonin	6	58/280	45/772	P=0.25; I ² =24%	3.09	1.99–4.81	<0.00001
Increased total bilirubin	2	20/158	65/725	P=0.52; I ² =0%	1.48	0.87–2.53	0.15
Increased alanine aminotransferase	4	77/248	164/858	P=0.32; I ² =14%	1.89	1.34–2.66	0.0003
Increased aspartate aminotransferase	7	141/319	194/1,000	P=0.09; I ² =45%	3.09	1.97–4.84	<0.00001
Increased C-reactive protein level	6	370/411	806/1,298	P=0.05; I ² =56%	4.33	2.07–9.07	0.0001

* , heterogeneity: I²<50%, P>0.1, suggesting that the homogeneity of each test was good, and the meta-analysis was performed using the fixed effect model (FE), while in contrast (I²>50%, P<0.1), the random effects model (RE) was used. ^a, P values indicate differences between severe and non-severe patients. P<0.05 was considered statistically significant. ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease.

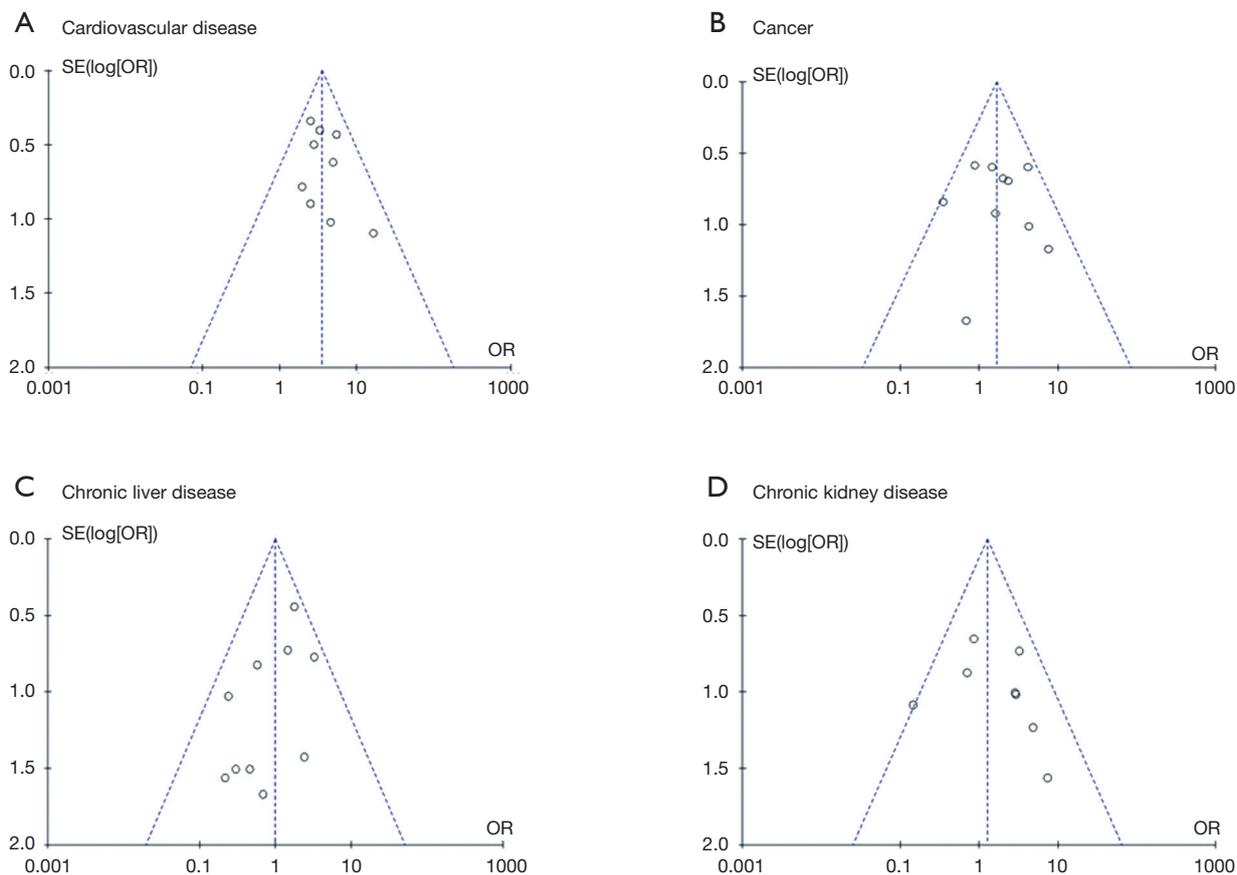


Figure 2 Funnel plots of the comparison of cardiovascular disease, cancer, chronic liver disease, and chronic kidney disease between the two groups. The middle lines represent the OR value of each study: (A) cardiovascular disease: 3.35; (B) cancer: 1.66; (C) chronic liver disease: 0.99; (D) chronic kidney disease: 1.26.

frequently in the treatment of severe patients than non-severe patients.

The mortality in the group of severe patients was much higher than that in the group of non-severe patients (OR =25.85, $P < 0.00001$), but the difference of discharge rate (OR =0.20, $P = 0.001$) in the group of severe patients was lower than non-severe patients. Moreover, the hospitalization rate between the two groups had no statistical significance ($P = 0.20$) (Table 3).

Meta-regression analysis: multivariate analysis

In Table 4, meta-regression analysis showed that patient age, gender, and proportion of severe cases did not significantly impact on the outcomes of any clinical indexes that showed high degree of heterogeneity in the meta-analysis.

Discussion

