Clinical Characteristics, Laboratory Findings, Radiographic Signs and Outcomes of 52,251 Patients with Confirmed COVID-19 Infection: A Systematic Review and Meta-analysis

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Abstract

Introduction: The 2019 novel coronavirus (COVID-19) is very contagious, and can be transmitted to other people by droplet, aerosol, sneezing, infected surface, and cough. There is no vaccine or effective treatment at this time. Therefore, the prevention of COVID-19 and the rapid diagnosis of infected patients is crucial.

Method: We searched all relevant literature published up to February 28, 2020, from Embase, Scopus, PubMed, Web of Science, and the Cochrane library to collect the studies that reported clinical and laboratory characteristics of COVID-19 infected patients. The study quality was assessed with the Critical Appraisal Checklist. Depending on the heterogeneity test, we used either random or fixed-effect models to analyze the appropriateness of the pooled results.

Result: Twenty studies were included in the meta-analysis, including a total of 52,251 patients with confirmed COVID-19 infection. 69.5% (95% CI 54.5-81, $p < 0.001$) of patients had a history of recent travel to Wuhan, contact with people from Wuhan, or lived in Wuhan. The most common symptoms among COVID-19 infected patients were fever 85.6 % (95% CI 73 -93, $p < 0.001$), and cough 63 % (95% CI 55.5-70, $p < 0.001$), respectively. The laboratory analysis showed that thrombocytosis was present in 91% (95% CI 81-98, $p < 0.001$) CRP was elevated in 81% (95% CI 65-91, $p < 0.001$), and lymphopenia in 62.5% of cases (95% CI 42-79, $p < 0.001$).

The most common radiographic signs were bilateral involvement in 76.8% (95% CI 62.5-87, $p < 0.001$) and consolidation in 75.5% (95% CI 50.5-91, $p < 0.001$) of patients. Most patients (85.4%) were hospitalized, 20.6% of patients were admitted to the ICU in critical condition, and the mortality rate was 5.6%.

Conclusions: Fever and cough are the most common symptoms of COVID-19 infection in the literature published to date. Thombocytosis, lymphopenia, and increased CRP were common lab findings although most patients included in the overall analysis did not have laboratory values reported. The most common radiographic sign was bilateral involvement in and consolidation. Among Chinese patients with COVID-19, rates of hospitalization, critical condition, and hospitalization were high in this study, but these findings may be biased by reporting only confirmed cases.

Keywords: COVID-19; SARS-CoV-2, coronavirus; severe acute respiratory syndrome coronavirus; meta-analysis

Introduction

In December 2019, the new COVID-19 coronavirus was recognized as a cause of respiratory illness. The first reports of pneumonia were from people who worked or lived in the Huanan seafood wholesale market in Wuhan, China raising concerns about a zoonotic viral infection[1,2]. Phylogenetic analysis showed that the COVID-19 belong to the beta-coronavirus[1]. Epidemiological studies have shown that the virus is spread relatively easily and can be transmitted by aerosol, droplets, and through infected surfaces[3]. The COVID-19 has now spread to more than 50 countries from December 2019 to February 2020[4]. Most symptoms are non-specific in patients with respiratory disease. According to the latest WHO report, out of 83652 confirmed cases of COVID-19 worldwide, 2791 deaths occurred in China and 67 deaths is recorded in other countries[4].

Thus far, 6 coronaviruses that are able to infect humans have been identified, coronavirus infections are typically asymptomatic or associated with mild respiratory symtoms[1]. The first coronavirus to cause severe disease in humans was the Severe Acute Respiratory Syndrome virus (SARS), which was appeared in the Guangdong province of southern China in 2002, there were 8098 reported case and 774 deaths[5]. In Saudi Arabia in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), which was transmitted from the camels to humans, caused 2458 infections with 848 deaths[6].

