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ORIGINAL ARTICLE

Characterisation of clinical, laboratory and imaging factors related to mild vs. severe covid-19 infection: a systematic review and meta-analysis

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ABSTRACT

Background: Early detection of disease progression associated with severe COVID-19, and access to proper medical care lowers fatality rates of severe cases. Currently, no studies had systematically examined the variables in detecting severe COVID-19.

Method: Systematic searching of electronic databases identified observational studies which recruited participants with confirmed COVID-19 infection who were divided into different groups according to disease severity were identified.

Results: To analysis 41 studies with 5064 patients were included.Patients who are elderly (SMD, 1.90; 95% CI, 1.01 to 2.8), male (OR, 1.71; 95% CI, 1.39 to 2.11) and have comorbidities or flu-like symptoms were significantly associated with the development to severe cases. Severe cases were associated with significant increased WBC (OR, 5.83; 95% CI, 2.76 to 12.32), CRP (OR, 3.62; 95% CI, 1.62 to 8.03), D-dimer (SMD, 1.69; 95% CI, 1.09 to 2.28), AST (OR, 4.64; 95% CI, 3.18 to 6.77) and LDH (OR, 7.94; 95% CI, 2.09 to 30.21). CT manifestation of bilateral lung involvement (OR, 4.55; 95% CI, 2.17 to 9.51) was associated with the severe cases.

Conclusions and Relevance: Our findings offer guidance for a wide spectrum of clinicians to early identify severe COVID-19 patients, transport to specialised centres, and initiate appropriate treatment.

KEY MESSAGES

- This systematic review and meta-analysis examined 41 studies including 5,064 patients with confirmed COVID-19. Severe cases were associated with age, male gender, and with fever, cough and respiratory diseases, increased WBC, CRP, D-dimer, AST and LDH levels. Furthermore, CT manifestation of bilateral lung involvement was associated with the severe cases.
- These findings provide guidance to health professionals with early identification of severe COVID-19 patients, transportation to specialised care and initiate appropriate supportive treatment.

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COVID-19; clinical characteristics; disease severity; laboratory indicators; meta-analysis

Introduction

Since December 2019, a severe acute respiratory infection (SARI) named Corona Virus Disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), began to spread from Wuhan throughout China, and indeed the world [1,2]. Although most patients have mild symptoms and good prognosis, COVID-19 can develop to severe illnesses including pneumonia, pulmonary edoema, acute respiratory distress syndrome, multiple organ failure or death [3]. As of April 2, 2020, there were 827,419 confirmed cases globally. Furthermore, COVID-

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Supplemental data for this article can be accessed here.

19 had caused 40, 777 deaths worldwide.In a recent report summarising the epidemiological characteristics of 44,415 Chinese patients with COVID-19, 2,087 (5%) were diagnosed as severe cases, defined as severe hypoxaemia and/or the presence of other organ failure [4]. Patients with severe COVID-19 may develop rapidly worsening respiratory failure and acute respiratory distress syndrome (ARDS) [5]. These characteristics indicate that the transition time from mild to severe disease is short, and it is difficult to recognise early. Notably, many patients develop respiratory failure with hypoxaemia but without any signs of respiratory distress, especially for elder individuals ("silent hypoxemia") [6].

To date, the effects of conventional methods on predicting those patients who will go on to develop severe COVID-19 are limited. Hence, there is an urgent need to find the significant clinical signs or biomarkers for the transition from mild to severe cases. Previous retrospective studies or meta-analysis have provided information on common factors for severe cases, including age, fever, cough, fatigue, comorbidities and chest computed tomography (CT) changes [7–25]. However, the prevalence of clinical manifestations in severe patients with COVID-19 were inconsistent and highly variable across outcome measures, populations, and assessment methods, such as fever (43–98%), cough (60–96%), fatigue (10–80.6%), comorbidity (32–100%), and bilateral pneumonia changes (45–87.2%) [9–25] depending on the subjects, the severity of illness, and the definition of severe cases. In addition, previous studies described the characteristics between severe and non-severe cases with COVID-19, while without statistical comparison and subgroup analysis on detailed demographic, geographic, clinical, or laboratory parameters [25].

Currently, we perform this systematic review and meta-analysis to reveal the proportion on unduplicated reports regarding the demographical and geographical-specific clinical characteristics, laboratory variables and imaging manifestations of COVID-19 illness ranging from symptomless to more severe diseases, which could help policymakers and healthcare workers for making decision.

Methods

Search strategy

A systematic review and meta-analysis on the clinical and image features at different stages of patients with COVID-19 was undertaken by group of evidence-based study on COVID-19. The search included all relevant studies published prior to 1 April 2020. Search terms were as follows: COVID19 virus or COVID-19 virus or coronavirus disease 2019 or SARS-CoV-2 or SARS2 or 2019-nCoV or 2019 novel coronavirus or 2019 novel coronavirus infection AND COVID-19 or coronavirus disease 2019 or 2019-nCoV disease or 2019 novel coronavirus pneumonia or 2019-nCoV infected pneumonia.

