The Clinical Characteristics and Risk Factors of Severe COVID-19

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Keywords

Coronavirus disease 2019 · Severe acute respiratory syndrome-CoV-2 · 2019-nCoV · Coronavirus · Pandemic

Abstract

Objective: We aim to investigate the clinical characteristics and risk factors for the severe cases of coronavirus disease 2019 (COVID-19) in comparison with the non-severe patients. **Methods:** We searched PubMed, EMBASE, Web of Science, and CNKI to collect all relevant studies published before July 26, 2020, and a total of 30 papers were included in this meta-analysis. **Results:** In the severe COVID-19 patients, 60% (95% CI = 56–64%) were male, 25% (95% CI = 21–29%) were over 65 years old, 34% (95% CI = 24–44%) were obese, and 55% (95% CI = 41–70%) had comorbidities. The most prevalent comorbidities were hypertension (34%, 95% CI = 25–44%), diabetes (20%, 95% CI = 15–25%), and cardiovascular disease (CVD; 12%, 95% CI = 9–16%). The most common blood test abnormalities were elevated C-reactive protein (CRP; 87%, 82–92%), decreased lymphocyte count (68%, 58–77%), and increased lactate dehydrogenase (69%, 95% CI = 57–81%). In addition, abnormal laboratory findings revealing organ dysfunctions were frequently observed in the severe cases, including decrease in albumin (43%, 95% CI = 24–63%) and increase in aspartate aminotransferase (47%,

95% CI = 38–56%), alanine aminotransferase (28%, 95% CI = 16–39%), troponin I/troponin T (TnI/TnT; 29%, 95% CI = 13–45%), and serum Cr (SCr; 10%, 95% CI = 5–15%). **Conclusion:** The male, elderly and obese patients and those with any comorbidities, especially with hypertension, diabetes, and CVD, were more likely to develop into severe cases. But the association between hypertension, diabetes, CVD, and severity of COVID-19 was declined by the increase of age. A significant elevation in cardiac TnI/TnT, the hepatic enzymes, and SCr and the reduction in lymphocytes with elevated CRPs are important markers for the severity. Specific attention should be given to the elderly male and obese patients and those with indications of severe immune injury in combination with bacterial infection and indication of multi-organ dysfunction or damages.

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Introduction

In early December 2019, the coronavirus disease 2019 (COVID-19) broke out in Wuhan, China, and shortly reported over the world [1–4]. COVID-19 was caused by a previously unknown betacoronavirus, named 2019-nCoV or severe acute respiratory syndrome (SARS)-CoV-2 [5]. In this pandemic, the urban medical facilities

in many countries have been overwhelmed with the treatment of severe cases [6]. Understanding the clinical characteristics and the risk factors of severe cases is critically important to improve the efficacy and outcome for the COVID-19 treatment. More and more studies have been published during the COVID-19 crisis. Here, we collected all relevant publications up to July 26, 2020, to reveal the clinical characteristics and the risk factors of severe COVID-19 to help identifying patients who are likely to develop to severe cases.

Methods

Protocol and Search Strategy

Our study followed PRISMA statement. We searched all relevant papers from PubMed, EMBASE, Web of Science, and CNKI with the following keywords: “2019-nCoV,” “COVID-19,” or “SARS-CoV-2” and “clinical characteristics,” “clinical finding,” “clinical feature,” “clinical study,” or “clinical case.” The search period was updated to July 26, 2020. Then 2 researchers did a further artificial selection to screen eligible papers independently.

The Inclusive and Exclusive Criteria

In this article, we focused on the clinical characteristics of severe patients with COVID-19 and the differences between the severe and non-severe COVID-19 patients. The studies on observation of clinical characteristics in severe and non-severe patients with COVID-19 were included, and studies without severe patients' data or the comparison between the severe and non-severe patients or lack of clear diagnostic criteria were excluded.

The severe patients in our article included the patients hospitalized in intensive care unit and the severe/critical patients defined by the seventh guideline for the diagnosis and treatment of COVID-19 issued by the Chinese National Health Commission & State Administration of Traditional Chinese Medicine. Because of the difficulty of obtaining original data, the classification was achieved based on the authors' statement presented in papers.

The severe illness of COVID-19 was defined if satisfying at least one of the following criteria: (a) breathing rate ≥ 30 /min; (b) pulse oximeter oxygen saturation $\leq 93\%$ at rest; or (c) ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ≤ 300 mm Hg (1 mm Hg = 0.133 kPa). Critical illness was defined if satisfying at least one of the following criteria: (a) respiratory failure with required mechanical ventilation; (b) shock; or (c) failure of other organs and received medical care in the intensive care unit. The reference intervals of laboratory findings varied in different studies, which was presented in online supplementary Table S1 (see www.karger.com/doi/10.1159/000513400 for all online suppl. material).

Data Extraction

The papers we searched and screened were imported to End-Note (version 8) to remove all duplicates. We then screened the titles and abstracts of retrieved papers in the list. All useful data were extracted in a form after reading the full text. Due to the reality in clinical practice and ethical restrictions, all included studies were cross-sectional studies.