Clinical studies have shown that COVID-19 can rapidly cause pulmonary damage and severe respiratory symptoms[3]. There is no vaccine or targeted treatment currently available for COVID-19 infection. Treatment is largely supportive although multiple experimental antiviral medications are being evaluated[7,8]. Thus, prevention and rapid diagnosis of infected patients is crucial. To date, the published clinical studies are quite small and give variable findings. With this in mind, here

we evaluate the clinical features and laboratory findings using a large sample size of COVID-19 infected patients in order to assist in its understanding, prevention and treatment.

Methods

Search strategy

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) guidelines [9]. We searched all studies published up to February 28, 2020 from the following databases: Embase, Scopus, PubMed, Web of Science and the Cochrane library. Search medical subject headings (MeSH) terms used were: “COVID-19”, "Coronavirus", “severe acute respiratory syndrome coronavirus”, and all their synonyms like “Wuhan Coronavirus”, “SARS-CoV-2”, and "COVID-19". Moreover, we searched for unpublished and grey literature with Google scholar, Centre for Disease Controls (CDC) and WHO databases. We also examined references of included articles to find additional relevant studies. There was no language restriction and all included studies are written in English or Chinese languages, the latter were translated by https://translate.google.com/. Additional search strategy details are provided in **Table S1 (supplementary material)**.

Study selection

Duplicate studies were removed using EndNote X7 (Thomson Reuters, New York, NY, USA). Records were initially screened by title and abstract by independently two authors (AP, SG). The full-text of potentially eligible records was retrieved and examined. Any discrepancies were resolved by consensus.

Inclusion criteria

Studies had to fulfil the following pre-determined criteria to be eligible for inclusion in our meta-analysis. Studies were included if they reported the number of confirmed cases of patients with demographic data, [AND] [OR] clinical data, [AND] [OR] laboratory data, [AND] [OR] risk factor data. Confirmed patients were defined as any patient with positive nucleic acid testing (most of the studies with Real-Time PCR) or those meeting CDC and WHO criteria at the time of their publication.

Exclusion criteria

Studies were excluded if they did not report number of confirmed cases, were letters to the editor or individual case reports or reviews. News reports were also excluded.

Data extraction

All included publications were published in 2020 and all patients are from China. The following items were extracted from each article: first author, Center and study location in China, sample collection time period, patient follow-up time, reference standard for infection confirmation, number of confirmed cases, and all demographic, clinical, laboratory data, and risk factor data. Two of our authors (AP and SG) independently extracted data and differences were resolved by consensus.

Quality assessment

Quality assessments of studies were performed by two reviewers independently according to the Critical Appraisal Checklist recommended by the Joanna Briggs Institute [10], and disagreements were resolved by consensus. The checklist is composed of nine questions that reviewers addressed for each study. The 'Yes' answer for each question received one point. Thus, final scores for each study could range from zero to nine (**Table S2** in Supplementary Material).

Analysis

Data cleaning and preparation was done in Microsoft Excel 2010 (Microsoft©, Redmond, WA, USA) and further analyses were carried out via Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Englewood, NJ). Determination of heterogeneity among the studies was undertaken using the chi-squared test (Cochran's Q) to assess the appropriateness of pooling data. Depending on the heterogeneity test, we used either Random or Fixed effect models for pooled results. In the case of high heterogeneity (I2 >50 %) a random effect model (M-H heterogeneity) was applied, while in low heterogeneity cases (I2 < 50 %), a fixed effect model was used [11]. P values reflect study heterogeneity with <0.05 being significant. We also used the Begg's and Egger's tests based on the symmetry assumption to detect publication bias.

Results

Characteristics of included studies

The process of study selection is displayed in **Fig 1**. A total of 36115 reports were screened for the analysis of patients with COVID-19, 36014 were excluded after title and abstract screening and the full text of 81 reports were reviewed in full text. We excluded studies that did not report sufficient data and finally 20 studies met the inclusion criteria (**Figure 1**). Characteristics of the selected articles are summarized in **Table 1**. Of the 20 studies that were included in the analysis, 19 studies were in English and the one of them was in the language of Chinese[12]. All studies were retrospective, published in 2020, and all patients were from China.

