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MINI REVIEW

# A digitized catalog of COVID-19 epidemiology data

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**COVID-19 is now rapidly spreading worldwide. While the majority of COVID-19 patients show only mild or moderate symptoms, some could deteriorate quickly and may succumb to a sudden death. It is therefore important to identify who will be more likely to develop severe outcomes and be treated with particular or preventive care. Here in this literature survey, we collected epidemiologic and clinical data from 36 articles on 51,270 patients with different severity of COVID-19, aiming to characterize the population that are prone to severe condition and bad outcomes. These data reveal that old males and those with high BMI or underlying diseases, especially cardiovascular disease, hypertension and diabetes, are overrepresented among severe cases. High leukocyte and lymphopenia are common features in severe and critical patients. Upon deterioration of the disease, both $CD4^+$ and $CD8^+$ T cells are decreased, while almost all serum cytokines, especially pro-inflammatory cytokines, increased.**

**Keywords:** COVID-19; severity; epidemiology; immune cells; cytokine

## BACKGROUND

Since December 2019, a new coronavirus SARS-CoV-2 spread rapidly worldwide. The virus was named SARS-CoV-2, due to its similarity of SARS-CoV, another coronavirus that caused SARS epidemic in 2003. The disease caused by SARS-CoV-2 was named COVID-19. SARS-CoV-2 infection may cause pneumonia and other comorbidities, which poses a huge threat to the health of people worldwide. As of May 9, 2020, the World Health Organization (WHO) has reported 3,855,788 laboratory-confirmed cases globally, mainly distributed in Western Pacific Region, South-East Asia, Europe and North America, and relatively fewer cases in Africa, with an alarming number of 265,862 deaths [1].

In the early days of the COVID-19 outbreak, a study in *The Lancet* [2] provided the first glimpse of the epidemiological features of the disease. Since then, numerous epidemiological data have been produced to provide more detailed descriptions of patients' age, sex, basic chronic disease and biochemical indicators, which not only provided important information for research and first-line clinical practice, but also provided assistance in the identification of susceptible populations and for diagnostic indicators of the possible drug targets. However, since these epidemiological studies are often based on different purposes and study designs, the emphasis is different from each other, and the sample size is relatively limited, making it difficult to reach a unified conclusion. Therefore, a combined and unified catalog of the existing literature is more helpful to obtain stable and accurate conclusions. A correspondence in *The Lancet* [3] suggests that patients be given different treatment options based on the severity of the symptoms to improve outcomes. To achieve this, the first step is to accurately characterize the characteristics of patients with severe COVID-19 symptom that may facilitate an accurate severity prediction in the future. Therefore, we summarized and tabulated the currently published or preprinted SARS-CoV-2 epidemiological articles, focusing on combing COVID-19 patients with different degrees of severity in terms of gender, age, past medical

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history, number of immune cells and various cytokines. We hope that a relatively uniform conclusion from these studies will provide guidance for the current clinical work and the prevention and treatment of similar infections in the future.

## RESULTS

A total of 3224 articles were retrieved according to the strategy in “Method”, among which 3037 papers were removed after reading titles and abstracts, 151 were eliminated after reading the full text. 36 papers were included in our analysis in the end, including a total of 51,270 patients from 31 Chinese provinces and 2 countries outside China. The specific operation flow according to PRISMA-protocol [4] is shown in Fig.1, and the characteristics of the literature are shown in Table 1.

Table 2 shows the distribution of different patient age, gender, BMI and underlying diseases in different severity group. We can see from the table that the median ages of the whole infected patients are among 40–60 years. Median ages of severe and critical patients are generally over 50 years and those of deaths are older than 60 years. There is no obvious gender bias among all infected patients, but in all relevant studies males make up the majority of critical and dead patients. In addition, the median BMI value of severe group, which are in the scale of overweight [39] ( $>24$), are generally higher than that of non-severe group. The odds ratio (OR) of obese patient ($\geqslant 28$) is as high as 7.8 comparing severe with non-severe group.

Patients with underlying diseases tend to be in more severe conditions, and among all the chronic diseases, cardiovascular disease, hypertension and diabetes are most commonly seen in COVID-19 patients, and are more likely to show up in severe, critical and death groups comparing with non-severe group.

The relative number of peripheral blood cells of patients with different severity are listed in Table 3. It can be seen that in most cohort studies, white blood cells, neutrophils, and monocytes of the all infected patients are in the normal range, while lymphocytes, especially T cells, are below normal levels. For severe and critical cases, both white blood cells and neutrophils have a tendency to increase, while T cell levels have dropped significantly compared with mild cases. Among T cells, both $CD4^+$ and $CD8^+$ cells are significantly reduced, with a possible greater decline of $CD8^+$ cells (as reported by some, $CD4^+/CD8^+$ T cells are higher in severe and critical groups). With the deterioration of the disease, NK cells are not found to have a consistent direction of change. In addition, the levels of eosinophils in the blood of severe patients are generally lower than those of non-severe patients.

The cytokine table (Table 4) consists of 11 studies, including a total of 1478 patients and 17 healthy people.

