Systematic Review and Meta-Analysis

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Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19

A systematic review and meta-analysis without cases duplication

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Abstract

Background: The pandemic of COVID-19 poses a challenge to global healthcare. The mortality rates of severe cases range from 8.1% to 38%, and it is particularly important to identify risk factors that aggravate the disease.

Methods: We performed a systematic review of the literature with meta-analysis, using 7 databases to identify studies reporting on clinical characteristics, comorbidities and complications in severe and non-severe patients with COVID-19. All the observational studies were included. We performed a random or fixed effects model meta-analysis to calculate the pooled proportion and 95% confidence interval (CI). Measure of heterogeneity was estimated by Cochran's *Q* statistic, I^2 index and *P* value.

Results: A total of 4881 cases from 25 studies related to COVID-19 were included. The most prevalent comorbidity was hypertension (severe: 33.4%, 95% CI: 25.4%–41.4%; non-severe 21.6%, 95% CI: 9.9%–33.3%), followed by diabetes (severe: 14.4%, 95% CI: 11.5%–17.3%; non-severe: 8.5%, 95% CI: 6.1%–11.0%). The prevalence of acute respiratory distress syndrome, acute kidney injury and shock were all higher in severe cases, with 41.1% (95% CI: 14.1%–68.2%), 16.4% (95% CI: 3.4%–29.5%) and 19.9% (95% CI: 5.5%–34.4%), rather than 3.0% (95% CI: 0.6%–5.5%), 2.2% (95% CI: 0.1%–4.2%) and 4.1% (95% CI: −4.8%–13.1%) in non-severe patients, respectively. The death rate was higher in severe cases (30.3%, 95% CI: 13.8%–46.8%) than non-severe cases (1.5%, 95% CI: 0.1%–2.8%).

Conclusion: Hypertension, diabetes and cardiovascular diseases may be risk factors for severe COVID-19.

Abbreviations: AKI = acute kidney injury, ARDS = acute respiratory distress syndrome, COVID-19 = corona virus disease 2019, CI = confidence interval, IQR = interquartile range, MERS-CoV = Middle East respiratory syndrome coronavirus, RR = relative risk, SARS = severe acute respiratory syndrome, SD = standard deviation, WHO = world health organization.

Keywords: coronavirus disease 2019 (COVID-19), meta-analysis, severe

1. Introduction

Since the end of 2019, there's been a surge in cases of COVID-19 with 24,257,989 laboratory-confirmed cases and 827,246 deaths as of August 28st. COVID-19 causes an adverse influence globally, especially in increasing the burden on healthcare. According to latest report,[1–3] case fatality of severe cases (8.1%-38%) is significant high.[4] Severe patients often have dyspnea or hypoxemia 1 week after onset, which may rapidly progress to ARDS, septic shock, metabolic acidosis that is difficult to correct, and coagulation dysfunction. Therefore, it's critical to reveal

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The datasets generated and analysed for this study are available from the corresponding author upon reasonable request.

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early risk factors of severe cases during COVID-19 pandemic, which is helpful for precise treatment and prognosis improvement. Notably, previous studies have clarified that patients particularly vulnerable to severe disease are those with pre-existing medical conditions such as diabetes, cardiovascular diseases, renal failure, obesity, and immunodeficiency.[5,6] Wang et al reported 138 cases of COVID-19 and the result indicated that almost half of hospitalized patients had comorbidities, and patients admitted to ICU with comorbidities was twice as high as without comorbidities.[2] To sum up, evaluating the prevalence of underlying diseases is fundamental to mitigate COVID-19 complications. However, this effort has been hindered by the limited number of cases and confounding classification in preexisting studies.

The present study was undertaken to provide a systematic evaluation without cases duplication to compare the proportion of demographic, comorbidities, symptoms, complications and outcomes between severe and non-severe COVID-19 cases. This assessment may aid the public health sector while developing policies for surveillance and response to COVID-19 and its severe outcomes.

2. Aims

- To compare the differences in the field of demographic, comorbidities, clinical symptoms, complications and outcomes between severe and non-severe COVID-19.
- To conclude the potential risk factors to severe COVID-19 patients.

3. Methods

We registered the study protocol with PROSPERO (registration number ID: CRD42020177414) (Supplemental material: study protocol & PRISMA Checklist).

4. Search strategy

We searched PubMed, Web of Science, Cochrane Library, CBM (Chinese Biomedical), CNKI (China National Knowledge Infrastructure), WanFang, and VIP databases up to March 16, 2020. The search terms were used as follows: "Wuhan coronavirus" OR "COVID-19" OR "novel coronavirus" OR "2019-nCoV" OR "coronavirus disease" OR "SARS-CoV-2" OR "SARS2" OR "severe acute respiratory syndrome coronavirus 2"; the full search strategy is shown in Supplemental material: search strategy. The search was limited to English and Chinese language. We hand-searched included papers' reference lists and contacted experts in the field to ensure a comprehensive review.

