The Association between Presence of Comorbidities and COVID-19 Severity: A Systematic Review and Meta-Analysis

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Abstract

Aim: Several studies reported the accompaniment of severe COVID-19 with comorbidities. However, there is not a systematic evaluation of all aspects of this association. Therefore, this meta-analysis aimed to assess the association between all underlying comorbidities in COVID-19 infection severity. *Methods:* Electronic literature search was performed via scientific search engines. After the removal of duplicates and selection of articles of interest, 28 studies were included. A fixed-effects model was used; however, if heterogeneity was high ($I^2 > 50\%$) a random-effects model was applied to combine the data. *Results:* A total of 6,270 individuals were assessed (1,615 severe and 4,655 non-severe patients). The median age was 63 (95% confidence interval [CI]: 49–74) and 47 (95% CI: 19–63) years in the severe and non-severe groups, respectively. Moreover, about 41% of patients had comorbidities. Severity was higher in patients with a history of cerebrovascular disease: OR 4.85 (95% CI: 3.11–7.57). The odds of being in a severe group increase by 4.81 (95% CI: 3.43–6.74) for a history of cardiovascular disease (CVD). This was 4.19 (95% CI: 2.84–6.19) for chronic lung disease and 3.18, 95% CI: 2.09–4.82 for cancer. The odds ratios of diabetes and hypertension were 2.61 (95% CI: 2.02–3.3) and 2.37 (95% CI: 1.80–3.13), respectively. *Conclusions:* The presence of comorbidities is associated with severity of COVID-19 infection. The strongest association was observed for cerebrovascular disease, followed by CVD, chronic lung disease, cancer, diabetes, and hypertension.

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Introduction

On December 31, 2019, several cases with pneumonia of unknown etiology were detected in Wuhan City, Hubei Province of China. Different potential causes such as influenza, avian influenza, adenovirus, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV) were assessed; however, the pathogen was not identified [1, 2]. Consequently, the causative viral disease called COVID-19 by the World Health Organization [1].The recent COVID-19 Situation Report of the World Health Organization reported nearly 32.7 million diagnosed cases with 991,000 deaths around the world until September
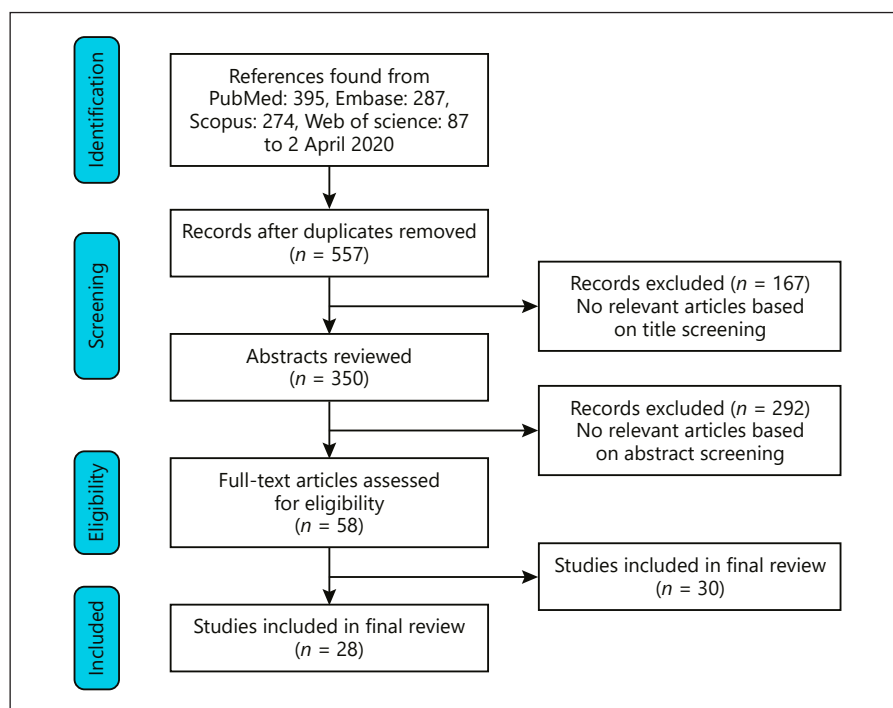
Fig. 1. Flowchart of literature search and article selection.