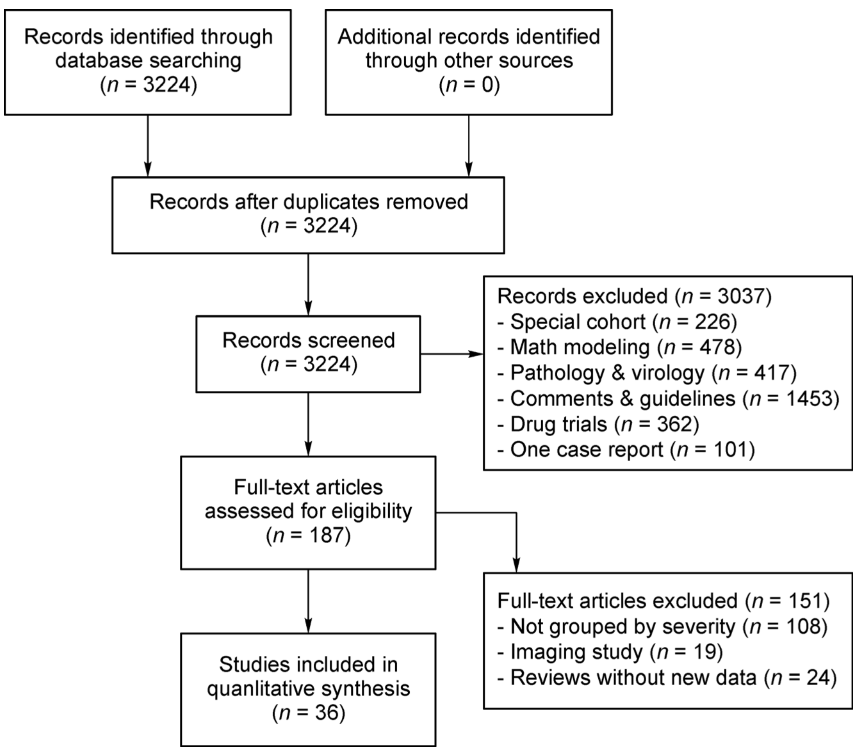


**Figure 1. PRISMA diagram of the literature survey workflow.**

**Table 1 Characteristics of the literatures**

| Ref. | Publication date | Data resources | Groups | Number in each group |
|---|---|---|---|---|
| Huang *et al*. 2020 [2] | 1.24 | Jinyintan Hospital, Wuhan | Total | 41 |
| | | | Non-critical | 28 |
| | | | Critical | 13 |
| Chen *et al*. 2020 [5] | 2.6 | Tongji Hospital, Wuhan, Huazhong University of Science and Technology | Severe | 9 |
| | | | Critical | 5 |
| | | | Non-severe | 15 |
| Wang *et al*. 2020 [6] | 2.7 | Zhongnan Hospital of Wuhan University | Total | 138 |
| | | | Non-critical | 102 |
| | | | Critical | 36 |
| Liu *et al*. 2020 [7] | 2.9 | Shenzhen Third People's Hospital | Total | 12 |
| | | | Non-severe | 4 |
| | | | Severe | 8 |
| Team, 2020 [8] | 2.17 | Reported cases by CCDC | Total | 44,672 |
| | | | Death | 1023 |
| Zhang *et al*. 2020 [9] | 2.19 | No.7 hospital of Wuhan | Total | 140 |
| | | | Non-severe | 82 |
| | | | Severe | 58 |
| Yang *et al*. 2020 [10] | 2.21 | Jinyintan Hospital, Wuhan | Critical | 52 |
| | | | Survivor | 20 |
| | | | Death | 32 |
| Tian *et al*. 2020 [11] | 2.27 | Beijing Emergency Medical Service | Total | 262 |
| | | | Non-severe | 216 |
| | | | Severe | 46 |
| Guan *et al*. 2020 [12] | 2.28 | 552 hospitals in Chinese mainland | Total | 1099 |
| | | | Non-severe | 926 |
| | | | Severe | 173 |
| Young 2020 [13] | 3.3 | 4 hospitals in Singapore | Total | 18 |
| | | | Non-severe | 6 |
| | | | Severe | 12 |
| Ruan *et al*. 2020 [14] | 3.3 | Jinyintan Hospital, Wuhan | Death | 68 |
| | | | Discharged | 82 |
| Zhou *et al*. 2020 [15] | 3.9 | Jinyintan Hospital, Wuhan, and Wuhan Pulmonary Hospital | Critical | 191 |
| | | | Survivor | 137 |
| | | | Death | 54 |
| Deng *et al*. 2020 [16] | 3.13 | Two tertiary hospitals in Wuhan | Death | 109 |
| | | | Discharged | 116 |
| CDC U.S. 2020 [17] | 3.18 | Reported cases by CDC in the U.S. | Hospitalization | 508 |
| | | | ICU | 121 |
| | | | Death | 44 |
| Chen *et al*. 2020 [18] | 3.26 | Tongji Hospitals, Wuhan | Total | 274 |
| | | | Death | 113 |
| | | | Discharged | 161 |
| Cao *et al*. 2020 [19] | Not peer reviewed | Xiangyang No. 1 Hospital | Total | 128 |
| | | | Non-severe | 107 |
| | | | Severe | 21 |

 

(*Continued*)

| Ref. | Publication date | Data resources | Groups | Number in each group |
|---|---|---|---|---|
| Chen *et al*. 2020 [20] | 5.1 | Tongji Hospital, Wuhan | Total | 21 |
| | | | Severe | 11 |
| | | | Non-severe | 10 |
| Deng *et al*. 2020 [21] | Not peer reviewed | Tongji Hospital, Wuhan | Severe | 59 |
| | | | Critical | 36 |
| | | | Non-severe | 19 |
| Diao *et al*. 2020 [22] | 5.1 | Two hospitals in Wuhan | Non-critical | 479 |
| | | | Critical | 43 |
| Liu *et al*. 2020 [23] | Not peer reviewed | Union Hospital, Wuhan, Huazhong University of Science and Technology | Total | 80 |
| | | | Non-severe | 11 |
| | | | Severe | 69 |
| Liu *et al*. 2020 [24] | 4.18 | Union Hospital, Wuhan | Non-severe | 27 |
| | | | Severe | 13 |
| Mao *et al*. 2020 [25] | 4.10 | Union Hospital, Wuhan, Huazhong University of Science and Technology | Total | 214 |
| | | | Non-severe | 126 |
| | | | Severe | 88 |
| Qian *et al*. 2020 [26] | 3.17 | 5 hospitals in east Zhejiang | Non-severe | 82 |
| | | | Severe | 9 |
| Qin *et al*. 2020 [27] | 3.12 | Tongji Hospital, Wuhan | Total | 452 |
| | | | Non-severe | 166 |
| | | | Severe | 286 |
| Liu *et al*. 2020 [28] | Not peer reviewed | 24 hospitals in Jiangsu | Total | 620 |
| | | | Severe | 33 |
| | | | Critical | 20 |
| | | | Asymptomatic/non-severe | 97 |
| | | | Non-severe | 470 |
| Wan *et al*. 2020 [29] | 4.17 | Chongqing Three Gorges Central Hospital | Total | 123 |
| | | | Non-severe | 102 |
| | | | Severe | 21 |
| Wang *et al*. 2020 [30] | Not peer reviewed | Renmin Hospital of Wuhan University | Total | 116 |
| | | | Non-severe | 59 |
| | | | Severe | 46 |
| | | | Critical | 11 |
| Wang *et al*. 2020 [31] | 3.30 | Zhongnan Hospital of Wuhan University | Total | 60 |
| | | | Non-severe | 41 |
| | | | Severe | 19 |
| | | | Healthy | 245 |
| Zheng *et al*. 2020 [32] | Not peer reviewed | Second Hospital of Nanjing | Mild | 71 |
| | | | Non-severe | 9 |
| | | | Severe | 8 |
| | | | Asymptomatic | 15 |
| Zhou *et al*. 2020 [33] | 3.22 | The First Affiliated Hospital of University of Science and Technology of China | Non-critical | 21 |
| | | | Critical | 12 |
| Zeng *et al*. 2020 [34] | Not peer reviewed | 3 Hospitals in Beijing & Shanghai | Non-critical | 113 |
| | | | Critical | 65 |

(*Continued*)

| Ref. | Publication date | Data resources | Groups | Number in each group |
|---|---|---|---|---|
| Liu *et al*. 2020 [35] | Not peer reviewed | Shenzhen Third People's Hospital | Non-severe | 4 |
| | | | Severe | 8 |
| | | | Healthy | 4 |
| Cai *et al*. 2020 [36] | 4.17 | Shenzhen Third People's Hospital | Non-severe | 240 |
| | | | Severe | 58 |
| Huang *et al*. 2020 [37] | 5.8 | 10 designated hospitals in Jiangsu | Total | 221 |
| | | | Non-severe | 196 |
| | | | Severe | 25 |
| Xu *et al*. 2020 [38] | Not peer reviewed | 7 ICUs in Guangdong | Critical | 45 |
| | | | Intubation | 20 |
| | | | Non-intubation | 25 |

The patients consist of 874 mild (Non-ICU and non-severe included), 476 severe, 128 critical (ICU included). Overall, the levels of cytokines in COVID-19 patients' blood are generally higher than normal levels. Among them, the levels of IL-2R, IL-6, IL-8 and IL-10 in severe (including critical) patients are significantly higher than those in non-critical cases, showing the characteristics of cytokine storms.

## DISCUSSION

So far there have been many reports and speculations about the susceptible populations of COVID-19. However, there has been no systematic analysis or catalog of the characteristics of patients with severe COVID-19 outcomes across different studies. According to WHO statistics, about 15% of COVID-19 patients worldwide are severely ill, and the rational allocations of facilities such as hospital beds are essential for these severe patients [40]. Therefore, it is necessary to collect basic information of the infected people and predict the patients' probability of transiting to severe outcomes.

It has been discovered that people in each age group have the possibility of SARS-CoV-2 infection, but cohort studies of children and infants showed that the majority of them showed no symptom or only mild symptoms [41–43]. In contrast, the epidemiological reports and statistics we summarized in Table 2 generally show that the symptoms of senior male patients are often more severe. Past reports of SARS and MERS have also shown correlations between severity and patient age or gender [44,45]. Researchers have somehow attributed these correlations to the immune system and the protective effects of sex hormones. Estrogen has been found to protect mouse-adapted SARS-infected mice from bad outcomes [46]. Our previous analysis of the expression quantitative loci (eQTL) in the database found that many estrogen receptors and some androgen receptor binding motifs are located near the regulatory site of ACE2, the recognized receptor of SARS-CoV-2. The expression of ACE2 were increased in some mouse tissues after estrogen or androgen treatment, and in the testis of transsexual humans (treated with estrogen), the proportion of Sertoli cells expressing ACE2 also increased [47], which suggest that sex hormones may play a certain role in regulating the expression of ACE2, thus making the condition differs between men and women. Since sex hormones decay with the age of adults [48], it may also be a factor affecting the severity of patients of different ages.

In addition to the possible specific differences in SARS-CoV-2-induced responses, the basal of immune systems also differ between different genders. In various kinds of animals, females generally have higher levels of immune responses than males to some extent. Human females are reported to have higher type I interferon (IFN) activity, T cell numbers, and antibody responses than males, which may indicate higher abilities for virus clearance. But in response to different pathogens, men and women have different effects and side effects [49].