5. Inclusion and exclusion criteria

We included studies which:

- Examined laboratory-confirmed patients with COVID-19.
- Examined the demographic, comorbidities (e.g., diabetes, hypertension, cardiovascular disease, etc), clinical symptoms, complications, and outcomes of severe and (or) non-severe patients with COVID-19.
- Reported mean ± SDs or proportion and 95% confidence interval (95% CI) of these factors.
- Observational studies.

We excluded papers which:

- Did not contribute to any variable (e.g., male, female, diabetes, hypertension, cardiovascular disease, COPD, fever, cough, ARDS, AKI, shock, hospitalization, discharge, death, etc) of this study. (We will include the maximum sample size of the same hospital according to each variable, so as to avoid the duplication of sample size.)
- Did not provide full-text.
- Did not publish in either English or Chinese.

6. Screening papers

After excluding duplicate papers, 1 researcher (ZW) screened the titles and abstracts using the eligibility criteria. Then 2 researchers (HD, CO) assessed the rest full-text articles for eligibility. The Kappa value for study inclusion between them was 0.82, which showed strong consistency. Consensus on the inclusion of all studies was agreed by 2 researchers (HD, CO) with any disagreements resolved in a discussion with researcher (ZW).

7. Data extraction and synthesis

Where available, the following information from each article was extracted using a standardized data extracted form: title, study design, study period, location, first author, publication year, sample size of severe or non-severe cases, sex distribution, any comorbidities, diabetes, hypertension, cardiovascular disease, COPD, fever, cough, ARDS, AKI, shock, hospitalization, discharge, death, etc. Particularly, we used the definition of eligible studies as the criteria for the type of disease.

We extracted the counting data as the number of occurrences of an event versus the total number of people reported for that event (n/N). Additionally, we used the mean and standard deviation (SD), or median and interquartile range (or median and range), to record the measurement data.

8. Data analysis

8.1. Quality assessment and analysis

Two researchers (CO, HD) assessed the risk of bias in individual papers using the Newcastle-Ottawa Scale for assessing the quality of cohort studies and case-control studies.[7] This considered the domains of selection, comparability and ascertainment of the outcome of interest. A study with a score of 0 to 3, 4 to 6 and 7 to 9 was considered as poor, intermediate and high quality, respectively. The Weighted Kappa value was 0.67 on quality rating criteria, and consensus was reached through discussion in cases of disagreement on individual rating criteria.

8.2. Statistical analysis

All analyses were conducted using STATA Version 15. Unit discordance for variables will be resolved by converting all units to a standard measurement for that variable. We conducted analyses by severity (severe vs non-severe). We used a random-effects model or a fixed-effects model to calculate the pooled proportion or mean and 95% confidence interval (95% CI) of all reported variables. All P values were based on 2-sided tests and were considered statistically significant at $P < .050$. Measure of heterogeneity, including Cochran's Q statistic and the I^2 index were estimated and reported. The pooled results from a random-

