Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis

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SUMMARY

Objective: To better inform efforts to treat and control the current outbreak with a comprehensive characterization of COVID-19.
Methods: We searched PubMed, EMBASE, Web of Science, and CNKI (Chinese Database) for studies published as of March 2, 2020, and we searched references of identified articles. Studies were reviewed for methodological quality. A random-effects model was used to pool results. Heterogeneity was assessed using I^2. Publication bias was assessed using Egger's test.
Results: 43 studies involving 3600 patients were included. Among COVID-19 patients, fever (83.3% [95% CI 78.4–87.7]), cough (60.3% [54.2–66.3]), and fatigue (38.0% [29.8–46.5]) were the most common clinical symptoms. The most common laboratory abnormalities were elevated C-reactive protein (68.6% [58.2–78.2]), decreased lymphocyte count (57.4% [44.8–69.5]) and increased lactate dehydrogenase (51.6% [31.4–71.6]). Ground-glass opacities (80.0% [67.3–90.4]) and bilateral pneumonia (73.2% [63.4–82.1]) were the most frequently reported findings on computed tomography. The overall estimated proportion of severe cases and case-fatality rate (CFR) was 25.6% (17.4–34.9) and 3.6% (1.1–7.2), respectively. CFR and laboratory abnormalities were higher in severe cases, patients from Wuhan, and older patients, but CFR did not differ by gender.
Conclusions: The majority of COVID-19 cases are symptomatic with a moderate CFR. Patients living in Wuhan, older patients, and those with medical comorbidities tend to have more severe clinical symptoms and higher CFR.

Introduction

In December 2019, a cluster of pneumonia cases of unknown cause appeared in Wuhan, China.[1] The National Health Commission (NHC) of the People's Republic of China later announced that a novel coronavirus, now named COVID-19 by the World Health Organization (WHO),[2] was responsible for the outbreak.[3] High-throughput sequencing identified COVID-19 as a betacoronavirus.

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This novel virus is genetically similar to bat coronaviruses, and shares about 79% and 50% of its genetic sequence with the coronaviruses responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively.[4] Although epidemiological evidence suggests most of the initial patients were exposed to the Huanan Seafood Market in Wuhan, the animal source of COVID-19 has not yet been identified.[1] Human-to-human transmission is now responsible for most new infections, including those among family members and health care workers.[5–7]

Pneumonia caused by 2019-nCOV, known as COVID-19, is of huge global concern, with confirmed cases in 34 Chinese provinces and nearly 30 countries across five continents. The WHO's International Health Regulations Emergency Committee declared this outbreak constitutes a Public Health Emergency of International Concern (PHEIC) on 30 January 2020.[2] As of 2 March 2020 the cumulative number of confirmed cases and deaths of COVID-19 in China has reached 80,302 and 2947, respectively. Outside of China, a total of 10,449 cases have been confirmed, including 170 deaths.[8]

Only one published systematic review and meta-analysis summarized clinical characteristics of COVID-19.[9] It reported a case-fatality rate (CFR) of 4.3% and that fever, sore throat, and muscle soreness or fatigue were the most common symptoms. In that review the incidence of abnormal chest computer tomography (CT) was 96.6%. However, this article analysed results from only ten studies, including one Chinese Center for Disease Control and Prevention (CDC) report that provides epidemiological data only, and four preprint articles (one was already withdrawn) that are not peer reviewed.[10] This article failed to report any clinical laboratory findings, treatments and geographical distribution of COVID-19 which are essential to a thorough understanding of clinical characteristics. Many cases have emerged inside and outside Wuhan over the past month.[1,5,6,11–50] Recent publications suggest there may be significant differences between clinical outcomes for COVID-19 between patients inside and outside Wuhan. Xu, et al. found that patients outside of Wuhan experienced milder illness and less pronounced laboratory abnormalities compared to counterparts inside Wuhan.[24]

Although the number of COVID-19 cases continues to grow worldwide, little attention has been paid to summarizing the clinical signs, risk factors, laboratory and chest CT findings, complications, and treatments of COVID-19. We performed a systematic review and meta-analysis to provide a comprehensive characterization of COVID-19 to better inform efforts to treat and control the current outbreak.

Methods

Search strategy and selection criteria

Our systematic review and meta-analysis was undertaken according to PRISMA and MOOSE guidelines.[51,52] We searched four databases, PubMed, EMBASE, Web of Science and CNKI (Chinese Database), to identify studies reporting COVID-19. Articles published on or before March 2, 2020 were eligible for inclusion. We used the following search terms: "coronavirus" or "nCoV" or "SARS-CoV-2″ or "COVID-19″. References of all retrieved studies were screened for additional eligible publications. Primary studies were eligible if they reported any information on COVID-19 patients in China without restriction on study type or study design. We excluded studies that focused on infection in infants, did not report original data or clear diagnostic criteria, and no reliable clinical data as well as research outside mainland China.

Two independent reviewers (LF and BW) screened the literature search and assessed each study for inclusion. Any disagreement was solved by consulting a senior investigator (HZ).

Data analysis

Four authors (TY, XC, BW, and LF) independently extracted relevant information, including first author, publication time, study designs, city, number of COVID-19 patients, mean or median age of patients, maximum follow-up duration (days), history of exposure in Wuhan, smoking history, diagnostic criteria of COVID-19, presence of medical comorbidities, clinical symptoms, radiologic findings, laboratory findings, complications, supportive treatment, and clinical outcome of COVID-19 patients. We also extracted the original author's guidelines for defining severe case and screened them according to Guidelines of Diagnosis and Treatment Of COVID-19 (Sixth Edition) from the NHC.[8] We classified patients admitted to intensive care units (ICU) as severe cases when authors did not report diagnostic criteria for disease severity. Studies that only reported data for critically ill patients were excluded in the overall meta-analysis but were included in the meta-analysis restricted to severe cases.

We used the quality assessment tool for case series studies published by the National Institutes of Health (NIH) to assess the methodological quality of included studies.[53] We scored 0 or 1 point for each item according to the criteria and added scores for all items to generate an overall quality score that ranged from 0 to 9. Based on the overall score, we classified studies as low ($\geq$7), moderate (5–6), or high risk of bias ($\leq$4). Any disagreement was resolved through discussion by all investigators.