Pubmed: (((COVID-19[Title/Abstract] OR novel coronavirus pneumonia [Title/Abstract]) OR NCP[Title/Abstract]) OR 2019-nCoV[Title/Abstract]) OR SARS-CoV-2[Title/Abstract] AND (("2020/01/01"[PDAT]: "2020/04/01"[PDAT]) AND "humans"[MeSH Terms])

Other databases: COVID-19[Title/Abstract] OR novel coronavirus pneumonia [Title/Abstract]) OR NCP[Title/Abstract]) OR 2019-nCoV[Title/Abstract]) OR SARS-CoV-2[Title/Abstract]

The inclusive criteria were: (1) Observation studies; (2) Enrolled participants with confirmed COVID 19; (3) Compared disease severity of COVID-19 (severe vs. non-severe); (4) Provided information on any of clinical symptoms, laboratory test or image feature outcomes. The exclusive criteria were: (1) Comments, news, letters, case report, case series, or viewpoint; (2) Non-human studies; (3) Duplicated sample or data; (4) Studies that did not report on outcomes of interest.

Data extraction and quality assessment

The following parameters were assessed: selection of study population, comparability, and ascertainment of exposure/outcome. Any discrepancy between the two reviewers was discussed by involving a third reviewer (LL). Two reviewers (X.M.W. and B.Z.) independently assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS) [10] (eTable 1).

Statistical analysis

An individual meta-analysis was performed for each feature. We distinguished whether the laboratory variables increased or decreased based on the reference values provided in the included studies. Odds ratio (OR) estimates with 95% confidence interval (CI) of clinical symptoms, binary classification of laboratory indicators and image features associated with severe COVID-19 cases were calculated by pooling study-specific estimates. Further, we also calculated the standardised mean difference (SMD) with 95% CI for changes in the laboratory variables of severe cases *vs.* non-severe cases because the scales of measurement of the laboratory variables varied. Subgroup analysis

based on the age (older than or equal to 45 years or less than 45 years), region (inside or outside Wuhan), sample size (more than or equal to 80 or less than 80). Random-effects meta-analyses were performed to pool the data. Heterogeneity was measured by I^2 variables. I2 > 50% or $p < .10$ was defined as substantial heterogeneity [11]. Outcomes from identified studies grouped according to prespecified study-level characteristics were compared using stratified meta-analysis. Egger's test were used to assess publication bias. Stata 12.0 software (Stata Corp, College Station, TX, USA) was applied to conduct this meta-analysis. P value less than 0.05 was defined as statistical significant.

Results

Search results

Initial literature review identified 1378 potential publications by the electronic database searches. After screening titles and abstracts, 1279 studies excluded. Then we evaluated the full-texts of the publications and 42 studies were excluded. Finally, 41 studies [21114-52] involved 5064 patients with COVID-19 were included in current meta-analysis. eFigure 1 in Supplementary 1 shows PRISMA flowchart of the including studies. Table 1 lists characteristics of the included studies in the meta-analysis. All of including studies ($n = 41$) were retrospective design. Quality assessment by the NOS indicates high-quality data for all including studies (eTable 2 in Supplementary 1). The PRISMA checklist is shown in eTable 3 in Supplementary 1.

Demographical characteristics and comorbidities

The overall difference in age, gender and comorbidities between patients with or without severe COVID-19 was shown in Figure 1. Age (SMD, 1.90; 95% CI, 1.01 to 2.8; $p < .001$) and male gender (OR, 1.71; 95% CI, 1.39-2.11; $p < .001$) were associated with a nearly 2-fold higher risk of severe SARS-CoV-2 infection. Diabetes (OR, 2.38; 95% CI, 1.59-3.57; $p < .001$), cardiovascular disease (OR, 3.16; 95% CI, 2.19-4.56, $p < .001$), cerebrovascular disease (OR, 3.34; 95% CI, 1.29-8.69, $p = .013$) and hypertension (OR, 2.63; 95% CI, 1.79-3.88; $p < .001$) were significantly involved in the development of severe COVID-19. Presence of chronic obstructive pulmonary disease (COPD) (OR, 6.92; 95% CI, 2.84-16.82; $p < .001$) and other lung diseases (OR, 4.45; 95% CI, 1.97-10.06; $p < .001$) were associated with a significantly higher rate of severe COVID-19 than other collected indicators. The results of subgroup analysis on demographical characteristics and comorbidities were shown in eTable4 (SMD) and eTable 5(OR).

Clinical manifestations

Regarding the clinical manifestations, dyspnoea (OR, 5.08; 95% CI: 2.61-9.86; $p < .001$) and shortness of breath (OR, 4.9; 95% CI: 1.28-18.74; $p = .02$) were more prevalent clinical manifestations associated with severe disease (Figure 2). The risk for development of severe COVID-19 disease was higher in patients who had fever (OR, 1.53; 95% CI: 1.09-2.13; $p = .013$), expectoration (OR, 1.53; 95% CI: 1.04-2.27; $p = .032$) and cough (OR, 1.52; 95% CI: 1.23-1.88; $p < .001$) and muscle ache/fatigue (OR, 1.75; 95% CI: 1.22-2.51; $p = .002$). Detailed subgroup analysis for the risk of severe COVID-19 cases was displayed in eTable 5 in Supplementary 1.