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27, 2020 [3]. Older men and those with comorbidities such as cardiovascular disease (CVD), diabetes, hypertension, and chronic obstructive pulmonary disease (COPD) were at the highest risk for the disease [4, 5] and higher rates of intensive care unit (ICU) admission [6].

Several studies reported the prevalence of comorbidities in COVID-19 patients [4, 7, 8]; however, a systematic evaluation of comorbidities to compare the relation of underlying medical conditions between severe and non-severe patients is lacking. Previous systematic reviews and meta-analyses explored some but not all aspects of this association. Therefore, this meta-analysis aims to assess the association between all underlying comorbidities in COVID-19 infection severity. The results could guide healthcare professionals to encounter properly with COVID-19. Besides, it will help policy-makers to design a prevention plan as well as respond to CO-VID-19 and its critical outcomes more preparedly.

Study Selection and Data Extraction

Inclusion and Exclusion Criteria
We included all relevant articles reporting clinical characteristics and epidemiological information on COVID-19 patients separately in a severe and non-se-

vere group. The criteria for severe disease include ICU admission, acute respiratory distress syndrome, need for supplemental oxygen or O_2 saturation <93%, critically ill cases, and severe outcome (e.g., cardiac injury or decompensation, organ failure, or death/not survived) [9–15]. Case series with incomplete information as well as review articles, opinion articles, and letters not presenting original data as well as any type of published data that only presented total patients were also excluded. The search strategy has been provided as supplementary file #1.

Data Extraction
Two authors (M.H. and R.A.) screened and evaluated the titles and abstracts of citations independently, and then a third author (M.E.Kh.) checked the screening results. Then, the full text of potentially eligible articles was obtained and reviewed for further assessment according to the inclusion and exclusion criteria. Data extraction forms including the following items were also filled out: name of the first authors, date of publication, DOI, the number of reported cases, age, sex, and coexisting underlying diseases such as diabetes/type 2 diabetes as well as the number of patients in severe and non-severe groups. Wherever there was the word "hypertension" and "high blood pressure," we considered them under the title of

Table 1. Demographics of the included studies

Study	Total, n	Age,* yr	Severity, n**		Male, n		Female, n	
			severe	non-severe	severe	non-severe	severe	non-severe
Zang (19 Feb 2020)	140	57	58	82	33	38	25	44
Guan (28 Feb 2020)	1,099	47	173	926	540	100	73	386
Wang (7 Feb 2020)	138	56	36	102	22	73	14	49
Huang (24 Jan 2020)	41	49	13	28	11	19	2	9
Liu (9 Feb 2020)	12	62.5	2	10	2	6	0	4
Yang (24 Feb 2020)	52	59.5	32	20	21	14	11	6
JieLi (12 Feb 2020)	17	45.1	12	5	5	4	7	1
Zhou (28 Mar 2020)	191	56	54	131	38	81	16	56
Wang (16 Mar 2020)	69	42	14	55	7	25	7	30
Yuan (19 Mar 2020)	27	60	17	10	4	8	3	12
Yuan (29 Mar 2020)	19	40	11	8	5	3	6	5
Chen (17 Mar 2020)	274	62	113	161	83	88	30	73
Young (3 Mar 2020)	18	47	6	12	2	7	4	5
Wu (27 Mar 2020)	280	43.12	83	197	45	106	34	91
Li, KunhuaMS (29 Feb 2020)	83	45.5	25	58	15	29	10	29
Wei-jie Guan (26 Mar 2020)	1,590	–	254	1,336	–	–	–	–
Gao (17 Mar 2020)	43	–	15	28	9	17	6	11
Chen (19 Feb 2020)	21	56.3	11	10	10	7	1	3
Chen (10 Mar 2020)	150	–	24	126	–	–	–	–
Yang-kai Li (30 Mar 2020)	61	51	36	25	10	14	4	22
Qin (12 Mar 2020)	452	58	286	166	155	80	131	86
Wang (31 Mar 2020)	116	54	57	59	33	34	24	25
Wan (21 Mar 2020)	135	47	40	95	21	51	19	44
Shi (18 Mar 2020)	487	49	438	46	36	223	13	215
Mo (16 Mar 2020)	155	85	70	54	55	31	30	39
Liu (28 Feb 2020)	78	11	67	38	7	32	5	35
Shi (25 Mar 2020)	416	82	334	64	44	63	38	173
Peng (1 Apr 2020)	112	16	96	62	7	52	9	44