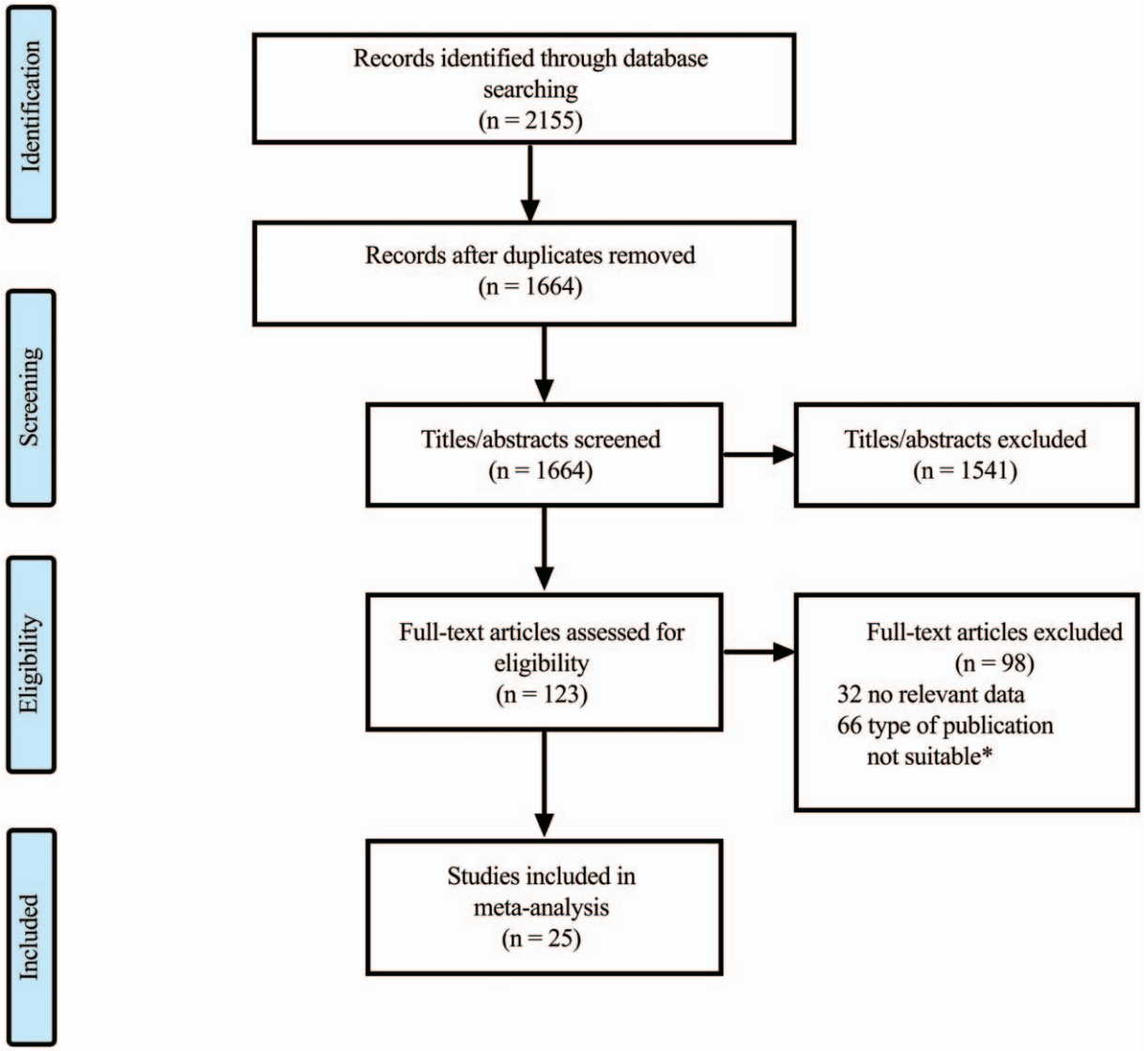

Figure 1. PRISMA flow diagram of included studies. "*" type of publications were reviews, case reports, comments or meta-analysis.

effects model would be reported when the $I^2 > 50\%$ and $P_{\text{heterogeneity}} < .100$, which indicated substantial heterogeneity. Publication bias was checked by visual inspection of funnel plots and tested using Egger's test when ten or more studies reported the variable, and the Egger test with $P < .050$ was considered to be an indication of substantial publication bias.

9. Results

We identified 25 studies[8–30] (Fig. 1) describing 4881 patients diagnosed COVID-19 from December, 2019 to March 16, 2020 (Table 1). All included studies were from hospitals in China mainland, with 12 from Hubei, 4 from Chongqing, 3 from Beijing and 1 each from Anhui, Henan, Hunan, Shanxi, Liaoning and Wenzhou. Publication bias was assessed with a funnel plot for the standard error by logit event, with no evidence of bias (Fig. 2). Additionally, the Egger test ($P = .312$) suggested that there was no notable evidence of publication bias. We analyzed 20 variables for the meta-analysis, the pooled results were all presented in detail in Table 2 and Supplementary online content Figure S1-40. (see Figure, Supplementary Content, which illustrate the demographic characteristics, comorbidities, clinical symptoms, complications and outcomes of the patients by forest plots.)

9.1. Demographic characteristics

The average age was higher in severe cases as compared with non-severe cases (48.5 vs 38.5, $P = .010$). The sex ratio (male to female) was 1.33 in severe cases and 0.95 in non-severe cases. Being aged or male were considered as risk factors to severe COVID-19 (relative ratio (RR) = 1.29, 95% CI: 1.12–1.47) (Fig. 3).

9.2. Comorbidities

The proportion of having comorbidities in severe cases was remarkably higher in severe cases (58.4%, 95% CI: 48.8%–67.9%) than non-severe cases (27.6%, 95% CI: 18.6%–36.6%) ($P < .050$). Meta-analysis showed that in both groups, the most

Table 1

Description of 25 studies retrieved from systematic search.

