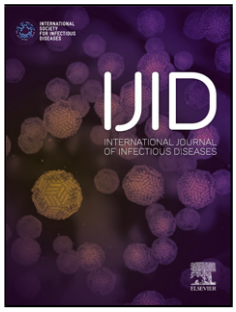
Journal Pre-proof



Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis

Jing Yang, Ya Zheng, Xi Gou, Ke Pu, Zhaofeng Chen, Qinghong Guo, Rui Ji, Haojia Wang, Yuping Wang, Yongning Zhou

PII: S1201-9712(20)30136-3

DOI: https://doi.org/10.1016/j.ijid.2020.03.017

Reference: IJID 4023

To appear in: *International Journal of Infectious Diseases*

Received Date: 28 February 2020

Revised Date: 4 March 2020

Accepted Date: 5 March 2020

Please cite this article as: Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y, Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis, *International Journal of Infectious Diseases* (2020), doi: https://doi.org/10.1016/j.ijid.2020.03.017

Prevalence of comorbidities in the Novel Wuhan Coronavirus (COVID-19) infection: a systematic review and meta-analysis.

Jing Yang[1,2,#], Ya Zheng[1,3,#], Xi Gou[1,4,#], Ke Pu[1,3], Zhaofeng Chen[1,4], Qinghong Guo[1,3,4], Rui Ji[1,3,4], Haojia Wang[1], Yuping Wang[1,3,*], Yongning Zhou[1,3,4,*]

1 Department of Gastroenterology, the First Hospital of Lanzhou University, Lanzhou, China

2 The First Clinical Medical School of Lanzhou University, Lanzhou, China

3 Key Laboratory for Gastrointestinal Diseases, Gansu Province, the First Hospital of Lanzhou University, Lanzhou, China

4 Gastrointestinal Endoscopy Center, Department of Gastroenterology, the First Hospital of Lanzhou University, Lanzhou, China

# These authors contributed equally to the work.

* Corresponding author:

Yongning Zhou, Department of Gastroenterology, Gastrointestinal Endoscopy Center, Key Laboratory for Gastrointestinal Diseases, Gansu Province, the First Hospital of Lanzhou University, Lanzhou, Gansu Province, 730000, China. Tel: +86-931-8356224. E-mail: zhouyn@lzu.edu.cn;

Yuping Wang, Department of Gastroenterology, Key Laboratory for Gastrointestinal Diseases, Gansu Province, the First Hospital of Lanzhou University, Lanzhou, Gansu Province, 730000, China. Tel: +86-931-8356323. E-mail: wangyuping@lzu.edu.cn.

Highlights

- COVID -19 cases now confirmed in multiple countries.
- assessed the prevalence of comorbidities in infected patients.
- comorbidities are risk factors for severe patients compare with Non-severe.

- help the health sector guide vulnerable populations and assess the risk of deterioration.

Background: An outbreak of Novel Coronavirus (COVID -19) in Wuhan, China, the epidemic is more widespread than initially estimated, with cases now confirmed in multiple countries.

Aims: The aim of the meta-analysis was to assess the prevalence of comorbidities in the COVID-19 infection patients and the risk of underlying diseases in severe patients compared to non-severe patients.

Methods: A literature search was conducted using the databases PubMed, EMBASE, and Web of sciences until February 25, 2020. Risk ratio (OR) and 95% confidence intervals (CIs) were pooled using random-effects models.

Results: Eight studies were included in the meta- analysis, including 46248 infected patients. The result showed the most prevalent clinical symptom was fever (91±3, 95% CI 86-97%), followed by cough (67±7, 95% CI 59-76%), fatigue (51±0, 95% CI 34-68%) and dyspnea (30±4, 95% CI 21-40%). The most prevalent comorbidity were hypertension (17±7, 95% CI 14-22%) and diabetes (8±6, 95% CI 6-11%), followed by cardiovascular diseases (5±4, 95% CI 4-7%) and respiratory system disease(2±0, 95% CI 1-3%). Compared with the Non-severe patient, the pooled odds ratio of hypertension, respiratory system disease, cardiovascular disease in severe patients were (OR 2.36, 95% CI: 1.46-3.83) ,(OR 2.46, 95% CI: 1.76-3.44) and (OR 3.42, 95% CI: 1.88-6.22)respectively.