Quality assessment

Quality assessment of included studies were performed based on the Critical Appraisal Checklist and the final scores for quality of included studies are represented in **Table S2** (in supplementary

material). In brief, studies by Chen[13], Wang[14], Huang[15], Guan[16], Zhang[17], Cheng[18], Li[19], Wei Xu[20], and Song[21] had the highest quality of the studies available in the purpose of this study.

Demographics, baseline characteristics, and clinical characterization

Overall, 52,251 confirmed patients with COVID-19 infection were included in the Meta-analysis, of which 53.7 % (95% CI 50-56.8, p < 0.001) were male. **Table 2** shows that most patients had fever 85.6 % (95% CI 73 -93, p < 0.001) (**Figure 2**) and cough 63 % (95% CI 55.5-70, p < 0.001). A much smaller proportion of patients had sore throat 12.3% (95% CI 7.8-17, p 0.06), headache 12.2% (95% CI 8.3-18, p < 0.001), diarrhea 7.3% (95% CI 4.6-11.4, p < 0.001), rhinorrhea 6% (95% CI 3-12, p 0.43) or nausea and vomiting 6% (95% CI 2.7-13, p < 0.001). Most patients required hospitalization 85.4% (95% CI 68-94, p < 0.001), 20.6% (95% CI 6.7-48, p < 0.001) were deemed to be in critical condition and the mortality rate was 5.6% (95% CI 2.5-12.5, p < 0.001) between all infected patients.

Clinical characteristics, and Comorbid conditions of patients infected with COVID-19

The majority of patients, 69.5% (95% CI 54.5-81, p < 0.001), had a history of recent travel to Wuhan, contact with people from Wuhan, or were Wuhan residents. A significant minority of patients (41.2%, 95% CI 20-66, p<0.001) had a history of chronic diseases and 24.3% (95% CI 9.6-49, p < 0.001) had exposure at the seafood market(s) (**Table 3).**

Laboratory findings of patients infected with COVID-19

The laboratory analysis and features showed that among a subset of patients 4.5 % (2361/52251) where data was available, the most infected patients had increased platelets 91% (95% CI 81-98, p < 0.001), and CRP 81% (95% CI 65-91, p < 0.001), while others showed decreased lymphocytes, 62.5% (95% CI 42-79, p < 0.001) (**Table 4**).

Chest X-ray and CT scan Findings in Patients infected with COVID-19

Analysis showed that the most abnormality which finding with Chest X-ray and CT are bilateral involvement of chest radiography 76.8% (95% CI 62.5-87, $p < 0.001$), consolidation 75.5% (95% CI 50.5-91, $p < 0.001$), and ground-glass opacity 71% (95% CI 40-90, $p < 0.001$) (**Table 5**).

Discussion

COVID-19 belongs to the Coronaviridae family and is the newest serious zoonotic virus after the related viruses SARS and MERS [22,23]. Prior to 2002, coronaviruses were associated with mild respiratory illness, but with the emergence of SARS in 2002, MERS in 2012, and now in late 2019, COVID-19, establishes that coronaviruses can be associated with severe respiratory disease. Genetic variation and phylogenetic analysis of these viruses show that the COVID-19 virus has 84% homology to other beta-coronaviruses, 96% sequence similarity at the whole genome level to a bat coronavirus and 79.5 % similarity to the SARS virus[8,24]. These results suggest that bats are important coronavirus reservoirs.

A study by Adam Bernheim, *et al*. showed that among 121 COVID-19 patients, fever, cough and sputum production were the most common clinical symptoms[3]. Our study found utilizing data from 52,251 patients with COVID-19 infection, that in additional to these, fatigue and myalgia (muscle soreness) were also common.