First Author	Year	Location	Study design	Number of patients	Study period	Quality score
Chaolin Huang[1]	2020	Wuhan, China (Jin-Yintan hospital)	Prospective study	41	By Jan. 2, 2020	7
Cheng Kebin[8]	2020	Wuhan, China (Jin-Yintan hospital)	Retrospective study	463	By Feb. 6, 2020	5
Xiaobo Yang[9]	2020	Wuhan, China (Jin-Yintan hospital)	Retrospective study	52	Dec. 2019 to Jan. 26, 2020	6
Xu Shen[10]	2020	Wuhan, China (Zhongnan hospital)	Retrospective study	62	Jan. 8, 2020 to Feb. 24, 2020	5
Dawei Wang[2]	2020	Wuhan, China (Zhongnan hospital)	Retrospective study	138	Jan. 1, 2020 to Jan. 28, 2020	7
Bai Peng[11]	2020	Wuhan, China (Xiehe hospital)	Retrospective study	58	Jan. 29, 2020 to Feb. 26, 2020	6
Peng Yudong[12]	2020	Wuhan, China (Xiehe hospital)	Retrospective study	112	Jan. 20, 2020 to Feb. 15, 2020	5
Wen Ke[13]	2020	Beijing, China (The Fifth Medical Center of Chinese PLA General Hospital)	Retrospective study	46	Jan. 20, 2020 to Feb. 8, 2020	4
Yuhuan Xu[14]	2020	Beijing, China (The Fifth Medical Center of Chinese PLA General Hospital)	Retrospective study	59	Jan. 2020 to Feb. 2020	5
Wan Qiu[15]	2020	Chongqing, China (Treatment center)	Retrospective study	153	Jan. 26, 2020 to Feb. 5, 2020	5
Yuan Jing[16]	2020	Chongqing, China (Treatment center)	Retrospective study	223	Jan. 24, 2020 to Feb. 23, 2020	6
Xiong Juan[17]	2020	Wuhan, China (Renmin Hospital of Wuhan University)	Retrospective study	89	Jan. 17, 2020 to Feb. 20, 2020	6
Lu Zilong[18]	2020	Wuhan, China (Renmin Hospital of Wuhan University)	Retrospective study	101	Jan. 15, 2020 to Feb. 15, 2020	4
Fang Xiaowei[19]	2020	Anhui, China	Retrospective study	79	Jan. 22, 2020 to Feb. 18, 2020	5
Xiao Kaihu[20]	2020	Chongqing, China (San-Xia hospital)	Retrospective study	143	Jan. 23, 2020 to Feb. 8, 2020	4
Kunhua Li[21]	2020	Chongqing, China (the Second Affiliated Hospital of Chongqing Medical University)	Retrospective study	83	Jan. 2020 to Feb. 2020	5
Cheng Jiuling[22]	2020	Henan, China	Cross sectional	1265	By Feb. 19, 2020	3
Dai Zhihui[23]	2020	Hunan, China	Retrospective study	918	Jan. 21, 2020 to Feb. 13, 2020	4
Gao Ting[24]	2020	Shanxi, China (Xianyang central hospital)	Retrospective study	11	Jan. 20, 2020 to Feb. 15, 2020	5
Li Dan[25]	2020	Liaoning, China	Retrospective study	30	Jan. 22, 2020 to Feb. 8, 2020	6
Chen Chen[26]	2020	Wuhan, China (Tongji hospital)	Retrospective study	150	Jan. 2020 to Feb. 2020	5
SiJia Tian[27]	2020	Beijing, China (Emergency center)	Retrospective study	262	By Feb. 10, 2020	5
Jin-jin Zhang[28]	2020	Wuhan, China (No.7 hospital of Wuhan)	Retrospective study	140	Jan. 16, 2020 to Feb. 3, 2020	5
Chen Min[29]	2020	Hubei, China (the third Renmin hospital of Jianghan university)	Retrospective study	54	Jan. 24, 2020 to Feb. 8, 2020	6
Wenjie Yang[30]	2020	Wenzhou, China	Retrospective study	149	Jan. 17, 2020 to Feb. 10, 2020	6

PLA = People's Liberation Ar.

prevalent comorbidity was hypertension (severe case: 33.4%, 95% CI: 25.4%–41.4%; non-severe cases: 21.6%, 95% CI: 9.9%–33.3%; $P < .050$), followed by diabetes (severe case: 14.4%, 95% CI: 11.5%–17.3%; non-severe cases: 8.5%, 95% CI: 6.1%–11.0%; $P < .050$). Having any comorbidity (RR = 1.96, 95% CI: 1.69–2.26), especially diabetes (RR = 1.53, 95% CI: 1.29–1.82), hypertension (RR = 1.40, 95% CI: 1.22–1.60), cardiovascular disease (RR = 1.79, 95% CI: 1.50–2.13) and COPD (RR = 2.10, 95% CI: 1.70–2.58) were considered as risk factors to severe COVID-19 (Fig. 3).