Conclusion: We assessed the prevalence of comorbidities in the COVID-19 infection patients and found underlying disease, including hypertension, respiratory system disease and cardiovascular, may be a risk factor for severe patients compared with Non-severe patients.

Keywords: 2019-nCoV, COVID-19, comorbidities, clinical characteristics, epidemiological, meta-analysis;

1. Introduction

On December 31, 2019, a cluster of cases of “pneumonia of unknown origin” in people associated with the Huanan Seafood Wholesale Market has been reported in Wuhan, China. Only a few days later, Chinese health authorities confirmed that this cluster was associated with a Novel Coronavirus [1] and was named COVID-19 by WHO. Confirmed by comparative homology analysis, COVID-19 is closely associated with bat-derived severe acute respiratory syndrome (SARS)-like coronavirus (bat-SL-covzc45 and bat-SL-covzxc21) (with 88% identity,) but is far away from SARS-Cov (about 79%) and MERS-Cov (about 50%) [2]. A total of 77 658 confirmed cases, including 9162 with severe illness, and 2663 death had been reported， as of February 25, 2020, by the National Health Commission of China. Huang et al first reported the clinical features of 41 confirmed patients, indicated 13 (32%) of them had underlying diseases [3], including cardiovascular disease, diabetes, hypertension, and chronic obstructive pulmonary disease. Subsequently, Wang et al reported findings from 138 cases of COVID-19 the results suggested that 64(46.4%) of them had comorbidities. Importantly, the patients admitted to the intensive care unit (ICU) had a higher number of comorbidities(72.2%) than those not admitted to the ICU（37.3%）. This suggests that complications may be a risk factor for adverse outcomes [4]. Assessing the prevalence of these chronic diseases is the basis for mitigating complications in patients with COVID-19 infections. However, the effort was hampered by the limited number of cases.

To get a more convincing result, we will provide a systematic evaluation and detail not only estimate the Prevalence of comorbidities in all patients, also assess the risk of underlying diseases in severe patients compared to non-severe patients. The result may aid the management while developing policies for prevention, and response to COVID-19 and its critical outcomes.

2. Methods

2.1. Search strategy and selection criteria

A systematic search was conducted on studies published from January 1, 2019 to February 25, 2020 in PubMed, EMBASE, and Web of Science databases. Records were managed by EndNote X 9.0 software to exclude duplicates. According to the indices of the various databases, we use the search term “2019 novel coronavirus and COVID-19” AND “comorbidities, clinical characteristics, epidemiological” without any language restriction. To identify missing studies, we had checked the reference list for each selected paper. Eligible studies should describe the epidemiological, clinical features of (COVID-19), and the prevalence of Chronic diseases in infected patients. Studies that (a) duplicate publications, (b) reviews, editorials, case reports, letters, and family-based studies, (c) only children cases, were excluded. The steps of the literature search are shown in Figure 1.

2.2. Data extraction and analysis

The two investigators (J Yang and YP Wang) who performed the literature search also independently extracted the data from included studies. Disagreements were resolved with a third investigator (YN Zhou) or by consensus. We extracted the following variables: author, date, age, gender, number of participates in severe and Non-severe, the prevalence of clinical symptoms such as fever, cough, fatigue, and dyspnea, together with comorbidities including hypertension, diabetes, respiratory system disease, and cardiovascular diseases. All calculations were performed by STATA MP version 13.0. The odds ratio (OR, 95% confidence intervals (CI)) was used to describe the ratio of the probability of the Coronavirus occurring in severe patients vs. Non-severe. Owing to heterogeneity within and between studies, a random effect model was used to estimating the average effect and its precision, which would give a more conservative estimate of the 95% CI. Using the I^2 statistic and Cochran's Q test to assess statistical heterogeneity.