We performed a meta-analysis of 16 current high-quality articles on COVID-19, which is the first comprehensive systematic review to compare the clinical characteristics of severe patients and non-severe patients in China. The virus was not only widespread in China, as of April 15, 2020, there were totally 1,946,523 confirmed patients in the world, with high mortality in some countries like Algeria (15.74%), France (15.18%), Belgium (13.35%), and Italy (11.35%), etc. Therefore, it is urgent to recognize the clinical characteristics of patients infected with the virus (especially severe patients) and take corresponding measures in advance to reduce mortality.

In this study, we found that severe patients were more likely to be manifested with dyspnea, hemoptysis, and the onset of these symptoms might help physicians identify

Table 3 The difference between severe and non-severe patients in treatments and prognosis

Treatment and prognosis	Included studies	No. (events/total)		Heterogeneity*	OR	95% CI	P value ^a
		Severe	Non-severe				
Use of corticosteroid	9	379/621	353/2,009	P<0.00001; I ² =92%	5.08	2.16–11.98	0.0002
Antiviral therapy	6	311/455	869/1,706	P=0.99; I ² =0%	1.71	1.35–2.18	<0.0001
Antibiotic therapy	5	390/463	839/1,581	P<0.0001; I ² =85%	5.56	2.00–15.94	0.001
Antifungal drugs	3	39/348	19/1,336	P=0.07; I ² =62%	9.29	2.12–40.80	0.003
Intravenous immune globulin	5	229/408	180/1,432	P<0.00001; I ² =92%	7.34	2.29–23.53	0.0008
Traditional Chinese medicine	2	48/123	110/292	P=0.98; I ² =0%	1.15	0.59–2.25	0.68
Mechanical ventilation							
Invasive	8	229/578	1/1,998	P=0.02; I ² =56%	213.88	44.06–1,038.32	<0.00001
Non-invasive	7	262/520	128/1,758	P<0.00001 I ² =83%	57.45	11.61–284.38	<0.00001
ECMO	7	37/538	0/1,903	P=0.99; I ² =0%	32.58	10.61–100.02	<0.0001
CKRT	5	28/313	3/1,209	P=0.57; I ² =0%	14.99	5.60–40.14	<0.00001
Prognosis							
Discharge	7	164/537	871/2,054	P<0.00001; I ² =87%	0.20	0.08–0.53	0.001
Mortality	7	64/490	8/1,959	P=0.88; I ² =0%	25.85	13.12–50.94	<0.00001
Hospitalization	7	310/537	1169/2,054	P<0.00001; I ² =93%	2.40	0.62–9.27	0.20