Laboratory variables

We classified laboratory variables into different categories (Figure 3). In terms of infection, nutrition, coagulation, organ function and internal environmental indicators and other indicators, a random-effects model meta-analysis showed that white blood cell count (WBC) (SMD, 2.03; 95% CI, 1.39 to 2.67; $p < .001$), neutrophils count (SMD, 2.59; 95% CI, 1.42 to 3.76; $p < .001$), C-reactive protein (CRP) (SMD, 3.25; 95% CI, 2.19 to 4.3; $p < .001$), procalcitonin (PCT) (SMD, 3.31; 95% CI, 2.04 to 4.57; $p < .001$), activated thromboplastin time (PT) (SMD, 1.26; 95% CI, 0.21 to 2.3; $p = .018$), D-dimer (D2) (SMD, 1.69; 95% CI, 1.09 to 2.28; $p < .001$), alanine aminotransferase (ALT) (SMD, 1; 95% CI, 0.25 to 1.74; $p = .009$), aspartate aminotransferase (AST) (SMD, 1.70; 95% CI, 0.78 to 2.63; $p < 0.001$), total bilirubin (TB) (SMD, 0.99; 95% CI, 0.22 to 1.76; $p = .012$), blood urea nitrogen (BUN) (SMD, 1.57; 95% CI, 0.61 to 2.54; $p = .001$), creatinine (Cr) (SMD, 1.02; 95% CI, 0.34 to 1.7; $p = .003$), lactate dehydrogenase (LDH) (SMD, 4.63; 95% CI, 2.71 to 6.54; $p < .001$), Troponin I (TnI) (SMD, 2.2; 95% CI, 1.25 to 3.16; $p < .001$), creatine kinase (Ck) (SMD, 1.67; 95% CI, 0.33 to 3.01; $p = .014$), serum amyloid A (SAA) levels (SMD, 1.43; 95% CI, 0.71 to 2.14; $p < .001$) were higher, while lymphocyte count (LC) (SMD, −2.09; 95% CI, −2.68 to −1.5; $p < .001$), albumin (ALB) levels (SMD, −2.35; 95% CI, −3.57 to −1.14; $p < .001$), haemoglobin (Hb) levels (SMD, −0.29; 95% CI, −0.49 to −0.0; $p = .005$) and partial pressure of oxygen (SMD, −5.49;

Table 1. Characteristics of the included studies.