3. Result

Terms initially searched a total of 108 articles. After we removed duplicates, checked the title and abstract, and reviewed full-text, eight studies [3-10] eventually met the predetermined inclusion and exclusion criteria. As of February 25, 2020, a total of

46248 participants were included in our meta- analysis. As presented in Table 1, the median age was 46.0 years and 23871 (51.6%) were men.

The result of this meta-analysis showed the most prevalent clinical symptom was fever (91±3, 95% CI 86-97%), followed by cough (67±7, 95% CI 59-76%), fatigue (51±0, 95% CI 34-68%) and dyspnea (30±4, 95% CI 21-40%). However, the I^2 varying from 84.9% to 96.4% in the evaluates of the clinical features showed significant statistic heterogeneity (p=0.00). The prevalence of comorbidities including hypertension, diabetes, respiratory system disease, and cardiovascular diseases. As shown in Figure 2 (inserts A, B, C, D), the most prevalent comorbidity were hypertension (17±7, 95% CI 14-22%) and diabetes (8±6, 95% CI 6-11%),followed by cardiovascular diseases (5±4, 95% CI 4-7%) and respiratory system disease(2±0, 95% CI 1-3%). In analysis by the proportion of comorbidities, the significant heterogeneity observed for estimates of hypertension, diabetes and cardiovascular diseases (p=0.000), but not respiratory system disease (p=0.126) with an I^2 index ranging from 39.9 to 87.5%.

In Figure 3, we analyzed the relationship between complications and severe group and Non-severe group. A higher risk of with hypertension, respiratory system disease, and cardiovascular diseases in the severe group compared to those in Non-severe, the result were (OR 2.36, 95% CI: 1.46-3.83), (OR 2.46, 95% CI: 1.76-3.44) and (OR 3.42, 95% CI: 1.88-6.22)respectively. They showed low heterogeneity, with I^2 from 0 to 39.3 %. However, it was not a statistically significant difference in diabetes, (OR 2.07, 95% CI: 0.89- 4.82).

4. Discussion

The meta-analysis was based on data from 8 studies with laboratory- confirmed COVID -19. All the cases were from hospitals in China. The result we observed more men than women, statistics about 23871:22377 in the COVID-19 infection. MERS-CoV and SARS- CoV have also been found to infect more males than females [11,12]. It is customary to think women are less likely to affect many bacteria and viruses than men, partly because of their more robust innate and adaptive immune responses [13].

However, it may be related to the occupational risk factors for men in Huanan wet market exposure history in Huang's report [3]. Aged people and severe patients are more susceptible to COVID-19, this may be associated with a higher frequency of comorbidities [9].

A meta-analysis of the comorbidities suggests that hypertension prevalent in approximately 17% of the patients, diabetes, cardiovascular diseases, and respiratory system disease were present in 8%, 5%, and 2% of the cases, respectively. Hypertension, diabetes mellitus consistent with the prevalence of hypertension and diabetes in China were 23.2%[14] and 10.9%[15] in adults. A recent study about influenza illness suggested that compared to patients with no comorbidities, the risk of death for severe patients more often in those who had chronic obstructive pulmonary disease (OR 1.49, 95% CI: 1.10-2.01), and in those who had cardiovascular disease(OR 2.92, 95% CI: 1.76-4.86), hypertension(OR 1.49,95% CI: 1.10-2.10)[16]. The comorbidities effect had also been noted to have similar effects in other respiratory illnesses, such as MERS-CoV [11]. In our study, the association also showed in hypertension, cardiovascular diseases, and respiratory system disease group. Overall, the severe patients were older [4] and had a more significant number of comorbid conditions than those Non-severe. These results suggest that age and comorbidities may be risk factors for critical patients.

