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Meta-analysis of COVID-19 Clinical Symptoms, Prevalence of Comorbidities and Influencing Factors of Severity and Mortality Cases

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Full Research Paper

Meta-analysis of COVID-19 Clinical Symptoms, Prevalence of Comorbidities and Influencing Factors of Severity and Mortality Cases

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Abstract: As the Corona Virus Disease 2019 (COVID-19) continues to spread globally, it is necessary to systematically understand the characteristics of the disease and cases. The purpose of this meta-analysis was to evaluate the clinical characteristics of patients infected with COVID-19 and the prevalence of comorbidities, as well as the risk of potential diseases in severe patients (or deceased patients) compared with non-severe patients (or survivors). As of July 31, 2020, we had used several databases for literature search. A random effects model was used to summarize the prevalence, odds ratio (OR) and 95% confidence interval (95% CI). The final meta-analysis included 79 studies, analyzing a total of 330,464 infected patients from countries in Asia, Europe and North America. The meta-analysis results showed that the average age of the patients was 55.46 years old, and there were more male patients than females. The most common clinical symptoms were fever, followed by cough, dyspnea, fatigue, sore throat, headache and diarrhea. Hypertension, diabetes and cardiovascular disease were the most common complications. In addition, chronic kidney disease, respiratory disease, cancer, chronic liver disease and HIV often appeared. We also observed that the prevalence of some clinical symptoms and complications varies from region to region. When compared with non-severe patients, the combined odd ratios of some comorbidities were all higher in severe patients. A comparison between deceased and surviving patients found that there was also a higher risk of comorbidities in deceased patients. Our research showed that comorbidities may be a risk factor that affects the development of COVID-19 into severe illness or death. We recommended that high-risk patients adopt more targeted infection prevention and treatment strategies to reduce the risk of future COVID-19 diseases.

Keywords: COVID-19, comorbidities, clinical features, epidemiology, meta-analysis

1. BACKGROUND

The novel coronavirus (SARS-CoV-2) is a pathogen not previously found in humans. It was reported for the first time in the bronchoalveolar lavage fluid samples of three patients in Wuhan Jinyintan Hospital on January 24, 2020, and it was confirmed as the cause of COVID-19 [1]. After in-depth research on the full-length genome, it was discovered that the virus is a new type of β-coronavirus that has not been detected in humans or animals. The new type of coronavirus pneumonia it caused was named COVID-19 by the World Health Organization (WHO). It was also named SARS-CoV-2 by the International Committee on Taxonomy of Viruses, and belongs to the same coronavirus family as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Since its outbreak in China at the end of 2019, SARS-CoV-2 has spread all over the world with its extremely contagious nature. On January 30, 2020, it was declared by the WHO that this was a public health emergency of international concern, and was later declared as a global pandemic on March 11, 2020.

The continuous outbreak of COVID-19 infection has seriously threatened international health and the

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economy. As the number of confirmed cases continues to increase, clinical research on patients and antiviral drugs is accelerating. Many countries have already started vaccine research. China, the United Kingdom, the United States and other countries developed related vaccines, but have not yet put them into large-scale use. At present, it is still useful to take preventive measures to reduce the movement and gathering of people. Simultaneously, more and more retrospective studies have reported the clinical manifestations and information of patients with COVID-19. The research of Alfonso et al. [3] shows that some underlying diseases may be risk factors for aggravation and death of patients. In previous studies on SARS and MERS, clinical and risk factors were reported. Badawi and Ryoo reported that the prevalence of chronic diseases is higher in MERS-CoV patients [4]. With the increase in the number of published studies, there are certain differences in the impact of comorbidities on the severity of COVID-19 and the outcome of death. Some studies have reported an association between the severity of COVID-19 and the outcome of previous diseases, while some other reports are not related. In order to further explore the clinical characteristics of COVID-19 and the prevalence of comorbidities and its relationship with worse outcome (i.e., severe disease), and to obtain more convincing results, we searched related literature and adopted meta-analysis methods, to assess the demographic characteristics, clinical symptoms, and prevalence of comorbidities of patients, including subgroup analysis by country or region. The risk of underlying diseases in severe patients (or deceased patients) compared with non-severe patients (or surviving patients) is also assessed. The findings of this article may be beneficial to patient management in the clinical stage, help identify patients who are susceptible to severe diseases, and facilitate tailor-made treatment plans for patients. It may also help clinicians to take corresponding treatment measures at an earlier stage.