* Age is reported as median for all studies. ** N is the absolute number in each column.

"hypertension." "Chronic obstructive pulmonary disease, COPD, Chronic lung diseases" were known as "chronic lung disease" in our study. "Cardiovascular disease, Coronary heart disease, heart disease" were defined as "Cardiovascular disease." The medical term "Cancer" included "Malignant tumor, Malignancy, Cancer, Carcinoma." Besides, "Cerebrovascular diseases, Cerebral infraction" were considered under the title of "Cerebrovascular diseases."

Risk of Bias Assessment
Newcastle-Ottawa Scale was used to evaluate quality of the included studies. The Funnel plots were used to investigate possible publication bias.

Statistical Analysis
All Statistical analyses were performed using Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14, StataCorp LP, College Station, TX, USA). We employed "metaprop" command to calculate the pooled prevalence estimates of comorbidities with 95% confidence. The associations between comorbidities and severity of disease, were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity among the primary studies was evaluated by the forest plots, Cochran's Q statistic, and I^2 statistic. A random-effects model was used if heterogeneity was high ($I^2 > 50\%$); otherwise, a fixed-effects model was applied. Also, the publication bias was formally tested with Egger's regression asymmetry tests to determine the asymmetry of the funnel plots, where $p < 0.10$ was considered as evidence of bias.
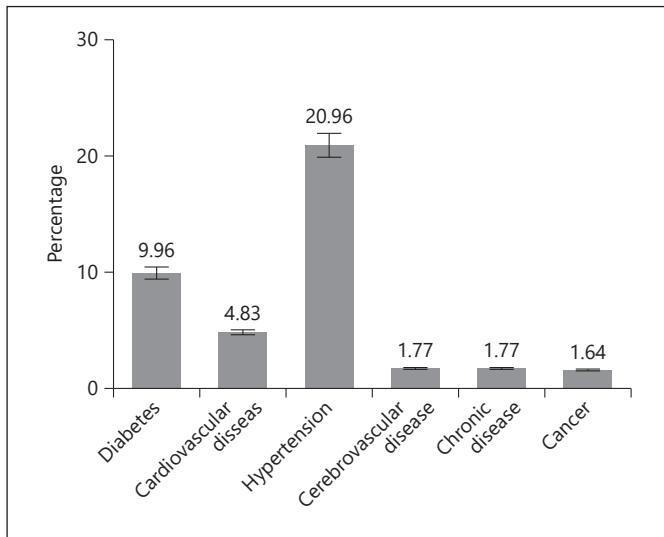
Fig. 2. Pooled prevalence of comorbidities in included studies. CVD, cardiovascular disease.