The diseases such as hypertension, diabetes, respiratory system disease, cardiovascular diseases, and their susceptibility conditions, may be linked to the pathogenesis of COVID-19. Chronic diseases share several standard features with infectious disorders, such as the proinflammatory state, and the attenuation of the innate immune response. For instance, diabetes occurs in part because the accumulation of activated innate immune cells in metabolic tissues leads to the release of inflammatory mediators, especially, IL-1β and TNFα, which promotes systemic insulin resistance and β-cell damage [17]. Besides, metabolic disorders may lead to low immune function by impairing macrophage and lymphocyte function [18], which may make individuals more susceptible to disease complications [11]. Recently, Guo et al [19] retrospectively analyzed the clinical data of patients with viral pneumonia and found

that the absolute count levels of CD3+ T cell, CD3+ CD8+ T cell and CD3+ CD4+ T cell in the death group were significantly lower than those in the survival group, suggesting that the levels of various inflammatory factors in the death group were higher than those in the survival group. A prospective case control study about seasonal influenza was conducted by Hong et al [20], Their result showed that diabetes and chronic cardiovascular disease were significantly related to development of complications, and diabetes was an independent risk factor for severe seasonal influenza (odds ration OR: 3.63, 95% CI(1.15-11.51)， P=0.02). Furthermore, a study analyzed the risk factors for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) patients, finding diabetes, Smoking, and heart disease were also significantly associated with MERS-CoV illness [21].

Limitations of this meta-analysis should be addressed. First, the high statistic heterogeneity could be found. This may relate to the study designs and large variation among studies in the sample size (9 to 46248 patients). Second, different lengths of follow-up may miss the event leading to heterogeneity. Owing to some patients are still in hospital in the included studies. Third, because only a few studies compared the comorbidities of severe and Non-severe patients, we did not conduct sensitivity analysis and subgroup analysis.

If causality exists between chronic diseases and COVID-19, it will help the health sector guide vulnerable populations and assess the risk of deterioration. Lau et al [22] followed up the vaccinations of 91,605 people with diabetes, the results showed that the flu vaccine could make the incidence of influenza and pneumonia in people with diabetes aged (<65 years) decreased by 43%, and diabetes in the elderly (≥65 years) people fell 55%. The symptoms of COVID-19 are similar with those of influenza (e. g, fever, cough or fatigue), and outbreaks occur during the year of a high prevalence of respiratory diseases caused by influenza, respiratory syncytial virus, and other respiratory viruses. Vaccines can still be useful in helping prevent flu and will reduce possible confusion with the COVID-19 infection [23].

Hypertension, diabetes, respiratory system disease, and cardiovascular disease period were identified as potentially important risk factors that should be included in future

vaccination recommendations. Given the limited level of evidence, more adequately and powered study should be conducted to prove the association. The prevalence of chronic diseases is increasing year by year, targeted public health vaccination interventions must be adopted to better protect people with chronic diseases from COVID-19 and other respiratory infections.

Funding Source

This project is supported by the Gansu Provincial COVID-19 Science and Technology Major Project, China; Talent Innovation and Entrepreneurship Project of Lanzhou, China (2019-RC-33); Excellence Program of the First Clinical Medical College of Lanzhou University, China.

Ethics

The study does not require ethical approval because the meta-analysis are based on published research and the original data are anonymous.

Conflict of interest

The authors declared that they have no conflicts of interest to this work.