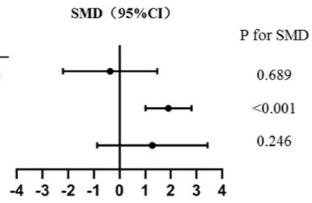
First Author	Sample period (DD/MM/YEAR)	Region	Diagnostic criteria*	Total (Non-Severe + Severe*)	Criteria for grouping	Gender -male (%)	Age (mean or median)
Chuan Liu [12]	23/01/2020-08/02/2020	Multicenter	5th edition	32 (28 + 4)	Non-Severe or Severe	20 (62.50)	38.5
Chaolin Huang [2]	16/12/2019-02/01/2020	Hubei Wuhan	WHO interim guidance	41 (28 + 13)	No ICU or ICU	30 (73.17)	49.0
Chen Chen [26]	01/01/2020-29/02/2020	Hubei Wuhan	6th edition	150 (126 + 24)	Non-Severe or Severe	84 (56.00)	59.0
Dan Fang [27]	27/01/2020-14/02/2020	Hubei Wuhan	5th edition	305 (259 + 46)	Non-Severe or Severe	146 (47.87)	57.0
Dan Li [28]	22/02/2020-15/02/2020	Liaoning	5th edition	30 (20 + 10)	Non-Severe or Severe	18 (60.00)	43.0
Dawei Wang [22]	01/01/2020-28/01/2020	Hubei Wuhan	WHO interim guidance	138 (102 + 36)	No ICU or ICU	75 (54.35)	56.0
Jianzhong Liu [29]	01/01/2020-08/02/2020	Shanxi	5th edition	15 (12 + 3)	Non-Severe or Severe	10 (66.67)	46.5
Jinjin Zhang [9]	16/01/2020-03/02/2020	Hubei Wuhan	3-5th edition	140 (82 + 58)	Non-Severe or Severe	69 (49.29)	57.0
Juan Xiong [17]	17/01/2020-20/02/2020	Hubei Wuhan	6th edition	89 (58 + 31)	Non-Severe or Severe	41 (46.07)	53. 0
Ke Wen [19]	20/01/2020-08/02/2020	Beijing	5th edition	46 (35 + 11)	Non-Severe or Severe	27 (58.70)	41.8
Kebin Cheng [30]	01/01/2020-06/02/2020	Hubei Wuhan	5th edition	463 (282 + 181)	Non-Severe or Severe	244 (52.70)	51.0
Keke Hou [31]	01/01/2020-29/02/2020	Sichuan	6th edition	56 (38 + 18)	Non-Severe or Severe	29 (51.79)	48.0
Kunhua Li [32]	01/01/2020-29/02/2020	Sichuan	5th edition	83 (58 + 25)	Non-Severe or Severe	44 (53.01)	45.5
Lei Chen [33]	14/01/2020-29/01/2020	Hubei Wuhan	4th edition	29 (15 + 14)	Non-Severe or Severe	21 (72.41)	56.0
Lu Huang [34]	01/01/2020-31/01/2020	Hubei Wuhan	5th edition	103 (58 + 45)	Non-Severe or Severe	61 (59.22)	65.0
Min Liu [35]	10/01/2020-31/01/2020	Hubei Wuhan	5th edition	30 (26 + 4)	Non-Severe or Severe	10 (33.33)	35.0
Ming Xu [16]	22/01/2020-29/01/2020	Henan	4th edition	23 (19 + 4)	Non-Severe or Severe	15 (65.22)	46.0
Qiu Wan [23]	26/01/2020-05/02/2020	Sichuan	5th edition	153 (132 + 21)	Non-Severe or Severe	77 (50.33)	45.4
Shi Chen [36]	24/12/2019-28/01/2020	Hubei Wuhan	5th edition	109 (65 + 44)	Non-Severe or Severe	48 (44.04)	52.5
Sijia Tian [24]	20/01/2020-10/02/2020	Beijing	2-5th edition	262 (216 + 46)	Non-Severe or Severe	127 (48.47)	47.5
Tianxin Xiang [18]	21/01/2020-27/01/2020	Jiangxi	4th edition	49 (40 + 9)	Non-Severe or Severe	33 (67.35)	42.9
Wei Liu [37]	30/12/2019-15/01/2020	Hubei Wuhan	4th edition	78 (67 + 11)	Improvement/Stabilization or Progression#	39 (50.00)	38.0
Wen Chen [38]	01/01/2020-29/02/2020	Hubei Jingmen	7th edition	91 (70 + 21)	Non-Severe or Severe	43 (47.25)	41.6
Xiaohu Li [39]	26/01/2020-18/02/2020	Anhui	6th edition	60 (58 + 2)	Non-Severe or Severe	40 (66.67)	39.0
Xiaowei Fang [40]	22/01/2020-18/02/2020	Anhui	6th edition	79 (55 + 24)	Non-Severe or Severe	45 (56.96)	45.1
Yaling Shi [41]	01/01/2020-29/02/2020	Guangdong	5-6th edition	164 (150 + 14)	Non-Severe or Severe	75 (45.73)	50.0
Yan Deng[42]	01/01/2020-21/02/2020	Hubei Wuhan	6th edition	225 (109 + 116)	Recovered or Death	124 (55.11)	Not provided
Yudong Peng [43]	20/01/2020-15/02/2020	Hubei Wuhan	1-6th edition	112 (96 + 16)	Non-Severe or Severe	53 (47.32)	62.0
Yuhuan Xu [15]	01/01/2020-29/02/2020	Beijing	5th edition	50 (37 + 13)	Non-Severe or Severe	29 (58.00)	43.9
Zhongliang Wang [20]	16/01/2020-29/01/2020	Hubei Wuhan	3th edition	69 (55 + 14)	SpO2 $\geq$ 90% or not	32 (46.38)	42.0
Wen Gao [44]	01/01/2020-29/02/2020	Beijing	6th edition	90 (57 + 33)	Non-Severe or Severe	42 (46.67)	53
Li Dong [45]	15/01/2020-31/01/2020	Hebei	6th edition	71 (57 + 14)	Non-Severe or Severe	43 (60.56)	44.25
Guangxiao Tang [25]	24/01/2020-04/02/2020	Sichuan	5th edition	83 (70 + 13)	Non-Severe or Severe	44 (53.01)	44.9
Shuxiang Zhang [14]	22/01/2020-04/02/2020	Ningxia	5th edition	34 (29 + 5)	Non-Severe or Severe	20 (58.82)	41
Kunwei Li [32]	18/01/2020-07/02/2020	Guangdong	7th edition	78 (70 + 8)	Non-Severe or Severe	38 (48.72)	44.6
Shi Y [46]	01/01/2020-29/02/2020	Zhejiang	1-6th edition	487 (438 + 49)	Non-Severe or Severe	259 (53.18)	46
Yun Ling [47]	20/01/2020-10/02/2020	Shanghai	5th edition	292 (271 + 21)	Non-Severe or Severe	154 (52.74)	49.9
Fei Zhou [13]	29/12/2019-31/01/2020	Hubei Wuhan	WHO interim guidance	191 (137 + 54)	Recovered or Death	119 (62.30)	56
Tao Chen [48]	13/01/2020-12/02/2020	Hubei Wuhan	6th edition	274 (161 + 113)	Recovered or Death	171 (62.41)	62
Rong Wang [21]	20/01/2020-14/02/2020	Hubei Wuhan	5th edition	96 (42 + 54)	Non-Severe or Severe	46 (47.92)	Not provided
Huan Han [49]	31/01/2020-10/02/2020	Hubei Wuhan	5th edition	94 (49 + 45)	Non-Severe or Severe	48 (51.06)	Not provided

*National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for novel coronavirus pneumonia (1–7th edition).

#progression group (common-type changed to severe- or critical-type, or death; severe-type changed to critical-type or death; critical-type progressed to death) and improvement/stabilization group (common-, severe-, and critical-types remained unchanged; severe-type changed to common-type; critical-type changed to severe- or common-type).