Results

Characteristics of Included Studies

In the initial search, 1,043 articles were found in different databases. 486 papers were excluded due to being duplicates. All papers were screened by reading their title and abstract, and 489 studies were excluded because of irrelevant data. Figure 1 shows the search details, and Table 1 shows the details of the included studies. In total, 28 studies (27 retrospective cross-sectional and 1 case series article) on 6,276 patients (32.2% female) were included (Fig. 1). All studies were conducted between January and April 2020 during the novel coronavirus (SARS-2-CoV) outbreak. The heterogeneity of all selected studies was low (I^2 between 0.0–30) except for hypertension (I^2 = 58.6). A total of 1,615 individuals were identified as severe disease whereas 4,655 individuals had the non-severe disease. The median age was 63 (95% CI: 49–74) years in the severe group compared to 47 (95% CI: 19–63) years in the non-severe group. The proportions of males/females, overall and by COVID-19 severity, were 1.18 and 1.35, respectively. The disease was more common in men overall (54.2%) and by COVID-19 severity (68%).

Prevalence of Underlying Diseases in COVID-19

We found that 41.1% of patients had associated comorbidities such as hypertension (20.9%), diabetes (9.96%), and CVD (4.8%) (Fig. 2; Table 2).

Figure 3 illustrates the relationship between associated comorbidities and disease severity. The most strongly associated comorbidities with severity of COVID-19 were cerebrovascular disease (OR 4.85, 95% CI: 3.11–7.57), CVD (OR 4.81, 95% CI: 3.43–6.74), and chronic lung disease (OR 4.19, 95% CI: 2.84–6.19) followed by cancer (OR 3.18, 95% CI: 2.09–4.82), diabetes (OR 2.61, 95% CI: 2.02–3.39), and hypertension (OR 2.37, 95% CI: 1.80–3.13), respectively (Fig. 3).

Discussion

Care of COVID-19 patients is presenting a major challenge for health care systems. This includes dealing with rapidly growing numbers of patients, inadequate response to current treatments, limited care staffing, and inadequate medical supplies [16]. Moreover, many factors can lead to severe COVID-19, especially in older adults. Disease severity was defined as the need for hospitalization, admission to an ICU, and death [17]. Classification of COVID-19 patients into severe and non-severe cases improves patient outcomes by providing the chance of effective individual assessment of patients [18]. Previous studies demonstrated that comorbidities such as diabetes, COPD, hypertension, and malignancy may lead to poorer prognosis [16, 19–22]. Therefore, in this study, we tried to explore the impact of comorbidities on the prognosis of the COVID-19 infection (Fig. 3).

We found disease severity was highly associated with the presence of cerebrovascular disease (OR 4.85, $p < 0.01$, I^2: 2.2%). It seems that the nervous system disease may be linked to the pathogenesis of COVID-19. In addition to the respiratory tract system, the nervous system may be invaded by SARS-CoV-2 via a hematogenous system or retrograde neuronal route, the same as SARS and MERS viruses leading to a wide spectrum of neurological manifestations from taste and smell impairment to acute cerebrovascular diseases and impaired consciousness [23]. Furthermore, lymphocyte counts are lower for patients with CNS involvement. This might be explained by immune suppression in patients with COVID-19 with CNS involvement, especially in severe cases. Moreover, an acute cerebrovascular disease with severe infection leads to rapid clinical deterioration contributing to a high mortality rate [23].

Preexisting CVD is also an important underlying disease for more severe COVID-19 accompanied by worse clinical outcomes [24]. Our meta-analysis revealed that preexisting CVD is associated with a nearly 4.8-fold sig-