We performed data analyses using meta packages in R (version 3.6.0). Random-effects meta-analysis was used to calculate pooled estimated prevalence with 95% confidence intervals of clinical symptoms, laboratory findings, chest CT findings, complications, treatment, and fatality of COVID-19 patients.[54] To minimize the impact of studies with extremely small or extremely large prevalence estimates on overall estimates, Freeman-Tukey double arcsine transformation was used to stabilize the variance of specific prevalence rates before using random-effects meta-analysis models to pool data.[54]

We assessed heterogeneity between studies using I^2, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively.[55] If substantial heterogeneity (I^2>75%) was detected, we further explored the possible source of heterogeneity through subgroup analysis and used the following grouping variables: age, sex, region, and underlying medical comorbidities. We also performed subgroup analyses to explore whether the prevalence of outcomes differed by these subgroups. If a meta-analysis included more than three studies, publication bias was assessed by Egger's test.[56]

Results

Our search produced 2247 publications. Of these, 1648 were unique records, from which 1434 records were excluded after screening their titles and abstracts (Fig. 1). We assessed the eligibility of 214 full-text papers, of which 99 did not report original data, 47 did not report clinical features of COVID-19 (e.g., epidemiological characteristics, mathematical models, virus structure), six did not include clear diagnostic criteria, 17 had a sample size smaller than four, two were conducted outside mainland China, and one focused on patients aged less than one year. After excluding these studies, 43 eligible studies with 3600 patients were included. Among included studies, one study only reported data on critically ill patients and was excluded from the overall meta-analysis but was included in the meta-analysis restricted to patients with severe illness.[1,5,6,11–50]

Table 1 summarizes characteristics of included studies. Included studies were published between 24 January 2020 and 28 February 2020, among which 25 (58.1%) were in Chinese and the

Table 1
Characteristics of studies reporting clinical characteristics of COVID-19.

Study	Publication date	Enrolment duration	Maximum follow-up duration (days)	Duration between onset of symptoms and hospitalization (median [range], days)	Study design (RCS/SD/PS)	City	No. of cases	Diagnosis method	Age (median/ mean [range/ IQR], years)	Males (%)	Traveled to or resident of Hubei Province (%)	No. Family -cluster (family)	Current Smokers (%)	Health workers (%)	Underlying diseases					Severe Cases (%)	Diagnosis of severity
															Hyper tension (%)	Diabetes (%)	Cancer (%)	Chronic respiratory /lung diseases (%)	Having any coexisting medical condition (%)		
Guan et al	Feb-06	NA	NA	NA	PS	Multi-city*	1099	L	47† (35–58)	640 (58.2)	676 (61.5)	NA	137 (12.4)	32 (2.9)	164 (15.0)	81 (7.4)	10 (0.9)	12 (1.1)	255 (23.2)	173 (15.7)	ATS
Chang et al	Feb-07	NA	NA	NA	RCS	Beijing	13	NA	34† (34–48)	10 (77.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zhang et al	Feb-	Jan 18 -Feb 3	NA	NA	RCS	Beijing	9	L	36 (15–48)	5 (55.0)	7 (78.0)	2	NA	1 (11.0)	NA	1 (11.0)	0	NA	NA	NA	NA
Yu et al	Feb-17	Jan 21	NA	NA	RCS	Beijing	40	NA	40 (21–57)	26 (65.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zhuang et al	Feb-19	Jan 1 -Feb 18	49	NA	RCS	Beijing	26	L	39.77† (3–79)	18 (77.0)	14 (54.0)	NA	NA	NA	4 (15.0)	3 (12.0)	NA	NA	9 (35.0)	NA	NA
Li et al	Feb-10	Jan 22 -Feb 10	20	NA	RCS	Dazhou	17	L	45 (22–65)	9 (53.0)	11 (65.0)	NA	3 (18.0)	NA	1 (6.0)	0	0	0	3 (18.0)	NA	NA
Chung et al	Feb-06	Jan 18 -Jan 27	NA	NA	RCS	Guangzhou	21	L	51† (29–77)	13 (62.0)	18 (86.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Zhang et al	Feb-19	Jan 19 -Feb 5	17	NA	RCS	Nanjing	42	L	43.02† (19–96)	23 (55.0)	23 (55.0)	5	NA	NA	NA	NA	NA	NA	5 (12.0)	0	NA
Wang et al	Jan-30	Jan 21 -Jan 24	14	4 (1–11)	RCS	Shanghai	4	L	47.5 (19–63)	3 (75.0)	3 (75.0)	NA	NA	NA	NA	0	0	0	1 (25.0)	2 (50.0)	NA
Song et al	Feb-02	NA	NA	NA	RCS	Shanghai	51	NA	49 (16–76)	25 (49.0)	50 (98.0)	NA	NA	NA	1 (2.0)	3 (6.0)	NA	1 (2.0)	NA	NA	NA
Lu et al	Feb-3	NA	NA	NA	RCS	Shanghai	50	L	50 (NA)	28 (56.0)	37 (74.0)	NA	NA	NA	8 (16.0)	3 (6.0)	NA	4 (8.0)	18 (36.0)	NA	NA
Chan et al	Jan-24	Jan 10 -Jan 15	14	7 (6–10)	RCS	Shenzhen	6	L	50 (10–66)	3 (50.0)	5 (83.3)	1	NA	NA	2 (33.0)	1 (17.0)	1 (17.0)	1 (17.0)	4 (67.0)	NA	NA
Liu et al	Feb-09	Jan 11 -Jan 20	10	8.5 (5–16)	RCS	Shenzhen	12	L	63 (10–66)	8 (67.0)	11 (91.7)	2	NA	NA	3 (25.0)	2 (16.7)	0	1 (8.0)	7 (58.0)	5 (42.0)	Guidelines
Wang et al	Feb-07	Jan 1 -Jan 28	34	7	RCS	Wuhan	138	L	56 (22–92)	75 (54.3)	138 (100.0)	NA	NA	40 (29.0)	43 (31.2)	14 (10.1)	10 (7.2)	4 (2.9)	61 (44.2)	36 (26.1)	ICU
Huang et al	Jan-24	Dec 16 -Jan 2	37	7 (4–8)	PS	Wuhan	41	L	49 (41–58)‡	30 (73.0)	41 (100.0)	1	3 (7.3)	NA	6 (14.6)	8 (19.5)	1 (2.4)	1 (2.4)	13 (31.7)	13 (31.7)	ICU
Liu et al	Jan-24	Jan 10 -Jan 15	15	7 (1–20)	RCS	Wuhan	137	L	57 (20–83)	61 (44.0)	137 (100.0)	NA	NA	NA	13 (10.0)	14 (10.0)	2 (2.0)	2 (2.0)	NA	NA	NA
Li et al	Feb-09	NA	NA	NA	SD	Wuhan	425	L	59 (15–89)	240 (56.0)	21 (50.0)	NA	NA	15 (4.0)	NA	NA	NA	NA	NA	NA	NA
Chen et al	Jan-29	Jan 1-Jan 20	25	NA	RCS	Wuhan	99	L	55.5 (21–82)	67 (68.0)	49 (49.0)	1	NA	NA	0	13 (13.0)	1 (1.0)	1 (1.0)	50 (51.0)	23 (23.0)	ICU
Pan et al	Feb-6	Dec 30 -Jan 31	31	NA	RCS	Wuhan	63	L	44.9† (NA)	33 (52.0)	63 (100.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pan et al	Feb-13	Jan 12-Feb 6	26	NA	RCS	Wuhan	21	L	40 (25–63)	6 (29.0)	21 (100.0)	NA	NA	NA	NA	NA	NA	NA	NA	0	NA
Chen et al	Feb-4	Jan 14 -Jan 29	NA	NA	RCS	Wuhan	29	NA	56 (26–79)	21 (72.0)	29 (100.0)	NA	2 (7.0)	NA	8 (28.0)	5 (17.0)	1 (3.0)	NA	16 (55.0)	14 (48.0)	Guidelines
Gong et al	Feb-18	Dec 20 -Jan 22	NA	NA	RCS	Wuhan	33	L	51 (23–79)	13 (39.0)	33 (100.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