* , heterogeneity: I² < 50%, P>0.1, suggesting that the homogeneity of each test was good, and the meta-analysis was performed using the fixed effect model (FE), while in contrast (I²>50%, P<0.1), the random effects model (RE) was used; ^a, P values indicate differences between severe and non-severe patients. P<0.05 was considered statistically significant. ECMO, extracorporeal membrane oxygenation; CKRT, continuous kidney replacement therapy.

the severe patients with poor prognosis. In terms of age, the severe patients was generally at a higher level than that of non-severe patients (3-7,9-11,13-18), which might be related to the lower immunity, more health issues and more comorbidities of older patients (6). In addition, this also indicated that the old-age was one of the risk factors leading to serious disease and might have contributed to the poor prognosis in some cases (19). Except for the elderly, patients with diabetes, HIV infection, long-term immunosuppressive therapy, and pregnant women also have relatively low body immunity (20). Therefore, strengthening the immunotherapy could appropriately reduce the severity and mortality of the disease.

Interestingly, our study found that patients' disease severity was related to past smoking history, but not associated with current smoking history. Because there was a lack of research on smoking history of patients infected with COVID-19, the relationship between smoking and COVID-19 was not clear (6), but there had been previous studies (21,22) confirmed that Ex-smoking was one of the

risk factors for community-acquired pneumonia (CAP), and the authors (21) also found a significantly decrease in CAP risk in the second year following smoking cessation, which had been attributed to normalisation of immune and inflammatory function of lung tissue. Brake *et al.* (23) had shown that smoking can upregulate the angiotensin-converting enzyme 2 (ACE2) receptor, which was a known receptor for severe acute respiratory syndrome -coronavirus (SARS-CoV) and human respiratory coronavirus NL638. Additionally, the patients' cumulative smoking volume is more important, and it can indirectly contribute to the severity of the COVID-19 by causing many comorbidities like COPD, malignancy and cardiovascular diseases, etc.

The underlying comorbidities like hypertension, Cardiovascular disease, malignancy, COPD, cerebrovascular disease, diabetes, and HIV or other immunosuppression disease were more prevalent among severe patients, which proved that the above-mentioned comorbidities as risk factors could make the disease worse and also might be associated with increased mortality (20). It is worth noting

Table 4 The outcomes of meta-regression analysis: multivariate analysis

Clinical indexes	Multivariate analysis (P value)			
	Severe cases	Gender	Age	Interaction
Symptoms				
Fever	0.606	0.943	0.725	0.699
Cough	1.169	0.280	0.051	0.137
Headache	0.702	0.528	0.305	0.545
Dyspnea	0.483	0.754	0.703	0.669
Diarrhea	0.964	0.874	0.868	0.907
Sputum production	0.942	0.963	0.844	0.954
Anorexia	0.328	0.349	0.318	0.329
Pharyngalgia	0.860	0.814	0.884	0.847
Muscle ache	0.407	0.480	0.356	0.404
Complications				
AKI*	0.148	0.698	0.953	–
Acute cardiac injury*	0.485	0.901	0.486	–
Comorbidities				
Any	0.533	0.519	0.241	0.495
Hypertension	0.186	0.074	0.131	0.178
Laboratory indicators				
White blood cell ($\times 10^9/L$)				
>10	0.345	0.588	0.898	0.512
<4	0.492	0.766	0.109	0.521
4–10	0.518	0.755	0.688	0.563
Decreased lymphocyte count	0.907	0.778	0.248	0.566
Increased D-dimer	0.972	0.529	0.550	–
Increased creatinine	0.659	0.832	0.703	0.754
Increased lactate dehydrogenase	0.313	0.367	0.374	0.271
Increased C-reactive protein level	0.787	0.748	0.727	0.613
Treatment				
Use of corticosteroid	0.847	0.984	0.766	0.898
Antibiotic therapy*	0.431	0.089	0.680	–
Antifungal drugs*	0.331	0.418	0.332	–
Intravenous immune globulin*	0.097	0.096	0.526	–
Invasive mechanical ventilation	0.537	0.501	0.794	0.620
Non-invasive mechanical ventilation	0.752	0.450	0.222	0.481
Prognosis				
Discharge	0.948	0.989	0.916	0.985
Hospitalization	0.503	0.705	0.558	0.556

*, due to the limited number of included studies, the multivariate analysis can't be performed in these indexes, so we just performed the univariate analysis. P values in these indexes represents the outcomes of univariate analysis.

that according to previous research, we found that very few cancer patients were infected with this virus, which was contrary to the phenomenon that cancer patients had low immunity and were easily infected. According to our clinical data, the reason may be that cancer patients realized their condition was not ideal, and paid more attention to personal protection and rarely went out to contact with outsiders, thus greatly reducing the risk of infection. But once cancer patients were infected, their prognosis would be worse than that of patients without cancer (24).