The large data set here finds that 85.4% of patients required hospitalization, 20.6% were found to be in critical condition and the mortality rate was 5.6% between all infected patients. The mortality rate is lower than some studies (for example, 11% in Nanshan, *et al*[13]), but still higher than many

viral infections. It should be recognized that these numbers are bias due to the data set including publications related to screening practices (e.g. only those with symptoms being screened) increased the % value. The true mortality rate from COVID-19 is almost certainly much lower than that found in this study. As more data emerges from screening asymptomatic or mildly symptomatic individuals in China and around the world, the true mortality rate will be better understood. Additionally, at the time of submission of this manuscript only ~50% of reported infected patients had recovered (gisanddata.maps.arcgis.com). Lymphopenia, age, multilobular infiltration, smoking history, hypertension, and bacterial co-infection have been reported as mortality risk factors. Underlying cardiovascular disease (40%) and bilateral pneumonia (75%) were common among those who have died. Recent travel to Wuhan, contact with people from Wuhan or residency in Wuhan, exposure to persons with respiratory symptoms, and seafood market exposures were common amongst those contracting COVID-19. Among 2,361 COVID-19 patients with laboratory data available, leukocytosis was found in 13.3% and leukopenia in 26% with lymphocytopenia in 62.5%. Among 2200 patients, thrombocytosis occurred in 91% and in a smaller sample (n=290) CRP was increased in 81%.

A study by Yu Zhao et al showed that ACE2 is a COVID-19 virus receptor and that it is normally expressed on pulmonary alveolar epithelial cells[25]. ACE2 activates the RAS cascade, which can lead to hypertension. The pathology in this pathway can also stimulate fibrogenesis, inflammation, cell hypertrophy, and cell proliferation[26,27]. ACE2 expression is increased in people with pulmonary ARDS and acute respiratory injury[28]. The data collected here shows that ARDS occurred in 10.6 % of reported patients with COVID-19 infection.

Limitations

Several limitations of this study exist. Publication bias and study heterogeneity are unavoidable in this type of study, therefore it should be considered when interpreting the outcomes of the reports and our final data set. Further, this study likely overestimates disease severity due to lack of screening of asymptomatic or mildly symptomatic individuals and subsequent publication bias related to these factors. It is very likely that many infected persons have not been detected, thus falsely elevating the rates of hospitalization, critical condition, and mortality. The lower quality analysis and reporting in some of the included publications is another limitation of the study. To prevent language bias, we included reports in languages other than English. In addition, we searched a variety of sites and databases to prevent internet platform bias. Using Egger's regression test we did not find significant publication bias. Journal bias is an issue facing those who carryout meta-analysis, yet it does not usually affect the general conclusions[29]. However, we cannot reject the occurrence of other biases in this study, such as choice bias, since there are several journals that are not indexed in Embase, Scopus, PubMed, Web of Science and the Cochrane library and unpublished data from some regions of world.

Conclusions

Fever and cough are the most common symptoms of COVID-19 infection in the literature published to date. Thombocytosis, lymphopenia, and increased CRP were common lab findings although most patients included in the overall analysis did not have laboratory values reported. The most common radiographic sign was bilateral involvement in and consolidation. Among Chinese patients with COVID-19, rates of hospitalization, critical condition, and hospitalization were high in this study, but these findings may be biased by reporting of only confirmed cases.

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Author Contributions:

Conceived and designed the study: AP, SG

Comprehensive research: SG, AK, AP

Analyzed the data: A P, MAM

Wrote and revised the paper: AP, SG, BB, AK, RT, MAM, NB, DK, JPI

Participated in data analysis and manuscript editing: AP, SG, BB, AK, RT, MAM, NB, DK, JPI

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Ethical statement: The manuscript is a systematic review, so the ethical approval was not required for the study.

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Figures:

Figure 1. Flow Diagram of Literature Search and Study Selection (PRISMA flow chart).