(*continued on next page*)

Table 1 (*continued*)

Study	Publication date	Enrolment duration	Maximum follow-up duration (days)	Duration between onset of symptoms and hospitalization (median [range], days)	Study design (RCS/SD/PS)	City	No. of cases	Diagnosis method	Age (median/ mean [range/ IQR], years)	Males (%)	Traveled to or resident of Hubei Province (%)	No. Family -cluster (family)	Current Smokers (%)	Health workers (%)	Underlying diseases					Severe Cases (%)	Diagnosis of severity
															Hyper tension (%)	Diabetes (%)	Cancer (%)	Chronic respiratory /lung diseases (%)	Having any coexisting medical condition (%)		
Zhong et al	Feb-13	NA	NA	NA	RCS	Wuhan	30	L	50 (22–81)	18 (60.0)	30 (100.0)	NA	NA	NA	NA	NA	NA	NA	10 (30.0)	8 (26.7)	Guidelines
Xia et al	Feb-18	Jan 15 -Feb 8	NA	(7.44±2.99)	RCS	Wuhan	52	L	54 (23–82)	24 (46.0)	52 (100.0)	NA	NA	NA	25 (48.0)	26 (50.0)	NA	NA	NA	12 (23.0)	Guidelines
Yang et al	Feb-21	Dec 24 -Jan 26	NA	NA	RCS	Wuhan	52	L	59 (13.3)	35 (67.0)	52 (100.0)	NA	2 (4.0)	NA	NA	9 (17.0)	2 (4.0)	2 (4.0)	21 (40.0)	52 (100.0)	ICU
Du et al	Feb-9	Jan 27 -Feb 1	NA	NA	RCS	Xian	7	NA	40 (24–55)	4 (57.0)	2 (28.5)	3	0	0	NA	NA	NA	NA	NA	NA	NA
Gao et al	Feb-6	NA	NA	NA	RCS	Xian	10	L	41.8† (22–70)	6 (60.0)	9 (90.0)	NA	NA	NA	NA	NA	NA	NA	NA	0	NA
Liu et al	Feb-18	NA	NA	NA	RCS	Xiaogan	41	L	48 (19–64)	32 (78.0)	28 (68.0)	NA	NA	NA	5 (12.0)	2 (5.0)	NA	NA	NA	5 (12.0)	NA
Xu et al	Feb-20	Jan 10 -Jan 26	NA	2 (1–4)	RCS	Zhejiang	62	L	41† (32–52)	32 (58.0)	62 (100.0)	NA	NA	NA	5 (8.0)	1 (2.0)	NA	1 (2.0)	20 (32.0)	1 (2.0)	Guidelines
Yu et al	Feb-03	Jan 21 -Feb 2	NA	5.5 (3–13)	RCS	Beijing	25	L	37.9† (3–79)	16 (64.0)	23 (92.0)	3	NA	NA	1 (4.0)	3 (12.0)	NA	NA	NA	NA	NA
Huang et al	Feb-16	Jan 23 -Feb 24	NA	NA	RCS	Guangzhou	35	L	44 (12–74)	19 (54.0)	20 (57.0)	NA	5 (14.0)	NA	1 (3.0)	2 (6.0)	NA	1 (3.0)	NA	NA	NA
Wang et al	Feb-15	Jan 19 -Feb 3	NA	NA	RCS	Zhejiang	52	L	44 (13–73)	29 (56.0)	16 (30.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fang et al	Feb-25	Jan 22 -Feb 18	NA	NA	RCS	Hefei	79	L	45.1† (5–91)	18 (75.0)	NA	NA	NA	NA	11 (46.0)	NA	NA	NA	NA	24 (30.0)	Guidelines
Chen et al	Feb-19	Jan 24 -Feb 8	NA	7 (4–9.5)	RCS	Wuhan	54	L	58.5 (43–69)	27 (50.0)	NA	NA	NA	NA	13 (24.0)	NA	NA	NA	NA	31 (57.0)	Guidelines
Xian et al	Feb-17	Jan 21 -Jan 27	NA	NA	RCS	Nanchang	49	L	42.0† (18–78)	33 (67.0)	46 (94.0)	NA	3 (6.0)	NA	6 (12.0)	2 (4.0)	NA	NA	NA	9 (18.0)	Guidelines
Cao et al	Feb-28	Jan 1 -Feb 15	NA	NA	RCS	Wuhan	36	L	72.5† (61–82)	19 (55.5)	NA	NA	NA	NA	17 (47.2)	8 (22.2)	NA	0.583	NA	NA	NA
Li et al	Feb-24	Jan 26 -Feb 6	NA	NA	RCS	Anhui	12	L	37 (21–71)	8 (66.7)	12 (100.0)	NA	0.333	NA	2 (16.7)	NA	NA	NA	NA	0	NA
Sun et al	Feb-24	Jan 21 -Feb 8	NA	NA	RCS	Tianjin	88	L	48.5† (9–91)	49 (55.7)	26 (29.5)	NA	NA	NA	22 (25.0)	10 (11.4)	NA	NA	NA	32 (36.4)	Guidelines
Ji et al	Feb-24	Jan 19 -Feb 1	NA	NA	RCS	Jingzhou	45	L	45.4† (21–67)	27 (60.0)	37 (82.2)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Wang et al	Feb-24	Jan 1 -Feb 14	NA	NA	RCS	Wuhan	159	L	45.5† (20–84)	66 (41.5)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Yu et al	Feb-26	Jan 17 -Jan 28	NA	NA	RCS	Wenzhou	40	L	45.9† (23–67)	22 (55.0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
XIAO et al	Feb-27	Jan 23 -Feb 8	NA	NA	RCS	Chongqing	143	L	45.1†	73 (51.0)	76 (53.0)	NA	NA	NA	17 (12.0)	10 (7.0)	NA	4 (3.0)	NA	36 (25.0)	Guidelines
Wu et al	Feb-28	Jan 22 -Feb 14	NA	NA	RCS	Jiangsu	80	L	46.1†	39 (49.0)	80 (100.0)	5	NA	NA	25 (31.0)	5 (6.0)	1 (1.0)	1 (1.0)	NA	3 (4.0)	Guidelines
Xu et al	Feb-19	Jan 23 -Feb 4	NA	NA	RCS	Guangzhou	90	L	50 (18–86)	39 (43.0)	86 (96.0)	NA	NA	NA	17 (19.0)	5 (6.0)	2 (2.0)	1 (1.0)	45 (50.0)	NA	Guidelines