(A)

The basic information	No. of studies	Disease Severity		SMD (95%CI)	P for SMD
		Non-severe	Severe		
Incubation	3	62	15	-0.37(-2.21, 1.46)	0.689
Age	17	2374	596	1.9(1.01, 2.8)	<0.001
BMI	4	182	39	1.27(-0.88, 3.42)	0.246



(B)

The basic information and disease	No. of studies	Disease Severity				OR(95%CI)	P for OR
		Non-severe		Severe			
		No. of events(%)	No. of sapmle	No. of events(%)	No. of sapmle		
Sex-male	22	1345(49.48)	2718	495(62.11)	797	1.71(1.39, 2.11)	<0.001
Smoking	7	74(7.04)	1051	33(7.62)	433	1.26(0.69, 2.32)	0.453
Alcohol	1	7(35.00)	20	5(50.00)	10	1.86(0.4, 8.69)	0.432
Diabetes	17	153(8.53)	1794	128(18.77)	682	2.38(1.59, 3.57)	<0.001
CVD	13	143(9.40)	1522	89(15.70)	567	3.16(2.19, 4.56)	<0.001
Cerebrovascular disease	7	13(1.71)	760	25(5.52)	453	3.34(1.29, 8.69)	0.013
hypertension	18	400(21.94)	1823	277(40.32)	687	2.63(1.79, 3.88)	<0.001
Chronic liver disease	11	66(4.61)	1433	18(3.28)	549	0.81(0.47, 1.4)	0.451
COPD	6	7(1.42)	492	19(8.72)	218	6.92(2.84, 16.82)	<0.001
Other lung diseases	7	15(2.92)	513	32(11.51)	278	4.45(1.97, 10.06)	<0.001
Thyroid disease	4	7(1.78)	394	7(3.57)	196	2.56(0.63, 10.46)	0.19
Cancer	8	28(2.37)	1179	21(4.56)	461	1.89(1.03, 3.47)	0.039

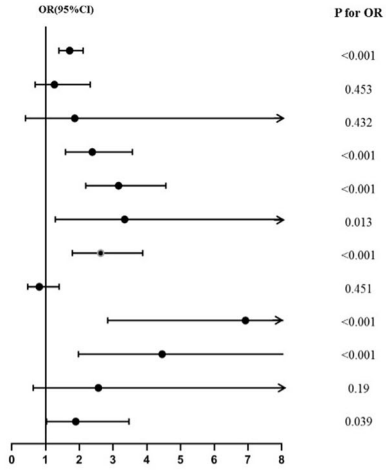


Figure 1. The results of basic information and disease in non-severe group and severe group. (A) The SMD of basic information and disease in non-severe group and severe group. (B) The OR of basic information and disease in non-severe group and severe group.

Clinical Symptom	No. of studies	Disease Severity				OR(95%CI)	P for OR
		Non-severe		Severe			
		No. of event(%)	No. of sapmle	No. of event(%)	No. of sapmle		
Nausea/vomiting	6	69(10.24)	674	29(8.98)	323	0.97(0.44, 2.14)	0.04
Diarrhea	14	248(16.89)	1468	75(12.80)	586	0.98(0.72, 1.34)	0.758
Dyspnea	12	245(19.82)	1236	254(45.85)	554	5.08(2.61, 9.86)	<0.001
Shortness of breath	3	29(17.68)	164	16(47.06)	34	4.9(1.28, 18.74)	0.209
Cough	19	927(59.58)	1556	484(72.56)	667	1.52(1.23, 1.88)	0.561
Expectoration	14	276(18.64)	1481	155(25.62)	605	1.53(1.04, 2.27)	0.071
Muscle ache/fatigue	16	492(33.20)	1482	261(43.50)	600	1.75(1.22, 2.51)	0.007
Stuffy/runny nose	4	25(4.31)	580	6(2.51)	239	0.91(0.36, 2.29)	0.529
Headache	12	92(7.85)	1172	40(7.92)	505	1.08(0.71, 1.63)	0.643
Sore throat	10	56(6.11)	917	29(6.44)	450	1.36(0.72, 2.56)	0.186
Chest pain	6	43(9.82)	438	38(20.77)	183	2.16(0.89, 5.25)	0.182
Chest tightness	6	97(15.16)	640	71(25.63)	277	2.56(0.97, 6.77)	0.04
Fever	17	1321(84.90)	1556	611(91.60)	667	1.53(1.09, 2.13)	0.779

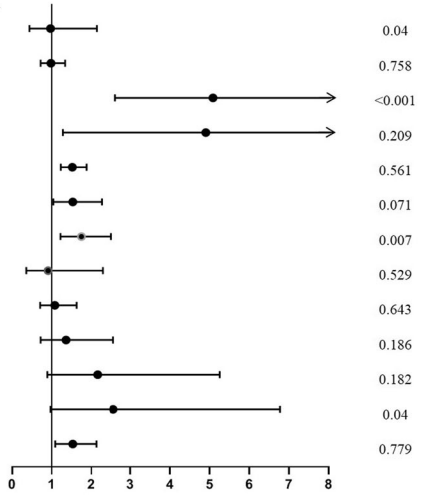


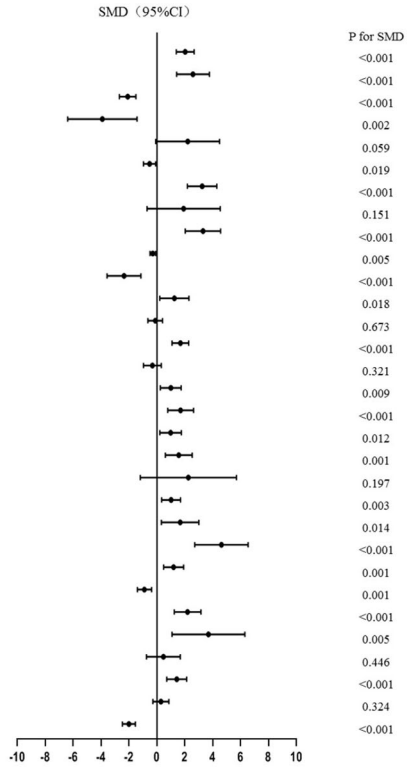
Figure 2. The OR of Clinical Symptom in non-severe group and severe group.