Statistical Analysis

Based on the selected articles and available data, we did a single-arm meta-analysis to summarize the most common clinical characteristics in the severe patients with COVID-19 and another meta-analysis to compare the differences of clinical manifestations and laboratory findings between the severe and non-severe COVID-19 patients. We used R (version 3.6.1) to calculate pooled estimated prevalence with 95% confidence intervals of basic characteristics, comorbidities, and laboratory findings, and Stata (version 12.0) was used to calculate OR and 95% CI to estimate every indicator of each paper. A random-effect model was used to calculate the combined ORs and its 95% CI. Cochran's Q test and I^2 statistics were used to evaluate the heterogeneity. Random-effects meta-regression was conducted to assess the effect of age on the association of comorbidities with severity of COVID-19. Sensitivity analyses were used to evaluate risk of bias and stability of the results. Egger's test was used to assess publication bias in which $p < 0.05$ indicated a significant publication bias.

Results

Literature Summary

We retrieved a total of 637 papers. 292 repetitive papers were removed and 131 papers were excluded after screening the titles and abstracts. 182 articles were eliminated due to lack of a comparison between non-severe and severe COVID-19 patients, short of original data or diagnosis criteria. At the end, 30 papers were included in our meta-analysis [1], [7–35]. The screening process was shown in Figure 1. The detailed information about basic characteristics, underlying diseases, and laboratory findings was summarized in Tables 1 and 2 and online supplementary Tables S1 and S2.

Because of the reality in clinical practice and medical ethics, all included studies are case series studies. A total of 6,685 individuals were involved in our study with the sample size ranging from 41 to 1,099.

Meta-Analysis Results

The Clinical Characteristics of Severe COVID-19

A total of 1,457 severe COVID-19 patients were included in this meta-analysis. In the severe COVID-19 patients, 60% (95% CI = 56–64%) were male, 25% (95% CI = 21–29%) were over 65 years old, 34% (95% CI = 24–44%) were obese, and 55% (95% CI = 41–70%) had comorbidities. The most prevalent comorbidities were hypertension (34%, 95% CI = 25–44%), diabetes (20%, 95% CI = 15–25%), and cardiovascular disease (CVD; 12%, 95% CI = 9–16%). For laboratory findings, the prevalence of elevated C-reactive protein (CRP) was 87% (82–92%), decreased lymphocyte count was 68% (58–77%), and increased lactate dehydrogenase (LDH) was 69%

Fig. 1. Flow diagram of the retrieval process.

(95% CI = 57–81%). In addition, significant decrease in albumin (43%, 95% CI = 24–63%) and increase in aspartate aminotransferase (AST; 47%, 95% CI = 38–56%), alanine aminotransferase (ALT; 28%, 95% CI = 16–39%), troponin I/troponin T (TnI/TnT; 29%, 95% CI = 13–45%), and serum Cr (SCr; 10%, 95% CI = 5–15%) were observed (Table 3).

The Differences of Clinical Characteristics between Severe and Non-severe Groups

As shown in Table 4, male (OR = 1.383, 95% CI = 1.183–1.616), age over 65 years old (OR = 2.250, 95% CI = 1.677–3.017), and obesity (OR = 2.519, 95% CI = 1.498–4.235) were associated with increased severity of COVID-19. The prevalence of comorbidity, such as hypertension, CVD, and diabetes in the severe patients was significantly higher (OR = 2.661, 95% CI = 1.700–4.163; OR = 2.041, 95% CI = 1.591–2.619; OR = 2.264, 95% CI = 1.705–3.007; OR = 2.156, 95% CI = 1.651–2.815) than non-severe cases. In the severe patients, increase in white blood cell count (OR = 2.784, 95% CI = 1.878–4.125) and decrease in lymphocyte (OR = 2.054, 95% CI = 1.641–2.571) and platelet count (OR = 1.852, 95% CI = 1.602–2.142) were common. Furthermore, the incidence rate of decreased albumin (OR = 2.257, 95% CI =

1.562–3.262) and increased levels of CRP (OR = 1.495, 95% CI = 1.353–1.652), procalcitonin (OR = 2.403, 95% CI = 1.727–3.343), AST (OR = 2.356, 95% CI = 1.917–2.896), ALT (OR = 1.857, 95% CI = 1.389–2.483), LDH (OR = 1.744, 95% CI = 1.384–2.199), TnI/TnT (OR = 4.707, 95% CI = 2.234–9.917), and SCr (OR = 2.245, 95% CI = 1.474–3.421) was significantly higher in the severe patients.

The Result of Meta-regression

The meta-regression analysis with age as a covariate indicated that age declined the association between hypertension ($p = 0.027$), diabetes ($p = 0.001$), CVD ($p = 0.003$), and severity of COVID-19.

Heterogeneity Test, Sensitivity Analysis and Publication Bias

We observed significant heterogeneity (I^2) varying from 52.1 to 96.2% in meta-analysis of the clinical characteristics of severe COVID-19 (Table 3). Significant publication bias ($p < 0.05$) was observed in the prevalence of CVD, increased white blood cells, increased CRP, and increased serum Cr (as shown in Table 3).

As for meta-analysis of the differences between severe and non-severe patients, heterogeneity varied from 0.0 to

