Clinical features of severe patients infected with 2019 novel coronavirus: a systematic review and meta-analysis

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Background: 2019 novel coronavirus disease (COVID-19) has posed significant threats to public health. To identify and treat the severe and critical patients with COVID-19 is the key clinical problem to be solved. The present study aimed to evaluate the clinical characteristics of severe and non-severe patients with COVID-19.

Methods: We searched independently studies and retrieved the data that involved the clinical characteristics of severe and non-severe patients with COVID-19 through database searching. Two authors independently retrieved the data from the individual studies, assessed the study quality with Newcastle-Ottawa Scale and analyzed publication bias by Begg's test. We calculated the odds ratio (OR) of groups using fixed or random-effect models.

Results: Five studies with 5,328 patients confirmed with COVID-19 met the inclusion criteria. Severe patents were older and more common in dyspnea, vomiting or diarrhea, creatinine >104 µmol/L, procalcitonin ≥ 0.05 ng/mL, lymphocyte count $<1.5\times10^{\circ}$ /L and bilateral involvement of chest CT. Severe patents had higher risk on complications including acute cardiac injury (OR 13.48; 95% CI, 3.60 to 50.47, P<0.001) or acute kidney injury (AKI) (OR 11.55; 95% CI, 3.44 to 38.77, P<0.001), acute respiratory distress syndrome (ARDS) (OR 26.12; 95% CI, 11.14 to 61.25, P<0.001), shock (OR 53.17; 95% CI, 12.54 to 225.4, P<0.001) and in-hospital death (OR 45.24; 95% CI, 19.43 to 105.35, P<0.001). Severe group required more main interventions such as received antiviral therapy (OR 1.69; 95% CI, 1.23 to 2.32, P=0.001), corticosteroids (OR 5.07; 95% CI, 3.69 to 6.98, P<0.001), CRRT (OR 37.95; 95% CI, 7.26 to 198.41, P<0.001) and invasive mechanical ventilation (OR 129.35; 95% CI, 25.83 to 647.68, P<0.001).

Conclusions: Severe patients with COVID-19 had more risk of clinical characteristics and multiple system organ complications. Even received more main interventions, severe patients had higher risk of mortality.

Keywords: 2019 novel coronavirus; acute respiratory disease; clinical features; disease severity; meta-analysis

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Introduction

A newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously been named as 2019 novel coronavirus or 2019-nCoV)-infected pneumonia (NCIP), which was also declared as 2019 novel coronavirus disease (COVID-19) from February 11, 2020, by the World Health Organization (WHO) (1), has strong ability of early human-to-human transmission (2,3). COVID-19 has posed significant threats to public health since December 2019 (4). Thus far (as of 24:00 on February 11), more than 42,638 confirmed cases, including cumulative 1,016 death cases and 7,333 severe cases in total, have been identified throughout the whole of China (5). Internationally, quite a lot of cases have been confirmed in other countries. The WHO announced that the outbreak of the SARS-CoV-2 has become a Public Health Emergency of International Concern (PHEIC) (6). Unfortunately, the numbers of both infected patients and fatalities are still growing rapidly.

To identify and treat the severe and critical patients with COVID-19 bears on reducing the mortality, which is the key clinical problem to be solved. Several studies have described the clinical manifestations of affected patients with COVID-19 (4,7-10), and two studies (4,7) also evaluated the difference on clinical characteristics between severe and non-severe cases. However, the sample size of these studies has been still insufficient to delineate the epidemiological severe cases. Recently, analysis with significantly larger sample sizes throughout China has been conducted to differentiate these cases (11) (preprint). Thus, the present study aimed to evaluate the clinical characteristics of severe and non-severe patients with COVID-19.

Methods

Literature search strategy and inclusion criteria

This study was performed according to the PRISMA recommendations and criteria for the reporting of metaanalysis guidelines (12). An electronic database search without language restrictions was systematically performed by two reviewers (DZH and XJL) in PubMed, Web of Science, MEDLINE, CNKI (China Knowledge Resource Integrated Database) and the Cochrane Central Register of Controlled Trials (CENTRAL) from December 1, 2019, to February 12, 2020. In addition, we also sought ongoing and unpublished trials through ClinicalTrials.gov. Studies that involved clinical characteristics between severe and non-severe patients with COVID-19 were included. The search terms included the following: "2019-nCoV", "Novel Coronavirus", "2019 Novel Coronavirus", "COVID-19".

The included studies had to meet the following criteria: (I) clinical trials including the cohort or case-control or descriptive studies; (II) human studies involved identified COVID-19 patients; (III) contained the information on clinical characteristics of patients with COVID-19. Patients who were admitted to ICU and non-ICU were also categorized into a severe and non-severe subgroup. We also included the studies which were preprint. If the studies focused on pregnant patients and other coronaviruses, such as the Middle East respiratory syndrome (MERS) or severe acute respiratory syndrome (SARS) human coronavirus, they were excluded. In addition, studies lacking the information on grouping between severe and non-severe patients were also excluded after attempting to obtain the data from the authors.

Data extraction and quality evaluation

Two independent reviewers conducted the data extraction and checked by each other (FES and FM). When there were disagreements, they resolved through discussion. For each included study, a record of the first author, publication date, number of patients, mean age, the proportion of males, smoking status and history of exposure to the market of the participant were extracted. We mainly focused on the clinical characteristics including symptoms and signs (fever, vomiting, diarrhea, headache, myalgia), laboratory indicators (creatinine, white blood cell count, procalcitonin), bilateral involvement of chest CT, complications [acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury (AKI), shock], treatment [antiviral therapy, use of corticosteroid, continuous renal replacement therapy (CRRT), oxygen support], and in-hospital death.