9.3. Clinical symptoms

Both in severe and non-severe case, the most common clinical symptom was fever (severe: 90.0%, 95% CI: 86.7%–93.3%; non-severe: 78.4%, 95% CI: 70.7%–86.2%; $P < .050$), followed by cough (severe: 69.0%, 95% CI: 60.4%–77.5%; non-severe: 54.2%, 95% CI: 47.0%–61.5%; $P < .050$). Myalgia or fatigue (severe: 36.7%, 95% CI: 25.5%–48.0%; non-severe: 28.8%, 95% CI: 20.2%–37.4%; $P < .050$) and sputum production (severe: 37.3%, 95% CI: 23.3%–51.3%; non-severe: 23.3%, 95% CI: 18.4%–28.1%; $P < .050$) were almost equally prevalent in 2 groups. The overall proportion of clinical symptoms was about 10% to 15% higher in severe patients (RR: 1.60–2.47) (Fig. 3).

9.4. Complications

Severe cases have significantly higher prevalence as compared with control group for ARDS (41.1% vs 3.0%, $P < .050$), AKI (16.4% vs 2.2%, $P < .050$), shock (19.9% vs 4.1%, $P < .050$). ARDS (RR = 5.06, 95% CI: 4.08–6.27), AKI (RR = 2.17, 95% CI: 1.81–2.60) and shock (RR = 3.17, 95% CI: 2.36–4.27) were all risk factors to severe COVID-19 (Fig. 3).

9.5. Outcomes

The mortality was obviously higher in severe cases than non-severe cases (30.3% vs 1.5%, $P < .050$). Severe patients were 2.30 times more likely to die than non-severe patients (RR = 2.30, 95% CI: 2.02–2.63) (Fig. 3).

10. Discussion

This is the first meta-analysis that avoids the phenomenon of included cases duplication, which compares severe and non-severe COVID-19 in the field of demographic features, clinical symptoms comorbidities, complications and outcomes. Based on 4881 laboratory-confirmed cases with COVID-19 in mainland China from 25 studies, we found that severe COVID-19 was more likely to occur in male. In terms of comorbidities, patients combining diabetes, hypertension, cardiovascular disease and COPD were more likely to develop severe COVID-19, which was consistent with the findings of Guan Wei-jie et al to some degree.[31] Fever and cough were the main clinical symptoms in both severe and non-severe cases, which was consistent with previous studies.[1,2,32] As for complications, ARDS, AKI or shock were much more likely to observed in severe cases, which

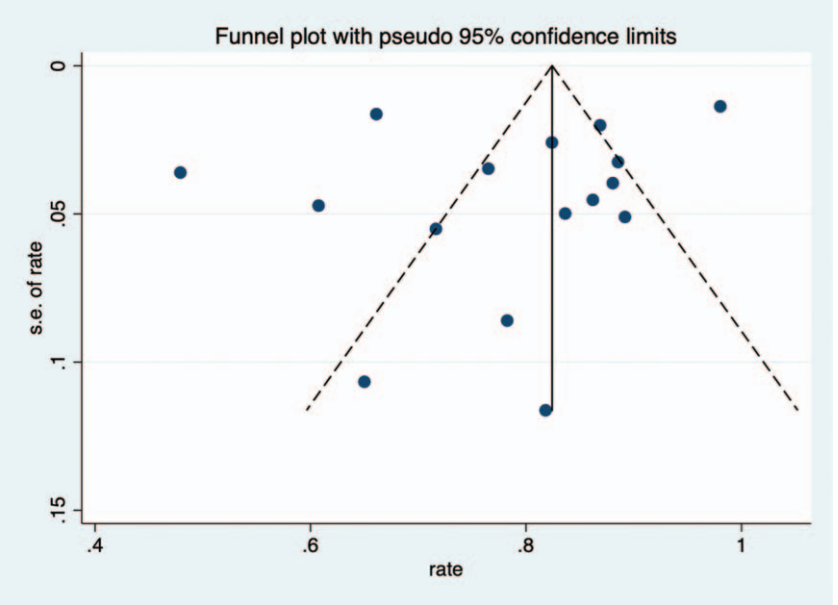

Figure 2. Funnel plot for the standard error by logit event that assess publication bias.

Table 2

The pooled result for each variable.