Conflict of Interest Statement

We declare that there are no potential conflicts of interest.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Hui DS, E IA, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. *Int J Infect Dis* 2020; **91**: 264-6.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-74.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 2020.
5. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020.
6. Kui L, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. *Chin Med J* 2020.
7. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China Life Sciences* 2020; **63**: 364-74.
8. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)-China, 2020. *China CDC Weekly* 2020; **2**: 113-22.
9. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. *Allergy* 2020; **00**: 1-12.
10. Zhang MQ, Wang XH, Chen YL, Zhao KL, Cai YQ, An CL, et al. Clinical features of 2019 novel coronavirus pneumonia in the early stage from a fever clinic in Beijing. *Zhonghua jie he he hu xi za zhi* 2020; **43**: E013.
11. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis* 2016; **49**: 129-33.
12. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *Journal of immunology* 2017; **198**: 4046-53.
13. Jaillon S, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. *Clinical reviews in allergy immunology* 2019; **56**: 308-21.
14. Hu S, Gao R, Liu L, Zhu M, Wang W, Wang Y, et al. Summary of the 2018 report on cardiovascular diseases in China. Chin Circ J 2019; **34**: 209.
15. Liu M, Liu SW, Wang LJ, Bai YM, Zeng XY, Guo HB, et al. Burden of diabetes, hyperglycaemia in China from to 2016: Findings from the 1990 to 2016, global burden of disease study. Diabetes Metab 2019; **45**: 286-93.
16. Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013;

347: f5061.
17. Odegaard JI, Chawla A. Connecting type 1 and type 2 diabetes through innate immunity. *Cold Spring Harbor perspectives in medicine* 2012; **2**: a007724.
18. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *The Lancet Infectious diseases* 2009; **9**: 737-46.
19. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. *Front Microbiol* 2019; **10**: 2752.
20. Hong KW, Cheong HJ, Choi WS, Lee J, Wie SH, Baek JH, et al. Clinical courses and outcomes of hospitalized adult patients with seasonal influenza in Korea, 2011-2012: Hospital-based Influenza Morbidity & Mortality (HIMM) surveillance. *Journal of infection and chemotherapy* 2014; **20**: 9-14.
21. Alraddadi BM, Watson JT, Almarashi A, Abedi GR, Turkistani A, Sadran M, et al. Risk Factors for Primary Middle East Respiratory Syndrome Coronavirus Illness in Humans, Saudi Arabia, 2014. *Emerging infectious diseases* 2016; **22**: 49-55.
22. Lau D, Eurich DT, Majumdar SR, Katz A, Johnson JA. Effectiveness of influenza vaccination in working-age adults with diabetes: a population-based cohort study. *Thorax* 2013; **68**: 658-63.
23. Patel A, Jernigan DB. Initial public health response and interim clinical guidance for the 2019 novel coronavirus outbreak - United States, December 31, 2019-February 4, 2020. *American journal of transplantation* 2020; **20**: 889-95.