We evaluated all included literature using the Newcastle-Ottawa Scale (NOS) (13). In this study, two investigators (ZWL and YFL) conducted the assessment scores for

Annals of Translational Medicine, Vol 8, No 9 May 2020

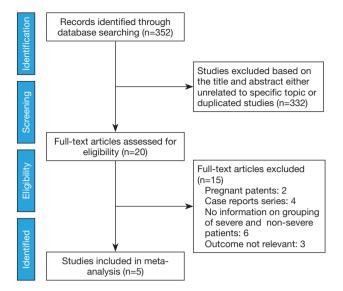


Figure 1 Flow chart for the selection of studies.

quality of each included study, of which a maximum of 1 point for each item in the selection and exposure perspectives and a maximum of 2 points in comparability. They also resolved the discrepancies by consensus. If they could not reach a consensus, other investigators helped to make a final decision through a vote majority.

Statistical analysis

We used the odds ratio (OR) with 95% confidence interval (CI) for the dichotomous outcomes and weighted mean difference (MD) with 95% CI for the continuous outcomes. To determine the between-study heterogeneity, we used Cochran's Q test (P>0.10 for statistical significance) and I^2 test (considered I^2 values <25%) to represent low heterogeneity, 25-50% to moderate heterogeneity, and >50% to severe heterogeneity). A fixedeffects model was applied if there was minimal significant heterogeneity, while the random-effects model was used if moderate to severe heterogeneity. To examine the possibility of publication bias, Funnel plots and Begg's tests were generated. Begg's test with P>0.1 was considered as no publication bias. Leave-one-out sensitivity analysis was also performed to evaluate the robustness of the results. A two-tailed P value <0.05 was considered significant. We used Review Manager version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata version 14 (Stata Corp LP, College Station, TX, USA) to perform the meta-analysis and produce the graph.

Results

Characteristics of the included studies

Literature searches identified and screened 352 potential abstracts, of which 20 underwent a full-text review. Of these, 15 studies were excluded for the following reasons: pregnant patients, case reports, no information on the grouping of severe and non-severe patients and irrelevant outcome. Consequently, 5 studies (4,7,11,14,15) met the inclusion criteria and entered final meta-analysis (*Figure 1*), of which 2 studies were preprint (11,15). A total of 5,328 patients (4,972 patients contained the information of disease severity) with confirmed COVID-19 in 5 studies were from China, with a mean/median age of between 47 and 56 years. Other information was listed in the table of characteristics of included studies (*Table 1*). In addition, all included studies were of high quality with a NOS score ≥ 6 (*Table 2*).

Presenting clinical characteristics

On admission, a total of 1,171 and 3,801 patients were categorized into severe and non-severe subgroups, respectively. Studies from Yang et al. (15) and Chen et al. (14) lacked some information of characteristics. Patents in severe group were 8.87 years more than those in non-severe group in a random-effects model (MD 8.87; 95% CI, 5.42 to 12.32, P<0.001), with severe heterogeneity ($I^2=71\%$, P=0.01). There were no significant differences between the two groups regarding the gender (OR 1.29; 95% CI, 0.99 to 1.67, P=0.06; I²=39%, P=0.18). For signs and symptoms, there was a statistically significance on higher risk of dyspnea (OR 5.50; 95% CI, 2.45 to 12.33, P<0.001; I²=61%, P=0.08) and gastrointestinal symptoms including vomiting and diarrhea (OR 1.86; 95% CI, 1.19 to 2.89, P=0.006; $I^2=0\%$, P=0.47) in the severe group than non-severe group. However, there were no significant differences between the two groups regarding the headache (OR 1.17; 95% CI, 0.77 to 1.78, P=0.46), fever (OR 1.25; 95% CI, 0.91 to 1.73, P=0.17), myalgia or arthralgia (OR 1.20; 95% CI, 0.83 to 1.74, P=0.32), with minimal heterogeneity. For laboratory findings, patents in severe group had higher risk compared to those in non-severe group on procalcitonin ≥0.05 ng/mL (OR 6.92; 95% CI, 3.02 to 15.86, P<0.001; I²=42%, P=0.18), creatinine >104 µmol/L (OR 2.90; 95% CI, 1.16 to 7.26, P=0.02; $I^2=0\%$, P=0.47) and lymphocyte count <1.5×10⁹/L (OR 4.39; 95% CI, 3.06 to 6.30, P<0.001; $I^2=0\%$, P=0.92). However, there were no significant differences between the two groups regarding the blood

Table 1 Charac	Table 1 Characteristics of the included studies	ncluded studies									
Author, study a	Author, study data, and country/region		Study design	Total number of patients (n)	Mean/median age (years)	Men (n)	Women (n)	Seafood market or wildlife exposure (n)	Smoking (n)		Medical staff (n)
Dawei Wang, 2020 02, China	020 02, China	Ď	Descriptive	138	56	75	63	12	I	7	40
Chaolin Huang	Chaolin Huang, 2020 01, China		Descriptive	41	49	30	11	27	ო		I
Weijie Guan, 2020 02, China	320 02, China	Ō	Descriptive	1,099	47	643	456	13	158		23
Lei Chen, 2020 02, China	02, China	Ō	Descriptive	29	56	21	80	N	0		I
Yang Yang, 2020 02, China	20 02, China	Ŏ	Descriptive	4,021	49	2,212	1,809	I	I	N	247
		Sele	Selection		Comparability	bility		Exposure			
Study	Adequate definition of cases	Representativene the cases	ess of Selection controls	ion of Definition rols controls	Representativeness of Selection of Definition of Control for important Ascertainment of the cases controls controls factor ^a exposure	nportant	Ascertainment c exposure	Same method of ascertainment for cases and controls		Non- response rate	Scores
Wang <i>et al.</i>	44	44	*	47 J	谷 42		44	*		1	8
Huang <i>et al.</i>	25	44	*	د ۲۶	25 25		275	44		I	8
Guan <i>et al.</i>	275	44	**	د ۲۶	25 25		275	44		I	ø
Chen <i>et al.</i>	275	44	I	¥.	**		275	44		I	9

