Impact of cardiovascular and metabolic diseases on the severity of COVID-19: a systematic review and meta-analysis

Meng Meng[1,*], Qianwen Zhao[2,*], Rahul Kumar[3,*], Chen Bai[4], Yunlei Deng[5], Bo Wan[6]

[1]Digestion Center, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China
[2]Department of Gastroenterology and Hepatology, Sichuan University-Oxford University Huaxi Gastrointestinal Cancer Centre, West China Hospital, Sichuan University, Chengdu, China
[3]Department of Gastroenterology and Hepatology, Changi General Hospital, Singapore
[4]Beijing University of Chinese Medicine, Beijing, China
[5]Department of Nephrology, The Third People's Hospital of Chengdu, Chengdu, China
[6]Centre for Stem Cells and Regenerative Medicine, King's College London, Guy's Hospital, Great Maze Pond, London, UK
*Equal contribution and co-first authors

Correspondence to: Bo Wan; **email:** bo.wan@kcl.ac.uk

ABSTRACT

We examined the effects of coronary heart disease (CHD), hypertension and diabetes on the development of severe COVID-19. We performed a comprehensive, systematic literature search for studies published between December 2019 and July 5, 2020 in five databases. The prevalence of severe COVID-19 in patients with CHD, hypertension and diabetes was evaluated through a meta-analysis. Thirty-five articles with 8,170 patients were included, and all the available studies were case series. The pooled odds ratio for the development of severe COVID-19 was 3.21 for patients with CHD (fixed-effects model, 95% CI: 2.58-3.99), 2.27 for patients with hypertension (random-effects model, 95% CI: 1.79-2.90) and 2.34 for patients with diabetes (random-effects model, 95% CI: 1.79-3.05). The heterogeneity of the studies was moderate for the effect of CHD on COVID-19 severity, but was high for the effects of diabetes and hypertension. Funnel plots and Egger's tests revealed no publication bias in the CHD and hypertension analyses, but suggested publication bias in the diabetes analysis. This bias was corrected using the trim-and-fill method, and was ultimately found to have no effect on the results. Our findings suggest patients with CHD, hypertension and diabetes are at greater risk for developing severe COVID-19 than those without these conditions.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was newly discovered in December 2019 [1]. By March 2020, the outbreak had spread to more than 200 countries, rapidly evolving into a pandemic. At the time of the World Health Organization's situation report on July 12, 2020, over 12 million laboratory-confirmed cases and 550,000 deaths had been documented globally.

Elderly patients and those with pre-existing health conditions are more likely to progress to severe COVID-19 [2, 3]. Coronary heart disease (CHD), hypertension and diabetes are the most prevalent diseases worldwide, as their prevalence increases with advancing age. A previous meta-analysis indicated that patients with pre-existing cardiovascular and metabolic

diseases may be at increased risk for intensive care unit admission and poor outcomes upon infection with SARS-CoV-2 [4]. However, the analysis only included six studies with relatively high heterogeneity, raising some questions about the reliability of the conclusions. Therefore, the risk of COVID-19 progression in patients with cardiovascular and metabolic diseases requires further investigation.

Herein, we conducted a meta-analysis to investigate the relationship between severe COVID-19 and underlying CHD, hypertension and diabetes.

RESULTS

Research study selection and quality assessment

Based on our search strategy, 29,617 studies were retrieved from five online databases. Duplicate records were deleted, such that 18,924 records were retained. Of these, 18,852 articles were excluded based on their titles and abstracts, and 37 of the remaining 72 articles were deleted for various other reasons (Figure 1). Ultimately, 35 articles (one in Chinese and the remainder in English) were included in the meta-analysis [5–39]. The characteristics and patient demographics of the included studies are shown in Table 1. The quality of the included articles was also evaluated, as shown in Table 2. The Methodological Index for Non-Randomized Studies (MINORS) scores of the studies ranged from 10-14.

Characteristics of the included studies

Of the 8,170 patients in the 35 studies included in this meta-analysis, 2,415 patients (29.56%) met the criteria for severe COVID-19. Ten studies did not report the prevalence of CHD [9, 18, 19, 22, 24, 27, 31, 32, 35, 37], five studies did not report the prevalence of hypertension [14, 20, 32, 36, 39] and three studies did not report the prevalence of diabetes [24, 34, 36]. The remaining studies reported the prevalence of CHD, hypertension and diabetes in their respective patient pools. In the original data, the prevalence of each disease in severe or non-severe COVID-19 patients was presented. To better visualize the risk, we converted the data and presented the incidence of severe COVID-19 in the populations with CHD, hypertension and diabetes.
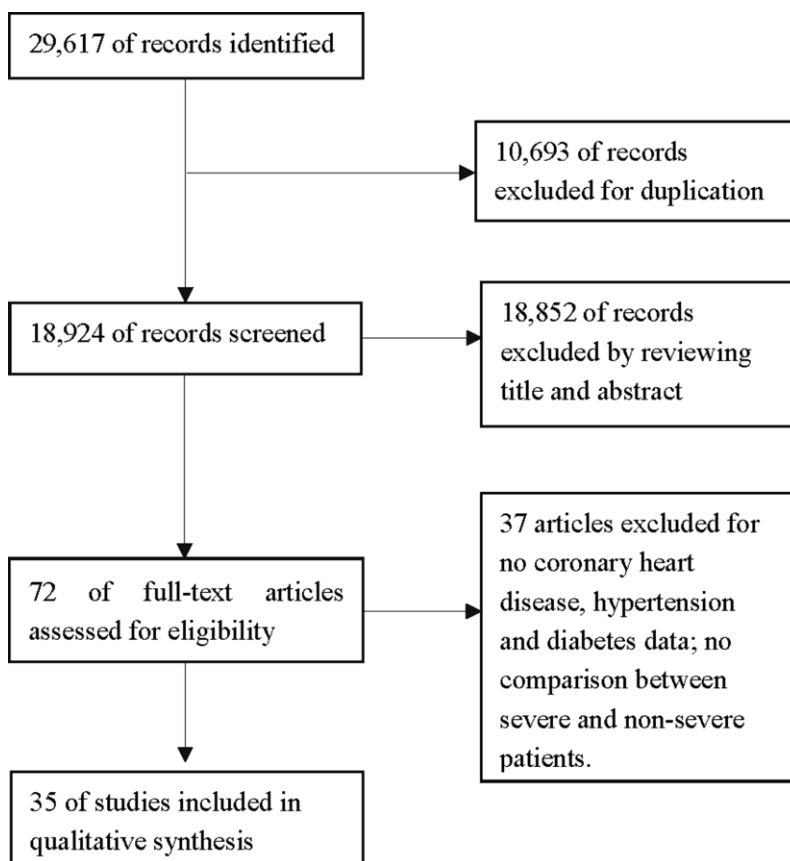

Figure 1. Flow diagram of the literature screening.