Figure Legend

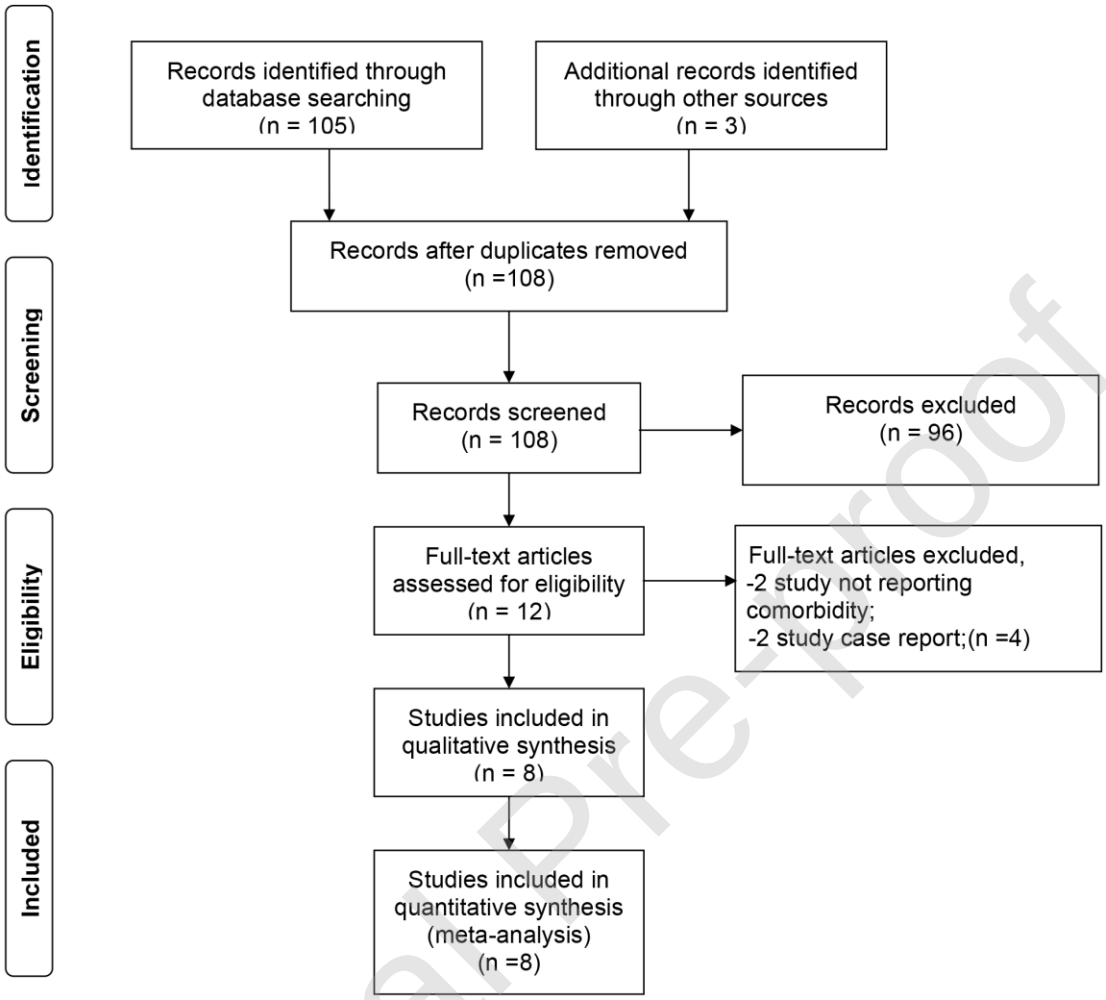


Figure 1 Flow diagram of the number of studies screened and included in the meta-analysis.

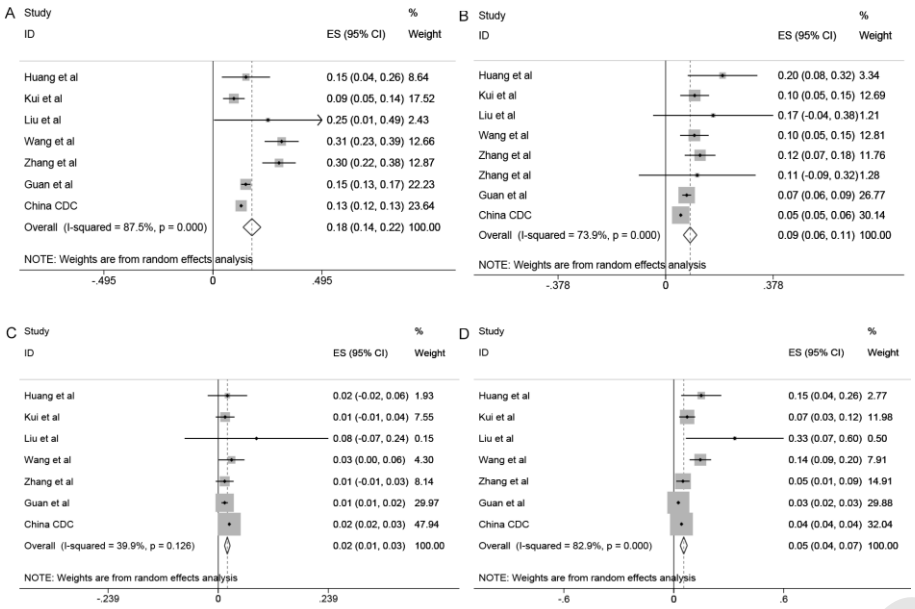


Figure 2 Meta-analysis of the proportion of comorbidities in COVID-19 cases. A, B, C, D represent proportions of hypertension, diabetes, Respiratory system disease, and Cardiovascular disease.