Table 1. The basic characteristics and comorbidities of patients with COVID-19

Studies	Disease severity	Patients, <i>n</i>	Age, <i>n</i> (%)			Sex (male) <i>n</i> (%)	Obesity ^a <i>n</i> (%)	Comorbidity <i>n</i> (%)	Hypertension <i>n</i> (%)	Diabetes <i>n</i> (%)	CVD <i>n</i> (%)	Ref.
			>50 yr	>60 yr	>65 yr							
Guan, Weijie	Severe Non-severe	173 926	- -	- -	44/163 (27.0) 109/848 (12.9)	100 (57.8) 540 (58.3)	- -	67 (38.7) 194 (21.0)	41 (23.7) 124 (13.4)	28 (16.2) 53 (5.7)	10 (5.8) 17 (1.8)	[1]
Huang, Chaolin	Severe Non-severe	13 28	- -	- -	- -	11 (84.6) 19 (67.9)	- -	5 (38%) 8 (29%)	2 (15%) 4 (14%)	1 (8%) 7 (25%)	3 (23%) 3 (11%)	[7]
Zhang, Jinjin	Severe Non-severe	58 82	48 (82.8) 50 (61.0)	- -	- -	33 (56.9) 38 (46.3)	- -	46 (79.3) 44 (53.7)	22 (37.9) 20 (24.4)	8 (13.8) 9 (11.0)	4 (6.9) 3 (3.7)	[8]
Xu, Yuhuan	Severe Non-severe	13 37	5 (38.5) 10 (27.0)	- -	- -	7 (53.8) 22 (59.5)	- -	- -	- -	- -	- -	[9]
Li, Kunhua	Severe Non-severe	25 58	- -	- -	- -	15 (60) 29 (50)	- -	11 (44.0) 4 (6.9)	2 (8.0) 3 (5.2)	7 (28.0) 0 (0.0)	1 (4.0) 0 (0.0)	[10]
Wan, Suxin	Severe Non-severe	40 95	- -	- -	- -	21 (52.5) 52 (54.7)	- -	28 (70) 15 (16.3)	4 (10) 9 (9.4)	9 (22.5) 3 (3.1)	6 (15) 1 (1)	[11]
Cai, Qingxian	Severe Non-severe	58 240	50 (86.21) 88 (36.67)	- -	- -	39 (67.24) 106 (44.17)	- -	- -	22 (37.9) 25 (10.4)	8 (13.79) 13 (22.41)	12 (5.0)	[12]
Zhang, Gemin	Severe Non-severe	32 63	- -	7 (21.9) 10 (15.9)	- -	21 (65.6) 32 (50.8)	- -	- -	- -	- -	- -	[13]
Zheng, F.	Severe Non-severe	30 131	- -	- -	- -	14 (46.7) 66 (50.4)	- -	- -	12 (40) 10 (7.6)	2 (6.7) 5 (3.8)	2 (6.7) 2 (1.5)	[14]
Cheng, Kebin	Severe Non-severe	181 282	- -	- -	42 (23.2) 36 (12.77)	99 (54.7) 145 (51.42)	- -	- -	53 (29.28) 54 (19.15)	20 (11.05) 20 (7.09)	16 (8.84) 12 (4.26)	[15]
Xiao, Kaihu	Severe Non-severe	36 107	- -	- -	- -	20 (55.6) 52 (48.6)	- -	17 (47.2) 29 (27.1)	5 (13.9) 12 (11.2)	5 (13.9) 5 (4.7)	2 (5.6) 3 (2.8)	[16]
Yuan, Jing	Severe Non-severe	31 192	- -	- -	- -	18 (58.1) 88 (45.8)	- -	14 (45.2) 40 (20.8)	4 (12.9) 21 (10.9)	8 (25.8) 10 (5.2)	0 (0) 1 (0.5)	[17]
He, Xingwei	Severe	54	-	-	-	34 (63.0)	-	-	24 (44.4)	13 (24.1)	5 (9.3)	[18]
Deng, Qing	Severe Non-severe	67 45	- -	- -	- -	38 (56.7) 19 (42.2)	28 (41.8) 13 (28.9)	- -	24 (35.8) 12 (26.7)	14 (20.9) 5 (11.1)	11 (16.4) 4 (8.9)	[19]
Yao, Qingchun	Severe Non-severe	25 83	- -	- -	9/25 (36.0) 8/83 (9.6)	13 (52.0) 30 (36.1)	- -	13 (52.0) 12 (14.5)	9 (36.0) 7 (8.4)	3 (12.0) 2 (2.4)	2 (8.0) 2 (2.4)	[20]
Xu, Jing	Severe Non-severe	30 125	- -	- -	- -	20 (66.7) 67 (53.6)	- -	12 (40.0) 16 (12.8)	- -	- -	- -	[21]
Asghar, M.S.	ICU Ward	33 67	- -	- -	- -	- -	- -	- -	- -	- -	- -	[22]
Cao, Zhenhuan	Severe Non-severe	27 53	- -	- -	- -	16 (59.3) 22 (41.5)	- -	- -	4 (14.8) 16 (30.2)	3 (11.1) 3 (5.7)	5 (18.5) 5 (9.4)	[23]

Table 1 (continued)