Obesity might be another independent factor. In addition to the data shown in the results, two other cohort studies aiming at SARS-CoV-2 infected medical stuffs and patients with underlying cardiovascular diseases, respectively [50,51], also showed that higher BMI often indicated higher severity and worse clinical outcomes. In addition, there is a well-known close relationship between obesity and diabetes. Taking the United States as an example, about 90%–95% of patients with type 2 diabetes (T2D) show the characteristics of obesity [52], and in our statistics, after the infection of SARS-CoV-2, the proportion of diabetes in severe cases is generally greater than that in non-severe cases (Table 2). While most of the literature did not indicate whether these diabetic patients suffer from type 1 or type 2 and how many of them are obese, they nevertheless showed some trends. Fat tissue is a large source of pro-inflammatory cytokines and

**Table 2 Age, gender, BMI and underlying diseases of patients in different severity groups**

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| Median age | 41 | 49.0 years | 49.0 years | | 49.0 years | | | Huang *et al.* 2020 [2] |
| | 138 | 56.0 years | 51.0 years | | 66.0 years | | | Wang, *et al.* 2020 [6] |
| | 12 | 62.5 years | 35.5 years | 64.0 years | | | | Liu *et al.* 2020 [7] |
| | 52 | | | | 51.9 years | 64.6 years | | Yang *et al.* 2020 [10]* |
| | 1099 | 47.0 years | 45.0 years | 52.0 years | | | | Guan *et al.* 2020 [12] |
| | 12 | 47.0 years | 37.0 years | 56.0 years | | | | Young 2020 [13] |
| | 214 | 52.7 years | 48.9 years | 58.2 years | | | | Mao *et al.* 2020 [25] |
| | 191 | | | | 56.0 years | 69.0 years | | Zhou *et al.* 2020 [15] |
| | 262 | 47.5 years | 44.5 years | 61.4 years | | | | Tian *et al.* 2020 [11] * |
| | 620 | 44.5 years | 44.5 years | 59.2 years | 61.6 years | | | Liu *et al.* 2020 [28]* |
| | 452 | 58.0 years | 53.0 years | 61.0 years | | | | Qin *et al.* 2020 [27] |
| | 40 | 53.0 years | 56.0 years | 31.0 years | | | | Liu *et al.* 2020 [23] |
| | 116 | 54.0 years | 45.0 years | 52.0 years | 67.0 years | | | Wang *et al.* 2020 [30] |
| | 150 | | | | | 67.0 years | | Ruan *et al.* 2020 [14] |
| | 114 | | | | | 69.0 years | | Deng *et al.* 2020 [16] |
| | 298 | | 40.0 years | 64.0 years | | | | Cai *et al.* 2020 [36] |
| | 221 | 45.0 years | 44.0 years | 51.0 years | | | | Huang *et al.* 2020 [37] |
| | 45 | | | | 56.7 years | | | Xu *et al.* 2020 [38]* |
| | 274 | 62.0 years | | | | 68.0 years | | Chen *et al.* 2020 [18] |
| | 140 | 57.0 years | 51.4 years | 64.0 years | | | | Zhang et al 2020 [9] * |
| < 49 | 41 | 51.2% | | | | | | Huang *et al.* 2020 [2] |
| | 12 | 25.0% | 75.0% | 0.0% | | | 0.0 | Liu *et al.* 2020 [7] |
| | 44,672 | 46.4% | | | | 6.3% | | Team 2020 [8] |
| | 52 | | | | 45.0% | 9.0% | | Yang *et al.* 2020 [10] |
| | 1099 | 56.0% | 58.7% | 41.7% | | | 0.5 | Guan *et al.* 2020 [12] |
| | 214 | 42.1% | 52.4% | 27.3% | | | 0.3 | Mao *et al.* 2020 [25] |
| | 128 | 46.1% | 48.6% | 33.3% | | | 0.5 | Cao *et al.* 2020 [19] |
| | 262 | 46.9% | 52.3% | 21.8% | | | 0.3 | Tian *et al.* 2020 [11] **** |
| | 508 | 21.0% | | | 12.0% | | | CDC U.S. 2020 [17]*** |
| | 221 | 65.6% | 67.9% | 48.0% | | | 0.4 | Huang *et al.* 2020 [37] |
| | 140 | 30.0% | 39.0% | 17.2% | | | 0.3 | Zhang *et al.* 2020 [9] *** |

(*Continued*)

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| 50–64 | 41 | 34.0% | | | | | | Huang *et al.* 2020 [2] |
| | 12 | 16.7% | 25.0% | 12.5% | | | 0.4 | Liu *et al.* 2020 [7] |
| | 44,672 | 22.4% | | | | 12.7% | | Team 2020 [8] ** |
| | 52 | | | | 20.0% | 28.0% | | Yang *et al.* 2020 [10] ** |
| | 1099 | 28.9% | 28.4% | 31.3% | | | 1.1 | Guan *et al.* 2020 [12] |
| | 128 | 35.1% | 33.6% | 42.9% | | | 1.5 | Cao *et al.* 2020 [19] |
| | 262 | 34.7% | 34.7% | 34.8% | | | 1.0 | Tian *et al.* 2020 [11] **** |
| | 508 | 35.0% | | | 36.0% | | | CDC U.S. 2020 [17]*** |
| | 221 | 19.0% | 18.4% | 24.0% | | | 1.4 | Huang *et al.* 2020 [37]** |
| | 140 | 49.3% | 50.0% | 48.3% | | | 0.9 | Zhang *et al.* 2020 [9] *** |
| >65 | 41 | 14.6% | | | | | | Huang *et al.* 2020 [2] |
| | 12 | 58.3% | 0.0% | 87.5% | | | # | Liu *et al.* 2020[7] |
| | 44,672 | 31.2% | | | | 81.0% | | Team 2020 [8] ** |
| | 52 | | | | 35.0% | 62.0% | | Yang *et al.* 2020 [10] ** |
| | 1099 | 15.1% | 12.9% | 27.0% | | | 2.5 | Guan *et al.* 2020 [12] |
| | 128 | 18.8% | 17.8% | 23.8% | | | 1.4 | Cao *et al.* 2020 [19] |
| | 262 | 18.3% | 13.0% | 43.5% | | | 5.2 | Tian *et al.* 2020 [11] **** |
| | 508 | 43.0% | | | 53.0% | 80.0% | | CDC U.S. 2020 [17] |
| | 221 | 15.4% | 13.8% | 28.0% | | | 2.4 | Huang *et al.* 2020 [37]** |
| | 274 | 56.0% | | | | 83.0% | | Chen *et al.* 2020b [18] ** |
| | 140 | 20.7% | 11.0% | 34.5% | | | 4.3 | Zhang *et al.* 2020 [9] |

(*Continued*)

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| Male | 41 | 73.0% | 68.0% | | 85.0% | | 2.7 | Huang *et al.* 2020 [2] |
| | 138 | 54.3% | 52.0% | | 61.1% | | 1.5 | Wang *et al.* 2020 [6] |
| | 12 | 66.7% | 100.0% | 50.0% | | | 0.0 | Liu *et al.* 2020 [7] |
| | 44,672 | 51.4% | | | | 63.8% | | Team 2020 [8] |
| | 52 | | | | 70.0% | 66.0% | | Yang *et al.* 2020 [10] |
| | 1099 | 58.2% | 58.3% | 57.8% | | | 1.0 | Guan *et al.* 2020 [12] |
| | 12 | 50.0% | 58.0% | 33.0% | | | 0.4 | Young 2020 [13] |
| | 214 | 40.7% | 34.1% | 50.0% | | | 1.9 | Mao *et al.* 2020 [25] |
| | 128 | 46.9% | 44.9% | 57.1% | | | 1.6 | Cao *et al.* 2020 [19] |
| | 191 | | | | 62.0% | 70.0% | | Zhou *et al.* 2020 [15] |
| | 262 | 48.5% | 46.8% | 56.5% | | | 1.5 | Tian *et al.* 2020 [11] |
| | 620 | 52.6% | 52.6% | 57.6% | 80.0% | | 1.8 | Liu *et al.* 2020 [28] |
| | 452 | 52.0% | 48.2% | 54.2% | | | 1.3 | Qin *et al.* 2020 [27] |
| | 40 | 42.5% | 9.1% | 47.8% | | | 9.2 | Liu *et al.* 2020 [23] |
| | 116 | 57.8% | 57.6% | 58.7% | 52.0% | | 1.1 | Wang *et al.* 2020 [30] |
| | 150 | | | | | 72.1% | | Ruan *et al.* 2020 [14] |
| | 114 | | | | | 73.0% | | Deng *et al.* 2020 [16] |
| | 298 | | 46.3% | 56.7% | | | 1.5 | Cai *et al.* 2020 [36] |
| | 221 | 57.0% | 55.0% | 72.0% | | | 2.1 | Huang *et al.* 2020 [37] |
| | 45 | | | | 64.4% | | | Xu *et al.* 2020 [38] |
| | 274 | 62.0% | | | | 73.0% | | Chen *et al.* 2020 [18] |
| | 140 | 50.7% | 46.3% | 56.9% | | | 1.5 | Zhang *et al.* 2020 [9] |
| BMI median (IQR) | 298 | | 22.9 (20.5–25.2) | 23.9 (22.0–26.7) | | | | Cai *et al.* 2020 [36] |
| | 221 | 24.2 (22.2–26.1) | 24.0 (22.0–26.0) | 26.4 (23.2–29.7) | | | | Huang *et al.* 2020 [37] |
| | 45 | | | | 24.2 (22.0–26.7) | | | Xu *et al.* 2020 [38] |
| BMI⩾28 | 221 | 13.3% | 9.5% | 45.0% | | | 7.8 | Huang *et al.* 2020 [37] |