**Table 2.** Baseline underlying disease of patients with COVID-19

| Study	Diabetes, n		CVD, n		Hypertension, n		Cerebrovascular disease, n		Chronic lung disease, n		Cancer, n	
	severe	non-severe	severe	non-severe	severe	non-severe	severe	non-severe	severe	non-severe	severe	non-severe
Zang (19 Feb 2020)	8	9	4	3	22	20	–	–	2	0	–	–
Guan (28 Feb 2020)	28	53	10	17	40	123	4	11	4	6	3	7
Wang (7 Feb 2020)	8	6	6	1	21	22	6	1	3	1	4	6
Huang (24 Jan 2020)	1	7	3	3	2	4	–	–	1	0	0	1
Liu (9 Feb 2020)	0	1	1	3	1	2	–	–	1	0	0	0
Yang (24 Feb 2020)	7	2	3	2	–	–	7	0	2	2	1	1
JieLi (12 Feb 2020)	–	–	–	–	1	0	–	–	–	–	–	–
Zhou (28 Mar 2020)	17	19	13	2	26	32	–	–	4	2	0	2
Wang (16 Mar 2020)	6	1	5	3	–	–	–	–	2	2	1	3
Yuan (19 Mar 2020)	6	0	3	0	–	–	1	0	–	–	1	0
Yuan (29 Mar 2020)	2	0	4	0	3	0	–	–	–	–	–	–
Chen (17 Mar 2020)	24	23	17	7	54	39	4	0	11	7	5	2
Young (3 Mar 2020)	1	0	–	–	4	0	–	–	–	–	–	–
Wu (27 Mar 2020)	–	–	–	–	–	–	–	–	4	0	3	2
Li (29 Feb 2020)	7	0	1	0	2	3	–	–	4	1		
Guan (26 Mar 2020)	45	85	20	39	88	181	15	15	15	9	9	9
Gao (17 Mar 2020)	6	1	1	2	6	7	–	–	–	–	–	–
Chen (19 Feb 2020)	2	1	–	–	4	1	–	–	–	–	–	–
Chen (10 Mar 2020)	5	15	6	3	14	35	–	–	–	–	–	–
Yang (30 Mar 2020)	2	0	6	2	2	2	–	–	7	3	–	–
Qin (12 Mar 2020)	53	22	24	3	105	30	8	3	9	3	10	4
Wang (31 Mar 2020)	10	8	–	–	20	23	6	1	–	–	–	–
Wan (21 Mar 2020)	9	3	6	1	4	9	–	–	–	–	3	1
Shi (18 Mar 2020)	7	22	4	7	26	73	–	–	–	–	2	3
Mo (16 Mar 2020)	12	3	7	0	22	15	7	0	–	–	5	2
Liu (28 Feb 2020)	2	3	–	–	2	6			1	1	2	2
Shi (25 Mar 2020)	20	40	36	29	49	78	13	9	6	6	7	2
Peng (1 Apr 2020)	4	19	–	–	10	82	–	–	–	–	–	–

CVD, cardiovascular disease.

nificantly increased risk of severe COVID-19 disease (Fig. 3). In a meta-analysis on 6 published studies on 1,527 patients with COVID-19 from China, the prevalence of diabetes, cardio-cerebrovascular disease and hypertension was reported to be 9.7, 16.4 and 17.1%, respectively [24]. Besides, diabetes and hypertension were shown to increase the risk of severity or requiring ICU admission by 2-fold while this figure was reported to be 3-fold for cardio-cerebrovascular disease [24]. Also, in a study by Clerkin et al. [24], CVD was associated with disease severity and ICU admission by 4.4 times (95% CI 2.64–7.47). Furthermore, disease severity is associated with higher case fatality rate. In addition, in a study by Shi et al. [25], it was shown that preexisting CVDs may predispose COVID-19 patients to COVID-19-induced heart injury.

Our study also showed that chronic lung disease was significantly related to the development of severe COVID-19 infection (OR 4.19 $p < 0.01$) (Fig. 3). Severe COPD is also a risk factor for severe COVID-19. In a meta-analysis conducted on 7 studies, COPD was shown to increase the risk of developing severe COVID-19 infections [21]. In a case series report from the Chinese Center for Disease Control and Prevention, the overall case fatality rate was 2.3%, while this figure was 6.3% for people with COPD [26]. In a study by Jain and Yuan [27], COPD was shown as the strongest predictive factor for disease severity (OR 6.42, 95% CI 2.44–16.9) as well as ICU admission (OR 17.8, 95% CI 6.56–48.2).