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^a, a maximum of 2 stars can be allotted in this category, one for age, the other for other controlled factors; –, not available.

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white leukocyte count $<4\times10^{9}$ /L (OR 1.02; 95% CI, 0.05 to 22.09, P=0.99), with severe heterogeneity (I²=87%, P=0.005). Patents in severe group had higher risk compared to those in non-severe group on bilateral involvement of chest CT (OR 5.66; 95% CI, 3.84 to 8.34, P<0.001; I²=0%, P=0.42) (*Figures S1-S12*).

Complications and death

Patents in severe group had higher risk on the incidence of acute cardiac injury (OR 13.48; 95% CI, 3.60 to 50.47, P<0.001) or AKI (OR 11.55; 95% CI, 3.44 to 38.77, P<0.001), ARDS (OR 26.12; 95% CI, 11.14 to 61.25, P<0.001), and shock (OR 53.17; 95% CI, 12.54 to 225.4, P<0.001) than non-severe group. For in-hospital death, there was a statistically significance of higher risk in severe group (OR 45.24; 95% CI, 19.43 to 105.35, P<0.001; $I^2=0\%$, P<0.60). The results all were with minimal heterogeneity (*Figure 2*).

Main interventions

Patents in severe group had higher risk on the received antiviral therapy (OR 1.69; 95% CI, 1.23 to 2.32, P=0.001), corticosteroids (OR 5.07; 95% CI, 3.69 to 6.98, P<0.001), CRRT (OR 37.95; 95% CI, 7.26 to 198.41, P<0.001) than non-severe group, with minimal heterogeneity. In addition, invasive mechanical ventilation (OR 129.35; 95% CI, 25.83 to 647.68, P<0.001, I^2 =23%, P=0.27) and non-invasive mechanical ventilation (OR 119.75; 95% CI, 9.22 to 1,556.24, P<0.001, I^2 =69%, P=0.04) was more required in severe group than non-severe group (*Figure 3*).

Examination of the funnel plot

There was no apparent systematic publication bias among the included trials according to the result of Begg's test (P=0.69) for in-hospital death. The funnel plot was relatively symmetrical (*Figure 4*). However, there were inevitably publication bias if the number of included studies were small.

Discussion

The present meta-analysis and systematic review mainly described the clinical characteristics of severe patients with COVID-19. We considered data from clinical characteristics, complications and main interventions between severe and non-severe patients, allowing better targeting of the population of interest.

The definition and classification of COVID-19 were in accordance with the selected articles, respectively. They were referred to the WHO interim guidance (16) or the standard protocol issued by the National Health Commission of the People's Republic of China (17). From the 5 selected articles, a large set of clinical indices were assessed, showing both the large panel of clinical symptoms and laboratory features could be considered clinical signs for prediction and diagnosis of severe COVID-19. The symptoms of the COVID-19 were non-specific. Fever was the most frequently assessed clinical signs. However, no significance was found for gender, fever, myalgia or arthralgia, headache and blood leukocyte count $<4\times10^{9}/L$ of severe cases compared to non-severe cases. To note, the recent report revealed COVID-19 was more prone to male patients (18), while the present study was difficult to differentiate the gender between severe and nonsevere patients. Based on the data, we found age, dyspnea, vomiting or diarrhea, creatinine >104 µmol/L, procalcitonin \geq 0.05 ng/mL, lymphocyte count <1.5×10⁹ and bilateral involvement of chest CT to be significantly associated with severe cases. However, the heterogeneity of the dyspnea and procalcitonin ≥ 0.05 ng/mL was apparent and we performed the leave-one-out sensitivity analysis to evaluate the robustness of the results, of which a study from Guan et al. (11) had a more prominence. The study also showed severe cases had more proportion of dyspnea and procalcitonin ≥0.05 ng/mL as compared with non-severe cases (11). Recent studies found SARS-CoV-2 induced diarrhea as onset symptom in a patient with COVID-19 (without high fever, cough, dyspnea and chest pain) (19) and SARS-CoV-2 could be found in stool samples of patients with abdominal symptoms (20), which increased the evidence for gastrointestinal infection of SARS-CoV-2 and spreading through fecal oral route. Therefore, diarrhea should not be underestimated and the digestive system for severe patients should be paid more attention to. In terms of laboratory tests, the reduced absolute value of lymphocyte may be a common feature of patients with COVID-19. A recent pathological finding of COVID-19 associated with ARDS indicated lymphocytopenia may be a key factor associated with disease severity and mortality (21). The present study suggests that SARS-CoV-2 might more act on lymphocytes in severe patients, which indicated damage to T lymphocytes might be an important factor leading to exacerbations of patients (21). Pan et al. demonstrated that