(*Continued*)

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| Underlying diseases | 41 | 32.0% | 29.0% | | 38.0% | | 1.5 | Huang *et al.* 2020[2] |
| | 138 | 46.4% | 37.3% | | 72.2% | | 4.4 | Wang *et al.* 2020 [6] |
| | 12 | 58.3% | 0.0% | 87.5% | | | # | Liu *et al.* 2020 [7] |
| | 44,672 | 26.0% | | | | 67.2% | | Team 2020 [8] |
| | 52 | | | | 20.0% | 53.0% | | Yang *et al.* 2020 [10] |
| | 1099 | 23.2% | 20.5% | 37.6% | | | 2.3 | Guan *et al.* 2020 [12] |
| | 12 | 28.0% | 8.0% | 67.0% | | | 23.3 | Young 2020 [13] |
| | 214 | 38.8% | 32.5% | 47.7% | | | 1.9 | Mao *et al.* 2020 [25] |
| | 191 | | | | 48.0% | 67.0% | | Zhou *et al.* 2020 [15] |
| | 452 | 44.0% | 33.1% | 51.0% | | | 2.1 | Qin *et al.* 2020 [27] |
| | 40 | 35.0% | 27.3% | 36.2% | | | 1.5 | Liu *et al.* 2020 [23] |
| | 150 | | | | | 63.2% | | Ruan *et al.* 2020 [14] |
| | 114 | | | | | 72.5% | | Deng *et al.* 2020 [16] |
| | 221 | 27.1% | 24.5% | 48.0% | | | 2.8 | Huang *et al.* 2020 [37] |
| | 45 | | | | 57.8% | | | Xu *et al.* 2020 [38] |
| | 274 | 49.0% | | | | 63.0% | | Chen *et al.* 2020 [18] |
| | 140 | 64.3% | 53.7% | 79.3% | | | 3.3 | Zhang *et al.* 2020 [9] |
| Cardiovascular disease | 41 | 15.0% | 11.0% | | 23.0% | | 2.4 | Huang *et al.* 2020 [2] |
| | 138 | 14.5% | 10.8% | | 25.0% | | 2.8 | Wang *et al.* 2020[6] |
| | 12 | 33.3% | 0.0% | 50.0% | | | # | Liu *et al.* 2020 [7] |
| | 44,672 | 4.2% | | | | 22.7% | | Team 2020 [8] |
| | 52 | | | | 10.0% | 10.0% | | Yang *et al.* 2020 [10] |
| | 1099 | 2.5% | 1.5% | 5.8% | | | 4.0 | Guan *et al.* 2020 [12] |
| | 214 | 7.0% | 6.3% | 8.0% | | | 1.3 | Mao *et al.* 2020 [25] |
| | 191 | | | | 8.0% | 24.0% | | Zhou *et al.* 2020 [15] |
| | 620 | 2.1% | 1.3% | 9.1% | 5.0% | | 6.2 | Liu *et al.* 2020 [28] |
| | 452 | 5.9% | 1.8% | 8.4% | | | 5.0 | Qin *et al.* 2020 [27] |
| | 40 | 7.5% | 0.0% | 8.7% | | | # | Liu *et al.* 2020 [23] |
| | 150 | | | | | 18.0% | | Ruan *et al.* 2020 [14] |
| | 114 | | | | | 11.9% | | Deng *et al.* 2020 [16] |
| | 221 | 2.3% | 2.0% | 4.0% | | | 2.0 | Huang *et al.* 2020 [37] |
| | 45 | | | | 13.3% | | | Xu *et al.* 2020 [38] |
| | 274 | 8.0% | | | | 14.0% | | Chen *et al.* 2020 [18] |
| | 140 | 5.0% | 3.7% | 6.9% | | | 1.9 | Zhang *et al.* 2020 [9] |

(*Continued*)

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| Hypertension | 41 | 15.0% | 14.0% | | 15.0% | | 1.1 | Huang *et al.* 2020 [2] |
| | 138 | 31.2% | 21.6% | | 58.3% | | 5.1 | Wang *et al.* 2020 [6] |
| | 12 | 25.0% | 0.0% | 37.5% | | | # | Liu *et al.* 2020 [7] |
| | 44,672 | 12.8% | | | | 39.7% | | Team 2020 [8] |
| | 1099 | 14.9% | 13.3% | 23.7% | | | 2.0 | Guan *et al.* 2020 [12] |
| | 12 | | 8.0% | 66.7% | | | 23.0 | Young 2020 [13] |
| | 214 | 23.8% | 32.5% | 47.7% | | | 1.9 | Mao *et al.* 2020 [25] |
| | 191 | | | | 30.0% | 48.0% | | Zhou *et al.* 2020 [15] |
| | 620 | 15.5% | 14.3% | 36.4% | 30.0% | | 3.1 | Liu *et al.* 2020 [28] |
| | 452 | 29.5% | 18.1% | 36.7% | | | 2.6 | Qin *et al.* 2020 [27] |
| | 40 | 17.5% | 0.0% | 20.3% | | | # | Liu *et al.* 2020 [23] |
| | 116 | 37.1% | 38.9% | 32.6% | 45.5% | | 0.9 | Wang *et al.* 2020 [30] |
| | 150 | | | | | 42.6% | | Ruan *et al.* 2020 [14] |
| | 114 | | | | | 36.7% | | Deng *et al.* 2020 [16] |
| | 221 | 14.5% | 14.3% | 16.0% | | | 1.1 | Huang *et al.* 2020 [37] |
| | 45 | | | | 46.7% | | | Xu *et al.* 2020 [38] |
| | 274 | 34.0% | | | | 48.0% | | Chen *et al.* 2020 [18] |
| | 140 | 30.0% | 24.4% | 37.9% | | | 1.9 | Zhang *et al.* 2020 [9] |
| Diabetes | 41 | 20.0% | 25.0% | | 8.0% | | 0.3 | Huang *et al.* 2020 [2] |
| | 138 | 10.1% | 5.9% | | 22.2% | | 4.6 | Wang *et al.* 2020 [6] |
| | 12 | 16.7% | 0.0% | 25.0% | | | # | Liu *et al.* 2020 [7] |
| | 44,672 | 5.3% | | | | 19.7% | | Team 2020 [8] |
| | 52 | | | | 10.0% | 22.0% | | Yang *et al.* 2020 [10] |
| | 1099 | 7.4% | 5.7% | 16.2% | | | 3.2 | Guan *et al.* 2020 [12] |
| | 12 | | 8.0% | 16.7% | | | 2.3 | Young 2020 [13] |
| | 214 | 14.0% | 11.9% | 17.0% | | | 1.5 | Mao *et al.* 2020 [25] |
| | 191 | | | | 19.0% | 31.0% | | Zhou *et al.* 2020 [15] |
| | 620 | 6.5% | 4.9% | 12.1% | 20.0% | | 3.4 | Liu *et al.* 2020 [28] |
| | 452 | 16.4% | 13.3% | 18.5% | | | 1.5 | Qin *et al.* 2020 [27] |
| | 40 | 13.8% | 0.0% | 15.9% | | | # | Liu *et al.* 2020 [23] |
| | 116 | 15.5% | 13.6% | 13.0% | 36.4% | | 1.4 | Wang *et al.* 2020 [30] |
| | 114 | | | | | 15.6% | | Deng *et al.* 2020 [16] |
| | 150 | | | | | 17.6% | | Ruan *et al.* 2020 [14] |
| | 221 | 9.5% | 5.6% | 40.0% | | | 11.2 | Huang *et al.* 2020 [37] |
| | 45 | | | | 28.9% | | | Xu *et al.* 2020 [38] |
| | 274 | 17.0% | | | | 21.0% | | Chen *et al.* 2020 [18] |
| | 140 | 12.1% | 11.0% | 13.8% | | | 1.3 | Zhang *et al.* 2020 [9] |