Malignancy was also a risk factor for COVID-19 severity. The results of our pooled analysis also show that preexisting cancer is associated with up to 3.18-fold higher risk of severe COVID-19 (Fig. 3). Infections are the lead-
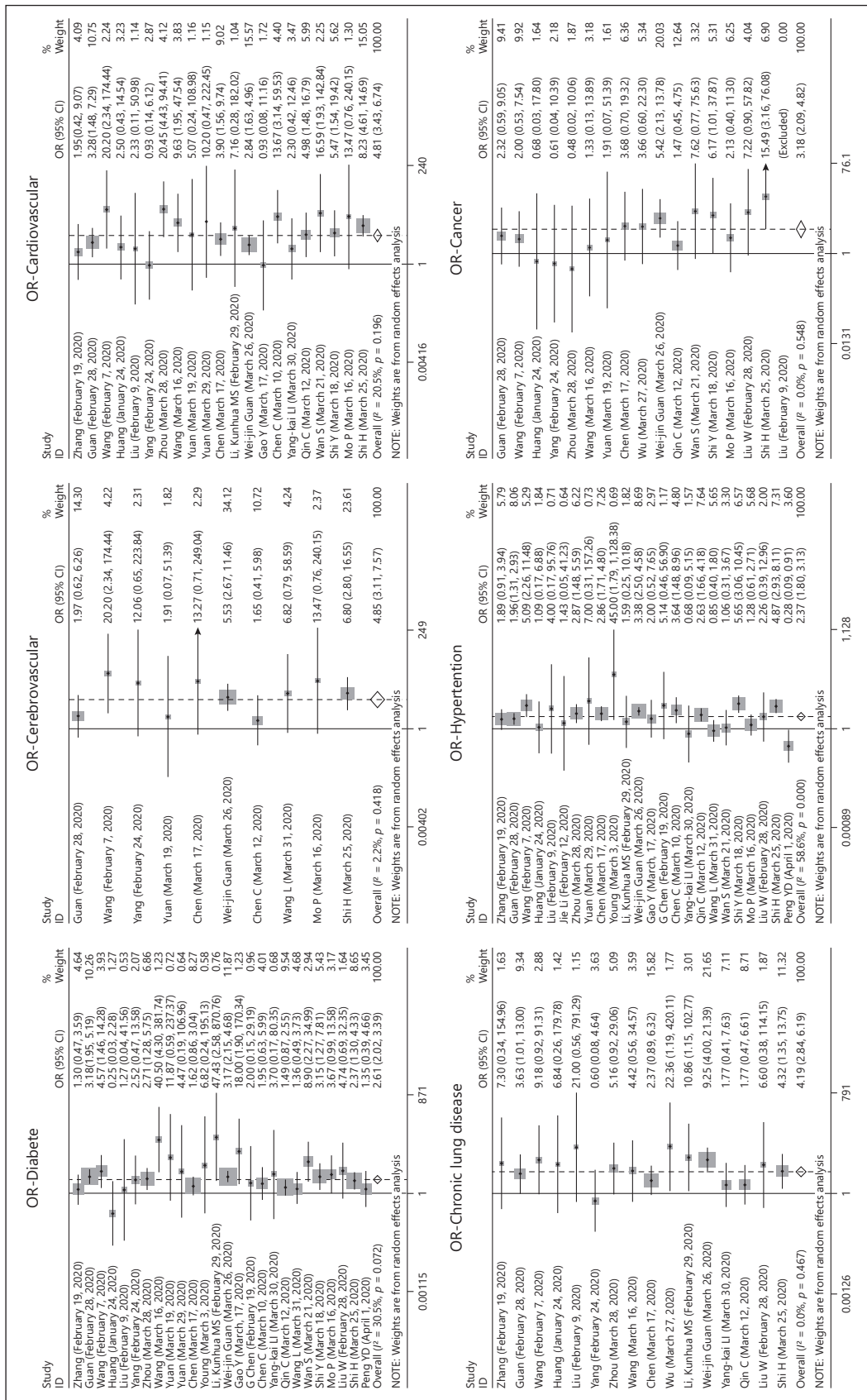