Studies	Disease severity	Patients, <i>n</i>	Age, <i>n</i> (%)			Sex (male) <i>n</i> (%)	Obesity ^a <i>n</i> (%)	Comorbidity <i>n</i> (%)	Hypertension <i>n</i> (%)	Diabetes <i>n</i> (%)	CVD <i>n</i> (%)	Ref.
			>50 yr	>60 yr	>65 yr							
Pellaud, Charlotte	ICU	49	-	34 (70.0)	-	30 (61.0)	28 (19)	40 (82.0)	27 (55)	11 (22)	6 (12)	[24]
	Ward	147		114 (77.0)		89 (60.0)	13 (27)	122 (83.0)	91 (62)	41 (28)	20 (14)	
Chen, Qingqing	Severe	43	-	34 (70.0)	-	23 (53.5)			9 (20.9)	7 (16.3)		[25]
	Non-severe	102		114 (77.0)		56 (54.9)			13 (12.7)	7 (6.9)		
Liu, Changquan	Severe	42				28 (66.7)		41 (97.6)				[26]
	Non-severe	236				102 (43.2)		197 (83.5)				
EBinger, Joseph E.	ICU	77				57 (74.0)	17 (22.1)		49 (63.6)	26 (33.8)	18 (23.4)	[27]
	Ward	137				78 (56.9)	27 (19.7)		68 (49.6)	40 (29.2)	27 (19.7)	
Hong, Kyung Soo	ICU	13			6 (46.2)	6 (46.2)		5 (38.5)	5 (38.5)	3 (23.1)	0 (0)	[28]
	Not-ICU	85			23 (27.1)	32 (37.6)		33 (38.8)	25 (29.4)	6 (7.1)	11 (12.9)	
Huang, Rui	Severe	23			5 (21.7)	17 (73.9)	8 (44.4)	9 (39.1)	2 (8.7)	8 (34.8)	1 (4.3)	[29]
	Non-severe	179			21 (11.7)	99 (55.3)	16 (10.4)	46 (25.7)	27 (15.1)	11 (6.1)	6 (3.3)	
Liu, Fang	Severe	33				8 (24.2)			22 (66.7)	12 (36.4)	13 (39.4)	[30]
	Non-severe	107				41 (38.3)			41 (38.3)	22 (20.6)	22 (20.6)	
Shahriarirad, Reza	ICU	11			3 (27.3)	7 (63.6)		7 (63.6)	5 (45.5)	3 (27.3)	4 (36.4)	[31]
	Not-ICU	102			25 (24.5)	64 (62.7)			17 (16.7)	13 (12.7)	12 (11.8)	
Geehan, Suleyman	ICU	141			92 (65.3)	80 (56.7)	37 (26.2)		111 (78.7)	73 (51.8)	26 (18.4)	[32]
	Not-ICU	214			110 (51.4)	85 (39.7)	38 (17.8)		147 (68.7)	83 (38.8)	30 (14.0)	
Zheng, Yufen	Severe	29				16 (55.2)		11 (37.9)				[33]
	Non-severe	112				58 (51.7)		58 (51.8)				
Almazeedi, Sulaiman	ICU	42				32 (76.2)			17 (40.5)	18 (42.9)	8 (19.0)	[34]
	Not-ICU	1,054				856 (81.2)			160 (15.2)	137 (13.0)	33 (3.1)	
Cao, Min	ICU	19			15 (78.9)	17 (89.5)			6 (31.6)	2 (10.5)	5 (26.3)	[35]
	Not-ICU	179			54 (30.1)	84 (46.9)			36 (20.1)	13 (7.3)	7 (3.9)	
COVID-19, coronavirus disease 2019; ICU, intensive care unit. ^a Obesity: BMI >30 or 28 kg/m ² (China).												