Table 1. Characteristics and demographic data of the included studies.

author	year	origin	language	outcome	mean age	male n(%)	severe cases /total cases —no./total no. (%)	severe cases in Coronary heart disease/total cases of Coronary heart disease —no./total no. (%)	severe cases in Hypertension / total cases of Hypertension — no./total no. (%)	severe cases in Diabetes/ total cases of Diabetes — no./total no. (%)
COVID-19 Australia Incident Room Surveillance Team	2020	Australia	English	ICU	58.67	306(51.00%)	157/600(26.17%)	NR	NR	38/107(35.51%)
D. Colombi	2020	Italy	English	ICU	68.00	177(75.00%)	108/236(45.76%)	77/127(60.63%)	NR	22/37(59.46%)
M. Choi	2020	South Korea	English	Composite End Point	33.33	214(73.04%)	36/293(12.29%)	NR	9/29(31.03%)	10/21(47.62%)
Y. Deng	2020	China	English	Death	55.83	124(55.11%)	109/225(48.44%)	13/17(76.47%)	40/58(68.97%)	17/26(65.83%)
X. Fang	2020	China	Chinese	Composite End Point	45.10	45(56.96%)	24/79(30.38%)	2/3(66.67%)	11/16(68.75%)	4/8(50.00%)
P. Goyal	2020	US	English	Composite End Point	61.50	238(60.60%)	130/393(33.08%)	NR	70/197(35.53%)	36/99(36.36%)
W. Guan	2020	China	English	Composite End Point	46.67	640(58.23%)	67/1099(6.10%)	10/27(37.04%)	41/165(24.85%)	18/81(22.22%)
Y. Gao	2020	China	English	Composite End Point	44.08	26(60.47%)	15/43(34.88%)	1/3(33.33%)	6/13(46.15%)	6/7(85.71%)
C. Huang	2020	China	English	ICU	49.33	30(73.17%)	13/41(31.71%)	3/6(50.00%)	2/6(33.33%)	1/8(12.50%)
S. Huang	2020	China	English	ICU	NR	NR	51/310(16.45%)	NR	27/113(23.89%)	NR
K. Li	2020	China	English	Composite End Point	45.50	44 (53.00%)	25/83(30.12%)	1/1(100.00%)	2/5(40.00%)	7/7(100.00%)
W. Liu	2020	China	English	Composite End Point	42.67	39 (50.00%)	11/78(14.10%)	NR	2/8(25.00%)	2/5(40.00%)
X. Li	2020	China	English	Composite End Point	59.00	279(50.90%)	269/548(49.09%)	28/34(82.35%)	104/166(62.65%)	52/83(62.65%)
Y. Liu	2020	China	English	Composite End Point	53.67	8(66.67%)	3/12(25.00%)	1/4(25.00%)	1/3(33.33%)	1/2(50.00%)
F. Montastruc	2020	France	English	Composite End Point	57.47	76(79.17%)	71/96(73.96%)	NR	32/43(74.42%)	16/27(59.26%)
L. Myers	2020	US	English	ICU	61.33	212(56.20%)	113/377(29.97%)	NR	58/164(35.37%)	45/118(38.14%)
B. Nowak	2020	Poland	English	Death	63.70	87 (51.50%)	46/169(27.22%)	22/58(37.93%)	27/80(33.75%)	16/32(50.00%)
Y. Nie	2020	China	English	Composite End Point	43.00	367(56.03%)	72/655(10.99%)	8/70(11.43%)	5/60(8.33%)	1/12(8.33%)
C. Qin	2020	China	English	Composite End Point	57.33	235(52.00%)	286/452(63.27%)	24/27(88.89%)	105/135(77.78%)	53/75(70.67%)
A. Simonnet	2020	France	English	Composite End Point	60.33	90(73.00%)	85/124(68.55%)	NR	48/60(80.00%)	23/28(82.14%)
C. Wu	2020	China	English	Composite	51.33	128(63.68%)	84/201(41.79%)	5/8(62.50%)	23/39(58.97%)	16/22(72.73%)

				End Point			%)			
D. Wang	2020	China	English	ICU	55.33	75(54.35%)	36/138(26.09%)	9/20(45.00%)	21/43(48.84%)	8/14(57.14%)
F. Wang	2020	China	English	ICU	68.60	21(75.00%)	14/28(50.00%)	4/4(100.00%)	10/15(66.67%)	NR
L. Wang	2020	China	English	Composite End Point	53.67	67(57.80%)	57/116(49.14%)	NR	20/43(46.51%)	10/18(55.56%)
S. Wan	2020	China	English	Composite End Point	46.00	72(53.30%)	40/135(29.63%)	6/7(85.71%)	4/13(30.77%)	9/12(75.00%)
X. Wang	2020	China	English	Composite End Point	49.00	59(45.04%)	69/131(52.67%)	2/3(66.67%)	3/4(75.00%)	2/2(100.00%)
Y. Wang	2020	China	English	Death	62.67	165(47.97%)	133/344(38.66%)	22/40(55.00%)	69/141(48.94%)	30/64(46.88%)
Z. Wang	2020	China	English	Composite End Point	46.33	32(46.38%)	14/69(20.29%)	5/8(62.50%)	5/9(55.56%)	6/7(85.71%)
Y. Xie	2020	China	English	Composite End Point	64.00	27(43.55%)	24/62(38.71%)	17/33(51.52%)	NR	NR
Z. Xiong	2020	China	English	Composite End Point	50.67	214(50.83%)	59/421(14.01%)	NR	8/44(18.18%)	3/13(23.08%)
L. Yang	2020	China	English	ICU	55.00	98(49.00%)	29/200(14.50%)	1/11(9.09%)	9/45(20.00%)	4/21(19.05%)
X. Yang	2020	China	English	Death	59.70	35(67.31%)	32/52(61.54%)	3/5(60.00%)	NR	7/9(77.78%)
F. Zhou	2020	China	English	Death	56.33	119(62.30%)	54/191(28.27%)	13/15(86.67%)	26/58(44.83%)	17/36(47.22%)
J. Zhang	2020	China	English	Composite End Point	56.33	71(50.71%)	58/140(41.43%)	4/7(57.14%)	22/42(52.38%)	8/17(47.06%)
J. Zhao	2020	China	English	Composite End Point	51.00	14(48.28%)	21/29(72.41%)	9/10(90.00%)	NR	7/7(100.00%)

*Composite end point in original studies was defined as SpO2<90% or requirement of an intensive care or the use of mechanical ventilation, or death.

Table 2. Bias risk assessment.