Fig. 3. Prevalence of comorbid conditions among patients with severe COVID-19 compared with non-severe patients. CVD, cardiovascular disease; OR, odds ratio; CI, confidence interval.
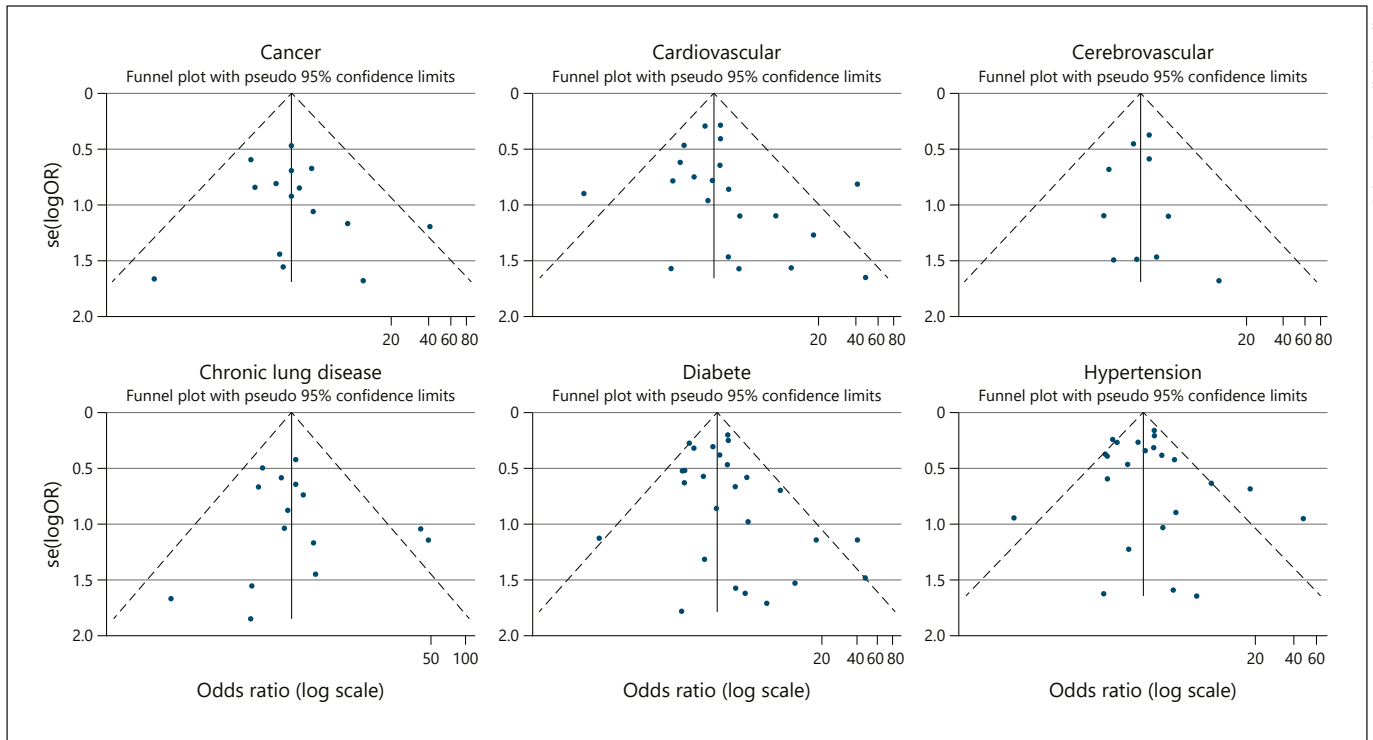
Fig. 4. Funnel plot for meta-analysis of the prevalence of comorbidity in COVID-19 patients. OR, odds ratio.