Variable	Group	Number*	Event	n	Percentage (95% CI)	Heterogeneity			Test for subgroup differences	
						Q	I^2	*P* value	RR (95% CI)	*P* value
Age†	Severe	14	–	599	48.5 (42.7–54.4)	823.14	98.4%	<.100	–	0.010
	Non-severe	15	–	1586	38.5 (34.3–42.6)	2530.23	99.4%	<.100		
Male	Severe	14	351	613	57.8% (53.9%–61.6%)	13.22	1.7%	.430	1.29 (1.12–1.47)	<0.050
	Non-severe	15	778	1600	48.2% (44.6%–51.8%)	26.95	48.0%	.020		
Female	Severe	14	263	613	42.4% (38.5%–46.2%)	13.50	3.7%	.410	0.78 (0.68–0.90)	<0.050
	Non-severe	15	822	1600	51.8% (48.2%–55.4%)	26.95	48.0%	.020		
Any comorbidity	Severe	9	281	500	58.4% (48.8%–67.9%)	36.95	78.3%	<.100	1.96 (1.69–2.26)	<0.050
	Non-severe	10	337	1061	27.6% (18.6%–36.6%)	100.21	91.0%	<.100		
Diabetes	Severe	12	85	551	14.4% (11.5%–17.3%)	9.05	0.0%	.620	1.53 (1.29–1.82)	<0.050
	Non-severe	12	100	1189	8.5% (6.1%–11.0%)	19.85	49.6%	.030		
Hypertension	Severe	13	188	569	33.4% (25.4%–41.4%)	45.16	75.6%	<.100	1.40 (1.22–1.60)	<0.050
	Non-severe	13	277	1212	21.6% (9.9%–33.3%)	410.13	97.1%	<.100		
Cardiovascular disease	Severe	12	56	521	10.4% (6.4%–14.4%)	19.03	47.5%	.040	1.79 (1.50–2.13)	<0.050
	Non-severe	6	33	891	3.3% (1.1%–5.4%)	20.02	75.0%	<.100		
COPD	Severe	8	31	413	6.8% (4.3%–9.2%)	5.73	0.0%	.450	2.10 (1.70–2.58)	<0.050
	Non-severe	7	13	769	1.8% (0.8%–2.9%)	1.38	0.0%	.850		
Malignancy	Severe	6	17	388	3.5% (1.6%–5.4%)	4.89	18.3%	.300	1.09 (0.76–1.57)	0.650
	Non-severe	5	22	579	3.7% (0.9%–6.4%)	10.82	63.0%	.030		
Chronic liver disease	Severe	7	16	423	3.5% (1.7%–5.3%)	2.17	0.0%	.830	0.93 (0.62–1.42)	0.740
	Non-severe	8	37	889	3.8% (2.5%–5.1%)	5.81	0.0%	.450		
Fever	Severe	14	600	672	90.0% (86.7%–93.3%)	23.31	48.5%	.030	2.47 (1.96–3.10)	<0.050
	Non-severe	16	1711	2323	78.4% (70.7%–86.2%)	364.59	95.9%	<.100		
Cough	Severe	14	454	646	69.0% (60.4%–77.5%)	82.55	84.3%	<.100	1.86 (1.59–2.16)	<0.050
	Non-severe	16	1204	2314	54.2% (47.0%–61.5%)	164.90	90.9%	<.100		
Myalgia or fatigue	Severe	13	220	652	36.7% (25.5%–48.0%)	130.41	90.8%	<.100	1.60 (1.40–1.84)	<0.050
	Non-severe	15	476	2234	28.8% (20.2%–37.4%)	416.18	96.6%	<.100		
Sputum production	Severe	9	192	492	37.3% (23.3%–51.3%)	88.94	91.0%	<.100	1.68 (1.44–1.96)	<0.050
	Non-severe	9	420	1723	23.3% (18.4%–28.1%)	35.20	77.3%	<.100		
ARDS	Severe	4	67	144	41.1% (14.1%–68.2%)	43.54	93.1%	<.100	5.06 (4.08–6.27)	<0.050
	Non-severe	5	7	360	3.0% (0.6%–5.5%)	1.37	0.0%	.500		
Acute kidney injury	Severe	4	36	170	16.4% (3.4%–29.5%)	21.56	86.1%	<.100	2.17 (1.81–2.60)	<0.050
	Non-severe	4	6	211	2.2% (0.1%–4.2%)	2.23	10.2%	.330		
Shock	Severe	3	17	80	19.9% (5.5%–34.4%)	5.29	62.2%	.070	3.17 (2.36–4.27)	<0.050

(*continued*)

Table 2

(continued).