(*Continued*)

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| Chronic kidney disease | 138 | 2.9% | 2.0% | | 5.6% | | 2.9 | Wang *et al.* 2020 [6] |
| | 12 | 16.7% | 0.0% | 25.0% | | | # | Liu *et al.* 2020 [7] |
| | 1099 | 0.7% | 0.5% | 1.7% | | | 3.3 | Guan *et al.* 2020 [12] |
| | 214 | 2.8% | 3.2% | 2.3% | | | 0.7 | Mao *et al.* 2020 [25] |
| | 191 | | | | 1.0% | 4.0% | | Zhou *et al.* 2020 [15] |
| | 620 | 0.6% | 0.6% | 0.0% | 5.0% | | 3.2 | Liu *et al.* 2020 [28] |
| | 452 | 2.2% | 2.4% | 2.1% | | | 0.9 | Qin *et al.* 2020 [27] |
| | 150 | | | | | 2.9% | | Ruan *et al.* 2020 [14] |
| | 274 | 1.0% | | | | 4.0% | | Chen *et al.* 2020 [18] |
| | 116 | 4.3% | 0.0% | 10.9% | 0.0% | | # | Wang *et al.* 2020 [30] |
| Chronic liver disease | 41 | 2.0% | 4.0% | | 0.0% | | 0.0 | Huang *et al.* 2020 [2] |
| | 138 | 2.9% | 3.9% | | 0.0% | | 0.0 | Wang *et al.* 2020 [6] |
| | 1099 | 2.1% | 2.4% | 0.6% | | | 0.2 | Guan *et al.* 2020 [12] |
| | 620 | 0.5% | 0.4% | 0.0% | 5.0% | | 4.8 | Liu *et al.* 2020 [28] |
| | 452 | 1.3% | 1.8% | 1.0% | | | 0.6 | Qin *et al.* 2020 [27] |
| | 150 | | | | | 1.5% | | Ruan *et al.* 2020 [14] |
| | 221 | 2.7% | 3.1% | 0.0% | | | 0.0 | Huang *et al.* 2020 [37] |
| | 40 | 1.3% | 0.0% | 1.5% | | | # | Liu *et al.* 2020 [23] |
| Respiratory system disease | 41 | 2.0% | 0.0% | | 8.0% | | | Huang *et al.* 2020 [2] |
| | 138 | 2.9% | 1.0% | | 8.3% | | 9.2 | Wang *et al.* 2020 [6] |
| | 12 | 8.3% | 0.0% | 12.5% | | | # | Liu *et al.* 2020 [7] |
| | 44,672 | 2.4% | | | | 7.9% | | Team 2020 [8] |
| | 1099 | 1.1% | 0.6% | 3.5% | | | 5.5 | Guan *et al.* 2020 [12] |
| | 191 | | | | 3.0% | 7.0% | | Zhou *et al.* 2020 [15] |
| | 150 | | | | | 2.9% | | Ruan *et al.* 2020 [14] |
| | 221 | 3.2% | 3.1% | 4.0% | | | 1.3 | Huang *et al.* 2020 [37] |
| | 45 | | | | 8.9% | | | Xu *et al.* 2020 [38] |
| | 274 | 7.0% | | | | 10.0% | | Chen *et al.* 2020 [18] |
| | 452 | 2.6% | 1.8% | 3.1% | | | 1.7 | Qin *et al.* 2020 [27] |

(*Continued*)

| | Total number (N) | All | Non-severe (mild) | Severe | Critical | Death | OR[a] | Ref. |
|---|---|---|---|---|---|---|---|---|
| Malignancy | 41 | 2.0% | 4.0% | | 0.0% | | 0.0 | Huang *et al.* 2020 [2] |
| | 138 | 7.2% | 5.9% | | 11.1% | | 2.0 | Wang *et al.* 2020 [6] |
| | 44,672 | 0.5% | | | | 1.5% | | Team 2020 [8] |
| | 52 | | | | 0.0% | 0.0% | | Yang *et al.* 2020 [10] |
| | 1099 | 0.9% | 0.8% | 1.7% | | | 2.3 | Guan *et al.* 2020 [12] |
| | 214 | 6.1% | 6.3% | 5.7% | | | 0.9 | Mao *et al.* 2020 [25] |
| | 191 | | | | 1.0% | 0.0% | | Zhou *et al.* 2020 [15] |
| | 620 | 1.1% | 1.3% | 0.0% | 5.0% | | 1.5 | Liu *et al.* 2020 [28] |
| | 40 | 8.8% | 27.3% | 5.8% | | | 0.2 | Liu *et al.* 2020 [23] |
| | 150 | | | | | 2.9% | | Ruan *et al.* 2020 [14] |
| | 114 | | | | | 5.5% | | Deng *et al.* 2020 [16] |
| | 221 | 1.4% | 1.5% | 0.0% | | | 0.0 | Huang *et al.* 2020 [37] |
| | 45 | | | | 6.7% | | | Xu *et al.* 2020 [38] |
| | 274 | 3.0% | | | | 4.0% | | Chen *et al.* 2020 [18] |
| | 116 | 10.3% | 1.7% | 10.9% | 52.0% | | 14.0 | Wang *et al.* 2020 [30] |
| Immunodeficiency | 138 | 1.4% | 2.0% | | 0.0% | | 0.0 | Wang *et al.* 2020 [6] |
| | 1099 | 0.2% | 0.2% | 0.0% | | | 0.0 | Guan *et al.* 2020 [12] |
| | 45 | | | | 2.2% | | | Xu *et al.* 2020 [38] |
| | 620 | 0.3% | 0.4% | 0.0% | 0.0% | | 0.0 | Liu *et al.* 2020 [28] |

[a] OR: odds ratio of severe (including severe and critical groups combined) with non-severe group