Study	1	2	3	4	5	6	7	8	Score
COVID-19 Australia Incident Room Surveillance Team	2	2	2	2	2	1	2	0	13
D. Colombi	2	2	2	2	2	0	0	0	10
M. Choi	2	2	2	2	2	2	1	0	13
Y. Deng	2	2	2	2	2	0	0	0	10
X. Fang	2	2	2	2	2	1	2	0	13
P. Goyal	2	2	2	2	2	0	0	0	10
W. Guan	2	2	2	2	2	0	0	0	10
Y. Gao	2	2	2	2	2	0	0	0	10
C. Huang	2	2	2	2	2	1	2	0	13
S. Huang	2	2	2	2	2	0	0	0	10
K. Li	2	2	2	2	2	0	0	0	10
W. Liu	2	2	2	2	2	1	2	0	13
X. Li	2	2	2	2	2	2	1	0	13
Y. Liu	2	2	2	2	2	0	0	0	10
F. Montastruc	2	2	2	2	2	0	0	0	10
L. Myers	2	2	2	2	2	2	2	0	14
B. Nowak	2	2	2	2	2	0	0	0	10
Y. Nie	2	2	2	2	2	2	1	0	13

	1	2	3	4	5	6	7	8	
C. Qin	2	2	2	2	2	0	0	0	10
A. Simonnet	2	2	2	2	2	0	0	0	10
C. Wu	2	2	2	2	2	0	0	0	10
D. Wang	2	2	2	2	2	1	2	0	13
F. Wang	2	2	2	2	2	2	1	0	13
L. Wang	2	2	2	2	2	0	0	0	10
S. Wan	2	2	2	2	2	0	0	0	10
X. Wang	2	2	2	2	2	0	0	0	10
Y. Wang	2	2	2	2	2	0	0	0	10
Z. Wang	2	2	2	2	2	1	2	0	13
Y. Xie	2	2	2	2	2	0	0	0	10
Z. Xiong	2	2	2	2	2	0	0	0	10
L. Yang	2	2	2	2	2	0	0	0	10
X. Yang	2	2	2	2	2	1	2	0	13
F. Zhou	2	2	2	2	2	0	0	0	10
J. Zhang	2	2	2	2	2	0	0	0	10
J. Zhao	2	2	2	2	2	2	2	0	14

1 A clearly stated aim;

2 Inclusion of consecutive patients;

3 Prospective collection of data;

4 Endpoints appropriate to the aim of the study;

5 Unbiased assessment of the study endpoint;

6 Follow-up period appropriate to the aim of the study;

7 Loss to follow up less than 5%;

8 Prospective calculation of the study size.

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies.

The patients in the studies were from China (27 studies), Italy (1 study), the United States (2 studies), France (2 studies), Australia (1 study), Poland (1 study) and South Korea (1 study). The average age of the patients ranged from 33.3 to 68.6 years. The incidences of CHD, hypertension and diabetes in all the included patients were 6.71%, 22.24% and 12.55%, respectively. The incidences of CHD, hypertension and diabetes in severe patients were 12.01%, 33.54% and 20.50%, respectively. Men were more likely than women to develop severe pneumonia (61.55% of severe cases were men).

CHD and the severity of COVID-19

A forest plot was used to evaluate the association between CHD and COVID-19 severity. In the forest plot, the odds ratio (OR) indicates the strength of the association between the basic disease and the severity of COVID-19. The vertical line indicating no effect crosses the horizontal axis at an OR of 1. The length of each horizontal line represents the range of the 95% confidence interval (CI) of the corresponding study. The small square in the middle of the line demonstrates the position of the OR, and the size of the square represents the weight of the study. If the combined OR for all the studies does not intersect

with the vertical line of no effect, the results are statistically significant.

Twenty-five studies reported the relationship between CHD and the severity of COVID-19. The pooled OR is displayed in Figure 2A, which demonstrates that CHD increased the risk of severe COVID-19 at least three-fold (fixed-effects model, OR=3.21, 95% CI: 2.58-3.99). The heterogeneity among the included studies was moderate (I^2=38%, p=0.03).

A funnel plot and Egger's test were used to evaluate publication bias. In a funnel plot, studies with large sample sizes and high precision are distributed at the top of the plot and concentrated toward the center, while studies with small sample sizes and relatively low accuracy are distributed in the middle and lower parts of the plot in a symmetrical arrangement. Egger's test (p=0.7511) and the funnel plot indicated no publication bias for the studies examining the association between CHD and COVID-19 severity (Figure 2B).

Hypertension and the severity of COVID-19

Thirty studies reported the relationship between hypertension and the severity of COVID-19. The duration of hypertension was not reported in most studies. The

pooled OR is depicted in Figure 3A, which demonstrates that hypertension increased the risk of severe COVID-19 at least two-fold (random-effects model, OR=2.27, 95% CI: 1.79-2.90). The heterogeneity among the studies was high (I^2=65%, p<0.01). A sensitivity analysis revealed that the results were not influenced by any individual study. Egger's test (p=0.8984) and a funnel plot indicated no publication bias (Figure 3B).

Diabetes and the severity of COVID-19

Thirty-two studies analyzed the association between diabetes and severe COVID-19. The pooled OR is shown in Figure 4A, which demonstrates that diabetes increased the risk of severe COVID-19 roughly 2.3-fold (random-effects model, OR=2.34, 95% CI: 1.79-3.05). The heterogeneity among the studies was high (I^2=59%, p<0.01). A sensitivity analysis revealed that the results were not influenced by any individual study.