95% CI, −7.95 to −3.03; $p < .001$) were lower in severe cases compared with the non-severe group.

The results of categorical variables of indicators were shown that decreased WBC (OR, 0.49; 95% CI, 0.25 to 0.9; $p = .04$), increased WBC (OR, 5.83; 95% CI, 2.76 to 12.32; $p < 0.001$), increased CRP (OR, 3.61; 95% CI, 1.62 to 8.03; $p = 0.002$), AST level more than 40 (OR, 4.64; 95% CI, 3.18 to 6.77; $p < 0.001$), increased

(A)

Indicators		No. of studies	Disease Severity		SMD (95%CI)	P for SMD
			Non-severe	Severe		
Infection indicators	WBC	18	1669	667	2.03(1.39, 2.67)	<0.001
	NC	12	963	316	2.59(1.42, 3.76)	<0.001
	LC	19	1801	688	-2.09(-2.68, -1.50)	<0.001
	LR	4	304	223	-3.91(-6.39, -1.42)	0.002
	NLR	3	154	44	2.21(-0.08, 4.49)	0.059
	MC	7	570	244	-0.52(-0.96, -0.09)	0.019
	CRP	16	1662	598	3.25(2.19, 4.03)	<0.001
	IL-6	3	498	308	1.92(-0.7, 4.54)	0.151
	PCT	12	1432	520	3.31(2.04, 4.57)	<0.001
Nutrition indicators	hemoglobin	8	770	395	-0.29(-0.49, -0.09)	0.005
	ALB	11	1070	448	-2.35(-3.57, -1.14)	<0.001
Blood coagulation indexes	PT	9	670	311	1.26(0.21, 2.30)	0.018
	APT	9	570	270	-0.11(-0.64, 0.41)	0.673
	D-2	12	1133	439	1.69(1.09, 2.28)	<0.001
	PLT	11	970	449	-0.32(-0.96, 0.32)	0.321
Organ function and Internal environmental indicators	ALT	16	1557	559	1.00(0.25, 1.74)	0.009
	AST	16	1557	559	1.70(0.78, 2.63)	<0.001
	TB	11	1128	485	0.99(0.22, 1.76)	0.012
	BUN	8	672	311	1.57(0.61, 2.54)	0.001
	UA	3	297	138	2.26(-1.18, 5.7)	0.197
	Cr	14	1370	529	1.02(0.34, 1.7)	0.003
	CK	8	919	338	1.67(0.33, 3.01)	0.014
	LDH	12	1153	366	4.63(2.71, 6.54)	<0.001
	potassium	4	511	316	1.20(0.49, 1.92)	0.001
	sodium	3	229	135	-0.89(-1.39, -0.38)	0.001
	TnI	8	964	315	2.20(1.25, 3.16)	<0.001
	BNP	4	654	174	3.70(1.09, 6.30)	0.005
Other indicators	ESR	4	733	319	0.47(-0.74, 1.68)	0.446
	SAA	4	554	262	1.43(0.71, 2.14)	<0.001
Blood pressure	SBP	5	145	52	0.29(-0.28, 0.86)	0.324
	DBP	3	98	35	-2.00(-2.47, -1.54)	<0.001



(B)

Clinical Symptom		No. of studies	Disease Severity				OR(95%CI)	P for OR
			Non-severe		Severe			
			No. of event(%)	No. of sample	No. of event(%)	No. of sample		
Infection indicators	Decreased WBC	8	191(22.87)	835	57(13.51)	422	0.49(0.25, 0.97)	0.04
	Increased WBC	10	50(5.38)	929	122(27.17)	449	5.83(2.76, 12.32)	<0.001
	Decreased LC	11	403(40.34)	999	291(61.91)	470	3.27(1.95, 5.47)	<0.001
	Increased LC	7	411(56.30)	730	94(26.86)	350	0.28(0.15, 0.53)	<0.001
	Increased CRP	7	213(46.00)	463	168(74.01)	227	3.61(1.62, 8.03)	0.002
	Increased PCT	7	182(30.80)	591	126(42.57)	296	2.26(0.35, 14.76)	0.393
Blood coagulation indexes	Decreased PLT	3	25(7.60)	329	29(14.65)	198	2.04(1.16, 3.6)	0.013
Organ function and Internal environmental indicators	AST>40	6	119(21.64)	550	103(53.09)	194	4.64(3.18, 6.77)	
	Increased LDH	5	197(36.15)	545	247(76.00)	325	7.94(2.09, 30.21)	<0.001
	Increased CK	3	20(5.80)	345	26(11.87)	219	2.51(1.32, 4.78)	0.005

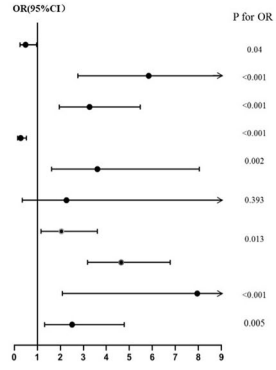


Figure 3. The results of Laboratory Findings in non-severe group and severe group. (A) The SMD of Laboratory Findings in non-severe group and severe group. (B) The OR of Laboratory Findings in non-severe group and severe group.