Table 2. The laboratory findings in patients with COVID-19

Studies	Disease severity	Patients, n	N (%)		Platelet ↓	Lymphocytes ↓ ²	CRP ↑	PCT ↑	Albumin ↓	ALT ↑	AST ↑	LDH ↑	TnI/TnT ↑	SCr ↑	Ref
			WBC ↑	WBC ↓											
Guan, Weijie	Severe	173	19/167 (11.4)	147/153 (96.1)	90/156 (57.7)	110/135 (81.5)	16/117 (13.7)	38/135 (28.1)	56/142 (39.4)	120/606 (19.8)	112/615 (18.2)	72/124 (58.1)	-	6/138 (4.3)	[1]
	Non-severe	926	39/811 (28.1)	584/726 (80.4)	225/713 (31.6)	371/685 (54.2)	19/516 (3.7)	19/516 (3.7)	112/615 (18.2)	120/606 (19.8)	112/615 (18.2)	72/124 (58.1)	-	6/14 (1.0)	
Huang, Chaolin	Severe	13	7/13 (54)	11/13 (85)	1/13 (8)	1/13 (8)	-	3/13 (25)	-	-	8/13 (62)	12/13 (92)	4 (31)	2 (15)	[7]
	Non-severe	28	5/27 (19)	15/28 (54)	1/27 (4)	1/27 (4)	-	0/27	-	-	7/28 (25)	17/27 (63)	1 (4)	2 (7)	
Zhang, Jinjin	Severe	58	13/56 (23.2)	46/56 (82.1)	-	-	53/55 (96.4)	-	-	-	-	-	-	-	[8]
	Non-severe	82	4/82 (4.9)	58/82 (70.7)	-	-	72/81 (88.9)	-	-	-	-	-	-	-	
Xu, Yuhuan	Severe	13	-	6 (46.1)	-	8 (61.5)	-	-	-	-	-	-	-	-	[9]
	Non-severe	37	-	8 (21.6)	-	18 (48.6)	-	-	-	-	-	-	-	-	
Li, Kunhua	Severe	25	4 (16.0)	22 (88.0)	-	23 (92.0)	21 (84.0)	23 (39.7)	-	-	-	-	-	-	[10]
	Non-severe	58	5 (8.6)	22 (37.9)	-	27 (46.6)	23 (39.7)	-	-	-	-	-	-	-	
Wan, Suxin	Severe	40	3 (7.5)	32 (80)	12 (30)	32 (80)	-	1 (2.5)	-	-	15 (37.5)	30 (75)	-	3 (7.5)	[11]
	Non-severe	95	6 (7)	36 (38)	11 (11.6)	36 (38)	-	0 (0)	-	-	15 (16)	28 (29)	-	3 (3)	
Cai, Qingxian	Severe	58	-	39 (67.2)	-	54 (93.1)	-	-	14 (24.1)	20 (34.5)	-	-	15 (25.9)	-	[12]
	Non-severe	240	-	75/235 (31.9)	-	142/233 (60.9)	-	-	11/240 (4.6)	19/240 (7.9)	-	-	5 (2.1)	-	
Zhang, Gemin	Severe	32	24 (75)	9 (28.1)	5 (15.6)	32 (100)	-	-	-	24 (75.0)	20 (75)	31 (96.9)	-	8 (25)	[13]
	Non-severe	63	1 (1.6)	2 (3.2)	6 (9.5)	47 (74.6)	-	-	-	28 (44.4)	28 (44.4)	43 (68.3)	-	14 (22.2)	
Zheng, F.	Severe	30	0 (0)	13 (43.3)	3 (10)	30 (100)	-	-	-	5 (16.7)	12 (40)	15 (50)	-	1 (3.3)	[14]
	Non-severe	131	3 (2.3)	29 (22.1)	8 (6.1)	91 (69.5)	-	-	-	8 (6.1)	10 (7.6)	23 (17.6)	-	1 (0.8)	
Cheng, Kebing	Severe	181	34 (18.78)	113 (62.43)	28 (15.47)	142 (78.45)	-	-	65 (35.91)	-	-	128 (70.72)	10/179 (5.59)	9 (4.97)	[15]
	Non-severe	282	22 (7.8)	135 (47.87)	23 (8.16)	170 (60.28)	-	-	60 (21.28)	-	-	132 (47.65)	6/260 (2.31)	5 (1.77)	
Xiao, Kaihu	Severe	36	1 (2.8)	20 (55.6)	-	29 (80.6)	3 (8.3)	-	-	-	-	15 (41.7)	-	-	[16]
	Non-severe	107	4 (3.7)	46 (43)	-	43 (40.1)	1 (0.9)	-	-	-	-	28 (26.2)	-	-	
Yuan, Jing	Severe	31	3 (9.7)	17 (54.8)	-	-	-	-	18 (58.1)	-	12 (38.7)	24 (77.4)	-	-	[17]
	Non-severe	192	5 (2.6)	30 (15.6)	-	-	-	-	45 (23.4)	-	20 (10.4)	35 (18.2)	-	-	
He, Xingwei	Severe	54	-	-	-	-	-	-	-	-	-	-	-	-	[18]
	Non-severe	45	-	-	-	-	-	-	-	-	-	-	-	-	
Deng, Qing	Severe	67	-	-	-	-	-	-	-	-	-	-	39 (58.2)	-	[19]
	Non-severe	45	-	-	-	-	-	-	-	-	-	-	3 (6.7)	-	
Yao, Qingchun	Severe	25	11/25 (44.0)	4 (16.0)	4 (16.0)	23 (92.0)	20 (80.0)	2 (8.0)	-	2 (8.0)	-	-	-	1 (4.0)	[20]
	Non-severe	83	1/83 (1.2)	6 (7.3)	6 (7.3)	46 (55.4)	41 (49.4)	4 (4.8)	-	4 (4.8)	-	-	-	3 (3.6)	
Xu, Jing	Severe	30	-	-	-	-	-	-	-	-	-	-	-	-	[21]
	Non-severe	125	-	-	-	-	-	-	-	-	-	-	-	-	
Asghar, M.S.	ICU	33	18/33 (54.5)	30/33 (90.9)	7/33 (21.2)	31/33 (93.9)	10/28 (35.7)	8/22 (36.4)	14/22 (63.6)	8/22 (36.4)	14/22 (63.6)	21/21 (100)	-	13/33 (39.4)	[22]
	Ward	67	11/63 (17.5)	27/63 (42.9)	7/63 (11.1)	45/59 (76.3)	2/8 (25.0)	14/55 (25.5)	18/55 (32.7)	14/55 (25.5)	18/55 (32.7)	33/40 (82.5)	-	6/67 (9.0)	
Hong, Kyung Soo	ICU	13	4 (30.8)	11 (84.6)	3 (23.1)	12 (100)	4 (33.3)	4 (33.3)	12 (92.3)	3 (23.1)	11 (84.6)	12 (100)	-	6 (46.2)	[28]
	Not-ICU	85	5 (5.9)	29 (34.1)	21 (24.7)	35 (43.2)	2 (2.4)	2 (2.4)	21 (25.3)	16 (18.8)	31 (36.5)	35 (43.2)	-	23 (23.1)	
Huang, Rui	Severe	23	6 (26.1)	11 (47.8)	-	12 (60)	10 (52.6)	35 (30.9)	-	-	-	0 (0.0)	-	-	[29]
	Non-severe	179	51 (28.5)	55 (30.7)	-	43 (34.6)	35 (30.9)	-	-	-	-	2 (2.2)	-	-	
Liu, Fang	Severe	33	-	-	-	31 (93.9)	5 (15.2)	3 (2.8)	-	-	-	-	-	-	[30]
	Non-severe	107	-	-	-	60 (56.1)	-	-	-	-	-	-	-	-	
Shahriariad, Reza	ICU	11	2 (18.2)	4 (36.4)	2 (18.2)	10 (90.9)	-	-	-	-	-	-	-	4 (36.4)	[31]
	Not-ICU	102	10 (9.8)5	10 (9.8)	10 (9.8)5	89 (87.3)	-	-	-	-	-	-	-	34 (33.5)	
Geethan, Suleyman	ICU	141	-	-	-	-	-	-	-	-	-	-	-	-	[32]
	Not-ICU	214	-	-	-	-	-	-	-	-	-	-	-	-	
Zheng, Yufen	Severe	29	2 (6.9)	24 (82.8)	7 (24.1)	-	-	-	-	-	-	-	-	-	[33]
	Non-severe	112	7 (6.3)	42 (37.5)	5 (4.4)	-	-	-	-	-	-	-	-	-	
Almazedi, Sulaiman	ICU	42	-	-	-	-	-	-	-	-	-	-	-	-	[34]
	Not-ICU	1,054	-	-	-	-	-	-	-	-	-	-	-	-	
Cao, Min	ICU	19	3 (15.8)	16 (84.2)	6 (31.6)	11 (78.6)	5 (26.3)	5 (26.3)	16 (84.2)	3 (15.8)	8 (42.1)	9 (47.4)	-	3 (15.8)	[35]
	Not-ICU	179	3 (1.7)	1 (0.6)	28 (16.1)	61 (40.1)	50 (28.6)	18 (10.2)	63 (35.8)	18 (10.2)	26 (14.8)	13 (7.4)	-	7 (4.1)	