NA = Not available. RCS = Retrospective case series. SD = Surveillance data. PS = Prospective study. *L* = Laboratory-confirmed. Guideline = Guidelines of 2019-nCoV infection from the National Health Commission of the People's Republic of China. ICU = Being admitted to ICU. ATS = American Thoracic Society guideline on admission. **All studies were published in 2020. December belongs to 2019. If there is no mark, the median and range were used to represent age. *All cases originated from 31 provinces, municipalities and autonomous regions other than Hubei province. †These values are average values. ‡These data are interquartile range.**

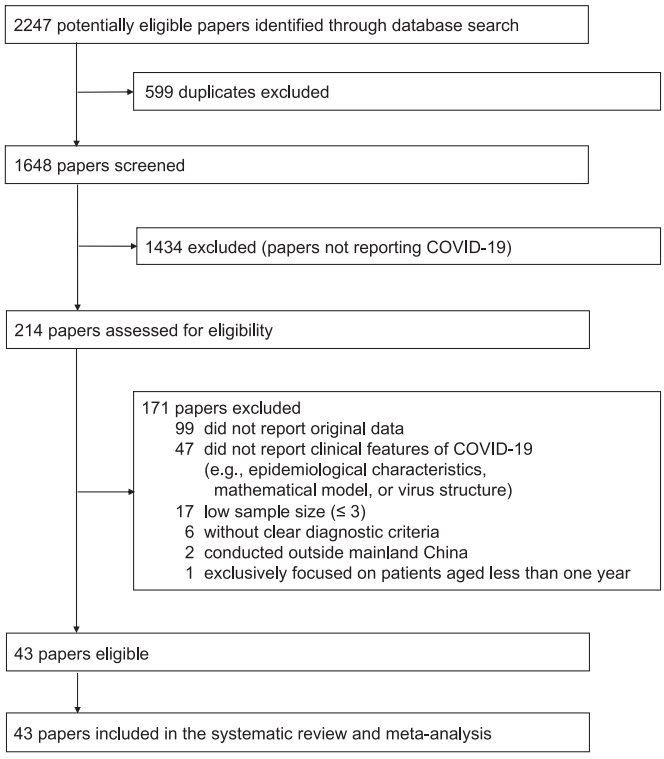

Fig. 1. Flow diagram of publication selection
*Figure legend: COVID-19: Corona Virus Disease 2019.

remaining was in English. The earliest enrollment time was 16 December 2019 and the latest was 27 January 2020. One publication was a letter, and the remainder were journal articles. Most included studies were retrospective case series (40 [90.3%]), 27 (62.8%) were from cities outside Wuhan, and 34 (79.0%) only included patients with laboratory confirmed COVID-19. The number of patients enrolled in each study ranged from 4 to 1099. Mean or median age of patients varied from 39 to 72 years (median 41 years; 43 studies). The proportion of male patients ranged from 29.0% to 77.0% (median 56.5%; 42 studies). The proportion of patients who had ever traveled to or were resident of Hubei Province varied from 28.5% to 100.0% (median 91.0%; 36 studies). The number of family-clusters ranged from 1 to 5 (10 studies). The proportion of patients who were current smokers ranged from 0.0% to 18.0% (median 7.2%; 9 studies), and health workers ranged from 0.0% to 29.0% (median 4.0%; 5 studies). The proportion of patients with hypertension ranged from 0.0% to 48.0% (median 16.0%;27 studies), diabetes ranged from 0.0% to 50.0% (median 10.1%; 26 studies), cancer ranged from 0.0% to 17.0% (median 1.0%; 15 studies), chronic respiratory/lung diseases ranged from 0.0% to 17.0% (median 2.0%; 16 studies), having any coexisting medical comorbidity ranged from 12.0% to 67.0%. The proportion of patients diagnosed with severe COVID-19 varied from 0.0% to 100.0% (median 26.5%; 21 studies), and the most commonly used diagnostic criteria was The Guidelines on 2019-nCoV Treatment and Prevention issued by the NHC (70.6) (17 studies). 9 (20.9%) of 43 studies were rated as low risk of bias, 30 studies (69.8%) as moderate, and all remaining studies rated as high risk of bias (supplementary Table 1).