Variable	Group	Number*	Event	n	Percentage (95% CI)	Heterogeneity			Test for subgroup differences	
						Q	I^2	*P* value	RR (95% CI)	*P* value
	Non-severe	3	4	188	4.1% (−4.8%–13.1%)	2.70	62.9%	.100		
Hospitalization	Severe	7	149	295	53.9% (32.6%–75.3%)	109.43	94.5%	<.100	0.90 (0.74–1.10)	0.310
	Non-severe	7	439	814	48.9% (28.7%–69.1%)	245.86	97.6%	<.100		
	Severe	7	89	295	30.4% (13.4%–47.4%)	90.02	93.3%	<.100	0.60 (0.48–0.75)	<0.050
	Non-severe	7	374	814	50.6% (30.5%–70.6%)	241.00	97.5%	<.100		
Death	Severe	7	77	267	30.3% (13.8%–46.8%)	103.70	94.2%	<.100	2.30 (2.02–2.63)	<0.050
	Non-severe	4	9	308	1.5% (0.1%–2.8%)	4.86	38.2%	.180		

* The number of available studies included in the analysis for each variable.

† Age expressed as mean and 95% CI.

was in accordance with the finding on Middle East respiratory syndrome coronavirus (MERS-CoV).[6,33]

Based on results of clinical symptoms, we found a significant difference between severe and non-severe patients with COVID-19 on overall factors. But in clinical practice, it is difficult to conclude whether a patient is more likely to develop severe or non-severe COVID-19 based on such clinical symptoms. Nonetheless, clinical symptoms are undoubtedly essential for the screening of suspected cases.

Based on our results, we found that severe COVID-19 patients may be usually combined with comorbidities on admission especially as diabetes, hypertension and cardiovascular disease,