2. METHOD

2.1 Search strategy and inclusion criteria

This research was based on the recommendations of the Preferred Reporting Project (PRISMA) of the meta-analysis. First, a systematic literature search was conducted on the research published in PubMed, Scopus, Embase, Web of Science, and the preprinted literature database bioRxiv. For related literature published before August 31, 2020, the following search terms were used: "Corona Virus Disease-2019", "2019 novel coronavirus", "COVID-19", "comorbidities", "clinical characteristics", "epidemiological", combined with Boolean logic operators (AND, OR). We also conducted a manual search and checked the reference list of included studies to identify missing studies. The obtained documentation results were managed by EndNote X9.0 software to eliminate duplicates.

First filter the initial search results based on the title and abstract, then read the full text of articles that meet the theme to check whether the article contains the information required. The inclusion criteria of the article are as follows: the study population is patients diagnosed with COVID-19, the research design is a case study, the outcome indicators include epidemiological, clinical features, and relevant descriptions of comorbidities in infected patients. Articles without clinical features, clinical experience, and case reports with a sample size of less than 10 are not included in the selection. We excluded studies that specifically targeted pregnant women, children, and elderly patients. The steps of document retrieval are shown in Figure 1.

2.2 Data collection and extraction

Extract data basic data such as author, study time, country, continent, age, gender, and number of cases from the literature. We also extracted the number and proportion of cases with clinical symptoms. The number and proportion of comorbidities were also extracted. Besides, if there is a study involving severe cases and deaths, the comorbidities in severe and deceased patients will be also within the statistical range.

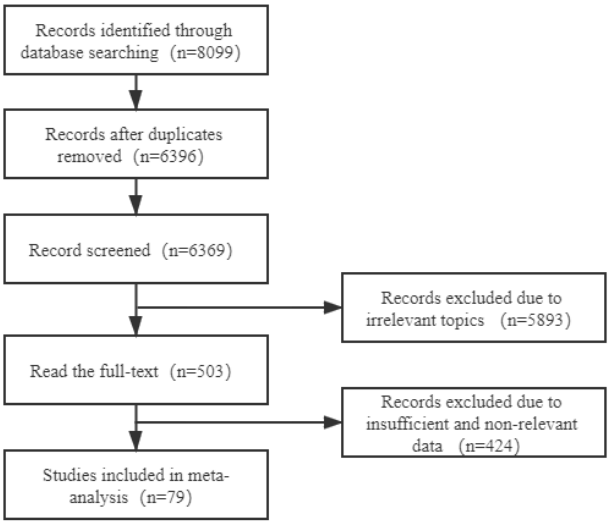

Figure 1. Study selection flow diagram

3. STATISTICAL METHODS

This article adopted the statistical method of meta-analysis, which aims to combine the scientific results of multiple comparable studies or experiments, and obtain aggregated estimates by summarizing relevant information, thereby improving statistical capabilities. In this study, the mean ± standard deviation was calculated to describe the distribution of continuous variables (such as age). For continuous data using median and quartile or number of samples, the estimation method proposed by Wan [5] was used to obtain the sample mean and standard deviation. The combined prevalence and its 95% confidence interval (95% CI) were used to summarize the weighted effect size of each study grouping variable. This study used odds ratio (OR) to describe the risk of comorbidities in severe and deceased patients.

The measures of heterogeneity were evaluated and reported, including Cochran's Q statistic and I^2 statistic. This study used a fixed effects model or a random effects model to assess the heterogeneity of the research. When the $P<0.10$ of Cochran's Q statistic [6], there is heterogeneity and it needs to be estimated using a random effects model. Higgin and Thompson's I^2 statistic expresses the percentage of effect size variability not caused by sampling error. When the I^2 statistic is medium (50%-74%) or high (75%), the random effects model will used to calculate the combined estimated value of the effect size [7]. For the group with high heterogeneity, subgroup analysis was conducted according to research region.

The publication bias was assessed by visual inspection of the funnel plot asymmetry and Egger regression test [8]. If the significance level P is greater than 0.05, it is considered to be unbiased. When evidence of publication bias is found, the trim-and-fill method is used to estimate and adjust the potential missing studies, and the effect size is recalculated accordingly [9]. All calculations are carried out by Comprehensive Meta Analysis 3.0 software.

4. RESULT ANALYSIS

4.1 Research selection and feature analysis

Initially, 8099 articles were retrieved using the search strategy. After deleting duplicate articles, 6396 articles were obtained. The abstract and title were further evaluated, and 503 articles were selected for full-text evaluation. Among them, 424 were excluded due to lack of relevant required information, and 79 articles reached the predetermined inclusion and exclusion criteria for quantitative meta-analysis. This study included 79 studies published as of June 28, 2020, and contains cases from 21 countries including the United States, China, Italy, Spain, India, the United Kingdom, South Korea, Kuwait, and Iran. A total of 330,464 patients were reported in all

studies.