We meta-analysed the prevalence of 16 clinical symptoms among COVID-19 patients (Fig. 2). Fever (83.3% [95% CI 78.4–87.7]), cough (60.3% [54.2–66.3]), and fatigue (38.0% [29.8–46.5]) were the most common, followed by increased sputum production, shortness of breath, and myalgia, with estimated prevalence just under 30% for each, respectively. Eleven studies reported the proportion of COVID-19 patients who did not exhibit obvious symptoms, and the pooled estimated prevalence was 5.6% (1.4–11.6). Among 16 commonly reported laboratory findings (Fig. 3), the

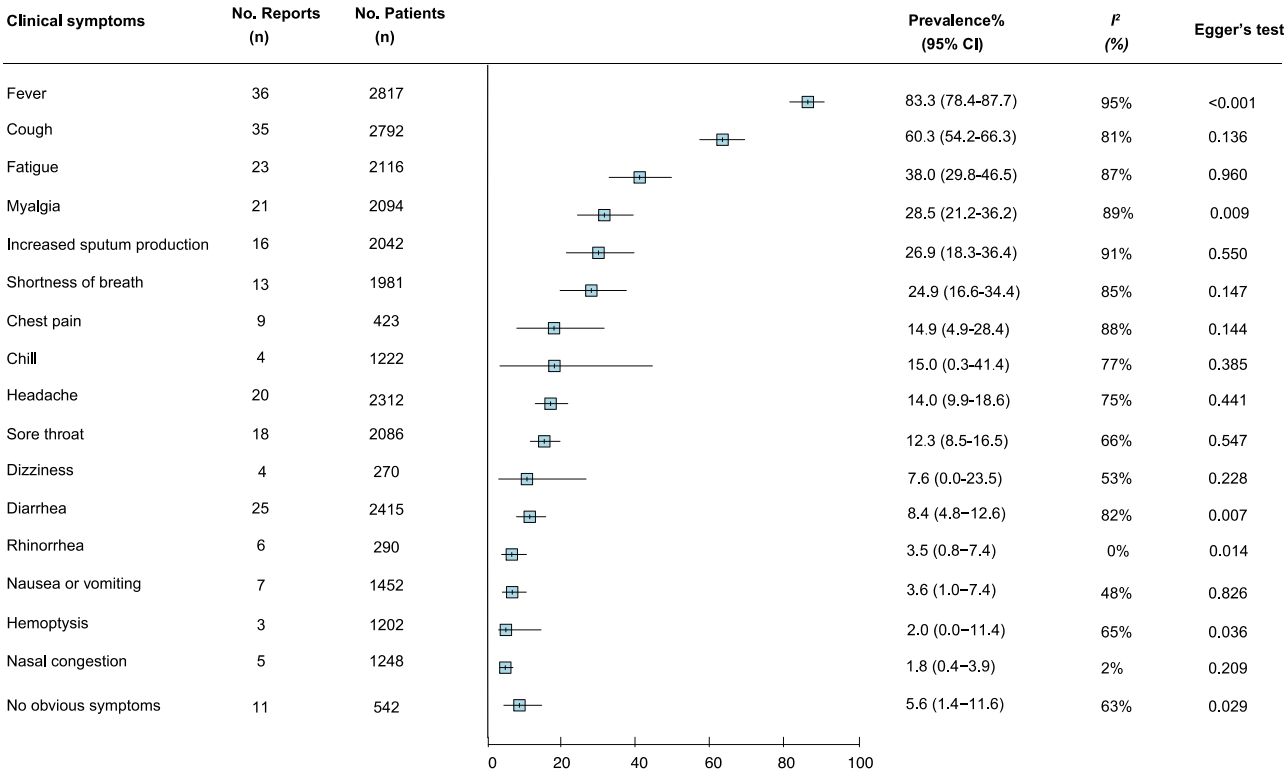

Fig. 2. Meta-analysis of the prevalence of clinical symptoms among COVID-19 patients.