LDH (OR, 7.94; 95% CI, 2.09 to 30.21; $p = 0.002$), increased CK (OR, 2.51; 95% CI, 1.32 to 4.78; $p = 0.005$) and decreased LC (OR, 3.27; 95% CI, 1.95 to 5.47; $p < 0.001$), decreased platelet count (PLT) (OR, 2.04; 95% CI, 1.16 to 3.6; $p = 0.013$), were associated with severe cases compared with the non-severe group.

Notably, the heterogeneity test showed a statistically significant heterogeneity with an I^2 of 60%. In addition, the results of laboratory variables subgroup analysis were shown in eTable 6 (SMD) and eTable 7 (OR) in supplementary 1.

Oxygen partial pressure, respiratory frequency and pulmonary CT manifestations

eFigure 2 in Supplementary 1 showed the oxygen partial pressure, respiratory frequency and pulmonary CT manifestations. Bilateral lung involvement (OR, 4.55; 95% CI: 2.17-9.51; $p < .001$) and interleaf thickening (OR, 1.89; 95% CI: 1.03-3.47; $p = .039$) were significantly associated with the disease progression. The results of CT manifestations subgroup analysis was in eTable 5 (OR) in Supplementary 1.

Subgroup analysis stratified by region

Subgroup analysis on region of China were divided into main geographical areas (Wuhan and outside Wuhan), which was shown in eFigure 3. Patients with dyspnoea, hypertension, diabetes, AST > 40 and increased WBC and CRP but lower LC levels were with high risk to develop severe COVID-19 both in and outside Wuhan (eTable 5). However, cerebrovascular disease (OR, 3.29; 95% CI: 1.14-9.45; $p = .027$), higher LDH (OR, 7.92; 95% CI: 1.85-33.98; $p = .005$) were independent risk factors for patients with severe COVID-19 on admission in Wuhan, while expectoration (OR, 2.24; 95%CI: 1.13-4.44; $p = .02$), muscle ache/fatigue (OR, 2.83; 95% CI: 1.42-5.67; $p = .003$) were significant for patients outside Wuhan (eTable 5).

Publication bias

Egger's test showed no significant publication bias in cough ($p = .08$), LC ($p = .26$) and bilateral lung involvement imaging ($p = .14$) studies, respectively.

Discussion

The COVID-19 is an emerging condition that primarily threatens the human life, health and safety [2]. Overall, most cases (81%) of China were classified as mild or common, 14% of confirmed cases were severe and only 5% were critical. The case fatality rate was 49% [4]. Facing a highly infectious disease, it demands efforts in epidemiological, diagnostic, therapeutic, and preventive fields during a pandemic [50]. However, we still have a lot of unknowns and blind spots about COVID-19, which are very harmful to deal with the serious consequences.

Factors regarding clinical, laboratory, and image features were associated with deterioration of the disease and outcomes, and constitute critical knowledge should be carefully studied in order to reduce mortality caused by COVID-19. In current comprehensive systematic review and meta-analysis which exactly ruled out possible duplicate cases, we found that several factors were associated with severe outcome: (i) individuals with higher age, male gender, a combination of lung diseases, diabetes, hypertension and cardiovascular/cerebrovascular diseases; (ii) typical clinical manifestations of hypoxia including dyspnoea and chest tightness; common symptoms including muscle ache/fatigue, expectoration and nausea/vomiting; (iii) abnormal laboratory indicators including infection (WBC, LC, lymphocyte ratio (LR), CRP, PCT), nutrition (ALB, Hb), coagulation (PT, D2), organ function and internal environmental indicators (ALT, AST, TB, BUN, CK, LDH, TNI); (iv) bilateral lung involvement shown in pulmonary CT. Together, our findings present concerns about the characteristics for developing severe outcomes among patients infected by the COVID-19.

Our results showed that males were more likely to be severely infected by SARS-CoV-2 than females, which was consistent with the results of a study performed by Guan et al. [51]. Older people are more susceptible to infection and have a higher risk of progression to severe disease, especially those with comorbidities. Recent report showed that no deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% case-fatality rate and even cases in those aged 80 years and older had a 14.8% case-fatality rate [4].

Compared with the non-severe patient, previous study reported that hypertension, respiratory system disease, cardiovascular disease were risk factors for patients with severe infection, which was consistent with our findings [52]. Interestingly, we found that people with previous chronic respiratory disease had a higher risk for severity. A recent study about influenza illness suggested that compared to patients with no comorbidities, the risk of death were more prevalent in those who had COPD (OR 1.49, 95% CI: 1.10–2.01) [52]. In our subgroup analysis stratified by age, compared with patients younger than 45 years, patients having chronic respiratory disease older than 45 years were more likely to be with severe disease. Therefore, healthcare workers should be closely monitoring the elderly male patients with chronic respiratory diseases in order to making early management contributed to the reduction in mortality.