[b] * mean value instead of median

** age threshold in this article is $<$ 49, 50–59, >60

*** age threshold in this article is $<$ 44, 45–64, >65

**** age threshold in this article is $<$ 49, 50–70, >70

**Table 3 Relative numbers of peripheral blood cells**

| Group | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Ref. |
|---|---|---|---|---|---|
| White blood cell | 41 | ~ | | +++ | Huang *et al.* 2020 [2] |
| | 138 | ~ | | ++ | Wang *et al.* 2020 [6] |
| | 1099 | ~ | - | | Guan *et al.* 2020 [12] |
| | 12 | ~ | -- | | Liu *et al.* 2020 [7] |
| | 33 | ~ | | + | Zhou *et al.* 2020b [33] |
| | 91 | ~ | ~ | | Qian *et al.* 2020 [26] |
| | 140 | ~ | ~ | | Zhang *et al.* 2020 [9] |
| | 128 | ~ | +++ | | Cao *et al.* 2020 [19] |
| | 214 | ~ | + | | Mao *et al.* 2020 [25] |
| | 12 | ~ | - | | Young 2020 [13] |
| | 620 | ~ | ~ | | Liu *et al.* 2020 [28] |
| | 452 | ~ | ~ | | Qin *et al.* 2020 [27] |
| Neutrophil | 41 | ~ | | ++++ | Huang *et al.* 2020 [2] |
| | 138 | ~ | | +++ | Wang *et al.* 2020 [6] |
| | 12 | ~ | ~ | | Liu *et al.* 2020 [7] |
| | 33 | ~ | | ++ | Zhou *et al.* 2020 [33] |
| | 91 | ~ | ~ | | Qian *et al.* 2020 [26] |
| | 214 | ~ | ++ | | Mao *et al.* 2020 [25] |
| | 12 | ~ | -- | | Young 2020 [13] |
| | 620 | ~ | + | | Liu *et al.* 2020 [28] |
| | 452 | ~ | + | | Qin *et al.* 2020 [27] |
| | 80 | ~ | ++ | | Liu *et al.* 2020 [23] |
| Monocyte count | 138 | ~ | | ~ | Wang *et al.* 2020 [6] |
| | 33 | ~ | | ~ | Zhou *et al.* 2020 [33] |
| | 91 | ~ | ~ | | Qian *et al.* 2020 [26] |
| | 620 | ~ | - | | Liu *et al.* 2020 [28] |
| | 452 | ~ | ~ | | Qin *et al.* 2020 [27] |
| Red-cell | 91 | ~ | ~ | | Qian *et al.* 2020 [26] |
| Eosinophil | 91 | ~ | --- | | Qian *et al.* 2020 [26] |
| | 140 | ~ | --- | | Zhang *et al.* 2020 [9] |
| | 620 | + | ---- | | Liu *et al.* 2020 [28] |
| Lymphocyte | 41 | - | | ---- | Huang *et al.* 2020 [2] |
| | 138 | - | | ~ | Wang *et al.* 2020 [6] |
| | 1099 | - | - | | Guan *et al.* 2020 [12] |
| | 12 | ~ | ---- | | Liu *et al.* 2020 [7] |

(*Continued*)

| Group | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Ref. |
|---|---|---|---|---|---|
| | 116 | ~ | --- | | Wang *et al.* 2020 [30] |
| | 33 | ~ | | -- | Zhou *et al.* 2020 [33] |
| | 91 | ~ | ~ | | Qian *et al.* 2020 [26] |
| | 91 | ~ | -- | | Qian, *et al.* 2020 [26] |
| | 140 | - | ~ | | Zhang *et al.* 2020 [9] |
| | 128 | ~ | ---- | | Cao *et al.* 2020 [19] |
| | 214 | ~ | -- | | Mao *et al.* 2020 [25] |
| | 12 | ~ | ~ | | Young, 2020 [13] |
| | 620 | ~ | --- | | Liu *et al.* 2020 [28] |
| | 452 | - | - | | Qin *et al.* 2020 [27] |
| | 80 | ~ | --- | | Liu *et al.* 2020 [23] |
| B cell | 116 | ~ | -- | | Wang *et al.* 2020 [30] |
| | 33 | ~ | | ~ | Zhou *et al.* 2020 [33] |
| | 91 | ~ | --- | | Qian *et al.* 2020 [26] |
| | 452 | ~ | ~ | | Qin *et al.* 2020 [27] |
| | 80 | ~ | ~ | | Liu *et al.* 2020 [23] |
| T cell | 522 | -- | | ---- | Diao *et al.* 2020 [22] |
| | 33 | - | | --- | Zhou *et al.* 2020 [33] |
| | 91 | ~ | ---- | | Qian *et al.* 2020 [26] |
| | 620 | ~ | --- | | Liu *et al.* 2020 [28] |
| | 178 | ~ | | ---- | Zeng *et al.* 2020 [34] |
| | 452 | -- | -- | | Qin *et al.* 2020 [27] |
| | 80 | ~ | - | | Liu *et al.* 2020 [23] |
| $CD4^+$ T cell | 12 | ~ | - | | Liu *et al.* 2020 [7] |
| | 522 | -- | | --- | Diao *et al.* 2020 [22] |
| | 116 | -- | -- | | Wang *et al.* 2020 [30] |
| | 33 | --- | | -- | Zhou *et al.* 2020 [33] |
| | 91 | ~ | --- | | Qian *et al.* 2020 [26] |
| | 620 | ~ | -- | | Liu *et al.* 2020 [28] |
| | 452 | - | -- | | Qin *et al.* 2020 [27] |
| | 178 | ~ | | ---- | Zeng *et al.* 2020 [34] |
| | 80 | ~ | ~ | | Liu *et al.* 2020 [23] |
| $CD8^+$ T cell | 12 | ~ | -- | | Liu *et al.* 2020 [7] |

(*Continued*)

| Group | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Ref. |
|---|---|---|---|---|---|
| | 522 | - - | | - - - - | Diao *et al.* 2020 [22] |
| | 116 | - | - - - | | Wang *et al.* 2020 [30] |
| | 33 | - | | - - - - | Zhou *et al.* 2020 [33] |
| | 91 | ~ | - - - - | | Qian *et al.* 2020 [26] |
| | 620 | ~ | - - | | Liu *et al.* 2020 [28] |
| | 178 | ~ | | - - - - | Zeng *et al.* 2020 [34] |
| | 452 | - - | - | | Qin *et al.* 2020 [27] |
| | 80 | ~ | - | | Liu *et al.* 2020 [23] |
| $CD4^+/CD8^+$ | 12 | ~ | + | | Liu *et al.* 2020 [7] |
| | 522 | ~ | | ++ | Diao *et al.* 2020 [22] |
| | 116 | ~ | ~ | | Wang *et al.* 2020 [30] |
| | 91 | ~ | +++ | | Qian *et al.* 2020 [26] |
| | 452 | ~ | ~ | | Qin *et al.* 2020 [27] |
| | 80 | ~ | ~ | | Liu *et al.* 2020 [23] |
| NK cell | 116 | ~ | - - | | Wang *et al.* 2020 [30] |
| | 33 | - | | - - | Zhou *et al.* 2020 [33] |
| | 91 | ~ | ++++ | | Qian *et al.* 2020 [26] |
| | 452 | ~ | - - | | Qin *et al.* 2020 [27] |
| | 178 | ~ | | - | Zeng *et al.* 2020 [34] |
| | 80 | ~ | ++++ | | Liu *et al.* 2020 [23] |

+, ++, +++ and ++++ indicate that the log2 values of ratio in the range of [0.25,0.5], [0.5,0.75], [0.75,1] and [1,]; -, - -, - - - and- - - - indicate that the log2 values of ratio in the range of [–0.5, –0.25], [–0.75, –0.5], [–1, –0.75] and [,–1]; Values between 0±0.25 are marked by "~".

**Table 4 Relative levels of serum cytokines**

| Cytokine | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Cited paper |
|---|---|---|---|---|---|
| IL-1α | 12 | ++++ | ++ | | Liu *et al*. 2020 [35] |
| | 29 | | ~ | ~ | Chen *et al*. 2020 [5] |
| | 452 | ~ | ~ | ~ | Qin *et al*. 2020 [27] |
| IL-1b | 41 | ++++ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | +++ | + | | Liu *et al*. 2020 [35] |
| IL-1ra | 41 | ++++ | | + | Huang *et al*. 2020 [2] |
| | 12 | +++ | ++++ | | Liu *et al*. 2020 [35] |
| IL-2 | 41 | ++++ | | + | Huang *et al*. 2020 [2] |
| | 12 | +++ | +++ | | Liu *et al*. 2020 [35] |
| | 80 | | ~ | | Liu *et al*. 2020 [23] |
| | 40 | | ~ | | Liu *et al*. 2020 [24] |
| IL-4 | 41 | ++ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ++++ | ++ | | Liu *et al*. 2020 [35] |
| | 123 | | ~ | | Wan *et al*. 2020 [29] |
| | 80 | | ~ | | Liu *et al*. 2020 [23] |
| | 40 | | ~ | | Liu *et al*. 2020 [24] |
| IL-5 | 41 | ~ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ~ | ~ | | Liu *et al*. 2020 [35] |
| IL-6 | 41 | ++++ | | + | Huang *et al*. 2020 [2] |
| | 12 | -- | ++++ | | Liu *et al*. 2020 [35] |
| | 522 | | | ++++ | Diao *et al*. 2020 [22] |
| | 123 | | ++++ | | Wan *et al*. 2020 [29] |
| | 21 | ++++ | ++++ | | Chen *et al*. 2020 [20] |
| | 80 | | ++++ | | Liu *et al*. 2020 [23] |
| | 114 | | ++++ | ++++ | Deng *et al*. 2020 [21] |
| | 29 | | ++ | ++++ | Chen *et al*. 2020 [5] |
| | 452 | +++ | +++ | | Qin *et al*. 2020 [27] |
| | 298 | ++++ | ++++ | | Cai *et al*. 2020 [36] |
| | 40 | | ++++ | | Liu *et al*. 2020 [24] |
| IL-7 | 41 | ++++ | | +++ | Huang *et al*. 2020 [2] |
| | 12 | +++ | + | | Liu *et al*. 2020 [35] |