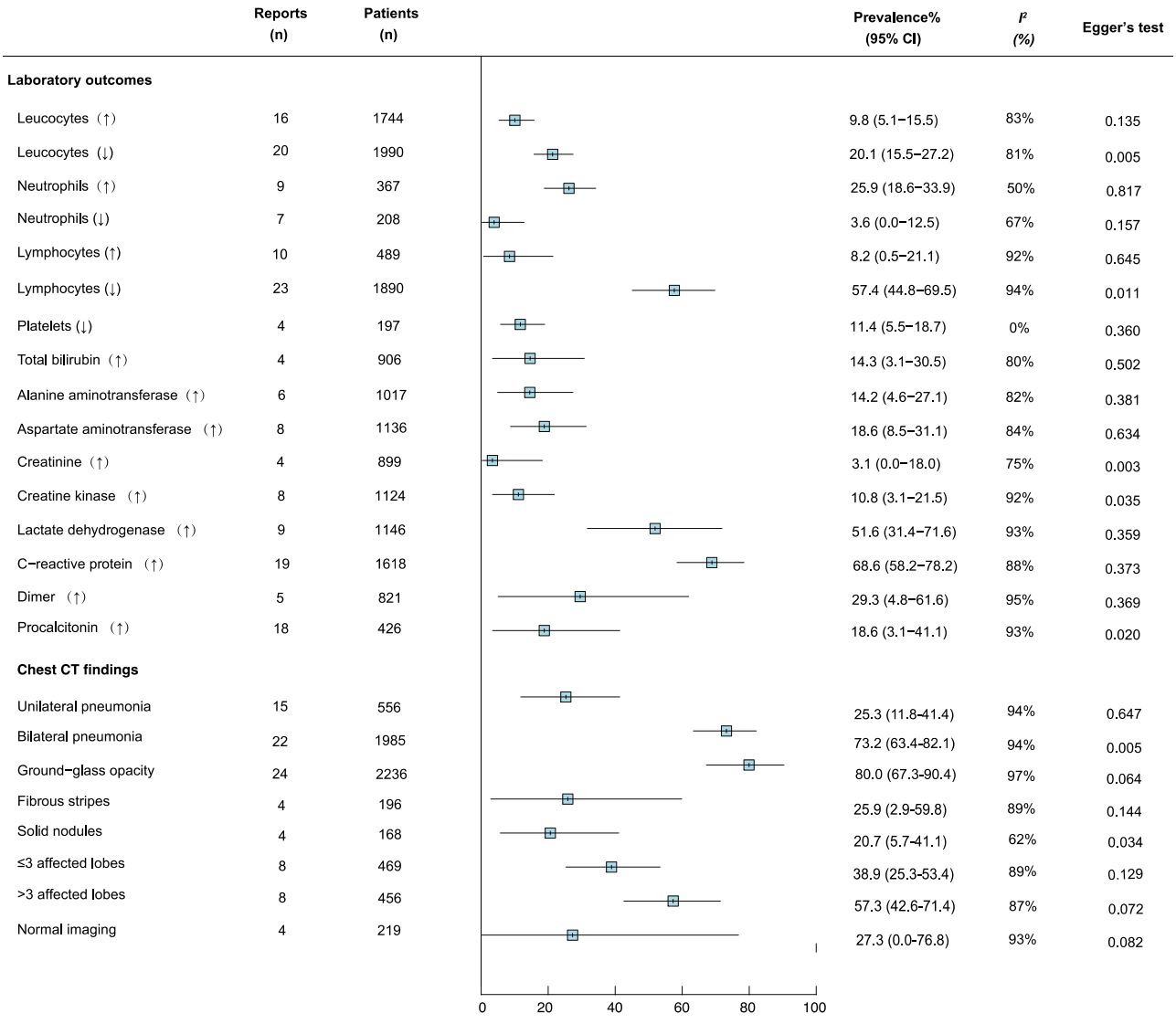

Fig. 3. Meta-analysis of the prevalence of laboratory findings among COVID-19 patients.

most common laboratory abnormalities were elevated C-reactive protein (68.6% [58.2–78.2]) and decreased lymphocyte count (57.4% [44.8–69.5]), as well as increased lactate dehydrogenase (51.6% [31.4–71.6]). Ground-glass opacities (80.0% [67.3–90.4]) and bilateral pneumonia (73.2% [63.4–82.1]) and were the most frequent chest CT findings (Fig. 3). The vast majority of patients received antiviral therapy (90.0% 74.1–99.0]), antibiotic treatment (71.5% [50.0–89.7]), and oxygen therapy (71•5% [28•0-99•7]). Acute respiratory distress syndrome (ARDS) was the most common complication (15.7% [5.0–30.4]). The overall estimated prevalence of severe case and death was 25.6% (17.4–34.9) and 3.6% (1.1–7.2), respectively (Fig. 4).

In subgroup analysis (supplementary Tables 2–5), studies from Wuhan had significantly higher prevalence of death, fever, fatigue, headache, elevated leukocyte count, and elevated lactate dehydrogenase, and elevated aspartate aminotransferase compared to patients from other cities (all $p<0.05$). Similarly, the prevalence of death, ARDS, headache, increased leukocyte count, and increased lactate dehydrogenase were significantly higher in studies in which the proportion of older patients was larger (all $p<0.05$), and the prevalence of diarrhea, and elevated lactate dehydrogenase were significantly higher in studies in which the proportion of patients with any coexisting medical condition was larger (all $p<0.05$). The prevalence of fatigue, myalgia, decreased leucocyte count were significantly higher in studies in which the proportion of male patients was smaller, whereas the reverse was true for the prevalence of elevated aspartate aminotransferase and lactate dehydrogenase (all $p<0.05$), though fatality did not differ by gender.

A total of eight studies reported separate results for severe cases and non- severe cases. Overall, the existence of clinical symptoms, abnormalities in laboratory and chest CT findings, and complications were higher among patients with severe illness compared to patients without severe illness (Table 2), however these differences were not statistically significant due to limited sample size and statistical power (data not shown).

Publication bias was found in the following subgroup outcomes: fever, myalgia, diarrhea, rhinorrhea, hemoptysis, decreased leucocytes, lymphopenia, increased creatine, creatine kinase, and procalcitonin, bilateral pneumonia, solid nodules, antiviral therapy, and immunoglobulin therapy (Figs. 2–4, all $p<0.005$ by Egger test). Substantial heterogeneity was present within most subgroups (Table 2 and Figs. 2–4).

Discussion

Our systematic review and meta-analysis of 43 studies involving 3600 patients provides the most comprehensive overview of clinical features, laboratory findings, chest imaging findings,

Table 2
Outcomes comparing severe cases and non-severe cases of COVID-19.

Outcomes	Critical illness				Non-critical illness			
	No. reports	No. patients	Prevalence% (95%CI)	I^2 (%)	No. reports	No. patients	Prevalence% (95%CI)	I^2 (%)
Clinical symptoms								
Fever	6	364	80.8 (41.1–100.0)	97	6	1299	71.2 (23.8–99.9)	98
Cough	6	364	65.6 (51.7–78.2)	67	6	1299	56.7 (39.5–73.2)	88
Sore throat	3	245	16.7 (0.0–53.2)	77	3	1135	11.2 (3.5–22.4)	63
Increased sputum production	3	222	32.1 (15.6–51.0)	19	3	1065	31.4 (23.1–40.5)	14
Shortness of breath	6	364	49.2 (21.5–77.2)	90	5	1216	13.3 (2.2–30.9)	85
Myalgia	5	351	17.6 (8.2–29.5)	57	5	1201	20.8 (10.0–33.9)	85
Fatigue	4	299	41.2 (5.2–84.0)	92	5	1201	34.5 (13.2–59.6)	93
Diarrhea	4	234	7.6 (0.0–24.0)	55	3	1053	4.3 (0.1–12.5)	54
Headache	4	274	11.3 (0.1–33.9)	74	5	1172	11.9 (5.8–19.7)	53
Laboratory findings								
Leucocytes (↑)	2	186	27.7 (0.0–100.0)	91	3	838	9.3 (0.0–1.0)	67
Leucocytes (↓)	3	216	33.7 (0.00–95.7)	92	3	957	27.2 (24.3–30.1)	0
Lymphocytes (↓)	3	203	81.5 (18.9–100.0)	94	4	883	59.6 (32.2–84.2)	99
Platelets (↓)	2	169	32.3 (0.0–100.0)	93	3	740	16.4 (0.0–1.0)	88
Aspartate aminotransferase (↑)	2	155	46.1 (0.0–100.0)	56	3	653	15.5 (0.0–50.8)	55
Creatinine (↑)	2	151	6.4 (0.0, 100.0)	57	2	642	2.3 (0.0, 97.1)	76
Creatine kinase (↑)	2	134	28.6 (0.0–100.0)	76	3	563	16.7 (0.0–1.0)	96
Lactate dehydrogenase (↑)	3	173	62.7 (55.7–100.0)	83	3	818	28.1 (0.0, 100.0)	99
C-reactive protein (↑)	2	171	40.3 (0.0–100.0)	99	5	1026	51.2 (38.6–63.8)	71
D-dimer (↑)	2	109	59.6 (50.2–68.7)	0	1	451	43.2 (38.7–47.8)	0
Procalcitonin (↑)	3	165	35.7 (0.0–100.0)	95	4	660	55.2 (0.0–33.8)	95
Chest CT findings								
Bilateral pneumonia	2	186	91.0 (0.0–100)	83	1	926	39.7 (36.6–42.9)	0
Complications								
ARDS	4	315	38.2 (3.2–83.0)	96	2	130	4.3 (2.8, 6.0)	0
Cardiac failure	4	155	17.1 (1.5–42.2)	78	2	130	1.9 (0.0, 26.0)	0
Shock	3	222	17.4 (0.0, 61.5)	87	.	.	.	.
Renal insufficiency	5	328	9.8 (0.1–28.7)	87	.	.	.	.