COVID-19, coronavirus disease 2019; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TnI/TnT, troponin I; SCr, serum Cr. ¹ Increased means over the upper limit of the reference range. ² Decreased means below the lower limit of the reference range.

Table 3. The clinical characteristics of severe patients with COVID-19

Clinical characteristic	Studies, <i>n</i>	Subgroup	Prevalence	95% CI	Quantifying heterogeneity, %	Egger test
Male	29	Total Severe ICU	0.60 0.58 0.65	[0.56; 0.64] [0.55; 0.61] [0.60; 0.70]	52.1 45.9 59.1	0.9551
Age	3 5 4	>50 yr >60 yr >65 yr	0.74 0.52 0.25	[0.57; 0.92] [0.30; 0.73] [0.21; 0.29]	82.3 92.5 0.0	0.7839
Obesity	6	Total Severe ICU	0.34 0.35 0.34	[0.24; 0.44] [0.26; 0.44] [0.17; 0.52]	77.7 19.5 89.2	0.1885
Comorbidity	15	Total Severe ICU	0.55 0.54 0.60	[0.41; 0.70] [0.37; 0.72] [0.32; 0.87]	95.1 95.9 83.4	0.4874
Hypertension	24	Total Severe ICU	0.34 0.28 0.52	[0.25; 0.44] [0.21; 0.34] [0.38; 0.67]	93.2 82.6 86.3	0.0963
Diabetes	26	Total Severe ICU	0.20 0.15 0.31	[0.15; 0.25] [0.12; 0.19] [0.19; 0.43]	81.8 52.2 82.8	0.0523
CVD	24	Total Severe ICU	0.12 0.11 0.17	[0.09; 0.16] [0.07; 0.14] [0.10; 0.24]	74.8 72.3 65.1	0.0017
WBC increased	17	Total Severe ICU	0.22 0.20 0.30	[0.15; 0.30] [0.12; 0.28] [0.10; 0.50]	90.5 91.4 74.8	0.0134
Lymphocyte decreased	20	Total Severe ICU	0.68 0.65 0.78	[0.58; 0.77] [0.54; 0.77] [0.60; 0.95]	92.2 93.5 76.3	0.269
Platelet decreased	14	Total Severe ICU	0.20 0.19 0.23	[0.11; 0.30] [0.08; 0.31] [0.14; 0.33]	89.0 92.3 0.0	0.0789
CRP increased	18	Total Severe ICU	0.87 0.87 0.92	[0.82; 0.92] [0.81; 0.92] [0.86; 0.98]	82.0 86.0 0.0	0.0055
PCT increased	12	Total Severe ICU	0.32 0.34 0.24	[0.19; 0.44] [0.15; 0.53] [0.18; 0.30]	93.1 95.5 0.0	0.1314
LDH increased	11	Total Severe ICU	0.69 0.67 0.78	[0.57; 0.81] [0.53; 0.81] [0.50; 1.00]	91.8 93.0 84.8	0.1586
Albumin decreased	5	Total Severe ICU	0.43 0.50 0.38	[0.24; 0.63] [0.0; 1] [0.23; 0.53]	91.5 96.4 81.1	1
AST increased	10	Total Severe ICU	0.47 0.43 0.56	[0.38; 0.56] [0.35; 0.50] [0.29; 0.84]	66.9 40.0 83.6	0.0892
ALT increased	9	Total Severe ICU	0.28 0.31 0.21	[0.16; 0.39] [0.15; 0.45] [0.11; 0.31]	86.1 91.0 0.0	0.8348
TnI/TnT increased	7	Total Severe ICU	0.29 0.23 0.42	[0.13; 0.45] [0.06; 0.40] [0.34; 0.49]	96.2 95.6 0.0	0.2931
SCr increased	10	Total Severe ICU	0.10 0.06 0.29	[0.05; 0.15] [0.03; 0.08] [0.13; 0.46]	70.6 31.1 52.8	0.0095

COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TnI/TnT, troponin I/troponin T; SCr, serum Cr.