(*Continued*)

| Cytokine | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Cited paper |
|---|---|---|---|---|---|
| IL-8 | 41 | ++++ | | +++ | Huang *et al*. 2020 [2] |
| | 12 | ++ | ++++ | | Liu *et al*. 2020 [35] |
| | 21 | ~ | ++++ | | Chen *et al*. 2020 [20] |
| | 29 | | + | +++ | Chen *et al*. 2020 [5] |
| | 452 | ~ | + | | Qin *et al*. 2020 [27] |
| IL-9 | 41 | + | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ~ | ~ | | Liu *et al*. 2020 [35] |
| IL-10 | 41 | ~ | | ++++ | Huang *et al*. 2020 [2] |
| | 12 | ++++ | ++++ | | Liu *et al*. 2020 [35] |
| | 522 | | | ++++ | Diao *et al*. 2020 [22] |
| | 123 | | +++ | | Wan *et al*. 2020 [29] |
| | 21 | ~ | ++ | | Chen *et al*. 2020 [20] |
| | 80 | | +++ | | Liu *et al*. 2020 [23] |
| | 29 | | + | ++ | Chen *et al*. 2020 [5] |
| | 452 | ~ | + | | Qin *et al*. 2020 [27] |
| | 40 | | +++ | | Liu *et al*. 2020 [24] |
| IL-12 (p40) | 12 | ++ | ++++ | | Liu *et al*. 2020 [35] |
| IL-12 (p70) | 41 | ++++ | | ++ | Huang *et al*. 2020 [2] |
| | 12 | ++ | +++ | | Liu *et al*. 2020 [35] |
| IL-13 | 41 | ++++ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ++++ | + | | Liu *et al*. 2020 [35] |
| IL-15 | 41 | ~ | | ++++ | Huang *et al*. 2020 [2] |
| | 12 | ~ | ~ | | Liu *et al*. 2020 [35] |
| IL-17 | 41 | + | | + | Huang *et al*. 2020 [2] |
| | 12 | + | ++ | | Liu *et al*. 2020 [35] |
| | 123 | | ~ | | Wan *et al*. 2020 [29] |
| Etotaxin | 41 | ~ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | + | + | | Liu *et al*. 2020 [35] |
| FGF basic | 41 | + | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ~ | + | | Liu *et al*. 2020 [35] |
| G-CSF | 41 | +++ | | + | Huang *et al*. 2020 [2] |
| | 12 | ++ | +++ | | Liu *et al*. 2020 [35] |
| GM-CSF | 41 | ~ | | ~ | Huang *et al*. 2020 [2] |

(*Continued*)

| Cytokine | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Cited paper |
|---|---|---|---|---|---|
| | 12 | +++ | + | | Liu *et al*. 2020 [35] |
| IFN-α2 | 12 | ++ | ++ | | Liu *et al*. 2020 [35] |
| | 123 | | + | | Wan *et al*. 2020 [29] |
| IFN-γ | 41 | ++++ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | +++ | ++++ | | Liu *et al*. 2020 [35] |
| | 40 | | + | | Liu *et al*. 2020 [24] |
| | 80 | | ++ | | Liu *et al*. 2020 [23] |
| IP-10 | 41 | ++++ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ++++ | ++++ | | Liu *et al*. 2020 [35] |
| MCP-1 | 41 | ++++ | | +++ | Huang *et al*. 2020 [2] |
| | 12 | +++ | ++++ | | Liu *et al*. 2020 [35] |
| MIP-1a | 41 | ++++ | | ++ | Huang *et al*. 2020 [2] |
| | 12 | ++ | +++ | | Liu *et al*. 2020 [35] |
| MIP-1b | 41 | ~ | | ++ | Huang *et al*. 2020 [22] |
| | 12 | ~ | ~ | | Liu *et al*. 2020 [35] |
| PDGF-bb | 41 | ++++ | | + | Huang *et al*. 2020 [2] |
| | 12 | ~ | ---- | | Liu *et al*. 2020 [35] |
| RANTES | 41 | ~ | | +++ | Huang *et al*. 2020 [2] |
| | 12 | ~ | -- | | Liu *et al*. 2020 [35] |
| TNF-α | 41 | ++ | | + | Huang *et al*. 2020 [2] |
| | 12 | ++ | ~ | | Liu *et al*. 2020 [35] |
| | 522 | | | + | Diao *et al*. 2020 [22] |
| | 21 | ~ | ++ | | Chen *et al*. 2020 [20] |
| | 80 | | ~ | | Liu *et al*. 2020 [23] |
| | 114 | | + | +++ | Deng *et al*. 2020 [21] |
| | 29 | | + | + | Chen *et al*. 2020 [5] |
| | 452 | ~ | ~ | | Qin *et al*. 2020 [27] |
| | 40 | | ~ | | Liu *et al*. 2020 [24] |
| VEGF | 41 | ++++ | | ~ | Huang *et al*. 2020 [2] |
| | 12 | ~ | + | | Liu *et al*. 2020 [35] |

(*Continued*)

| Cytokine | Total number (N) | Non-severe/healthy | Severe/non-severe (mild) | Critical/non-critical (mild) | Cited paper |
|---|---|---|---|---|---|
| M-CSF | 12 | ++ | +++ | | Liu *et al*. 2020 [35] |
| HGF | 12 | + | ++++ | | Liu *et al*. 2020 [35] |
| IL-2Rα | 12 | ~ | ++ | | Liu *et al*. 2020 [35] |
| IL-3 | 12 | +++ | +++ | | Liu, *et al*. 2020 [35] |
| IL-16 | 12 | ++++ | - - | | Liu *et al*. 2020 [35] |
| IL-18 | 12 | ++++ | ++ | | Liu *et al*. 2020 [35] |
| CTACK | 12 | +++ | ~ | | Liu *et al*. 2020 [35] |
| GRO-α | 12 | - | ~ | | Liu *et al*. 2020 [35] |
| LIF | 12 | ++++ | + | | Liu *et al*. 2020 [35] |
| MCP-3 | 12 | ++++ | ++++ | | Liu *et al*. 2020 [35] |
| MIF | 12 | + | - | | Liu *et al*. 2020 [35] |
| MIG | 12 | ++++ | ++++ | | Liu *et al*. 2020 [35] |
| b-NGF | 12 | ++++ | +++ | | Liu *et al*. 2020 [35] |
| SCF | 12 | ~ | +++ | | Liu *et al*. 2020 [35] |
| SCGF-b | 12 | + | ++ | | Liu *et al*. 2020 [35] |
| SDF-1α | 12 | ~ | ~ | | Liu *et al*. 2020[35] |
| TNF-b | 12 | ++++ | +++ | | Liu *et al*. 2020 [35] |
| TRAIL | 12 | + | ~ | | Liu *et al*. 2020 [35] |
| IL-2R | 21 | ~ | ++++ | | Chen *et al*. 2020 [20] |
| | 29 | | ++ | +++ | Chen *et al*. 2020 [5] |
| | 452 | ~ | ~ | | Qin *et al*. 2020 [27] |

+, ++, +++ and ++++ indicate that the log2 values of ratio in the range of [0.25,0.5], [0.5,0.75], [0.75,1] and [1,]; -, - -, - - - and- - - - indicate that the log2 values of ratio in the range of [–0.5, –0.25], [–0.75, –0.5], [–1, –0.75] and [,–1]; Values between 0±0.25 are marked by “~”.

chemokines [53]. Studies have shown that some fat tissue cytokines will increase with age, including IL-6 and TNF-α [54,55], which are increased in severe patients as shown in Table 4, suggesting a possibility that patients with high fat content are more likely to cause cytokine storms after infection, thereby aggravating the disease. Fat tissue can also produce angiotensin II (AngII), which is exactly the substrate of ACE2, and is related to pathological processes of human diseases such as hypertension and heart failure. Liu *et al*. confirmed that AngII was significantly increased in patients with COVID-19 [7], which may be related to its pathogenesis.