Moreover, clinical manifestations and laboratory abnormalities among patients with COVID-19 were also described in recent studies [53,54]. Inconsistent with the prior reports on clinical sings such as fever, cough, dyspnoea, expectoration, we found dyspnoea was associated with the majority of severe patients with COVID-19, which were also significant in subgroup analysis stratified by age, region and sample. This may be due to the lower tolerance of patients with ARDS to hypoxia [55], and studies with large number of patients are needed to further validate our findings. For laboratory variables, the previous evidence on laboratory abnormalities with severe COVID-19 among description studies were abnormal leukocyte count and lymphopenia but without statistical tests [51]. Our study found that pooled ORs of leukocytosis and lymphopenia were significantly associated with severe outcome, which may be related to different definitions of severe patients. However, due

to the different definitions of severe and non-severe cases in different studies, different conclusions have been drawn. Some studies had applied American Thoracic Society guidelines for community-acquired pneumonia classification criteria [51] and some studies had applied WHO interim guidance [56] or diagnosis and treatment protocol for novel coronavirus pneumonia (1-7th edition) made by National Health Commission of the People's Republic of China [57]. This may be the reason why leukocytosis and lymphopenia have different meanings. Although the cause and mechanism are still uncertain, careful attention should be paid to changes in these symptoms and indicators to prevent the disease from worsening.

In view of the high amount of cytokines induced by severe SARS-CoV-2 infection [58], immune system is activated by the inflammatory response, causing a series of secondary organ functions [39]. In our study, we found that there were significantly different degrees of abnormalities in multiple indicators of organ function, which was also in line with the clinical trend of severe patients with COVID-19. Consistent with the prior reports, pulmonary CT images could manifest different imaging features or patterns in COVID-19 patients with a different time course and disease severity [59].

We further searched the English (Pubmed) and Chinese (CNKI) database as well as preprint server (https://www.preprints.org) about systematic review and meta-analysis regarding COVID-19 clinical, laboratory and imaging findings. A brief report based on only ten studies, addressing limited variables, such as fever, cough, abnormal chest images, patients in critical ill and crude death of patients with COVID-19 [60]. Another single-arm meta-analysis investigated the clinical symptoms and laboratory findings of COVID-19 patients and explained the discharge rate and fatality rate [61]. Recently, in a similar study, Rodriguez-Morales *et al.* summarised the prevalence of clinical, laboratory, and imaging features in patients with COVID-19 using random-effects model meta-analysis as we did. They also evaluated the frequency of patients required intensive care unit, but they did not assess the risk of underlying diseases in severe patients compared to non-severe patients [53]. Yang *et al.* assessed the risk of comorbidities in the severe COVID-19 patients compared with the non-severe cases, and revealed hypertension, respiratory system disease, cardiovascular disease were significant risk factors which were consistent with our findings. However, there were no data on clinical manifestations, laboratory or imaging findings [62]. In addition, there were other pooled studies focus on comorbidities [62] and indicators such as thrombocytopenia, cardiac troponin I or procalcitonin [63,64]. Comparing these studies with ours, we compressively excluded duplicate cases or reports individually according to defined protocol, thus, provided strong evidence on the clinical, laboratory, and imaging characteristics of severe patients.

Strengths and limitations

The strengths of our study include a number of studies comprehensively reviewed with a non-duplicated samples and assessed the detailed clinical, laboratory, and imaging variables in detecting severe COVID-19 cases. Recently, hundreds of papers related to COVID-19, including research articles, case series, brief reports or systematic reviews have been published rapidly. Notably, Bauchner H *et al.* provided a concern on "Possible Reporting of the Same Patients With COVID-19 in Different Reports" [65], suggesting it may preclude valid meta-analyses. Arguably, during literature searching and data extraction process of our study, we carefully reviewed information which could indicate duplicates such as authors, affiliations, or time at admission of subjects, e.g. in order to remove duplicated reports. Thus, we believe that despite the observed heterogeneity, the conduct of current meta-analysis was appropriate and our conclusions valid. However, there were some limitations in our systematic review and meta-analysis. First, most of the included studies were retrospective or cross-sectional design and lacked of dynamic and continuous data, so this may restrict causal and relative deduction on the correlation between severity COVID-19 and its risk factors. Secondly, we did not have more information regarding the imaging variables; for example, most studies reported the chest CT findings as unilateral or bilateral. Third, all included studies were from China, which emphasising this gap in the literature. It is needed to conduct further studies worldwide, to get a more comprehensive understanding of COVID-19.

Implications of findings for clinical practice

The pooled overall, demographic and geographic characteristics of clinical symptoms, laboratory variables and image features for patients at different stages of COVID-19 are rare. Our systematic review and meta-analysis aimed to identify factors or biomarkers for the development of severe COVID-19 that could be useful in clinical practice. Age, male gender, chronic

respiratory diseases, abnormal laboratory parameters and chest CT changes may be risk factors for severe patients compared with non-severe patients with COVID-19. These findings provide guidance to health professionals with early identification of severe COVID-19 patients, transportation to specialised care and initiate appropriate supportive treatment.

Conclusion

The evidence currently support that development of severe COVID-19 cases is significantly associated with older age, male gender, with a combination of chronic diseases, laboratory and pulmonary CT abnormalities. These findings offer guidance for a wide spectrum of clinicians to early identify severe COVID-19 patients, transport to specialised centres, and initiate appropriate treatment. Furthermore, many studies with a broad geographic scope and prospective observation as well as a longer follow-up, involving more comprehensive features and biomarkers are needed.

Ethical approval

Overall ethical approval was not required as this study did not require use of patient identifiers.

Disclosure statement

We declare no competing interests.

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Data availability statement

Authors of included studies should be contacted individually regarding requests to share individual patient data.

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