4.2 Meta-analysis results

4.2.1 Prevalence of clinical symptoms and comorbidities

The variables of the meta-analysis research were shown in Table 1. The average age of the subjects studied was 55.46 (95% CI: 52.53-58.39) years old, and there were more male patients than females (59.96%, 95% CI: 57.46-62.40%, I^2=99.26%). The results of meta-analysis showed that the most common clinical symptom was fever, and the combined prevalence rate was 73.49% (95%CI: 67.07-79.05%, I^2=97.75%), followed by cough (62.91%, 95%CI: 57.15- 68.32%, I^2=97.38%), dyspnea (43.26%, 95%CI: 37.44–49.29%, I^2=96.79%) and fatigue (29.32%, 95%CI: 22.99–36.58%, I^2=97.15%). Other symptoms such as sore throat (14.87%, 95% CI: 12.01–18.26%, I^2=84.77%), headache (13.38%, 95% CI: 10.04–17.61%, I^2=91.65%) and diarrhea (12.43%, 95% CI: 9.67–15.83%, I^2=94.34%) also appeared from time to time.

Common comorbidities included hypertension, diabetes, respiratory disease, cardiovascular disease, chronic liver disease, chronic kidney disease, cancer and HIV. Among them, the most common comorbidities were hypertension (32.82%, 95%CI: 28.80–37.10%, I^2=99.75%), diabetes (19.77%, 95%CI: 17.21-22.61%, I^2=99.57%) and cardiovascular disease (11.10%, 95%CI: 8.86-13.81%, I^2=99.61%). A small proportion of patients developed chronic kidney disease (8.41%, 95%CI: 5.72-12.20%, I^2=99.84%), respiratory system diseases (7.53%, 95%CI: 5.62-10.02%, I^2= 99.72%), cancer (5.44%, 95%CI: 4.69–6.30%, I^2=96.82%), chronic liver disease (2.28%, 95%CI: 1.82–2.84%, I^2=98.24%), and HIV (1.03%, 95%CI: 0.58-1.82%, I^2=97.23). In the evaluation of clinical characteristics, I^2 was above 90%, showing statistical heterogeneity (P<0.001), as shown in Table 1. Through the analysis of the prevalence of comorbidities, it was observed that the Q statistic P<0.1, and the I^2 of the comorbidities are all above 90%, showing significant heterogeneity.

Table 1. Meta-analysis results

	N	Prevalence[a]	Lower limit	Upper limit	Q	P	I^2
Male	73	59.96%	57.46%	62.40%	9778.31	0.00	99.26
Fever	47	73.49%	67.07%	79.05%	2048.59	0.00	97.75
Cough	51	62.91%	57.15%	68.32%	1909.09	0.00	97.38
Fatigue	31	29.32%	22.99%	36.58%	1052.31	0.00	97.15
Dyspnea	43	43.26%	37.44%	49.29%	1306.92	0.00	96.79
Diarrhea	33	12.43%	9.67%	15.83%	565.69	0.00	94.34
Headache	31	13.38%	10.04%	17.61%	359.22	0.00	91.65
Sore Throat	23	14.87%	12.01%	18.26%	144.47	0.00	84.77
Hypertension	58	32.82%	28.80%	37.10%	22669.63	0.00	99.75
Diabetes	66	19.77%	17.21%	22.61%	14983.19	0.00	99.57
Respiratory System Disease	64	7.53%	5.62%	10.02%	22583.26	0.00	99.72
Cardiovascular Diseases	63	11.10%	8.86%	13.81%	15767.18	0.00	99.61
Chronic Liver Disease	32	2.28%	1.82%	2.84%	1761.60	0.00	98.24
Chronic Kidney Disease	55	8.41%	5.72%	12.20%	33793.63	0.00	99.84
Cancer	41	5.44%	4.69%	6.30%	1257.86	0.00	96.82
HIV	13	1.03%	0.58%	1.82%	433.11	0.00	97.23

[a] Meta-analysis for the prevalence was calculated from binary random-effects model analysis

4.2.2 Subgroup analysis

A subgroup analysis was conducted on the prevalence of clinical symptoms and comorbidities. The

subgroups were divided into Asian countries, European countries and North American countries according to regions. There were 32 studies from Asian countries, 15 of which were from China, 23 of European countries, 9 of which were from Italy, 6 from Spain, and 24 from North America, most of which were from the United States. The average age of patients from Asian countries was 48.23 (95% CI: 45.14–51.32), the proportion of male patients was 63.26% (95% CI: 55.42–70.46%). The average age of European patients was 65.23 (95% CI: 59.92–70.54), the proportion of male patients was 58.21% (95% CI: 54.48–61.85%). In North America, the average age of patients was 58.08 (95% CI: 55.09–60.07) years, 57.08% (95 %CI: 53.07–61.01%) were male patients. We had observed that the combined prevalence of some clinical symptoms and complications varies from region to region.