Table 4. The association of different patients' characteristics and clinical manifestations with increased severity of COVID-19

Clinical characteristic	Subgroup	Pooled OR	95% CI	I ² , %	p value	Egger test
Male	Total	1.383	1.183; 1.616	22.3	0.000	0.385
	Severe	1.306	1.144; 1.618	18.7	0.001	
	ICU	1.405	0.964; 2.047	39.0	0.077	
Age	>50 yr	4.153	1.426; 12.090	73.8	0.009	0.650
	>60 yr	1.841	0.905; 3.746	72.8	0.092	
	>65 yr	2.250	1.677; 3.017	0.0	0.000	
Obesity	Total	2.519	1.498; 4.235	81.7	0.000	0.198
	Severe	2.380	0.995; 5.695	71.6	0.051	
	ICU	1.267	0.706; 2.276	89.8	0.000	
Comorbidity	Total	2.661	1.700; 4.163	71.5	0.000	0.289
	Severe	3.258	1.955; 5.428	72.8	0.000	
	ICU	1.267	0.706; 2.276	8.2	0.427	
Hypertension	Total	2.041	1.591; 2.619	50.1	0.000	0.545
	Severe	2.170	1.586; 2.970	48.1	0.000	
	ICU	1.835	1.188; 2.833	56.8	0.006	
CVD	Total	2.264	1.705; 3.007	44.4	0.000	0.148
	Severe	2.353	1.815; 3.051	79.1	0.000	
	ICU	2.056	1.061; 3.983	0.0	0.033	
Diabetes	Total	2.156	1.651; 2.815	63.7	0.000	0.030
	Severe	2.569	1.906; 3.463	36.1	0.000	
	ICU	1.608	1.043; 1.043	76.8	0.032	
WBC increased	Total	2.784	1.878; 4.125	55.2	0.000	0.069
	Severe	2.530	1.546; 4.142	61.4	0.000	
	ICU	3.573	2.201; 5.800	0.1	0.000	
Lymphocyte decreased	Total	2.054	1.641; 2.571	91.7	0.000	0.094
	Severe	1.851	1.496; 2.289	89.9	0.000	
	ICU	4.262	1.817; 9.997	88.2	0.001	
Platelet decreased	Total	1.852	1.602; 2.142	0.0	0.000	0.635
	Severe	1.871	1.607; 2.178	0.0	0.000	
	ICU	1.680	1.037; 2.720	0.0	0.035	
CRP increased	Total	1.495	1.353; 1.652	79.3	0.000	0.009
	Severe	1.493	1.345; 1.658	77.8	0.000	
	ICU	1.523	1.087; 2.132	87.4	0.014	
PCT increased	Total	2.403	1.727; 3.343	54.7	0.000	0.002
	Severe	2.613	1.753; 3.894	57.2	0.000	
	ICU	2.151	0.930; 4.973	68.3	0.073	
Albumin decreased	Total	2.257	1.562; 3.262	69.9	0.000	0.585
	Severe	2.555	1.501; 4.350	77.2	0.001	
	ICU	1.352	0.260; 7.029	83.5	0.720	
ALT increased	Total	1.857	1.389; 2.483	41.1	0.000	0.645
	Severe	2.057	1.396; 3.032	60.6	0.000	
	ICU	1.407	0.830; 2.384	0.0	0.205	
AST increased	Total	2.356	1.917; 2.896	39.1	0.000	0.087
	Severe	2.468	1.810; 3.363	56.6	0.000	
	ICU	2.292	1.756; 2.990	0.0	0.000	
LDH increased	Total	1.744	1.384; 2.199	86.2	0.000	0.243
	Severe	1.860	1.487; 2.326	81.5	0.000	
	ICU	1.315	0.443; 3.901	96.3	0.622	
SCr increased	Total	2.245	1.474; 3.421	21.2	0.000	0.534
	Severe	2.003	1.247; 3.217	0.0	0.000	
	ICU	2.568	0.971; 6.792	66.8	0.057	
TnI/TnT increased	Total	4.707	2.234; 9.917	77.2	0.000	0.154
	Severe	6.034	2.758; 13.201	40.5	0.000	
	ICU	3.357	0.978; 11.520	90.2	0.054	

COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TnI/TnT, troponin I/troponin T; SCr, serum Cr.

91.7% (Table 4). Significant publication bias ($p < 0.05$) was observed in the prevalence of diabetes, increased CRP and procalcitonin (as shown in Table 4).

Sensitivity analysis was conducted by excluding any study, and the significant results remained unchanged. Detailed results of Egger's test were shown in Tables 3 and 4.

In summary of the meta-analysis results, the male, elderly, obese people, and patients with any comorbidities, especially with hypertension, diabetes, and CVD, were more likely to develop into severe cases. A significant percentage of severe patients had multi-organ dysfunctions or damages, including the damage of immune system.

Discussion/Conclusion

The original host of this virus is still not identified, although bats are the most possible suspect. A structural analysis study found that the SARS-CoV-2 external receptor-binding domain was similar to that of SARS-CoV. The angiotensin-converting enzyme 2 (ACE2) receptor in human cells is considered to be the binding site of SARS-CoV-2, which is also the cellular receptor for SARS coronavirus [36–38]. Further studies demonstrated that SARS-CoV-2 employed ACE2 for cell entry through the binding of the viral spike (S) proteins to cellular receptor ACE2 [39].

ACE2 is distributed in multiple organs, including the lungs, heart, kidneys, liver, and intestine [40–43]. Several studies found that in addition to the respiratory system, the damages in other systems might also be related to SARS-CoV-2 attack. Zheng et al. [44] reported that SARS-CoV-2 was responsible for acute cardiac injury and may be mediated by ACE2. In addition, Xiao et al. [45] reported that SARS-CoV-2 could infect the cytoplasm of gastric, duodenal, and rectum glandular epithelial cell. Also, the liver impairment might be directly caused by the viral infection or due to drug hepatotoxicity [46]. Furthermore, SARS-CoV-2 infection also promotes secretion of inflammatory cytokines and systemic inflammatory response, and in some cases leading to inflammatory storm. A recent autopsy revealed the deep airway inflammation, alveoli damage, exudative inflammation, and the hydropericardium and myocardial changes due to SARS-CoV-2 infection or pre-existing CVD were also observed [47]. These findings indicate that SARS-CoV-2 not only induces lung injury but also may cause systematic damages in COVID-19 patients.