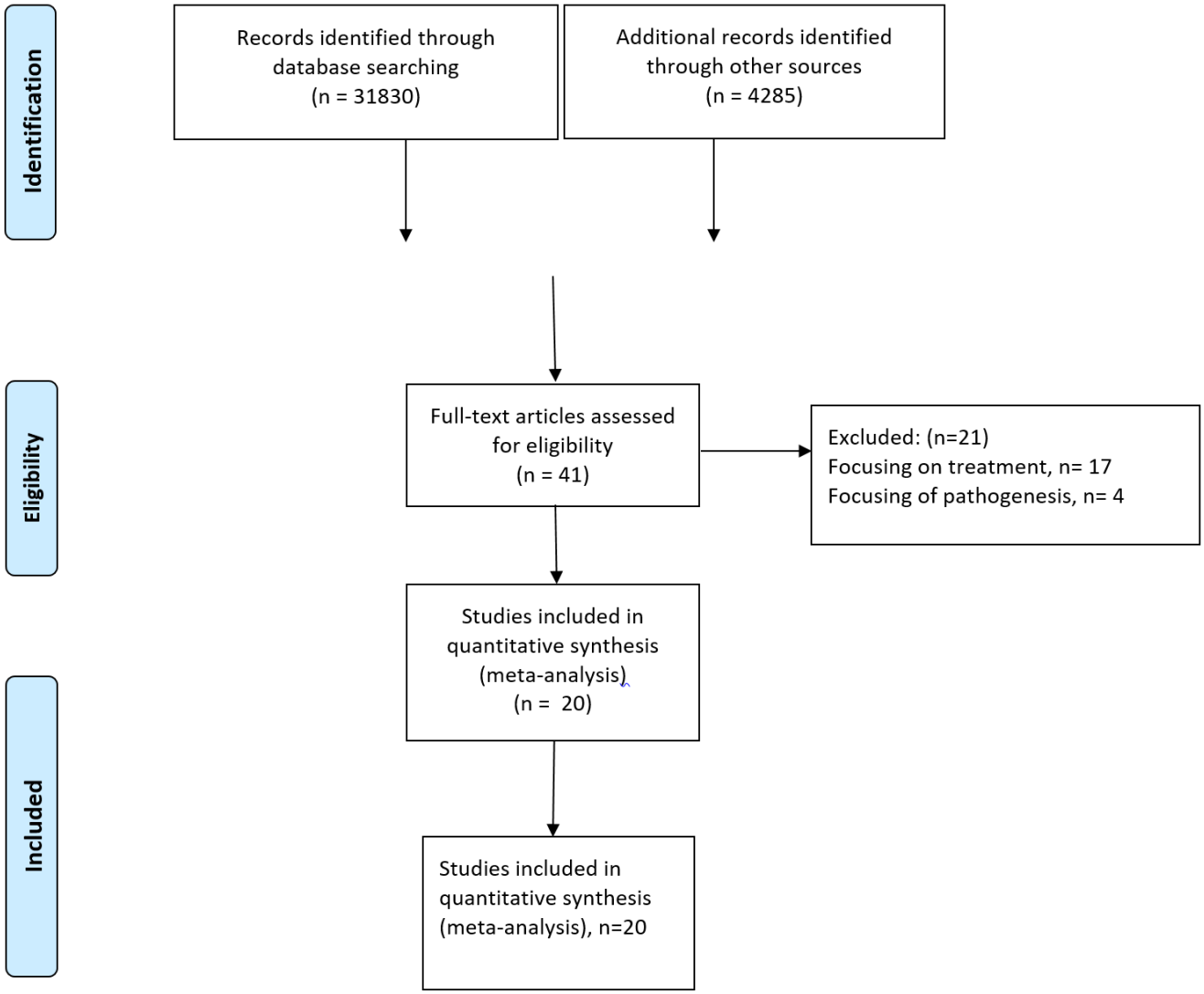

Figure 2. Forest plot of the meta-analysis on clinical presentation of fever in patients with Confirmed COVID-19.