In terms of clinical symptoms, fever and cough were the most prevalent manifestations in Asia, Europe and North America, and dyspnea and fatigue were also common symptoms. The prevalence of cough in North American patients exceeded fever, and was the most common clinical symptom. At the same time, the prevalence of dyspnea ($Q=20.77$, $P<0.001$) and diarrhea ($Q=30.13$, $P<0.001$) in North American were obviously higher than that in Asia and Europe.

As for comorbidities, the most common were hypertension and diabetes, and cardiovascular disease and respiratory system diseases also occurred from time to time. There were significant differences in the prevalence of some comorbidities in different regions. The prevalence of hypertension ($Q=43.33$, $P<0.001$), cardiovascular disease ($Q=11.56$, $P<0.001$) and cancer ($Q=10.99$, $P<0.001$) in European and North American patients was significantly higher than that in Asia. The prevalence of diabetes ($Q=47.93$, $P<0.001$), chronic kidney disease ($Q=12.36$, $P<0.001$) and HIV ($Q=11.91$, $P<0.001$) among North American patients was significantly higher than that of the other two regions.

Table 2. Subgroup analysis results

		N	Prevalence	Lower limit	Upper limit	Q	P	I^2
Male	Asia	31	63.26%	55.42%	70.46%	2468.36	0.00	98.78
	Europe	22	58.21%	54.48%	61.85%	1950.19	0.00	98.92
	North America	20	57.08%	53.07%	61.01%	2276.45	0.00	99.17
Fever	Asia	21	73.73%	64.13%	81.50%	368.62	0.00	94.57
	Europe	13	76.13%	65.46%	84.30%	768.69	0.00	98.44
	North America	13	68.89%	57.45%	78.41%	256.54	0.00	95.32
Cough	Asia	22	59.88%	50.18%	68.86%	554.22	0.00	96.21
	Europe	15	56.92%	47.26%	66.09%	743.66	0.00	98.12
	North America	14	73.42%	62.25%	82.22%	285.36	0.00	95.44
Fatigue	Asia	19	25.12%	15.39%	38.22%	657.97	0.00	97.26
	Europe	5	31.83%	21.05%	44.99%	131.58	0.00	96.96
	North America	7	39.42%	22.52%	59.30%	114.56	0.00	94.76
Dyspnea	Asia	17	26.19%	16.20%	39.44%	421.90	0.00	96.21
	Europe	15	46.38%	39.83%	53.07%	356.17	0.00	96.07
	North America	11	64.78%	55.08%	73.39%	100.37	0.00	90.04
Diarrhea	Asia	14	6.05%	3.86%	9.35%	86.56	0.00	84.98
	Europe	9	15.09%	11.15%	20.11%	92.76	0.00	91.38
	North America	10	23.89%	18.64%	30.08%	47.39	0.00	81.01
Headache	Asia	17	11.77%	7.62%	17.76%	221.12	0.00	92.76
	Europe	5	15.55%	5.73%	35.79%	93.06	0.00	95.70
	North America	9	15.92%	11.19%	22.13%	34.00	0.00	76.47
Sore Throat	Asia	10	17.98%	13.87%	23.00%	63.10	0.00	85.74
	Europe	3	11.27%	4.01%	27.86%	19.04	0.00	89.49
	North America	10	12.60%	8.24%	18.79%	51.68	0.00	82.59