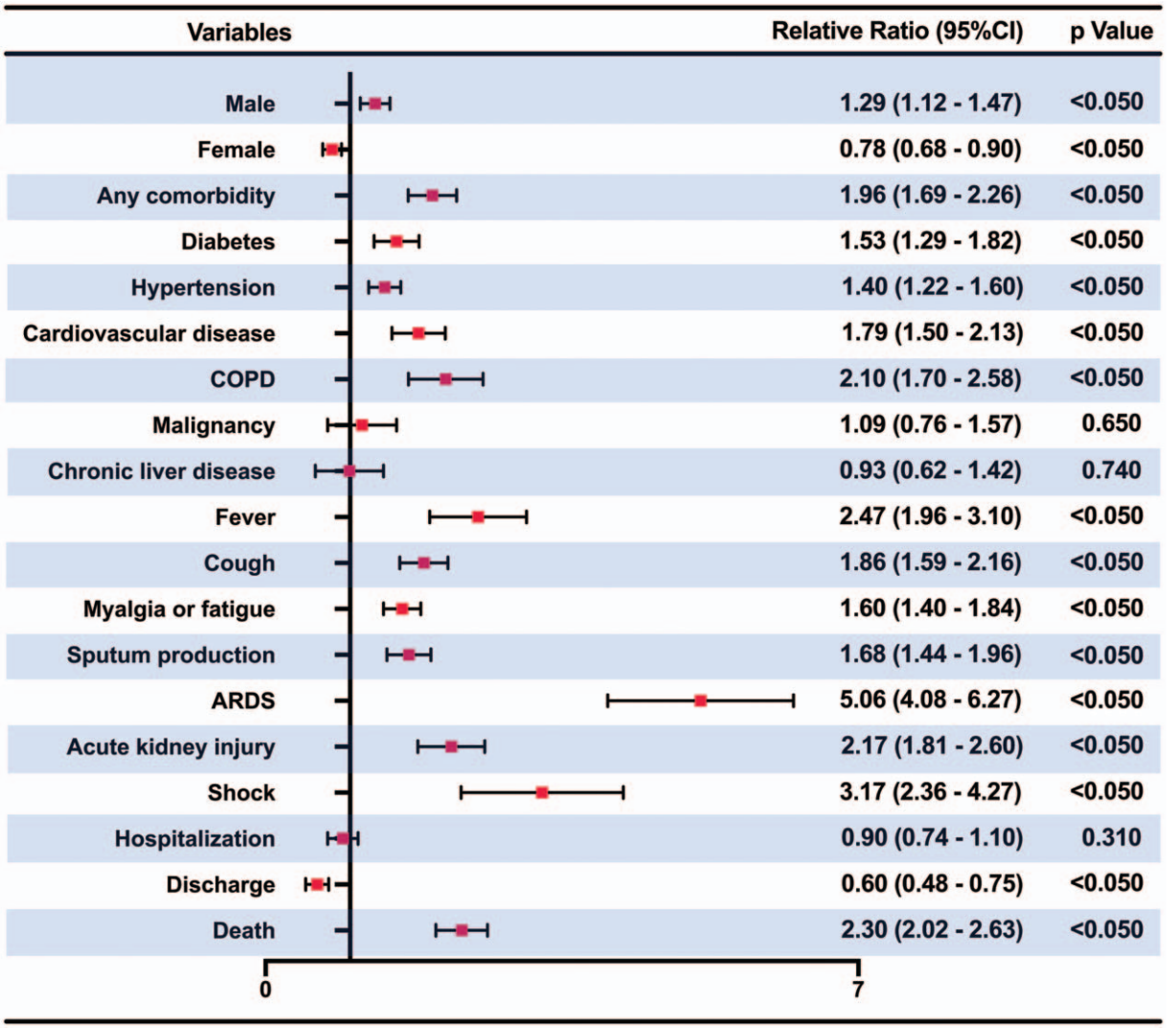

Figure 3. The relative ratio (RR) and the 95% confidence interval (95% CI) for the factors associated with the severe COVID-19.

which could affect some key mediators of the host's innate immune response.[33] Previous findings on MERS-CoV also found that people with severe illness were more likely to combine these underlying comorbidities.[33] This can be explained by the phenomenon of cytokine storm that a variety of cytokines gather in the body fluids. Early studies of MERS-CoV found that the amount of Th1/Th2 cytokines profile was higher in patients with diabetes, hypertension or cardiovascular disease which was linked with exacerbation of pro-inflammatory state and generation of oxidative stress.[17,34–38] Studies have shown that cytokine storm indicate poor prognosis and tissue damage.[10] So far in COVID-19 patients, research has shown that ICU patients had higher plasma levels of IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α compared with non-ICU patients.[1]

Considering that these cytokines mainly belong to Th1 or Th2 subgroups, we infer that patients with comorbidities, especially those with diabetes, hypertension or cardiovascular disease, are more likely to develop severe COVID-19. Therefore, we suggest that clinicians can pay more attention to patients with comorbidities, which may prevent the development of severe COVID-19 and its progressive complications with suitable care.

Also, it is believed that cytokine storm is also an important cause of ARDS and multiple organ failure in patients with viral infections.[39,40]

Therefore, we considered that patients having diabetes, hypertension or cardiovascular disease on admission were more likely to suffer from potentially fatal complications such as ARDS, AKI and shock during disease progression.

As mentioned on complications of severe and non-severe patients, we found that the incidence of ARDS, AKI and shock were remarkably higher in severe patients. This was also consistent with the conclusion of previous research that secondary pneumonia, ARDS, encephalitis, myocarditis and other potentially fatal complications could occur in severe patients.[6,33] These severe clinical manifestations caused by the underlying comorbidities can also be seen in other respiratory diseases such as influenza and influenza H1N1.[32,39,41] With evaluating the occurrence of complications induced by SARS-CoV-2 infection, it helps us fully understand the adverse impact and disease burden of severe COVID-19.

In general, figuring out differences on comorbidities, clinical symptoms and complications between severe and non-severe patients may provide an evidence base to clinicians through the meta-analysis approach. Besides, due to the similarity between COVID-19 with SARS and MERS to a certain extent, we could draw some experience in the previous studies of SARS and MERS while comparing with the studies of COVID-19 as well. We hope that this assessment may aid the public health sector while developing policies for surveillance and response to COVID-19 and its severe outcomes.

11. Strengths and limitations

We followed the PRISMA procedure in this meta-analysis for medical evidence searching. Additionally, we excluded the potential repeated cases from the same hospital or region according to every specific variable which we are about to analyze, avoiding to amplify the false effect of some factors by including many duplicate cases.

There are still some limitations in this study. First, all the included studies are conducted in mainland China, so the outcomes may not be suitable for the international situation at present. Second, because of the lack of available data, we could not make a statement of the comparison for geographic region (Wuhan, China vs outside Wuhan), which was designed in the study protocol. Third, there were some differences in the proportion of diabetes, hypertension or cardiovascular diseases between the studies, which may be a source of heterogeneity.

But these results can play a certain reference value and alert role for future epidemic prevention and treatment measures.

12. Conclusion

There is a significant difference between severe and non-severe patients with COVID-19 in terms of demographic features, clinical symptoms, comorbidities, complications and outcomes. Hypertension, diabetes and cardiovascular diseases may be risk factors for COVID-19 patients to develop into severe cases.

Author contributions

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