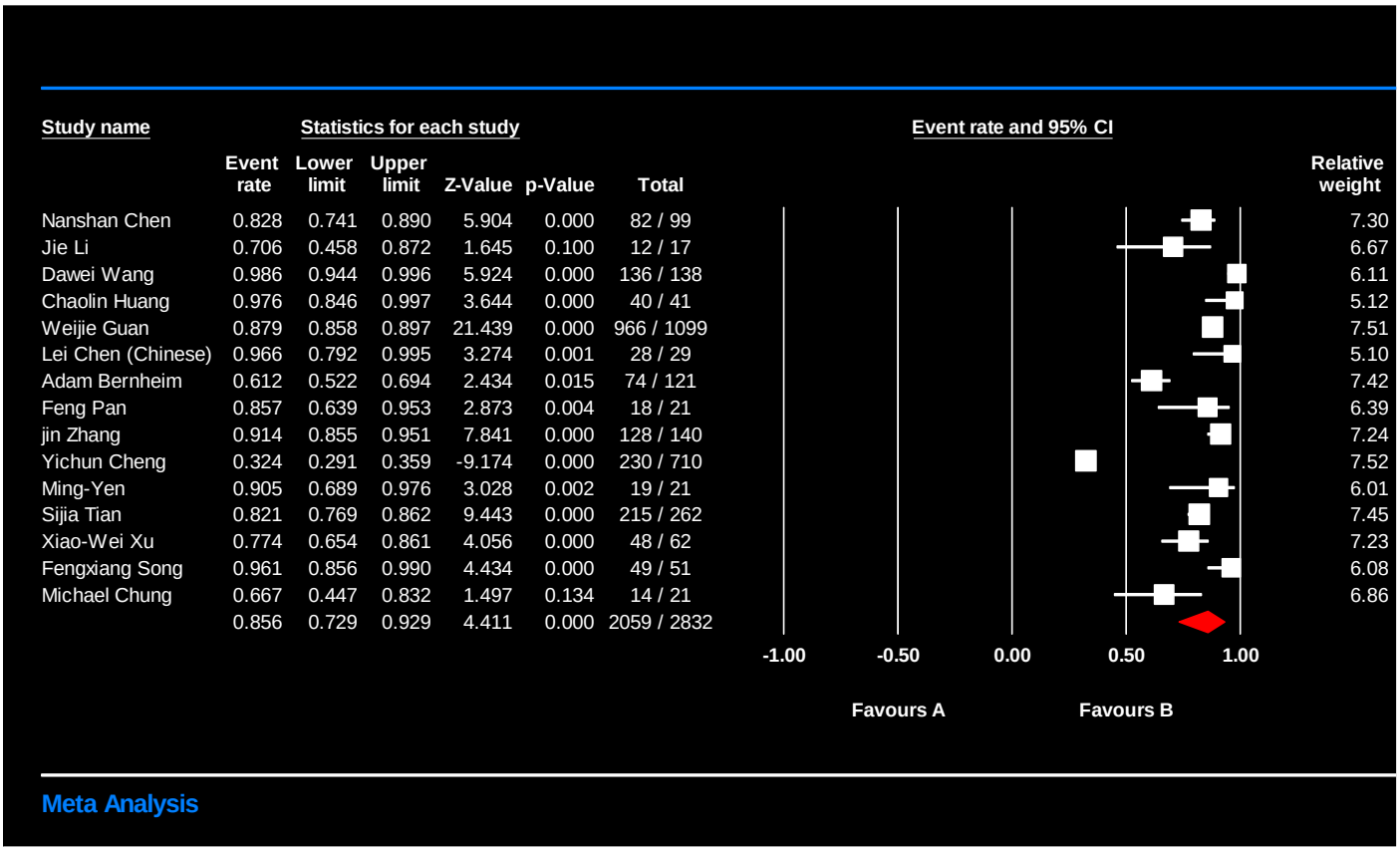

Table 1. Characterization of Included Studies with total 52, 251 COVID-19 Confirmed Patients. All Studies are Retrospective, from China, and Published in 2020.