Publication bias was assessed using a funnel plot (Figure 4B) and Egger's test, both of which revealed publication bias in this analysis (Egger's test, p=0.0497). The trim-and-fill method was used to deal with the publication bias (Figure 4C). After the addition of seven studies, the combined-effect OR in the
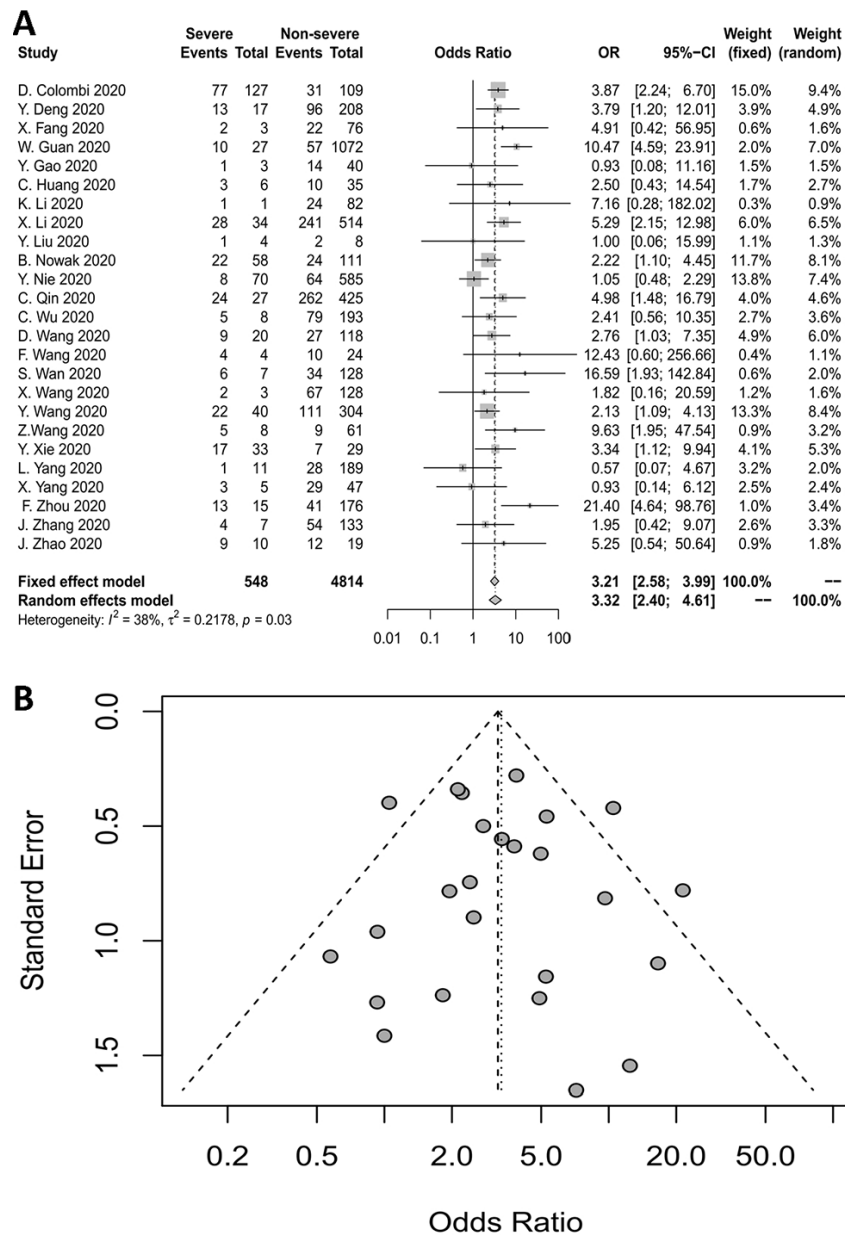

Figure 2. (**A**) Forest plot for CHD. (**B**) Funnel plot for CHD.

random-effects model was 1.7649 (95% CI: 1.32-2.36). The lack of obvious change indicated that the publication bias had little effect on the results, and the results were relatively stable.

DISCUSSION

Cardiovascular diseases and diabetes are the most prevalent chronic diseases globally. During this ongoing pandemic, large numbers of people with these underlying conditions are inevitably going to contract COVID-19. The present systematic analysis summarized the results of 35 studies from December 2019 to July 5, 2020, and demonstrated that CHD,

hypertension and diabetes each increased the risk of severe COVID-19 at least two-fold.

Regarding CHD, our meta-analysis of 25 qualifying studies indicated that the risk of developing severe COVID-19 was three times higher in patients with pre-existing CHD than in those without. Several possible explanations have been proposed for the impact of cardiovascular diseases on the progression of COVID-19 [40]. First, the acute pulmonary infection associated with COVID-19 may cause cardiac injury by inducing myocarditis [41], thus reducing systolic function and promoting heart failure. Second, the systemic inflammatory response to COVID-19 may cause
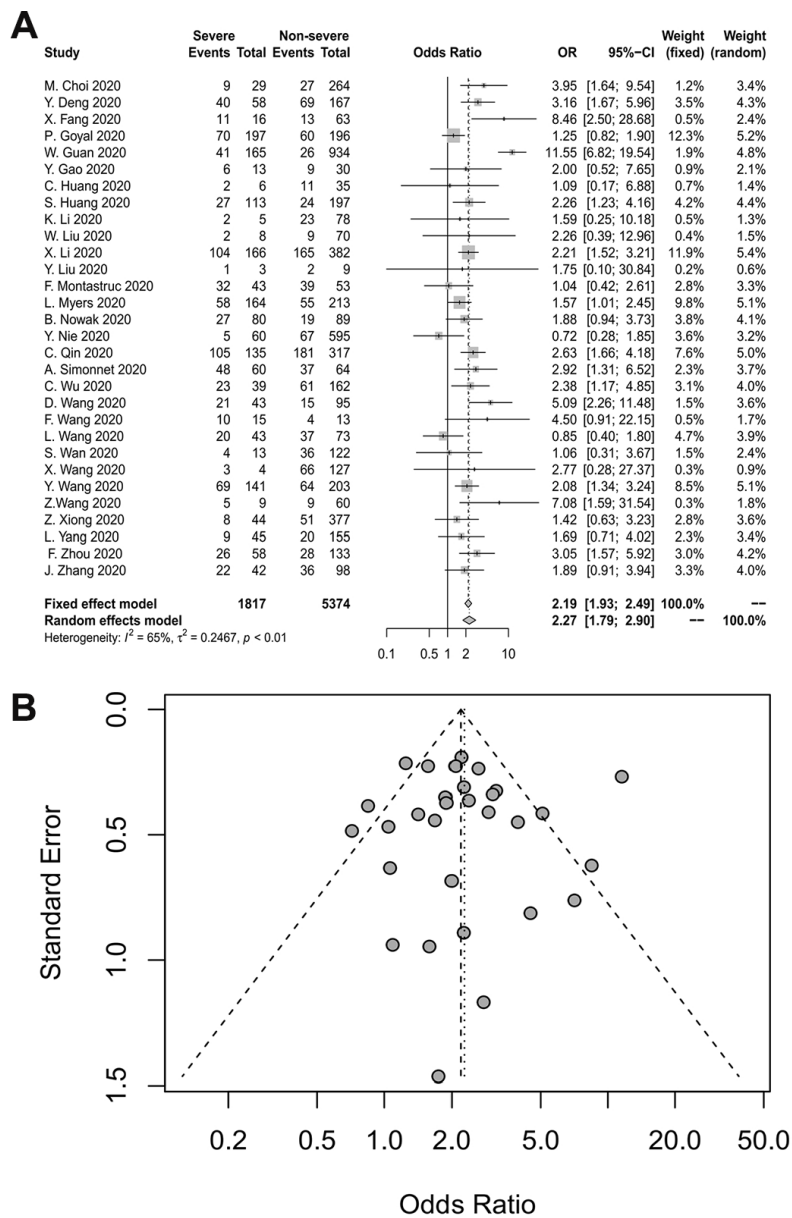