Acute cardiac injury

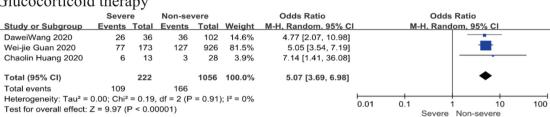
Study or Subgroup	Seve Events		Non-sev Events		Weight	Odds Ratio M-H, Fixed, 95% C			Odds Ratio I, Fixed, 95% Cl	
Chaolin Huang 2020		13	1	28		12.00 [1.18, 121.81]		IVI-I		
DaweiWang 2020	8	36	2	102	64.9%	14.29 [2.87, 71.12]				
Total (95% CI)		49		130	100.0%	13.48 [3.60, 50.47]				
Total events	12		3							
Heterogeneity: Chi ² =		1(P = 0)	-	0%			L			
Test for overall effect		,		070			0.01	0.1 Se	1 10 evere Non-severe	100
Acute kidney	injury									
	Seve	re	Non-sev	vere		Odds Ratio			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H	I, Fixed, 95% CI	
Chaolin Huang 2020	3	13	0	28	16.2%	19.00 [0.90, 399.79]				
DaweiWang 2020	3	36	2	102	63.5%	4.55 [0.73, 28.39]				
Wei-jie Guan 2020	5	173	1	926		27.53 [3.20, 237.12]				
Total (95% CI)		222		1056	100.0%	11.55 [3.44, 38.77]				
Total events	11		3							
Heterogeneity: Chi ² =				0%			0.01	0.1	1 10	10
Test for overall effect	t: Z = 3.96 (P < 0.0	001)				0.01		evere Non-severe	10
	Severe		lon-sever			Odds Ratio			dds Ratio	
			von-sever	e		Odds Ratio		C)dds Ratio	
	Events T	otal E	vents T	otal W		M-H, Random, 95% CI			Odds Ratio Random, 95% Cl	
Study or Subgroup Chaolin Huang 2020	Events T 11	Total E 13	ivents T	otal W	10.3% 14	M-H. Random, 95% Cl 48.50 [12.18, 1810.44]				
Chaolin Huang 2020 DaweiWang 2020	Events T 11 22	Total E 13 36	Events T 1 5	otal W 28 102	10.3% 14 35.6%	M-H, Random, 95% Cl 8.50 [12.18, 1810.44] 30.49 [9.94, 93.54]				
Chaolin Huang 2020	Events T 11	Total E 13	Events T 1 5	otal W 28 102	10.3% 14	M-H. Random, 95% Cl 48.50 [12.18, 1810.44]				
Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI)	Events 1 11 22 27	Total E 13 36	Events T 1 5 10	otal W 28 102	10.3% 14 35.6% 54.1%	M-H, Random, 95% Cl 8.50 [12.18, 1810.44] 30.49 [9.94, 93.54]				
Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events	Events 1 11 22 27 60	Total E 13 36 173 222	Events T 1 5 10 1 16	otal W 28 102 926 8 056 10	10.3% 14 35.6% 54.1%	M-H. Random, 95% CI [8.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73]				
Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Tau ² =	Events T 11 22 27 60 0.20; Chi ² =	Total E 13 36 173 222 3.05, d	Events T 1 5 10 1 16 f = 2 (P = 0	otal W 28 102 926 8 056 10	10.3% 14 35.6% 54.1%	M-H. Random, 95% CI [8.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73]	F	M-H, F		
Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2	Events T 11 22 27 60 0.20; Chi ² =	Total E 13 36 173 222 3.05, d	Events T 1 5 10 1 16 f = 2 (P = 0	otal W 28 102 926 8 056 10	10.3% 14 35.6% 54.1%	M-H. Random, 95% CI [8.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73]	H 0.01	M-H, F	Random, 95% Cl	• • 100
Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2	Events T 11 22 27 60 0.20; Chi ² = Z = 7.50 (P	Total E 13 36 173 222 3.05, d < 0.000	The second secon	otal W 28 102 926 8 056 11 0.22); 1 ²	10.3% 14 35.6% 54.1%	M-H. Random, 95% Cl 18.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73] 26.12 [11.14, 61.25]	F	<u>М-Н, F</u> 0.1 Sev	Random, 95% CI	
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Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Shock Study or Subgroup Chaolin Huang 2020	Events 1 11 22 27 60 0.20; Chi ² = Z = 7.50 (P Severe Events 3 3	otal E 13 36 173 222 3.05, d < 0.000	Events T 1 5 10 1 16 7 12 7 10 1	otal W 28 102 102 926 926 10 0.56 10 0.22); 12 12 rre Total 28 28	10.3% 14 35.6% 54.1% 00.0% = 34% <u>Weight</u> 32.4%	M-H. Random, 95% CI 8.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73] 26.12 [11.14, 61.25] Odds Ratio M-H. Fixed, 95% C 19.00 [0.90, 399.79]	0.01	<u>М-Н, F</u> 0.1 Sev	Aandom, 95% CI	
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Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Shock Study or Subgroup Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events	Events 1 11 22 27 60 0.20; Chi ² = Z = 7.50 (P Severe Events 1 3 11 11 25	Total E 13 36 173 222 3.05, d < 0.0000	Events T 1 5 10 11 16 6 1 2 0 1 0 1 0 1 0 1 1 0 1 1	otal W 28 102 102 926 926 10 0.22); I ² 10 re 102 926 102 926 102 926 102 926 102 926 1056	10.3% 14 35.6% 54.1% 00.0% = 34% <u>Neight</u> 32.4% 48.0% 19.6%	M-H. Random, 95% CI 18.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73] 26.12 [11.14, 61.25] Odds Ratio M-H. Fixed, 95% C 19.00 [0.90, 399.79] 44.44 [5.48, 360.52] 131.14 [7.69, 2236.25]	0.01	<u>М-Н, F</u> 0.1 Sev	Aandom, 95% CI	
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Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 2 Shock Study or Subgroup Chaolin Huang 2020 DaweiWang 2020 Wei-jie Guan 2020 Total (95% CI) Total events Heterogeneity: Chi ² = C	Events 1 11 22 27 60 0.20; Chi ² = Z = 7.50 (P Severe Events 1 3 11 11 25 0.86, df = 2 Z = 5.39 (P	Total E 13 36 173 222 3.05, d 3 305, d 173 222 3 173 222 2 173 36 173 222 (P = 0.000) 0 (P = 0.000) 0	Events T 1 5 10 11 16 7 1 2 (P = 10) 001) 10 Non-seve 0 1 0 1 0 1 0 1 0 355); I² = 0%	otal W 28	10.3% 14 35.6% 54.1% 00.0% = 34% <u>Neight</u> 32.4% 48.0% 19.6%	M-H. Random, 95% CI 18.50 [12.18, 1810.44] 30.49 [9.94, 93.54] 16.94 [8.03, 35.73] 26.12 [11.14, 61.25] Odds Ratio M-H. Fixed, 95% C 19.00 [0.90, 399.79] 44.44 [5.48, 360.52] 131.14 [7.69, 2236.25]	↓ 0.01	M-H. F 0.1 Sev M-H	Aandom, 95% Cl	