First Author	Sampling Center	Sample collection time	Patient follow up (days)	N Confirmed Patients	Mean age in years (IQR)	N sex (male)	Reference standard
Nanshan Chen[13]	Wuhan Jinyintan Hospital	Jan 1 to Jan 20, 2020	5-24	99	55·5 (21-82)	67	RT-PCR
Kaiyuan Sun[30]	Multicenter	Jan 20- Jan 29, 2020	42	288	49 (2-89)	62.3	CDC guideline
Jie Li[31]	Dazhou Central Hospital	22 January-10 February 2020	1-21	17	45.1 (32-65)	9	RT-PCR
Dawei Wang[14]	Zhongnan Hospital of Wuhan	January 1-January 28, 2020	6-34	138	56 (42-68)	75	RT-PCR
Chaolin Huang[15]	Jin Yintan Hospital (Wuhan)	Dec 31, 2019-UN	NA	41	49 (41-58)	30	RT-PCR
Weijie Guan[16]	Multicenter	NA	NA	1099	47 (35-58)	640	RT-PCR
Yang Yang[32]	NA	NA	51 days	4021	49	2211	NA
Lei Chen (Chinese)[12]	Tongji hospital in Wuhan	January 14-29, 2020	15 day	29	56 (26-79)	21	RT-PCR
Adam Bernheim[3]	Multicenter	January 18-February 2, 2020	12 days	121	45 (18-80)	61	RT-PCR & CT scan
Feng Pan[33]	Union Hospital	12 Jan-6 Fen 2020	NA	21	40 (25-63)	15	RT-PCR
jin Zhang[17]	No.7 hospital of Wuhan	Jan 16th to Feb 3rd 2020	NA	140	57 (25-87)	71	RT-PCR
Yichun Cheng[18]	Tongji hospital in Wuhan	January 28-February 11, 2020	10 (7-13)	710	63 (51-71)	374	RT-PCR
Ming-Yen[34]	Hong Kong-Shenzhen Hospital	NA	NA	21	56 (37-65)	13	RT-PCR
Sijia Tian[35]	Beijing Emergency Medical Service	Jan 20 to Feb 10, 2020	Feb.10 20	262	47.5 (1-94)	127	RT-PCR
Qun Li[19]	NA	NA	NA	425	15 -89 (26-82)	240	WHO guideline
De Chang[36]	3 hospitals in Beijing	January 16-January 29, 2020	Feb.4 2020	13	34 (34-48)	10	NA
Xiao-Wei Xu[20]	Zhejiang province	10 January - 26 January 2020	10 days	62	41 (32-52)	36	WHO guideline
Fengxiang Song[21]	Center for Disease Control, Shanghai	January 20-January 27, 2020	NA	51	49 (16-76)	25	CT scan & nucleic acid test
Michael Chung[37]	Multicenter	January 18-27, 2020	NA	21	51 (29-77)	13	CT scan, NA
Zunyou Wu (CDC)[38]	Multicenter	through February 11, 2020	15 days	44672	30-79	22981	nucleic acid test result

NA=not known, RT-PCR= Real Time Polymerase Chain Reaction, CDC= Centers for Disease Control and Prevention, WHO= World Health Organization, CT scan= CT scan of chest, N= number, IQR=interquartile range.

Table 2. Demographics, Baseline Characteristics, and Clinical Outcomes of Patients with Confirmed COVID-19.

	Clinical presentation*	Confidence interval 95%	Heterogeneity test, I2 (%)**	Heterogeneity test, P Value**	Number of Studies
Age, years	49.5 (mean)	46-52.5	98	<0.001	20
Sex (Male)	53.7 (%)	50-56.8	88.4	<0.001	20
Fever	85.6 (%)	73 -93	98	<0.001	15
Cough	63 (%)	55.5-70	86	<0.001	15
Fatigue	40.3 (%)	29-52.5	93	<0.001	11
Sputum production/ Expectoration	28 (%)	19-39	92	<0.001	7
Myalgia	26 (%)	14-43	92	<0.001	6
Dyspnea	20 (%)	12.6-32	92	<0.001	7
Sore throat	12.3 (%)	7.8-17	52	0.06	6
Headache	12.2 (%)	8.3-18	77	<0.001	10
Diarrhea	7.3 (%)	4.6-11.4	70	<0.001	11
Rhinorrhea	6 (%)	3-12	0	0.43	3
Nausea and vomiting	6 (%)	2.7-13	84	<0.001	4
		Outcome			
Hospitalized	85.4 (%)	68-94	95	<0.001	3
Critical condition/ ICU	20.6 (%)	6.7-48	99	<0.001	6
Death	5.6 (%)	2.5-12.5	98	<0.001	8

*Age is an exception, presented in mean age in years. ** Greater than 50% is considered high heterogeneity, less than 50% is considered low heterogeneity. A low p value (<.05) is consistent with high heterogeneity.