		N	Prevalence	Lower limit	Upper limit	Q	P	I^2
Hypertension	Asia	22	16.70%	12.45%	22.04%	960.67	0.00	97.81
	Europe	18	42.82%	35.27%	50.71%	4152.18	0.00	99.59
	North America	18	46.89%	38.33%	55.64%	9971.74	0.00	99.83
Diabetes	Asia	24	12.80%	9.94%	16.35%	576.24	0.00	96.01
	Europe	20	18.72%	14.89%	23.26%	2713.35	0.00	99.30
	North America	22	30.06%	26.92%	33.39%	1607.09	0.00	98.69
Respiratory System Disease	Asia	22	3.83%	1.33%	10.57%	4634.93	0.00	99.55
	Europe	21	10.64%	6.89%	16.08%	6588.69	0.00	99.70
	North America	21	9.13%	6.23%	13.19%	3350.17	0.00	99.40
Cardiovascular Diseases	Asia	23	6.91%	4.89%	9.67%	409.65	0.00	94.63
	Europe	21	13.90%	8.24%	22.50%	9556.89	0.00	99.79
	North America	19	14.37%	10.78%	18.90%	3096.77	0.00	99.42
Chronic Liver Disease	Asia	12	2.67%	1.10%	6.30%	298.66	0.00	96.32
	Europe	10	2.00%	1.01%	3.92%	751.82	0.00	98.80
	North America	10	2.08%	1.14%	3.75%	482.40	0.00	98.13
Chronic Kidney Disease	Asia	15	3.12%	1.72%	5.60%	335.00	0.00	95.82
	Europe	19	7.57%	5.90%	9.65%	897.45	0.00	97.99
	North America	21	17.09%	7.55%	34.20%	23953.92	0.00	99.92
Cancer	Asia	14	2.49%	1.22%	4.99%	369.16	0.00	96.48
	Europe	16	8.20%	6.60%	10.14%	781.64	0.00	98.08
	North America	11	6.71%	5.93%	7.59%	25.40	0.00	60.63
HIV	Asia	3	0.58%	0.13%	2.56%	10.68	0.00	81.27
	Europe	3	0.47%	0.23%	0.95%	45.52	0.00	95.61
	North America	7	1.70%	1.25%	2.32%	17.38	0.01	65.47

4.2.3 Non-severe and severe cases

A comparison between severe and non-severe patients found that the average age of severe patients was 62.17 (95% CI: 59.29-65.06), and the average age of non-severe patients was 53.02 (95% CI: 47.58-58.45). Compared with non-severe patients, severe patients presented a higher risk of complications. The ORs of cardiovascular disease, diabetes, hypertension, chronic liver disease, were 2.32 (95%CI: 1.31–4.10, I^2=80.73%), 2.02 (95%CI: 1.41–2.90, I^2=76.30%), 1.90 (95%CI: 1.31–2.74, I^2=83.10%), and 1.89 (95%CI: 1.42–2.52, I^2=0.24%) respectively. Respiratory system diseases (OR=1.79, 95%CI: 1.03–3.11, I^2=64.60%), chronic kidney disease (OR=1.54, 95%CI: 0.95–2.49, I^2=62.04%), cancer (OR=1.50, 95%CI: 0.94–2.39, I^2=30.66%) and HIV (OR=1.34, 95%CI: 0.30–5.93, I^2=0.00%) were also closely associated with severe disease.

4.2.4 Surviving and non-surviving cases

A comparison between the survivors and deceased patients found that the average age of the dead patients was 71.47 (95% CI: 67.56–75.38), and the average age of the survivors was 60.48 (95% CI: 57.61–63.35). Compared with surviving patients, deceased patients presented a higher risk of complications. The ORs for cardiovascular disease, chronic kidney disease, hypertension, cancer, were 4.05 (95%CI: 2.63–6.24, I^2=83.30%), 3.69 (95%CI: 2.13–6.41, I^2=92.02%), 2.46 (95%CI: 1.85–3.29, I^2=81.11%), and 2.30 (95%CI: 1.76–3.01, I^2=54.92%) respectively. Chronic liver disease (OR=2.26, 95%CI: 1.32–3.87, I^2=32.68%), respiratory system diseases (OR=2.24, 95%CI: 1.77–2.84, I^2=52.59%), diabetes (OR=2.04 ,95%CI: 1.7–2.65, I^2=79.16%), and HIV (OR=0.74, 95%CI: 0.43–1.27, I^2=0.00%) were also closely associated with severe diseases.

4.2.5 Publication bias and sensitivity analysis

The publication bias was evaluated by visually inspecting the symmetry of the funnel plot and Egger's

regression. Asymmetry was observed in the funnel plot of the prevalence of fatigue, diarrhea, and chronic liver disease, with Egger's P of 0.024, 0.0035, and 0.019 respectively. In the analysis of severe cases, the funnel plot of chronic liver disease showed asymmetry (Egger's P=0.0078), indicating the existence of publication bias. However, after using the trim-and-fill method to process it, and adjusting the size of the asymmetry of the funnel plot, the adjusted effect was still the same as the original effect, indicating that the result was reliable.

By omitting each study one by one to conduct sensitivity tests to assess the stability of the combined results, no obvious significant deviations were found. The one study removed method was used to exclude one document at a time, and the influence of each document on the results of the meta-analysis was studied. The results of the sensitivity analysis showed that the combined effect value of each study does not change much, suggesting that the results of this meta-analysis were relatively robust and credible.