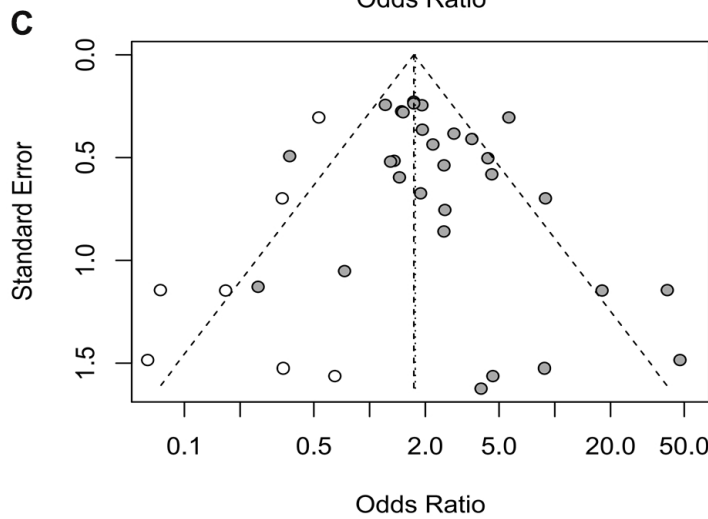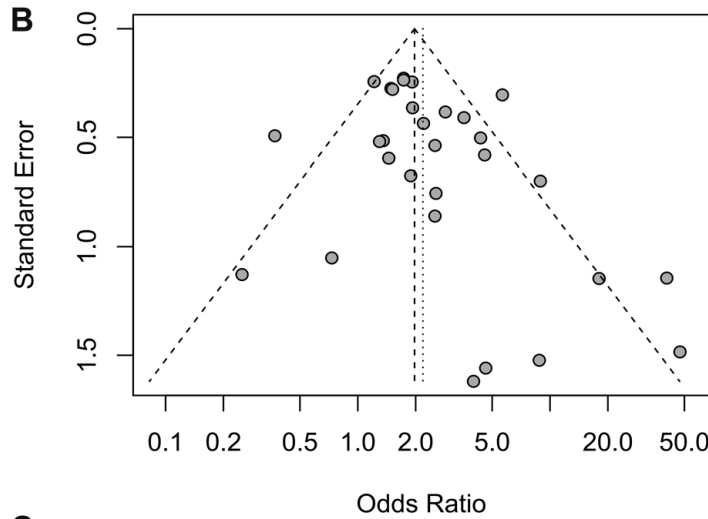**Figure 3.** (**A**) Forest plot for hypertension. (**B**) Funnel plot for hypertension.

A

Study	Severe Events	Total	Non-severe Events	Total	Odds Ratio	OR	95%−CI	Weight (fixed)	Weight (random)
COVID−19 Australia 2020	38	107	119	493		1.73	[1.11; 2.70]	11.0%	5.7%
D. Colombi 2020	22	37	86	199		1.93	[0.94; 3.93]	4.4%	4.6%
M. Choi 2020	10	21	26	272		8.60	[3.34; 22.17]	0.8%	3.6%
Y. Deng 2020	17	26	92	199		2.20	[0.93; 5.16]	3.0%	4.0%
X. Fang 2020	4	8	20	71		2.55	[0.58; 11.19]	0.8%	2.2%
P. Goyal 2020	36	99	94	294		1.22	[0.75; 1.96]	12.1%	5.6%
W. Guan 2020	18	81	49	1018		5.65	[3.11; 10.27]	2.3%	5.1%
Y. Gao 2020	6	7	9	36		18.00	[1.90; 170.34]	0.2%	1.2%
C. Huang 2020	1	8	12	33		0.25	[0.03; 2.28]	1.6%	1.2%
K. Li 2020	7	7	18	76		47.43	[2.58; 870.76]	0.1%	0.7%
W. Liu 2020	2	5	9	73		4.74	[0.69; 32.35]	0.3%	1.5%
X. Li 2020	52	83	217	465		1.92	[1.19; 3.10]	9.9%	5.6%
Y. Liu 2020	1	2	2	10		4.00	[0.17; 95.76]	0.1%	0.6%
F. Montastruc 2020	16	27	55	69		0.37	[0.14; 0.97]	5.1%	3.6%
L. Myers 2020	45	118	68	259		1.73	[1.09; 2.75]	10.6%	5.6%
B. Nowak 2020	16	32	30	137		3.57	[1.60; 7.96]	2.3%	4.2%
Y. Nie 2020	1	12	71	643		0.73	[0.09; 5.76]	1.0%	1.3%
C. Qin 2020	53	75	233	377		1.49	[0.87; 2.55]	9.1%	5.3%
A. Simonnet 2020	23	28	62	96		2.52	[0.88; 7.24]	2.0%	3.3%
C. Wu 2020	16	22	68	179		4.35	[1.62; 11.66]	1.6%	3.5%
D. Wang 2020	8	14	28	124		4.57	[1.46; 14.28]	1.0%	3.0%
L. Wang 2020	10	18	47	98		1.36	[0.49; 3.73]	2.6%	3.4%
S. Wan 2020	9	12	31	123		8.90	[2.27; 34.99]	0.6%	2.4%
X. Wang 2020	2	2	67	129		4.63	[0.22; 98.32]	0.2%	0.7%
Y. Wang 2020	30	64	103	280		1.52	[0.88; 2.62]	8.2%	5.3%
Z. Wang 2020	6	7	8	62		40.50	[4.30; 381.74]	0.1%	1.2%
Z. Xiong 2020	3	13	56	408		1.89	[0.50; 7.06]	1.1%	2.5%
L. Yang 2020	4	21	25	179		1.45	[0.45; 4.66]	1.7%	2.9%
X. Yang 2020	7	9	25	43		2.52	[0.47; 13.58]	0.8%	1.8%
F. Zhou 2020	17	36	37	155		2.85	[1.35; 6.05]	3.0%	4.4%
J. Zhang 2020	8	17	50	123		1.30	[0.47; 3.59]	2.6%	3.4%
J. Zhao 2020	7	7	14	22		8.79	[0.44; 174.04]	0.2%	0.7%
Fixed effect model		**1025**		**6745**		**2.03**	**[1.76; 2.35]**	**100.0%**	**−−**
Random effects model						**2.34**	**[1.79; 3.05]**	**−−**	**100.0%**