Typically, viral infection generally does not cause a significant increase in white blood cells compared with bacterial infection, which is also a critical consideration to differentiate the two clinically [56]. However, we can see from Table 3 that the leukocytes and neutrophils in the blood of severe patients, especially the critically ill patients, have increased significantly, which indicated possible co-infections of bacteria or other pathogens in severe patients. Therefore, when discussing the immune response of severe patients, the impact of these co-infection should be considered. That makes studying the immune response of patients with SARS-CoV-2 infection more complicated.

A study of immune response kinetics showed that at least in non-severe patients, SARS-CoV-2 infection could induce some normal immune responses such as the increase of antibody secreting cells (ASCs), follicular assist T cells (TFH cells), activated $CD4^+$ and $CD8^+$ T cells, as well as the secretion of SARS-CoV-2-binding immunoglobulin antibodies and very few pro-inflammatory cytokines and chemokines [57]. However, as can be seen in Tables 3 and 4, excessive immune responses of COVID-19 severe patients are generally reported, including two crucial features of lymphopenia and cytokine storms [6].

$CD4^+$ and $CD8^+$ T cells are generally reduced in severe cases and have been judged as independent factors related to severity in many cohort studies [58], but their status were hyperactivated. The first pathological study of a dead patient showed that the proportion of $CD4^+$ and $CD8^+$ T cells expressing HLA-DR significantly increased, suggesting an increase in their degree of activation. The ratio of pro-inflammatory $CCR4^+$ $CCR6^+$ Th17 cells and cytotoxic granules in $CD8^+$ cells also increased significantly, showing severe damage to the immune system of dead patients [59]. A correspondence in Cellular & Molecular Immunology revealed that severe patients lost the diversity of $CD4^+$ T cells, and their $CD8^+$ T cells showed significant exhaustion [60]. The pathological study by Zhou *et al.* further indicated that $CD4^+$ T cells have greatly changed into pathogenic GM-$CSF^+$ Th1 cells after infection, which further induced inflammatory $CD14^+$ $CD16^+$ monocytes, generating cytokines such as IL-6 [33]. These over-activated immune responses could cause dysfunctions of the immune cells, leading to deterioration and even acute death. At present, the complete mechanism of lymphopenia in severe COVID-19 patients is still inconclusive. In earlier studies of SARS patients, evidence of direct SARS-CoV infection was found in lymphocytes, especially T cells [61], but that has not yet been reported for COVID-19 patients. Considering that most severe patients are the seniors with poor immunity, whether people with fewer immune cells are more susceptible to severe illness, or disease deterioration can cause the decline of immune cells, still awaits more experimental data to resolve.

Various cytokines, especially pro-inflammatory cytokines, were generally elevated in patients with COVID-19, which could partially explain the hyperactivation of T cells. The accumulation of damaged cells attacked by the virus in the lungs and other organs is considered to induce these pro-inflammatory cytokines [62]. Functionally, cytokines like IL-2, IL-7, etc. can activate T cells and promote their proliferation; IL-6 and other pro-inflammatory cytokines induce $CD4^+$ T cells to differentiate into Th17 subset; IL-2, IL-6, IFN-γ, etc. can significantly promote T cells to transform towards cytotoxic T-cell (CTLs) [63,64]. All these cytokines mentioned showed significant differences between severe and non-severe cases in our catalog. Activated T cells and other cells like macrophages and monocytes can produce more pro-inflammatory cytokines, and eventually lead to the cytokine storm, causing more severe symptoms on patients, such as edema, ventilation dysfunction, acute respiratory distress symptoms, acute heart injury and secondary infections [2]. Prior to SARS-CoV-2, cytokine storms have been widely observed in viral infections, and been regarded to be correlated to the severity and mortalities of those infections, such as coronaviruses SARS [65] and MERS [66], and influenza viruses like H5N1 [67] and H7N9 [68]. At present, the sustained increase in IL-6 has been included in the "Early Indicators for Severe and Critical Cases" by the Guideline for the Diagnosis and Treatment of COVID-19 (7th version) [69], and its antibody Tocilizumab was suggested as an optional treatment for this kind of critical patients. Furthermore, mesenchymal stem cell therapy is also under development in order to prevent or reduce cytokine storms through its immunomodulatory effects [70]. Other therapies aiming at the cytokine storm, such as artificial-liver blood-purification system, also showed good prognosis [71].

In summary, previous epidemiologic and clinical data of patients with different severity of COVID-19, uniformly conclude that senior males and those with high BMI or underlying diseases, especially cardiovascular disease, hypertension and diabetes, tend to end up in severe conditions and bad outcomes. High leukocyte and lymphopenia are commonly seen in severe and critical patients. Both $CD4^+$ and $CD8^+$ T cells are decreased with the deterioration of disease, and almost all cytokines, in particular the pro-inflammatory cytokines in severe symptom patients' serum highly increased compared to mild cases.

## METHODS

We first searched literature databases, including Pubmed, Web of Science, Google Scholar, Chinese database CNKI, and some preprint databases medRxiv, bioXiv, SSRN, etc. Search keywords include "novel coronavirus", "novel coronavirus 2019", "2019-ncov", "COVID-19", "SARS-CoV-2", and collect documents from January 1, 2020 to March 26, 2020. No distinction is made between literature languages.

### Literature eligibility criteria

The following standard documents were included in this survey: Patients described were diagnosed with SARS-CoV-2 infection by RT-PCR, clinical, laboratory, and image features, and were classified into at least two groups according to the severity of the disease in the article. In principle, only the data in peer-reviewed and published articles were used, but for the patient's immune cell fraction and cytokine level data, because of the rarity of these data, some non-peer-reviewed data are included and noted when cited as unpublished articles.

### Data extraction

The survey includes information on the literature, publication journal, publication date, source of patient information (accurate to provinces, cities and hospitals), basic patient information (including the number of patients reported in the article, age, gender, underlying chronic diseases), patient biochemical data (blood routine, number of immune cells, and cytokine levels) and main conclusions of the article cited.

To compare the differences in age, gender, basic chronic diseases, clinical data and biochemical indicators between the severe cases and the mild cases, we use the following guidelines. The Guideline for the Diagnosis and Treatment of COVID-19 (7th version) [69] classifies the severity of patients into mild, common, severe and critical. Because the epidemic is a new type of virus and spreads rapidly, the diagnostic criteria have been partially changed as the epidemic continues. Therefore, in the literature published at different times, there is also a difference in the degree of illness. But in general, it can still be divided by the course of disease into "non-severe" (mild and common), "severe", "critical" and "dead" according to the description of the patient's condition in various literatures, and then study of different degrees of patients with basic information and clinical indicators can be carried out. Among the researches cited, ICU patients are classified as "critical" patients according to the Guideline for the Diagnosis and Treatment of COVID-19 (7th version) [69].

Data analysis statistics for the patients' gender, age, medical history and other information, the proportion of the number of corresponding indicators in the total number of corresponding groups has been counted. For cross-study analyses and comparisons of the clinical data and biochemical indicators of patients, instead of collecting the exact numbers from different literature, which are often derived from different platforms and are in different units, we adopted the relative values of the average data between groups on the log2 fold change of non-heavy / healthy, heavy / non-heavy (light) and critical / non-critical (light), respectively. These are annotated as "+", "++", "+++" and "++++" to indicate that the log2 values of each ratio are in the range of [0.25,0.5], [0.5,0.75], [0.75,1] and [1,]; "-", "--", "---"and "----" to indicate that the log2 values of each ratio are in the range of [–0.5, –0.25], [–0.75, –0.5], [–1, –0.75] and [,–1]; Values between "$0\pm0.25$" are marked by "~". The biochemical parameters of the dead patients are not included in the statistics due to the inconsistency in the blood sample collection stage before death.

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**COMPLIANCE WITH ETHICS GUIDELINES**

The authors Wanyu Tao, Zhengqing Yu and Jing-Dong J. Han declare that they have no conflict of interests.

All procedures performed in studies were in accordance with the ethical standards of the institution or practice at which the studies were conducted, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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