5. DISCUSSION

This study was based on 79 laboratory-confirmed COVID-19 research data. The results found that the proportion of male patients is greater than that of females (59.96%, 95% CI: 57.46-62.40%), which is in consistent with the conclusions of previous studies. In the previous two outbreaks of coronavirus respiratory system diseases, namely severe acute respiratory disease (SARS) and Middle East respiratory disease (MERS), it was also observed that the infection rate of men was significantly higher than that of women [4]. In Mohammad's study, it was also found that the hospital mortality rate of men among COVID-19 patients was significantly higher than that of women (OR 3.4, 95% CI: 1.2–9.1, P = 0.01) [10].

Many previous studies had shown that women are less likely to be infected by a variety of bacteria and viruses than men, partly because women have stronger innate and adaptive immune responses. The severity of the disease may be related to the immunomodulatory effects of hormones. Estrogen and testosterone sex hormones have the effect of regulating the immune response. In general, estrogen is conducive to enhancing immunity, and testosterone can suppress immunity, which may also be the reason why women are not susceptible to virus infection [11]. Some scholars had also raised the influence of smoking. According to research, angiotensin converting enzyme 2 (ACE2) is the receptor of SARS-CoV-2 in the lower respiratory tracts, and the expression of ACE2 in the lower respiratory tract of smokers is higher, which indicates that smokers have higher risk of COVID-19 illness [12]. The smoking prevalence of men in China is much higher than that of women (57.6% vs. 6.7%). In other countries, the smoking rate of men is also usually higher than that of women. These findings may reveal the reason for the higher risk of men in COVID-19. Although approximately 70% of health and care workers in the world are women, and they are more exposed to the risk of infection, most studies currently showed that men with COVID-19 have a higher overall infection and mortality rate [13]. More research is needed to explore gender differences during the COVID-19 pandemic.

We extracted data on the prevalence of the most common symptoms of COVID-19. These most common clinical manifestations were also similar to previous reports. Fever and cough were the most common clinical symptoms in COVID-19 patients. The prevalence of fever symptoms in COVID-19 patients was similar to that of SARS and MERS, but the prevalence of cough in SARS and COVID-19 was higher than that of MERS. (<50%) [14]. In North America, the prevalence of cough symptoms (73.42%) exceeded fever (68.89%), and became the most common clinical symptom. The analysis of subgroups divided by regions found that the prevalence of dyspnea (Q=20.77, P<0.001) and diarrhea (Q=30.13, P<0.001) in North American patients was significantly higher than that in Asia and Europe. The reason for this difference remained to be further investigated.

According to the results of our meta-analysis, the most common comorbidities were hypertension, diabetes, cardiovascular disease and so on. The analysis of regions divided into different subgroups showed that the prevalence of complications such as hypertension, cardiovascular disease, cancer, diabetes, chronic kidney disease,

and HIV also differs significantly in different regions. This may be caused by differences in the patients' environment, social conditions, and medical conditions, thus further research is needed to determine the reason for the difference. This was similar to the conclusion obtained by Sunny Goel et al.[15]. Their study also reported that the prevalence of respiratory system diseases (asthma and chronic obstructive pulmonary disease) and liver disease in American and European patients was significantly higher than that in Asia. However, no significant differences were observed in our study (respiratory system diseases: Q=3.27, P=0.19; chronic liver disease: Q=0.29, P=0.87).

Compared with non-severe patients, the risk of comorbidities was higher in severe people. Similarly, compared with survivors, non-survivors also had a higher risk of comorbidities. However, no higher risk of death has been observed in HIV patients (OR: 0.74, 95% CI: 0.43–1.27), which may be due to the fact that fewer relevant literatures were included. There is not much information reported on HIV comorbidities, and further research is needed to explain the relationship and interaction between HIV and COVID-19 pathogenesis.

According to age-based analysis, the average age of patients was 55.46 years, which was close to the number reported in previous studies [14]. In fact, it had been shown that elderly patients are more likely to have more serious complications and further deaths, which may be related to the relatively weak immune system of the elderly or the higher prevalence of comorbidities. Comorbidities and susceptibility diseases may damage the function of macrophage and lymphocyte function, thereby reducing immunity, which is related to the pathogenesis of COVID-19 [16]. Previous studies had also pointed out that diabetes and heart disease are also significantly related to MERS-CoV illness. The meta-analysis of Yang et al.[17] pointed out that age and comorbidities are highly correlated in COVID-19 patients. Another study also confirmed that the elderly and patients with comorbidities (including diabetes, hypertension, cardiovascular disease, liver disease, malignant tumors) are more likely to develop severe diseases (62.1%, 25.0%, $p < 0.001$).