ARDS=Acute Respiratory Distress Syndrome.

disease severity, and CFR of COVID-19 patients. Compared with the only previous published systematic review on the subject, we included 31 additional studies performed detailed subgroup analyses. Particularly our results suggest CFR and proportion of severe cases are both declining as 2019-nCOV spreads away from Wuhan.

The dominant clinical features of COVID-19 were fever, cough, and fatigue, while congestion, rhinorrhea, sore throat and diarrhea are rare.[13,16,19,24] The most frequently reported laboratory abnormalities were reduced lymphocyte count, elevated C-reactive protein, and elevated lactate dehydrogenase, all of which are generally consistent with previous reports of patients with COVID-19.[11,19,24] However, all these laboratory markers are very non-specific, making their clinical utility limited. When evaluating suspected cases, physicians cannot rely on these laboratory abnormalities to exclude or confirm the diagnosis of COVID-19. These abnormalities are similar to those previously observed in patients with SARS and MERS.[57–59] Previous research suggests these abnormalities may be related to the cytokine storm brought on by infection.[22] Recently, a study suggested that COVID-19 may primarily affect T lymphocytes, especially CD4+ *T* cells, resulting in significant lymphopenia as well as decreased IFN- γ production.[60] Additionally, by using a multiple linear regression model, a study showed that CD4+ *T* lymphocyte count may help predict the duration of viral RNA detection in patients' stools ($p=0.010$).[61] However, the number of cases currently reported is too small to draw firm conclusions, and further studies are required. The most frequently reported finding on CT imaging was ground-glass opacities, particularly bilateral opacities impacting three or more lobes. These results are also consistent with previous studies,[21] and are also frequently identified in MERS and SARS.[57–59]

In this systematic review and meta-analysis, we found a CFR of 3.6%, which is closer to the estimate (2.3%) in a report by the Chinese Center for Disease Control and Prevention (China CDC) that includes the epidemiological characteristics of 44,672 confirmed COVID-19 patients in mainland China (updated through February11, 2020).[10] CFR may have been higher in earlier reports because of belated treatment during the earlier stages of the outbreak or a decline in fatality after sustained human-to-human transmission.[1,14,19] Of note, roughly half of the studies included in our analysis were from outside Wuhan, the epicenter of the current outbreak, and our subgroup analysis found significantly lower prevalence of death among patients treated outside Wuhan. This may indicate fatality from COVID-19 is declining.

In our analysis, the proportion of severe cases (25.6%) was close to the estimate in the China CDC report (18.5%).[10] This is consistent with previous studies that patients from Wuhan had significantly higher prevalence of death, fever, elevated leucocyte count, and elevated aspartate aminotransferase compared with patients from other cities in China (all $p<0.05$).[1,14,19] Additionally, the China CDC report supports our finding that the overall CFR in Hubei (2.9%) is higher than that outside Hubei (0.4%).[10] This interpretation could be supported by a study that showed lower fatality in patients who did not have direct contact with the site of the original disease.[62] Similarly, the CFR, proportion of severe cases, ARDS, headache, increased leukocyte count, and increased lactate dehydrogenase were significantly higher in studies in which the proportion of older patients was larger (all $p<0.05$), which is consistent with previous publications.[62] This finding suggests COVID-19 may disproportionately impact the elderly or people living with medical comorbidities. This is consistent with a single-center retrospective study found that older patients (>65 years) with comorbidities and ARDS were at increased risk of death.[45] A multivariate Cox regression analysis results showed age and severe cases were identified as independent prognostic factors for virus clearance.[62] Furthermore, a study showed that children might be less likely to become infected or, if infected, may show milder symptoms.[16] Another study also confirmed that the elderly and those with comorbidities including diabetes, hypertension, cardiovascular disease, liver diseases, ma-