The patients with CVD deserve particular attention. Li et al. [48] concluded that there was a significant associa-

tion between COVID-19 mortality and cardiac injury. A study found that ACE2 activity is increased in patients with type 1 diabetes with vascular complications [49]. It is known that the ACE2 expression and activity are connected with Angiotensin-converting enzyme inhibitor (ACEI). ACEI is the drug for treating hypertension and heart failure by regulating blood pressure and prevention of ventricular remodeling via suppressing the elevated activity of renin-angiotensin-aldosterone system. During ACEI application, ACE2 activity is not inhibited. Instead, the upregulation of ACE2 expression and increased activity were observed [50, 51]. However, latest studies found that ACEI or ARB use was not associated with more severe COVID-19 disease [52], but the use of ARBs increased the risk of SARS-CoV-2 infection in younger patients [53].

Our study found that patients with hypertension, diabetes, and CVD are more sensitive to SARS-CoV-2 infection and transition to severity. However, the association between hypertension, diabetes, and CVD and severity of COVID-19 was decreased by age. It is likely that age itself is closely related with the propensity of comorbidities which contributes somewhat to the severity transition.

Also, male patients are more sensitive to the infection of bacteria, virus, parasite, and fungi [54]. This may be linked to their living habits. For instance, there are much more smokers in men than in women. In a recent meta-analysis study [55], Vardavas and Nikitara [55] reported that the smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to be admitted to an intensive care unit, need mechanical ventilation, or die compared to nonsmokers. This may be linked to an increased ACE2 gene expression in the smokers. From another point of review, in the smokers, unlikely to wear a mask and frequent hand-to-mouth contact may also increase the risk of SARS-CoV-2 infection. Given these, the male seems more easily to be attacked by SARS-CoV-2 and more likely to transit into severe cases.

In addition, obesity is a main risk factor of comorbidities such as hypertension, diabetes mellitus, and CVD [56]. Meanwhile, ACE2 abundantly expressed in adipose tissue. These may cause obese people vulnerable to SARS-CoV-2 as well [57].

COVID-19 patients were in some cases complicated with myocarditis. However, the diagnosis of myocarditis was largely based on troponin elevation. Actually, the myocardial injury could be likely caused by the viral infection-triggered inflammatory response, rather than the direct viral attack, and there was no SARS-CoV-2 observed in the heart tissue [58–61].

In terms of nervous injury, most publications included in our study only observed nonspecific neurological symptoms, such as headache, dizziness, and agitation. More specific manifestations like delirium were not generally reported. Mao et al. [62] and Julie Helms et al. [63] found delirium and/or neurological symptoms appeared more frequent in severe COVID-19 patients and were associated with worse prognosis. However, the direct evidence of COVID-19 invasion to nervous system is still limited. The RT-PCR test of SARS-CoV-2 was negative in cerebrospinal fluid and there was not remarkable pathological observation in the brain [61, 63].

Hypoalbuminemia in critically ill patients was statistically significant and associated with longer hospitalization and higher mortality [64]. Decreased albumin levels in severe COVID-19 patients could be the results of liver dysfunction or malnutrition due to gastrointestinal symptoms [65]. But hypoalbuminemia is a predictor of transition to the severity independent of age and comorbidity [66].

Comparing COVID-19 with SARS or Middle East Respiratory Syndrome, age, male gender, and comorbidities such as diabetes and hypertension were the mortality risk factors in common [67, 68]. Besides, laboratory findings including decreased lymphocytes, platelet count, and albumin level and increased AST, LDH, and CRP levels in patients diagnosed with COVID-19 were not remarkably different from those of patients diagnosed with SARS or Middle East respiratory syndrome [69].

We have to notice that the abnormal laboratory variants were obtained at the time of hospitalization but not always collected prior to the patient transition to the severe cases. In some cases, the results may be collected in patients who had already become a severe case at the time of hospital admission. Under this circumstance, we cannot rule out the possibility that these abnormalities were secondary to the disease development (present in online suppl. Tables S1, S2).

In summary, our study revealed that the elderly, male, obese people, and patients with any comorbidities, espe-

cially those with hypertension, CVD, or diabetes are more likely to develop to severe cases. A progressive elevation in cardiac TnI/TnT, the hepatic enzymes, and serum Cr and the advanced lymphocytopenia and leukocytosis are important alerting markers of mild to severe case transition.

A total of 30 papers were included in this meta-analysis. Although the literatures included in this study have good quality, some limitations remain. First, due to the inconsistency of the observation time of each study, heterogeneity and bias are inevitable. Second, all studies included in this meta-analysis are retrospective studies, and all the study objects were inpatients diagnosed with SARS-CoV-2 infection. Therefore, many patients who did not go to hospital were not included. A more solid conclusion can be achieved when more well-designed large-scale clinical trial studies become available.

Statement of Ethics

This study is exempt from Ethical Committee Approval since all human data were collected from the published sources.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The research idea and study design were guided by Yanggan Wang. The data extraction and analysis were done by Jianhua Hu. The manuscript was written by Jianhua Hu and modified by Yanggan Wang.

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