	Sever	re	Non-sev	vere		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
Chaolin Huang 2020	5	13	1	28	14.2%	16.88 [1.71, 166.21]				
Chen Lei 2020	2	14	0	15	14.7%	6.20 [0.27, 141.32]			•	
DaweiWang 2020	6	36	0	102	7.9%	43.69 [2.39, 797.75]				
Wei-jie Guan 2020	14	173	1	926	10.6%	81.45 [10.64, 623.70]				•
Yang Yang 2020	55	935	3	2730	52.6%	56.81 [17.73, 182.05]				-
Total (95% CI)		1171		3801	100.0%	45.24 [19.43, 105.35]			-	
Total events	82		5							
Heterogeneity: Chi ² = 2	2.73, df = 4	4 (P = 0	0.60); l ² =	0%					10	1000
Test for overall effect: 2	z = 8.84 (I	P < 0.0	0001)				0.001	0.1 1 Severe	I 10 Non-severe	1000

Figure 2 Forest plots of comparison severe versus non-severe cases for complications.

Antiviral therapy

	1.0									
	Sever	re	Non-se	vere		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Rand	lom, 95% Cl	
Chaolin Huang 2020	12	13	26	28	1.6%	0.92 [0.08, 11.20]			· · · · · · · · · · · · · · · · · · ·	
DaweiWang 2020	34	36	90	102	4.2%	2.27 [0.48, 10.66]				
Wei-jie Guan 2020	80	173	313	926	94.1%	1.68 [1.21, 2.34]				
Total (95% CI)		222		1056	100.0%	1.69 [1.23, 2.32]			•	
Total events	126		429							
Heterogeneity: Tau ² = (0.00; Chi ²	= 0.36	, df = 2 (P	= 0.83)	; I ² = 0%		0.01	0.1	+ + 1 10	100
Test for overall effect: 2	z = 3.23 (F	P = 0.0	01)				0.01	Severe		100
Glucocorticoid	1 thera	apy						Severe	11011-367616	



Continuous renal replacement therapy

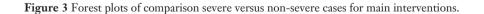
	Sever	re	Non-se	vere		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl	
Chaolin Huang 2020	3	13	0	28	38.2%	19.00 [0.90, 399.79]				
DaweiWang 2020	2	36	0	102	38.5%	14.86 [0.70, 317.07]		-		
Wei-jie Guan 2020	9	173	0	926	23.3%	107.01 [6.20, 1847.50]				• •
Total (95% CI)		222		1056	100.0%	37.95 [7.26, 198.41]				
Total events	14		0							
Heterogeneity: Chi ² = 1	07, df = 2	2 (P = 0	0.59); l ² =	0%			0.001	0.1	1 10	1000
Test for overall effect: Z	= 4.31 (P < 0.0	001)				0.001		Non-severe	1000

Invasive mechanical ventilation

	Seve	re	Non-se	vere		Odds Ratio		Odds	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixe	d, 95% Cl	
Chaolin Huang 2020	2	13	0	28	49.3%	12.39 [0.55, 278.55]		-		
DaweiWang 2020	17	36	0	102	25.7%	183.97 [10.62, 3188.55]				
Wei-jie Guan 2020	24	173	0	926	25.0%	303.67 [18.37, 5020.13]				_
Total (95% CI)		222		1056	100.0%	129.35 [25.83, 647.68]				
Total events	43		0							
Heterogeneity: Chi ² = 2	2.60, df =	2 (P = 0).27); l² =	23%			0.001	0.1 1	10	1000
Test for overall effect:	Z = 5.92 (P < 0.0	0001)				0.001	Severe	10 Non-severe	1000