Heterogeneity: $I^2 = 59\%$, $\tau^2 = 0.2675$, $p < 0.01$
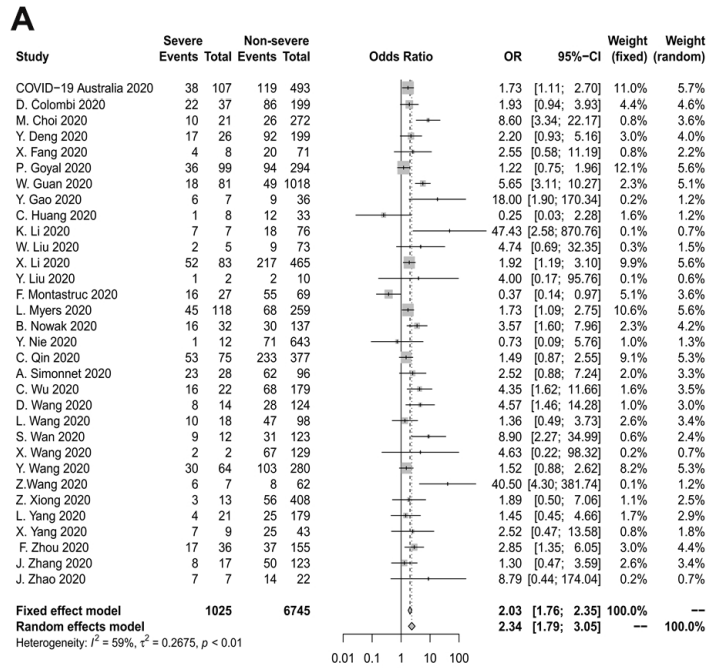
0.01 0.1 1 10 100

Figure 4. (**A**) Forest plot for diabetes. (**B**) Funnel plot for diabetes. (**C**) Funnel plot after used the trim-and-fill method for diabetes.

coronary plaque rupture or erosion in patients with pre-existing CHD and thus induce acute coronary syndrome. Third, COVID-19-induced hypoxemia may trigger atrial fibrillation in elderly patients with cardiovascular diseases. The clinical presentation of COVID-19 may be similar to that of acute coronary syndrome or decompensated cardiovascular disease if it includes dyspnea and fatigue, and this may lead to misdiagnosis at the early stages of infection, thus delaying medical intervention.

Our meta-analysis also demonstrated that the risk of developing severe COVID-19 was at least two times greater in patients with hypertension than in those without. It has been postulated that the progression of COVID-19 into severe COVID-19 in patients with hypertension may be due to prior and concomitant use of angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) [42]. This proposed mechanism is based on the notion that ACE inhibitors and ARBs upregulate the expression or prevent the degradation of angiotensin II converting enzyme (ACE2), a receptor with high binding affinity for SARS-CoV-2. However, as of now, there is no reliable scientific basis or clinical evidence to support this view. Thus, it is necessary to further explore the potential impact of ACE inhibitors and ARBs on the pathogenesis and prognosis of COVID-19.

In this meta-analysis, we also found that the risk of severe COVID-19 was nearly two-fold higher in patients with diabetes than in those without. ACE2, the entry receptor for SARS-CoV-2, is expressed in various tissues, including the lungs, heart, renal tubules, small intestinal cavity surface and blood vessels [43]. Many drugs used by diabetic patients can increase the expression of ACE2, including glucagon-like peptide-1 agonists and statins [44]. The increased expression of ACE2 in multiple tissues of diabetic patients may increase the risk of COVID-19 infection. In addition, uncontrolled hyperglycemia can promote abnormal ACE2 glycosylation in the lungs, nasal airways, tongue and oropharynx, potentially increasing the binding sites of SARS-CoV-2 and the severity of the disease [45]. The mortality rate of COVID-19 was reported to be 7.6% in diabetic patients, but only 0.9% in patients without comorbidities [16]. Insulin resistance and uncontrolled blood glucose are important contributors to the deterioration of COVID-19. In severe COVID-19 patients, blood glucose levels were found to be increased to varying degrees in patients with diabetes [46]. Therefore, strict control of blood glucose may be critical for improving the clinical results of COVID-19 patients. However, it is worth noting that the mean age in our analysis was middle-aged, and it is highly likely that middle-aged patients with CHD, hypertension or diabetes have other diseases or bad habits. Thus, further

study is needed to determine whether bad living habits aggravate COVID-19.

Our heterogeneity analysis revealed moderate heterogeneity among the CHD studies and high heterogeneity among the hypertension and diabetes studies. Sensitivity analyses indicated that the results were not influenced by any individual study. When we excluded samples one by one to observe the dynamic changes in the meta-analysis, the results were not altered significantly, suggesting that the data were more stable after they were merged and that a random-effects model could be used. However, the results should be interpreted carefully due to their high heterogeneity.

There were several possible sources of heterogeneity in this study. 1. The quality of the available scientific literature for this meta-analysis was not ideal, as all the studies were large observational case series; however, due to the rapid spread of COVID-19, randomized controlled trials and prospective observational studies have not been conducted so far. 2. The results of this study demonstrated that patients with CHD, hypertension and diabetes were at increased risk for severe COVID-19 among hospitalized patients; however, 70-80% of COVID-19 patients may be asymptomatic or not require in-patient care. Further observational studies involving asymptomatic and mildly symptomatic patients not requiring hospitalization will be needed to determine the true magnitude of the effect of pre-existing CHD and metabolic diseases on COVID-19 severity. 3. Most of the patients were from Asia, although we included data from seven countries. As COVID-19 spreads globally, further study will be needed to determine whether there are ethnic differences in risk. 4. All the studies were clinical case observations, so there may have been heterogeneity in whether or for how long patients were followed up. 5. COVID-19 is an infectious disease that spread in a sudden worldwide outbreak. Thus, in sharing patient data for the first time, many researchers did not describe the diagnostic criteria for basic diseases such as CHD, hypertension and diabetes in detail, or did not fully consider the staging, severity, blood glucose control or blood pressure control of patients with these underlying diseases, leading to heterogeneity. Despite these limitations, this meta-analysis demonstrated that hospitalized patients with pre-existing CHD, hypertension and diabetes were at two- to three-fold higher risk for developing severe COVID-19 than those without these diseases.

The results of this meta-analysis emphasize the importance of strictly limiting the spread of COVID-19 in patients with underlying cardiovascular and metabolic diseases, as they are the most vulnerable group. Clinicians should be aware of the approximately two- to three-fold higher risk of severe COVID-19 in

these patients. Since elderly patients, smokers and patients with lung diseases are also more likely than others to progress to severe COVID-19 [47], clinicians should consider the patient's age, underlying diseases, smoking status and other comprehensive factors when evaluating the prognosis of COVID-19. In addition, from a public health perspective, patients with co-morbid cardiovascular and metabolic conditions should be especially careful about hand hygiene and personal protection measures. Better control of blood glucose and blood pressure may improve the course of COVID-19, but further research is needed.

In summary, pre-existing cardiovascular and metabolic diseases increased the likelihood of severe COVID-19 and thus may promote a poor prognosis in COVID-19 patients.