ing cause of mortality in malignancy [28]. The underlying disease, malignancy-related treatments as well as accompanied comorbidities are 3 main reasons for susceptibility to infections in this group of patients. Both malignancy and its related treatment result in compromised immune systems and a higher risk of infection [28]. Moreover, accompanied comorbidities were previously shown to increase the risk of mortality in MERS-CoV infection [28]. Furthermore, Liang et al. [29] showed that among patients with malignancy, older age was the only risk factor for severe events (OR 1.43, 95% CI 0.97–2.12; $p = 0.072$).

In this meta-analysis, we found that diabetes (OR 2.61, 95% CI: 2.02–3.39) and hypertension (OR 2.37, 95% CI: 1.80–3.13) also increase the risk of severity in COVID-19. Diabetes was an important risk factor for mortality in patients infected with pandemic influenza A (H1N1), SARS-CoV as well as MERS-CoV [30]. In a study that was conducted by Fadini et al. [31], the pooled rate ratio of diabetes among patients with severe disease compared to those with the non-severe disease was 2.26 (95% CI 1.47–3.49). Moreover, diabetes-related complications as the indicators of advanced diabetes may increase the risk of mortality in COVID-19 [19].

Globally, hypertension is a prevalent disease reported in 26% of the population worldwide [22]. However, previous studies showed controversial results regarding the association between hypertension and COVID-19 severity [22]. In a study by Lippi et al. [22], hypertension was shown to increase both the severity and mortality of COVID-19 by ~2.5-fold. This effect was mainly demonstrated in people older than the age of 60, in a meta-regression [22]. Besides, Jain and Yuan [27] showed that hypertension increased disease severity and ICU admission by 3.7 times (95% CI 2.22–5.99). In a meta-analysis by Yang et al. [6] on 8 studies, comorbidities such as hypertension (OR 2.36, 95% CI: 1.46–3.83), respiratory system disease (OR 2.46, 95% CI: 1.76–3.44), and CVDs (OR 3.42, 95% CI: 1.88–6.22) were shown to impose a higher risk for disease severity. However, diabetes did not have a statistically significant effect (OR2.07, 95% CI: 0.89–4.82) [6].

In general, our findings indicate that individuals with associated comorbidities are more susceptible to severe COVID-19 infection. Those at the highest risk for severe disease include people with underlying conditions such as cerebro-cardiovascular disease, chronic respiratory disease, cancer, diabetes, and hypertension.

The key strengths of this study are its quality assessments of studies, large sample size, and desirable I^2 of chosen studies. The funnel plot results indicated that our selected studies had high precision which mostly plotted near the average (Fig. 4).

One issue with the current study was that the generalizability of findings to other populations was unclear because of published reports being restricted to China and a few other countries. Moreover, we do not have detailed data on the number of comorbidities/vascular risk factors and the severity of COVID-19. The heterogeneity of disease severity definition across studies was the other limitation of current study in which any of the following conditions are included as a severe case: ICU admission, receipt of mechanical ventilation or $SpO_2 < 90\%$, development of cardiac injury or end organ failure, and mortality.

In addition, most selected studies did not specify the type of cerebrovascular disease except for 2 in which cerebrovascular disease was defined as cerebral infarction. Furthermore, considering uncertainty about data collection methods and consistency, the results should be interpreted cautiously.

Conclusion

The findings indicate that the presence of associated comorbidities is associated with worse outcome in COVID-19 infection. Cerebrovascular disease was the most strongly predictive comorbidity for severe disease, followed by CVD, chronic lung disease, cancer, diabetes, and hypertension.

Statement of Ethics

This work is a systematic review and meta-analysis of the current available evidence. It was approved by the ethics committee of Iran University of Medical Sciences (IR.IUMS.REC.1396.070).

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

Author Contributions

Z.E. created a systematic search strategy. M.H. and R.A. screened and evaluated the titles and abstracts of citations independently, and then M.E.Kh. checked the screening results. L.J. performed statistical analysis. M.H. and R.A. wrote the manuscript and M.E.Kh. revised. All authors checked and approved the final version.

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