Noninvasive mechanical ventilation

	Seve	e	Non-sev	vere		Odds Ratio		Odds F	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H, Rando	m, 95% Cl	
Chaolin Huang 2020	8	13	2	28	38.9%	20.80 [3.37, 128.54]				_
DaweiWang 2020	15	36	0	102	30.3%	147.79 [8.51, 2565.93]				
Wei-jie Guan 2020	56	173	0	926	30.8%	891.02 [54.69, 14516.15]			-	
Total (95% CI)		222		1056	100.0%	119.75 [9.22, 1556.24]				
Total events	79		2							
Heterogeneity: Tau ² = 3	3.53; Chi²	= 6.49	df = 2 (P	= 0.04)	; I ² = 69%	, D	0.001	0.1 1	10	1000
Test for overall effect: 2	Z = 3.66 (P = 0.0	003)				0.001		Non-severe	1000



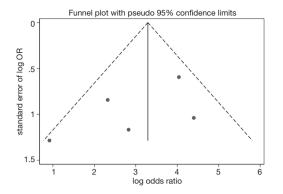


Figure 4 Funnel plot with 95% confidence interval (CI) to assess publication bias.

the manifestations of the new coronavirus pneumonia are diverse (22). At an early stage, patients may have a single lobe or multiple lobes involvement, but as the disease progressed, the lungs showed diffuse lesions, and the density of both lungs increased widely in the short-term. The present study showed bilateral involvement of chest was an indicator of severe case, which helps early diagnosis based on imaging findings.

A study using single-cell RNA-seq data analysis showed that the receptor ACE2 (angiotensin-converting enzyme II) as a cell entry receptor, expression in lung, esophagus, kidney, bladder, and ileum were as high as respiratory organs (lung). This result suggested that the multiple organs could be affected by COVID-19 (23), which may lead to the complications of ARDS, AKI, acute cardiac injury and shock. To note, the present study showed severe cases had a higher risk of acute cardiac injury (OR 13.48; 95% CI, 3.60 to 50.47, P<0.001). A study of 99 hospitalized patients with confirmed COVID-19 showed 40% of patients have a cardiovascular or cerebrovascular disease (18). However, pathological characteristics of biopsy samples from a patient who died from severe infection with SARS found no obvious histological changes in heart tissue, indicating that SARS-CoV-2 infection might not directly impair the heart (21). The association between COVID-19 and cardiac injury requiring further confirmed. According to the clinical guidance of COVID-19 from American College of Cardiology, it is advisable for patients with underlying cardiovascular disease of the potential increased risk to encourage additional and reasonable precautions and the medical staffs tailored guideline-directed therapies to individual patients in geographies with active COVID-19 transmission (24). Severe cases had a significantly higher

risk of progressed rapidly with complications, which was eventually followed by multiple organs failure. A report on the epidemiological and clinical outcomes of 41 laboratoryconfirmed cases infected with COVID-19 showed higher concentrations of GCSF, MIP1A, IP10, MCP1, and TNF α in patients who required ICU admission than those not requiring ICU admission, suggesting that the cytokine storm was related to disease severity (4). Thus, it may be of great significance to initiate the blood purification therapy (such as plasma exchange, immunoadsorption or CRRT) for the purpose of eliminating cytokines in the early stage, which have been previous demonstrated to play an important role on SARS, MERS and other sepsis treatment (25,26).

Patents in the severe group had higher risk on the received antiviral and corticosteroids therapy, as well as CRRT and invasive mechanical ventilation than the nonsevere group. However, for in-hospital death, there was a statistically significantly higher risk in the severe group. The reasons could be as follow. Firstly, until now, no specific treatment or antiviral agents have enough evidence to be recommended for treating COVID-19 infection. No unique clinical evidence exists to expect that patients with COVID-19 will benefit from corticosteroids (27). In addition, critically ill cases had a higher risk of progressing rapidly with ARDS, AKI, acute cardiac injury, and shock, leading to a higher possibility of death. Therefore, it might still be useful to identify cases that are at risk of admission to ICU and would benefit from critical care rather than merely oxygen therapy plus the provision of antiviral drugs.

There are several limitations of this study. Firstly, only a few articles with limited sample sizes were found, and all of them were observational studies and two studies were preprint, which may affect the quality of the present study. Secondly, non-severe cases that were not admitted to the hospital were ruled out in the analyses. This inclusion might have biased the discriminative value of measures for severe cases. Thirdly, since we have found no related studies focusing on patients of other races, the demonstration of the effect of the present study was limited to Chinese patients with COVID-19. Fourthly, some date on the grouping of severe and non-severe cases were missing because they were not measured or no reported in the included studies, which may lead to a lack of power or selective outcome reporting. Finally, although the funnel plots and Begg's test did not show publication bias, we could not rule out the possibility of publication bias as the number of included studies were small. However, the data in this study permit an early

Annals of Translational Medicine, Vol 8, No 9 May 2020

assessment of the clinical and laboratory characteristics to predict severe cases of COVID-19.