MATERIALS AND METHODS

Data source, search strategy and inclusion criteria

We carried out a comprehensive, systematic literature search in five online databases (PubMed, Cochrane, Web of Science, WanFang Data and CNKI) from December 2019 to July 5, 2020 to identify potential studies. The search terms and relative variants used were as follows: "COVID-19" OR "2019 novel coronavirus infection" OR "coronavirus disease 2019" OR "2019 novel coronavirus disease" OR "coronavirus 2019" OR "2019-nCoV" OR "SARS-CoV-2" OR "COVID19" OR "coronavirus disease-19". The literature search included both English- and Chinese-language publications.

The titles, abstracts and full texts of all the documents identified through this search strategy were screened by two investigators (M.M. and QW.Z.). The reference lists of the review articles and research articles were also reviewed to detect other eligible documents. Studies were included if they reported diabetes, hypertension or CHD data in COVID-19 patients with or without a severe presentation. The definition of severe COVID-19 varied among the included studies. In this study, we defined COVID-19 as severe if the patient required intensive care, received mechanical ventilation or died, consistent with most of the articles. All the search results were evaluated according to the MINORS statement. Case reports, letters, non-human studies and studies without adequate information were excluded from the present meta-analysis.

Data extraction and quality assessment

The data extraction and literature quality evaluation were conducted independently by two investigators (M.M. and QW.Z.). Microsoft Excel was used to record all the available information, including baseline details, clinical data, the discharge rate and the fatality rate. Any disagreement was resolved by another investigator (B.W.).

Data synthesis and statistical analysis

Microsoft Excel was used to analyze the combined results for patients with severe and non-severe disease. The meta-analysis was carried out using R software. Heterogeneity among the studies was assessed using the Cochran chi-square test and I^2. When I^2 was $< 50\%$, a fixed-effects model was used, and when I^2 was $> 50\%$, a random-effects model was selected. If there was statistical heterogeneity in the results, a further sensitivity analysis was conducted to determine the source of the heterogeneity. After significant clinical heterogeneity was excluded, a random-effects model was used for meta-analysis. Funnel plots and Egger's tests were used to detect publication bias. $P<0.05$ (two-sided) was considered statistically significant.

Abbreviations

COVID-19: Coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CHD: coronary heart disease; MINORS: Methodological Index for Non-Randomized Studies; OR: pooled odds ratio; ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; ACE2: angiotensin II converting enzyme.

AUTHOR CONTRIBUTIONS

Guarantor of the article: Bo Wan; Designed the study: Bo Wan; Interpreted data and wrote the manuscript: Meng Meng and Rahul Kumar; Screened and extracted data: Meng Meng and Qianwen Zhao; Statistical analyses: Bo Wan; Reviewed the results and made critical comments on the manuscript: Chen Bai, Yunlei Deng, Rahul Kumar; All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

All of the authors report no relationships that could be construed as a conflicts of interest

FUNDING

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, et al, and

China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382:727–33.
https://doi.org/10.1056/NEJMoa2001017
PMID:31978945

2. Lian J, Jin X, Hao S, Cai H, Zhang S, Zheng L, Jia H, Hu J, Gao J, Zhang Y, Zhang X, Yu G, Wang X, et al. Analysis of epidemiological and clinical features in older patients with coronavirus disease 2019 (COVID-19) outside Wuhan. Clin Infect Dis. 2020; 71:740–47.
https://doi.org/10.1093/cid/ciaa242 PMID:32211844

3. Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system? a call for epidemiologic investigations. Clin Infect Dis. 2020; 71:870–74.
https://doi.org/10.1093/cid/ciaa329 PMID:32215613

4. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, Bi Z, Zhao Y. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020; 109:531–38.
https://doi.org/10.1007/s00392-020-01626-9
PMID:32161990

5. Fang XW, Mei Q, Yang TJ, Zhang L, Yang Y, Wang YZ, Tong F, Ye CY, Gao Y, Huang Y, Geng SK, Pan AJ. Clinicalcharacteristics and treatment strategies of 79 patients with COVID-19. Chinese Pharmacol Bulletin. 2020; 4:453–59.
https://kns.cnki.net/kcms/detail/34.1086.r.20200224.1340.002.html

6. Gao Y, Li T, Han M, Li X, Wu D, Xu Y, Zhu Y, Liu Y, Wang X, Wang L. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. J Med Virol. 2020; 92:791–96.
https://doi.org/10.1002/jmv.25770 PMID:32181911

7. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B, Li LJ, Zeng G, et al, and China Medical Treatment Expert Group for Covid-19. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382:1708–20.
https://doi.org/10.1056/NEJMoa2002032
PMID:32109013

8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395:497–506.
https://doi.org/10.1016/S0140-6736(20)30183-5
PMID:31986264

9. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, Wei S, Deng Y, Liu J, Liu HG, Yang M, Hu Y. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl). 2020; 133:1032–38.
https://doi.org/10.1097/CM9.0000000000000775
PMID:32118640

10. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020; 63:364–74.
https://doi.org/10.1007/s11427-020-1643-8
PMID:32048163

11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020; 323:1061–69.
https://doi.org/10.1001/jama.2020.1585
PMID:32031570

12. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis. 2020; 71:769–77.
https://doi.org/10.1093/cid/ciaa272 PMID:32176772

13. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J, Wang S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; 180:934–43.
https://doi.org/10.1001/jamainternmed.2020.0994
PMID:32167524

14. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8:475–81.
https://doi.org/10.1016/S2213-2600(20)30079-5
PMID:32105632

15. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020; 75:1730–41.
https://doi.org/10.1111/all.14238
PMID:32077115

16. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395:1054–62.
https://doi.org/10.1016/S0140-6736(20)30566-3
PMID:32171076

17. Wang X, Xu H, Jiang H, Wang L, Lu C, Wei X, Liu J, Xu S. The clinical features and outcomes of discharged coronavirus disease 2019 Patients: A prospective cohort study. QJM. 2020; 113:657–65. https://doi.org/10.1093/qjmed/hcaa178 PMID:32442308

18. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of hospitalized adults with COVID-19 in an integrated health care system in California. JAMA. 2020; 323:2195–98. https://doi.org/10.1001/jama.2020.7202 PMID:32329797

19. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion TR Jr, Nahid M, Ringel JB, Hoffman KL, Alshak MN, Li HA, et al. Clinical characteristics of covid-19 in New York city. N Engl J Med. 2020; 382:2372–74. https://doi.org/10.1056/NEJMc2010419 PMID:32302078

20. Colombi D, Bodini FC, Petrini M, Maffi G, Morelli N, Milanese G, Silva M, Sverzellati N, Michieletti E. Well-aerated lung on admitting chest CT to predict adverse outcome in COVID-19 pneumonia. Radiology. 2020; 296:E86–96. https://doi.org/10.1148/radiol.2020201433 PMID:32301647

21. Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, Huang F, Zhou J, Zhang B, Yan F, Wang J. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med. 2020; 201:1430–34. https://doi.org/10.1164/rccm.202003-0736LE PMID:32267160