We also found that severe patients have significantly higher risk to have the complications of ARDS, AKI, acute cardiac injury, secondary infection, and shock, which were consistent with previous studies, and these complications might be the potential predictors of the severity of COVID-19 (3,5,11-18). In addition to these complications, previous studies had also reported that severe patients are prone to other complications such as acute liver injury etc., for example, as is shown in Xu *et al.*'s study (25), the liver biopsy specimens of the patient with COVID-19 showed moderate microvascular steatosis and mild lobular and portal activity.

In terms of laboratory indicators, severe patients have numerous laboratory abnormalities, such as higher levels of D-dimer, PCT, WBC, LDH, ALT, AST, creatine kinase and CRP, but lower levels of lymphocyte count and platelet count than non-severe patients. The higher CRP, PCT, D-dimer concentration and leukocyte counts might represent more prominent inflammation in severe patients, and the higher leukocyte count and PCT might also be due to secondary bacterial infection (6). The reduction of lymphocyte count indicated that this coronavirus might mainly act on lymphocytes and damage them, especially T lymphocytes. The translocation of lymphocyte from peripheral blood to lungs might also cause to the reduced lymphocytes (3,7,8,20). Neutrophilia might be related to cytokine storm induced by virus invasion, which generate a series of immune responses and cause changes in peripheral leukocytes and immune cells (20). The elevated LDH might be associated with myocardia injury, hepatic injury and kidney injury that related to direct effects of the virus, hypoxia, and shock (8). The elevating of ALT and AST might be also associated with the hepatic injury caused by the direct effects of the virus, drug hepatotoxicity or immune-mediated inflammation (such as cytokine storm and pneumonia-associated hypoxia, etc.) (3,26). A previous study has described that lymphocyte count, LDH, neutrophil count, and CRP were highly correlated to the acute lung

injury and might be predictors of disease severity (27), and the conclusion was almost in line with our study. Moreover, the higher D-dimer, PCT, WBC count, ALT, and AST might also be predictors of severity in this study.

The chest CT of severe patients mainly showed bilateral lung involvement, which is consistent with previous studies (28-31). Not only that, many research reports on COVID-19 indicated that most patients have CT manifestations with multiple lobes involvement (19,28,29), and showed patchy/punctate ground glass opacities, etc. (19,29-34). The posterior and peripheral lung predominant distribution in some studies was also very characteristic (28-31).

This study had several limitations: (I) all the studies are from China, so the results are difficult to represent the clinical characteristics of populations around the world. In contrast, the results of this study were more suitable for the Chinese population; (II) the combined indicators were not so comprehensive because of the limited numbers of included articles, such as some complications and comorbidities, so further study were necessary; (III) all studies included in this meta-analysis were retrospective studies with inevitable possible bias. Therefore, based on the above limitations, the conclusions of this meta-analysis still need to be verified by more relevant studies from multi-centers with larger sample size.

Conclusions

The severity of COVID-19 could be evaluated by age, radiologic finding, symptoms such as dyspnea, Hemoptysis etc., some laboratory indicators such as D-dimer, PCT, WBC count, LDH, ALT, AST, neutrophil count, C-reactive protein level and lymphocyte count etc., and smoking history, especially the ex-smokers. Compared with non-severe patients, severe patients were more likely to have complications such as ARDS, AKI, shock, etc. Comorbidities including hypertension, cardiovascular disease, COPD, and diabetes etc. were the risk factors for the disease to be severer and could also cause higher mortality, but the chronic liver disease and chronic kidney disease were not associated the severity of COVID-19.

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Footnote

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