Conclusions

Severe patients with COVID-19 had more risk of clinical characteristics (age, dyspnea, vomiting or diarrhea, creatinine >104 µmol/L, procalcitonin ≥ 0.05 ng/mL, lymphocyte count $<1.5\times10^{9}$ /L and bilateral involvement of chest CT) and multiple system organ complications (acute cardiac injury, ARDS, AKI, and shock). Even received more main interventions (antiviral and corticosteroids therapy, as well as CRRT and invasive mechanical ventilation), the mortality was extremely higher in severe patients than non-severe cases. Early identification and efforts to explore effective therapy for critically ill cases are a crucial concern.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at http://dx.doi. org/10.21037/atm-20-2124). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Huang et al. Clinical features of severe COVID-19

Page 10 of 10

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		Severe		No	on-severe			Mean Difference		Mear	Differe	nce	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Ra	ndom, 9	5% CI	
Chaolin Huang 2020	49	14.826	13	49	11.8608	28	10.5%	0.00 [-9.18, 9.18]			+		
DaweiWang 2020	66	15.5673	36	51	18.5325	102	17.7%	15.00 [8.77, 21.23]					
Wei-jie Guan 2020	52	18.5325	173	45	17.0499	926	31.8%	7.00 [4.03, 9.97]					
Yang Yang 2020	55	15	935	45	15	2563	39.9%	10.00 [8.88, 11.12]					
Total (95% CI)			1157			3619	100.0%	8.87 [5.42, 12.32]				٠	
Heterogeneity: Tau ² =				(P = 0.0	01); l² = 71	1%			-20	-10	0	10	20
Test for overall effect:	2 = 5.04	(P < 0.00	001)							Seve	ere Non	-severe	

Figure S1 Forest plots of comparison severe versus non-severe cases for age.

	Severe	Э	Non-se	/ere		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Chaolin Huang 2020	11	13	19	28	2.3%	2.61 [0.47, 14.30]	
DaweiWang 2020	22	36	53	102	9.8%	1.45 [0.67, 3.15]	
Wei-jie Guan 2020	100	173	540	926	32.8%	0.98 [0.70, 1.36]	
Yang Yang 2020	575	935	1438	2730	55.1%	1.44 [1.23, 1.67]	-
Total (95% CI)		1157		3786	100.0%	1.29 [0.99, 1.67]	◆
Total events	708		2050				
Heterogeneity: Tau ² =	0.03; Chi ² =	= 4.90,	df = 3 (P	= 0.18)	; l ² = 39%	-	
Test for overall effect:							0.1 0.2 0.5 1 2 5 10 Severe Non-severe

Figure S2 Forest plots of comparison severe versus non-severe cases for gender.

	Sever	e	Non-se	vere		Odds Ratio		0	dds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	М-Н,	Fixed, 95%	CI	
Chaolin Huang 2020	13	13	27	28	1.0%	1.47 [0.06, 38.60]			· · ·		_
Chen Lei 2020	14	14	14	15	0.7%	3.00 [0.11, 79.91]					
DaweiWang 2020	36	36	100	102	1.1%	1.82 [0.09, 38.73]			<u> </u>		
Wei-jie Guan 2020	82	173	391	926	97.3%	1.23 [0.89, 1.71]					
Total (95% CI)		236		1071	100.0%	1.25 [0.91, 1.73]			•		
Total events	145		532								
Heterogeneity: Chi ² = 0).35, df = 3	3 (P = 0).95); l ² =	0%						10	100
Test for overall effect: 2	Z = 1.39 (I	P = 0.1	7)				0.01	0.1 Sev	ere Non-s	10 evere	100

Figure S3 Forest plots of comparison severe versus non-severe cases for fever.

	Sever	e	Non-se	vere		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95%	6 CI	
Chaolin Huang 2020	0	13	3	28	5.7%	0.27 [0.01, 5.62]				
Chen Lei 2020	2	14	0	15	1.0%	6.20 [0.27, 141.32]				\rightarrow
DaweiWang 2020	3	36	6	102	7.4%	1.45 [0.34, 6.15]		<u> </u>		
Wei-jie Guan 2020	26	173	124	926	85.8%	1.14 [0.72, 1.81]				
Total (95% CI)		236		1071	100.0%	1.17 [0.77, 1.78]		•		
Total events	31		133							
Heterogeneity: Chi ² = 2	.09, df = 3	3 (P = 0).55); l ² =	0%			0.01 0.1		10	100
Test for overall effect: 2	z = 0.73 (I	P = 0.4	6)				0.01 0.1	Severe Non-s	10 evere	100

Figure S4 Forest plots of comparison severe versus non-severe cases for headache.

	Seve	re	Non-se	vere		Odds Ratio		(Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Random, 95% Cl		M-H, I	Random, 9	5% CI	
Chaolin Huang 2020	12	13	10	28	11.1%	21.60 [2.44, 191.38]					
DaweiWang 2020	23	36	20	102	36.1%	7.25 [3.14, 16.76]			1.	-	
Wei-jie Guan 2020	65	173	139	926	52.8%	3.41 [2.39, 4.87]			1	-	
Total (95% CI)		222		1056	100.0%	5.50 [2.45, 12.33]			-		
Total events	100		169								
Heterogeneity: Tau ² =	0.29; Chi ²	= 5.08	, df = 2 (P	= 0.08); l ² = 61%		0.01	0.1		10	100
Test for overall effect:	Z = 4.13 (P < 0.0	001)				0.01	0.1 Se	vere Non-	10 severe	100

Figure S5 Forest plots of comparison severe versus non-severe cases for dyspnea.

	Severe Non-sev			vere		Odds Ratio	Odds Ratio				
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% C	1	M-H. Fixed, 95% CI			
Chaolin Huang 2020	0	13	1	28	3.7%	0.68 [0.03, 17.80]					
DaweiWang 2020	9	36	10	102	15.5%	3.07 [1.13, 8.32]			_		
Wei-jie Guan 2020	22	173	74	926	80.7%	1.68 [1.01, 2.78]					
Total (95% CI)		222		1056	100.0%	1.86 [1.19, 2.89]			•		
Total events	31		85								
Heterogeneity: Chi ² =	1.49, df = :	2(P = 0)	0.47); l ² =	0%			0.01	0.1	-	10	100
Test for overall effect:	Z = 2.74 (P = 0.0	06)				0.01	0.1 Se	vere Non-s	10 evere	100

Figure S6 Forest plots of comparison severe versus non-severe cases for vomiting and diarrhea.