22. Choi MH, Ahn H, Ryu HS, Kim BJ, Jang J, Jung M, Kim J, Jeong SH. Clinical characteristics and disease progression in early-stage COVID-19 patients in South Korea. J Clin Med. 2020; 9:1959. https://doi.org/10.3390/jcm9061959 PMID:32585855

23. Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, Wang K, Leng F, Wei S, Chen L, Liu HG. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020; 133:1261–67. https://doi.org/10.1097/CM9.0000000000000824 PMID:32209890

24. Huang S, Wang J, Liu F, Liu J, Cao G, Yang C, Liu W, Tu C, Zhu M, Xiong B. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. Hypertens Res. 2020; 43:824–31. https://doi.org/10.1038/s41440-020-0485-2 PMID:32483311

25. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, Li C. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol. 2020; 55:327–31. https://doi.org/10.1097/RLI.0000000000000672 PMID:32118615

26. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146:110–18. https://doi.org/10.1016/j.jaci.2020.04.006 PMID:32294485

27. Montastruc F, Romano C, Montastruc JL, Silva S, Seguin T, Minville V, Georges B, Riu-Poulenc B, Fourcade O. Pharmacological characteristics of patients infected with SARS-Cov-2 admitted to intensive care unit in south of France. Therapie. 2020; 75:381–84. https://doi.org/10.1016/j.therap.2020.05.005 PMID:32425250

28. Nie Y, Li J, Huang X, Guo W, Zhang X, Ma Y, Wang H, Qi M, Tang X, Shen X, Dai X. Epidemiological and clinical characteristics of 671 COVID-19 patients in Henan Province, China. Int J Epidemiol. 2020. [Epub ahead of print]. https://doi.org/10.1093/ije/dyaa081 PMID:32588051

29. Nowak B, Szymański P, Pańkowski I, Szarowska A, Życińska K, Rogowski W, Gil R, Furmanek M, Tatur J, Zaczyński A, Król Z, Wierzba W. Clinical characteristics and short-term outcomes of patients with coronavirus disease 2019: a retrospective single-center experience of a designated hospital in Poland. Pol Arch Intern Med. 2020; 130:407–11. https://doi.org/10.20452/pamw.15361 PMID:32420710

30. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020; 71:762–68. https://doi.org/10.1093/cid/ciaa248 PMID:32161940

31. Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M, Caizzo R, Caplan M, Cousin N, et al, and LICORN and the Lille COVID-19 and Obesity study group. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. Obesity (Silver Spring). 2020; 28:1195–1199. https://doi.org/10.1002/oby.22831 PMID:32271993

32. COVID-19 National Incident Room Surveillance Team. COVID-19, Australia: epidemiology report 15 (reporting week to 23:59 AEST 10 May 2020). Commun Dis Intell (2018). 2020; 44.

https://doi.org/10.33321/cdi.2020.44.43
PMID:32438898

33. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, Lang C, Huang D, Sun Q, Xiong Y, Huang X, Lv J, Luo Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol. 2020; 92:797–806.
https://doi.org/10.1002/jmv.25783
PMID:32198776

34. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, Yu X, Shi X. CLINICAL CHARACTERISTICS OF 28 PATIENTS WITH DIABETES AND COVID-19 IN WUHAN, CHINA. Endocr Pract. 2020; 26:668–674.
https://doi.org/10.4158/EP-2020-0108
PMID:32357072

35. Wang L, Li X, Chen H, Yan S, Li D, Li Y, Gong Z. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol. 2020; 51:343–48.
https://doi.org/10.1159/000507471
PMID:32229732

36. Xie Y, You Q, Wu C, Cao S, Qu G, Yan X, Han X, Wang C, Zhang H. Impact of cardiovascular disease on clinical characteristics and outcomes of coronavirus disease 2019 (COVID-19). Circ J. 2020; 84:1277–83.
https://doi.org/10.1253/circj.CJ-20-0348
PMID:32536672

37. Wang W, Xin C, Xiong Z, Yan X, Cai Y, Zhou K, Xie C, Zhang T, Wu X, Liu K, Li Z, Chen J. Clinical characteristics and outcomes of 421 patients with coronavirus disease 2019 treated in a mobile cabin hospital. Chest. 2020; 158:939–46.
https://doi.org/10.1016/j.chest.2020.05.515
PMID:32437696

38. Yang L, Liu J, Zhang R, Li M, Li Z, Zhou X, Hu C, Tian F, Zhou F, Lei Y. Epidemiological and clinical features of 200 hospitalized patients with corona virus disease 2019 outside Wuhan, China: a descriptive study. J Clin Virol. 2020; 129:104475.
https://doi.org/10.1016/j.jcv.2020.104475
PMID:32485619

39. Zhao J, Gao HY, Feng ZY, Wu QJ. A retrospective analysis of the clinical and epidemiological characteristics of COVID-19 patients in Henan Provincial People's Hospital, Zhengzhou, China. Front Med (Lausanne). 2020; 7:286.
https://doi.org/10.3389/fmed.2020.00286
PMID:32582740

40. Yang C, Jin Z. An acute respiratory infection runs into the most common noncommunicable epidemic-COVID-19 and cardiovascular diseases. JAMA Cardiol. 2020; 5:743–44.
https://doi.org/10.1001/jamacardio.2020.0934
PMID:32211809

41. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8:420–22.
https://doi.org/10.1016/S2213-2600(20)30076-X
PMID:32085846

42. Marin GH. Facts and reflections on COVID-19 and anti-hypertensives drugs. Drug Discov Ther. 2020; 14:105–06.
https://doi.org/10.5582/ddt.2020.01017
PMID:32213760

43. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, Leopoldi A, Garreta E, Hurtado Del Pozo C, Prosper F, Romero JP, Wirnsberger G, Zhang H, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020; 181:905–13.e7.
https://doi.org/10.1016/j.cell.2020.04.004
PMID:32333836

44. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020; 41:bnaa011.
https://doi.org/10.1210/endrev/bnaa011
PMID:32294179

45. Erener S. Diabetes, infection risk and COVID-19. Mol Metab. 2020; 39:101044.
https://doi.org/10.1016/j.molmet.2020.101044
PMID:32585364

46. Smith SM, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, Dobesh DP, Brufsky A, Connor RI. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. J Med Virol. 2020. [Epub ahead of print].
https://doi.org/10.1002/jmv.26227
PMID:32589756

47. Zhao Q, Meng M, Kumar R, Wu Y, Huang J, Lian N, Deng Y, Lin S. The impact of COPD and smoking history on the severity of COVID-19: a systemic review and meta-analysis. J Med Virol. 2020. [Epub ahead of print].
https://doi.org/10.1002/jmv.25889
PMID:32293753