Hypertension is the most common comorbidity among COVID-19 patients. Previous studies had also explored the relationship between hypertension and the severity of COVID-19. A study from Zekavat et al. found that patients with hypertension patients have a higher risk of acute respiratory disease and chronic lower respiratory disease. A systematic review from Chen et al. showed that hypertension is one of the main comorbidities leading to the death of COVID-19.

Diabetes increases metabolic disorders and induces inflammatory infections, which makes diabetic patients more susceptible to SARS-CoV-2. At the same time, the blood glucose level of diabetic patients may fluctuate sharply due to viral infection, which is not conducive to the patient's recovery. Considering that diabetes can weaken the complexity of the human immune system, it is important to take preventive measures to combat the high incidence of COVID-19 in this vulnerable group. Such patients must be reminded to pay special attention to blood glucose control, blood glucose monitoring and timely treatment to avoid serious complications of COVID-19.

Heart disease patients with SARS-CoV-2 may develop serious diseases, which indicates that SARS-CoV-2 may cause more infections in cardiovascular disease patients and make their condition worse. Gaurav's research showed that cardiovascular disease is directly related to the severity of COVID-19 patients, and they found that cardiovascular disease is associated with an approximately three-fold increase in the probability of severe COVID-19 infection [18].

Chronic kidney disease usually causes various metabolic and electrolyte abnormalities, and can lead to serious consequences due to acute kidney injury. A report on COVID-19 indicated that 30% of cases developed moderate to severe kidney damage. According to research, its pathogenesis may be that kidney tissue is one of the main binding sites for COVID-19, where the expression of ACE2 increases [19].

Respiratory system diseases such as patients with chronic obstructive pulmonary disease have less resistance to viruses and are prone to acute respiratory distress syndrome. Similar to other respiratory infections, COVID-

19 mainly affects the lungs and invades pulmonary alveolar epithelial cells. Patients who have suffered from respiratory system diseases may have hypoxia at baseline, so they are more likely to be at risk of impaired lung function after infection [20]. Furthermore, according to studies by Imai et al., the expression of ACE2 (the main receptor of COVID-19) is higher in people with acute respiratory distress syndrome and acute respiratory injury. This may partly explain the relationship between patients with lung disease and severe COVID-19.

Liang et al. released a study of 1590 COVID-19 patients, including 18 cancer patients, which is higher than the cancer incidence rate of the entire Chinese population. Another cross-sectional study published by Jing et al. analyzed 1524 cancer patients in a hospital in Wuhan. It reported 12 cancer patients diagnosed with COVID-19 and concluded that the COVID-19 infection rate among cancer patients was higher than the cumulative incidence reported in Wuhan during the same period (0.79% vs 0.37%).

A study by Zhang et al. showed that the expression of ACE2 in the liver makes it easy to be injured by SARS-CoV-2 infection. Other drugs used to treat COVID-19, such as lopinavir/ritonavir may also adversely affect the liver, causing further liver damage.

For immunodeficiency and HIV patients, the risk of serious diseases associated with COVID-19 infection will greatly increase. Compared with SARS-CoV-2 single-infected patients, COVID-19 patients with HIV are also prone to increase the prevalence of other comorbidities, which may further lead to aggravation of the disease. However, in this study, it was found that there was no significantly higher risk of HIV comorbidities among patients who died from COVID-19, and the relationship between the two in terms of pathogenesis and therapeutic impact needs to be further explored.

Based on the results of our research, the following prevention strategy was proposed, that was, individuals with higher risk should receive immunization first. People with high blood pressure, diabetes, cardiovascular disease, chronic kidney disease, respiratory disease, cancer and chronic liver disease are at higher risk of worse outcome from COVID-19, so they should be given priority when allocating vaccines. Lau et al. investigated the influenza vaccination of 91,605 diabetic patients and found that influenza vaccine can significantly reduce the incidence of influenza and pneumonia in diabetic patients. The study of Remschmidt et al. also confirmed that in people with chronic comorbidities, influenza vaccination significantly reduced morbidity and mortality. In the season when respiratory system diseases caused by influenza, respiratory syncytial virus and other respiratory viruses are highly prevalent, influenza vaccination is still necessary. On the one hand, it can still be used to prevent influenza. On the other hand, it can help reduce the possibility of infection with COVID-19 confused. Therefore, patients with chronic diseases such as hypertension, diabetes, respiratory system diseases and cardiovascular diseases should be included in the influenza and future COVID-19 vaccination recommendations. In view of the limited level of evidence in this study, scholars in this field can conduct more adequate research to prove this association in the future. The prevalence of chronic diseases is increasing year by year, and targeted public health vaccination interventions must be taken to better protect people with chronic diseases from COVID-19 and other respiratory viruses.