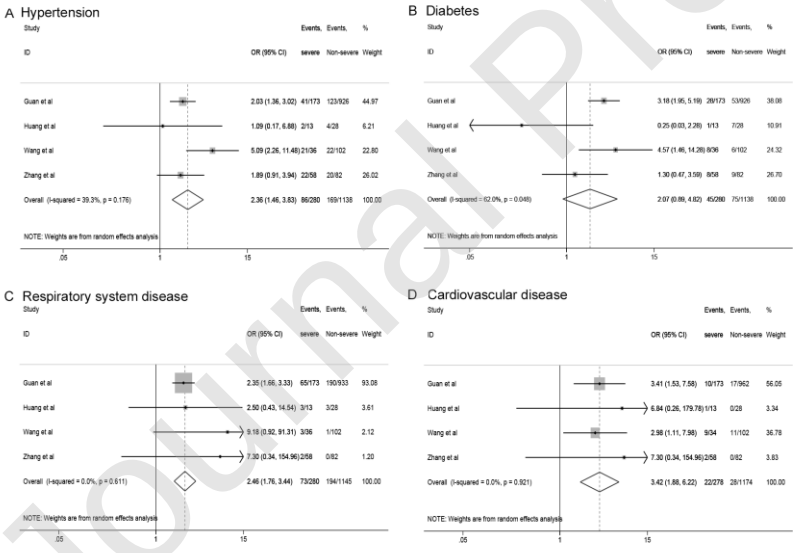


Figure 3 The risk of comorbidities in severe patients compared to Non-severe patients. (A) hypertension, (B) diabetes, (C) Respiratory system disease, (D) Cardiovascular disease.

Table 1 Main Characteristics of included studies in the meta-analysis.

Study	Date (month, day)	Patients （No.）		Age (year)	Symptoms (%)				Coronavirus (%)			
		All	Male		Fever	Cough	fatigue	Dyspnea	Hypertension	Diabetes	Respiratory system disease	Cardiovascular diseases
Huang et al	12.16-01.02	41	30	49.0	98.0	76.0	44.0	55.0	15.0	20.0	2.0	15.0
Kui et al	12.30-01.24	137	61	57.0	81.8	48.2	32.1	19.0	9.5	10.2	1.5	7.3
Liu et al	01.10-01.21	12	8	53.7	83.3	91.7			25.0	16.7	8.3	33.3
Wang et al	01.01-01.28	138	75	56.0	98.6	59.4	69.6	31.2	31.2	10.1	2.9	14.5
Zhang et al	01.06-02.03	140	71	57.0	91.7	75.0	75	36.7	30.0	12.1	1.4	5.0
Zhang et al	01.18-02.03	9	5	35.2	88.9	55.6	44.4		0	11.1	0	0
Guan et al	-01.29	1099	640	47.0	87.9	67.7	38.1	18.6	14.9	7.4	1.4	2.5
China CDC [c]	12.31-02.11	44672	22981	45.9					12.8	5.3	2.4	4.2
Total	12.16-02.03	46248	23871	46.0 [a]								
Prevalence ±SE [b]					91±3	67±7	51±0	30±4	17±7	8±6	2±0	5±4
95% CI					86-97	59-76	34-68	21-40	14.0-22.0	6.0-11.0	1.0-3.0	4.0-7.0
I^2 (%)					92.1	84.9	96.4	91.1	87.5	73.9	39.9	82.9
P for heterogeneity					0	0	0	0	0	0	0.126	0

a, average age; b, Meta-analysis for the prevalence was calculated from binary random-effects model analysis; c, The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team