	Sever	re	Non-severe			Odds Ratio		Odds Ratio			
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% C	M-H. Fixed. 95% CI				
Chaolin Huang 2020	7	13	11	28	6.4%	1.80 [0.48, 6.81]			-		
DaweiWang 2020	12	36	36	102	24.9%	0.92 [0.41, 2.05]			_		
Wei-jie Guan 2020	30	173	133	926	68.7%	1.25 [0.81, 1.93]					
Total (95% CI)		222		1056	100.0%	1.20 [0.83, 1.74]			•		
Total events	49		180								
Heterogeneity: Chi ² =	0.83, df = :	2 (P = (0.66); l ² =	0%			0.01	0.1		10	100
Test for overall effect:	Z = 0.99 (I	P = 0.3	2)				0.01	0.1 Se	vere Non-	10 severe	100

Figure S7 Forest plots of comparison severe versus non-severe cases for myalgia or arthralgia.

	Seve	re	Non-se	vere		Odds Ratio		Odds Ratio			
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Fixed, 95% Cl	i	M-H	CI		
Chaolin Huang 2020	11	13	15	28	5.2%	4.77 [0.89, 25.57]					-
Wei-jie Guan 2020	102	154	228	736	94.8%	4.37 [3.02, 6.32]					
Total (95% CI)		167		764	100.0%	4.39 [3.06, 6.30]					
Total events	113		243								
Heterogeneity: Chi ² =	0.01, df =	1 (P = (0.92); l ² =	0%			0.01	0.1	1	10	100
Test for overall effect:	0001)				0.01	0.1 Se	evere Non-se	10 evere	100		

Figure S8 Forest plots of comparison severe versus non-severe cases for lymphocyte count <1.5*10^9/L.

	Seve	re	Non-se	vere		Odds Ratio		Odds Ratio			
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% Cl		M-H. Random, 95% CI			
Chaolin Huang 2020	1	13	9	28	43.9%	0.18 [0.02, 1.57]		-			
Wei-jie Guan 2020	102	167	228	811	56.1%	4.01 [2.84, 5.68]			-		
Total (95% CI)		180		839	100.0%	1.02 [0.05, 22.09]					
Total events	103		237								
Heterogeneity: Tau ² =	4.37; Chi ²	= 7.84	, df = 1 (P	= 0.005	5); l ² = 879	16	- 01	01		100	
Test for overall effect:	Z = 0.01 (I	P = 0.9	9)				0.01	0.1 Seve	1 10 ere Non-severe	100	

Figure S9 Forest plots of comparison severe versus non-severe cases for white blood cell count <4*10^9/L.

	Sever	Severe Non-severe				Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		M-H. Random, 95% Cl		
Chaolin Huang 2020	3	12	0	27	6.8%	20.26 [0.96, 429.41]				\rightarrow
Chen Lei 2020	0	14	0	15		Not estimable				
DaweiWang 2020	27	36	22	102	41.9%	10.91 [4.48, 26.56]				
Wei-jie Guan 2020	16	117	19	516	51.4%	4.14 [2.06, 8.33]				
Total (95% CI)		179		660	100.0%	6.92 [3.02, 15.86]			•	
Total events	46		41							
Heterogeneity: Tau ² = 0).22; Chi ²	= 3.47	, df = 2 (P	= 0.18)	; l ² = 42%		L 01		1 10	100
Test for overall effect: Z	z = 4.57 (I	P < 0.0	0001)				0.01	0.1 Severe	1 10 Non-severe	100

Figure S10 Forest plots of comparison severe versus non-severe cases for procalcitonin ≥0.05 ng/mL.

	Sever	e	Non-sev	/ere		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95%	CI	
Chaolin Huang 2020	2	13	2	28	22.2%	2.36 [0.29, 18.97]				
Chen Lei 2020	2	14	2	15	34.2%	1.08 [0.13, 8.95]		-		
Wei-jie Guan 2020	6	138	6	614	43.6%	4.61 [1.46, 14.51]				
Total (95% CI)		165		657	100.0%	2.90 [1.16, 7.26]				
Total events	10		10							
Heterogeneity: Chi ² = 1	.50, df = 2	2 (P = 0		0.01 0.1	1	10	100			
Test for overall effect: 2	Z = 2.28 (F	P = 0.02	2)				0.01 0.1	Severe Non-s		100

Figure S11 Forest plots of comparison severe versus non-severe cases for serum creatinine >104 µmol/L.

	Sever	evere Non-severe				Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H	I. Fixed, 95%	6 CI	
Chaolin Huang 2020	13	13	27	28	2.6%	1.47 [0.06, 38.60]					_
DaweiWang 2020	36	36	102	102		Not estimable				_	
Wei-jie Guan 2020	137	173	368	926	97.4%	5.77 [3.91, 8.52]					
Total (95% CI)		222		1056	100.0%	5.66 [3.84, 8.34]				•	
Total events	186		497								
Heterogeneity: Chi ² = 0	Heterogeneity: Chi ² = 0.66, df = 1 (P = 0.42); l ² = 0%									10	100
Test for overall effect: Z = 8.77 (P < 0.00001)								0.1 Se	evere Non-s	10 severe	100

Figure S12 Forest plots of comparison severe versus non-severe cases for bilateral involvement of chest CT.