From a clinical point of view, this research was very relevant to the practice of patient care. Our research found that there is a certain correlation between comorbidities and the severity of COVID-19 disease and the outcome of death, which may help medical and health departments to guide susceptibility population prevention and assessment of the risk of patient deterioration. It can also contribute to guiding prevention and treatment strategies. Since the clinical results of COVID-19 are more related to the elderly, men, and comorbidities, more active hospital care measures may be needed for such patients. Abnormal examinations of the lungs, liver, and kidneys on admission can be used as predictors of disease severity. Susceptible patients with certain known risk factors may need to take additional preventive measures to help prevent SARS-CoV-2 infection. High-risk patients who are infected can be encouraged to seek medical attention in the early stages of the disease. In the case of

hospitalization, doctors should consider that the medical management of such patients may be more difficult because they are at higher risk of serious illness and death.

6. CONCLUSIONS

COVID-19 is a new type of virus. Its outbreak and epidemic are threatening the safety of all countries and the entire ecosystem in the world. In the face of this new clinical disease, it is necessary for all countries and departments to make joint efforts in the fields of epidemiology, diagnosis, treatment and prevention during the epidemic period in order to contain the further spread of the disease. In the context of the COVID-19 outbreak, the clinical symptoms, laboratory results, and imaging analysis of the disease should be systematically studied and evaluated to correctly understand the virus itself and the characteristics of the disease caused by it. This study analyzed 330,464 patients through a systematic review and random effects meta-analysis. Through the combined prevalence and 95% confidence interval estimation, the following summary was obtained: the most common clinical manifestation in COVID-19 patients was fever, symptoms such as cough, dyspnea and fatigue, sore throat, headache, diarrhea were common; the elderly, men, and the presence of comorbidities were some of the risk factors; among patients with comorbidities, the most common were hypertension, diabetes, cardiovascular disease, chronic kidney disease, respiratory disease, cancer, chronic liver disease and HIV also often appeared; through the analysis of the comorbidities of severe and non-severe patients (deceased and surviving patients), it was found that there was a higher risk of comorbidities in severe and deceased patients.

The symptoms, prevalence, and epidemiological characteristics of COVID-19 patients are an important topic in the research community, because more data can be obtained and more specific and stable discoveries can be obtained. Our study conducted a meta-analysis of patient characteristics and compared the performance of patient characteristics in different regions. The results of this study can help medical and public health professionals and the public better understand the symptoms associated with COVID-19. This study confirmed that patients with comorbidities have an increased risk of developing serious or death, which was consistent with the conclusions of other previous studies. Considering this higher risk, we suggested that people with one or more potential comorbidities need to pay more attention, especially those in areas with high infection rates, should be protected and avoid close contact with community members. In addition, with the development of effective antiviral treatments and vaccines, we must vigorously consider adopting key intervention measures to protect this vulnerable group.

However, there were still certain limitations in this study. First, the lack of reports on asymptomatic infections and mildly symptomatic patients may cause this study to overestimate the severity of the disease. Secondly, most of the studies included in this meta-analysis were not randomized controlled trials. In addition, the meta-analysis results found that there was a high heterogeneity statistical data, which may be related to the large difference in the sample size between the study design and the study. Some studies provided incomplete or insufficient patient clinical data, and missing information may lead to biased results. Moreover, patients had great heterogeneity, because the age, race, and economic status of patients in the study were not same, and different treatment methods and drug use during the treatment process may also affect statistics. In this study, we only considered the region as the basis for subgroup classification. Furthermore, the literature included in this study was not sufficient. As the pandemic spreads globally, future studies can obtain more regional data and collect more comprehensive data, higher-quality clinical trials for more reliable conclusions.

So far, whether it is a case report or a cross-field study, the clinical findings are basically the same. However, more data is needed to further determine the epidemiology, pathogenesis, duration of virus shedding, and clinical scope of the COVID-19 virus infection. Clinically, these data will help guide countries that are currently undergoing epidemics to conduct adequate clinical surveillance. Additionally, this study provided assistance in

the screening and prevention of COVID-19 in clinical practice, and the risk stratification and management of patients. Meanwhile, it was useful for decision makers, clinicians and researchers to take supportive interventions and implement infection control measures to prevent further spread.

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