Table 3. Clinical Characteristics and Comorbid Conditions of patients with confirmed COVID-19.

Risk Factor	Patients with risk factor (%)	Confidence interval 95%	Heterogeneity test, I2 (%)*	Heterogeneity test, P Value*	Number of Studies reporting
Recent travel to Wuhan/contact with people from Wuhan/ resident of Wuhan	69.5	54.5-81	96	<0.001	7
Chronic diseases	41.2	20-66	95	<0.001	3
Exposure to seafood market	24.3	9.6-49	95	<0.001	5
Sick contacts with respiratory illness	15	4.5-39.6	97	<0.001	4
Hypertension	15	8.5-24.6	97.5	<0.001	10
ARDS	10.6	4-26.7	95.7	<0.001	5
Diabetes	8	4-15	96	<0.001	8
Current smoker	7.7	3.7-15	69	0.01	5
Chronic liver disease	5.7	3.8-8.4	6	0.38	8
Digestive system disease	3.5	2.5-4.9	95	<0.001	2
Health care worker	3	2-4.6	79	0.008	3
Past smoker	3	1.1-7.5	80	0.02	2
Cardiovascular and cerebrovascular diseases	2.3	2.2-2.5	98	<0.001	8
Chronic respiratory disease	2.2	0.6-8	93	<0.001	4

Cancer	1.7	0.4-7.4	96.3	<0.001	6

ARDS=acute respiratory distress syndrome * Greater than 50% is considered high heterogeneity, less than 50% is considered low heterogeneity. A low p value (<.05) is consistent with high heterogeneity.

Table 4: Laboratory Features for Confirmed Patients with COVID-19

		Confidence interval 95%	normal range	Total Patient Number	Number of Studies
Leucocytes (WBCs)	5.55 (× 10^9 per L)	5.1-5.9	3.5-9.5	2361	11
Increased	13.3 (%)	6.4-25.6			
Decreased	26 (%)	20-33			
Neutrophils	3.6 (× 10^9 per L)	3.1-4.1	1.8-6.3	412	8
Lymphocytes	0.98 (× 10^9 per L)	0.9-1.06	1.1-3.2	2361	11
Decreased	62.5 (%)	42-79			
Platelets	186.5 (× 10^9 per L)	167-205	125-350	2200	9
Decreased	13 (%)	5-30			
Increased	91 (%)	81-98			
CRP*	29.6 (mg/L)	16.7-42.5	0-0.5	290	5
Increased	81 (%)	65-91			
Hemoglobin	119 (g/L)	106-132	130-175	2062	8
ESR**	42 (mm/h)	46-57	0-15	120	2
Albumin	36.8 (g/L)	24.5-46	40- 55	120	2
Decreased	80%	72-87			
Interleukin-6	7.9 (pg/mL)	6.8-8.6	0.0- 7	99	2
Increased	52%	42-61			
LDH***	280	268-294	120- 250	1783	9
Increased	70.3 (%)	58-83			

CRP= C Reaction Protein, ESR= Erythrocyte sedimentation rate. WBCs= White blood cells
*Increased or Decreased refers to values above or below the normal range

Table 5. Chest X-ray and CT scan Findings in Patients with Confirmed COVID-19.

	Abnormality (%)	Confidence interval 95%	Heterogeneity test, I2 (%)**	Heterogeneity test, P Value**	Number of Studies
Bilateral involvement of chest radiography	76.8	62.5-87	93	<0.001	12
Consolidation	75.5	50.5-91	89	<0.001	6
Ground-glass opacity	71	40-90	97	<0.001	12
Unilateral involvement of chest radiography	16.5	8.5-29.5	94	<0.001	6

** Greater than 50% is considered high heterogeneity, less than 50% is considered low heterogeneity. A low p value (<.05) is consistent with high heterogeneity. CT scan= CT scan.