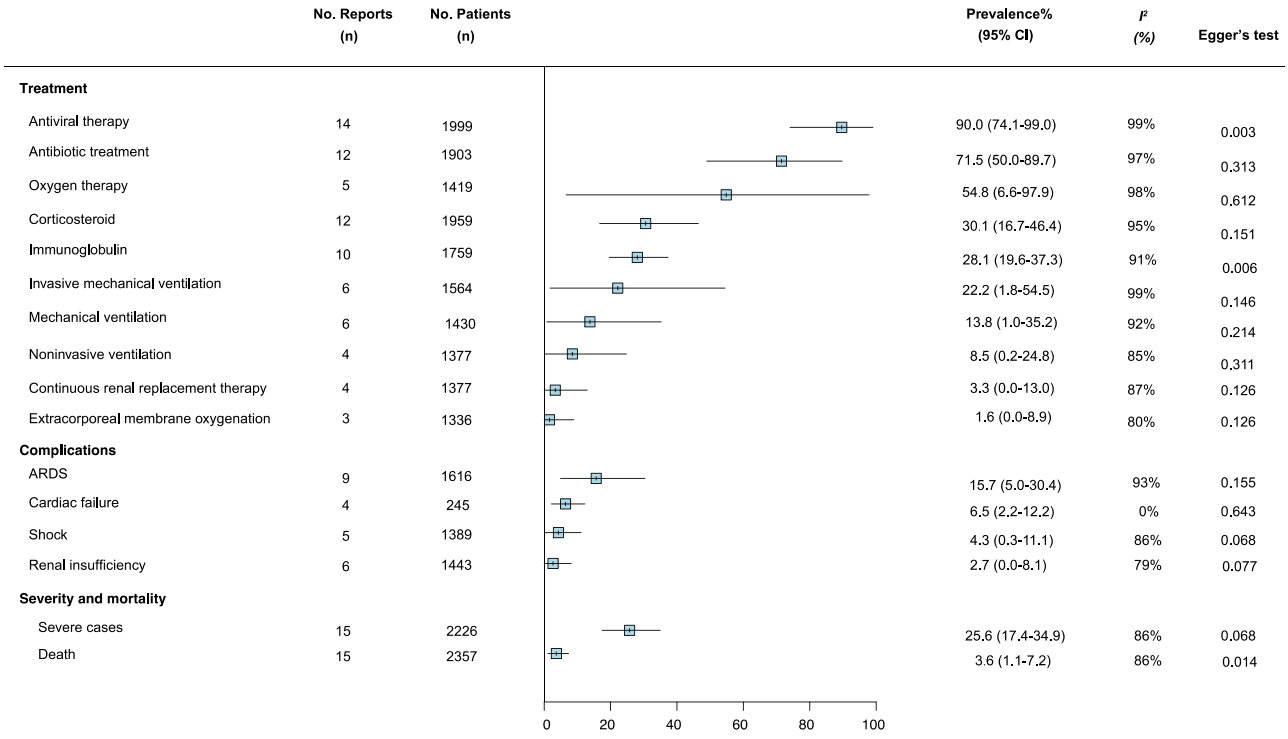

Fig. 4. Meta-analysis of the prevalence of chest CT findings, complications, severe cases, and mortality among COVID-19 patients
*Figure legend: ARDS=Acute Respiratory Distress Syndrome.

lignancy were more likely to develop critical illness (62.1%:25.0%, $p<0.001$).[62]

Our study did not find significant differences between men and women in terms of CFR and proportion of severe cases. This finding is similar to a previous study in which there was no difference in the proportion of men and women admitted to the intensive care unit (ICU) for treatment of COVID-19.[6] However, this differs from another study which found that men are more susceptible to COVID-19 than women,[63] as well as a recent publication reporting that seven of nine infant patients were female.[64] There is no clear explanation as to why men and women would be at different risk of infection, however some have proposed genetic mechanisms or sex-specific effects.[65] Whether there are differences in risk of infection between men and women requires further research.

We found the prognosis was worse among severe cases compared to non-severe cases, however these differences were not statistically significant, which is likely due to insufficient sample size. In our research, there was no significant difference in the degree of lymphocyte decline between severe cases and non-severe cases. This conclusion can be supported by this research that the expression level of lymphocyte counts has no significant correlation with the severity of the disease.[22] However, some studies showed that lymphocytopenia is a prominent feature of severe cases.[45] At present, it is unclear whether lymphocyte count is related to severity of disease. Further investigation is needed to establish whether lymphocytosis or lymphopenia can help predict mortality in COVID-19 patients.[62]

We found many patients were treated with antiviral and antibiotic therapy. Currently there is no treatment that can cure COVID-19. Supportive measures may reduce complications and fatality.[14] The impact of antivirals and antibiotics on patients' prognosis remains unknown and requires further clinical evaluation. Currently, clinical trials of lopinavir / ritonavir (LPV/r) and remdesivir registered in the Chinese clinical trial registry are ongoing.

The recently published systematic review and meta-analysis on the clinical characteristics of 50,466 patients may reflect a combination of fallacies.[9] Authors misuse fundamental terms. They mistake incidence for prevalence and odds ratio for proportion. They demonstrate the proportion of severe cases is 88% and case fatality rate is 42% in figures, which are misleading. PRISMA guidelines and test for heterogeneity were not mentioned. Authors state in Methods that "Only available data from published articles were collected. Data from unpublished papers were not included." However 4 out of 10 references were from Medrxiv, a platform that publishes non-peer reviewed reports. These reports, as it clearly states on Medrxiv's website, should not be relied on to guide clinical practice or health-related behavior and should not be reported as established information. One reference providing 4021 cases was already withdrawn from publication.[66] It is inappropriate to include the China CDC report providing epidemiological characteristics of 44,672 cases of COVID-19 (as of February 11, 2020) in a meta-analysis of its clinical characteristics.[10] This report, based on national surveillance data, provides epidemiological data only, including spatiotemporal distribution. Albeit this report includes a large sample, data on clinical symptoms that are not systematically reported, may not be reliable. For example, 53% did not report if they have co-morbidity or not. 9 out 10 studies included in the meta-analysis were published/submitted before February 11, 2020 so cases in these 9 studies must have already been included in the China CDC report. It is inappropriate to count an individual twice. After excluding the China CDC report and the four preprint articles, only 369 patients would be reportable in that review. Authors did not list specific imaging performance in abnormal imaging, nor did they list pulmonary fibrosis and its incidence. However in Discussion they use two lengthy paragraphs to explain the content of pulmonary fibrosis, which may cause readers to mistakenly believe that the imaging abnormality is pulmonary fibrosis. Author failed to report any clinical laboratory findings and treatments of COVID-19 which are essential to a thorough understanding of clinical characteristics. They also failed to report the diagnostic criteria for abnormal chest CT detection and severe cases.

Our systematic review and meta-analysis has limitations. First, we found substantial heterogeneity between studies and significant publication bias among several subgroups. Second, this study performs an analysis during an ongoing outbreak. Many regions affected by COVID-19 haven not yet published clinical datasets, which may skew the results of this analysis. All these datasets are retrospective, which prevents us from exploring risk factors. Additionally, our meta-analysis focused on Chinese people, not those infected in other countries, so geographical and ethnic differences were not excluded. Finally, the meta-analysis was performed by comparing entire datasets against one another, therefore there was no way to analyze data on the level of individual patients.

Conclusion

This review provides a comprehensive characterization of clinical features among COVID-19 patients. Patients living in Wuhan, older patients, and those with medical comorbidities tend to have more severe clinical symptoms and higher fatality. Better therapeutics are crucial for the treatment of severe cases. Our comprehensive characterization of COVID-19 will inform healthcare providers and public health policy makers in their efforts to treat and control the current outbreak.

Contributors

HZ, YS and LL conceived the study and designed the protocol with LF and BW. LF, BW, TY and XC conducted study selection and data extraction. LF, WB, TY, XC, YA contributed to statistical analysis and interpretation of data. LF, BW, TY, XC and HZ drafted the manuscript with all authors critically revising the manuscript.

Declaration of Competing Interest

The authors declare having no conflict of interest related to this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.03.041.

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