The Clinical Characteristics and Risk Factors of Severe COVID-19

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Abstract

Objective: We aim to investigate the clinical characteristics and risk factors for the severe cases of coronavirus disease 2019 (COVID-19) in comparison with the non-severe patients. Methods: We searched PubMed, EMBASE, Web of Science, and CNKI to collect all relevant studies published before July 26, 2020, and a total of 30 papers were included in this meta-analysis. Results: In the severe COVID-19 patients, 60% (95% CI = 56–64%) were male, 25% (95% CI = 21–29%) were over 65 years old, 34% (95% CI = 24–44%) were obese, and 55% (95% CI = 41–70%) had comorbidities. The most prevalent comorbidities were hypertension (34%, 95% CI = 25–44%), diabetes (20%, 95% CI = 15–25%), and cardiovascular disease (CVD; 12%, 95% CI = 9–16%). The most common blood test abnormalities were elevated C-reactive protein (CRP; 87%, 82–92%), decreased lymphocyte count (68%, 58–77%), and increased lactate dehydrogenase (69%, 95% CI = 57–81%). In addition, abnormal laboratory findings revealing organ dysfunctions were frequently observed in the severe cases, including decrease in albumin (43%, 95% CI = 24–63%) and increase in aspartate aminotransferase (47%, 95% CI = 38–56%), alanine aminotransferase (28%, 95% CI = 16–39%), troponin I/troponin T (TnI/TnT; 29%, 95% CI = 13–45%), and serum Cr (SCr; 10%, 95% CI = 5–15%). Conclusion: The male, elderly and obese patients and those with any comorbidities, especially with hypertension, diabetes, and CVD, were more likely to develop into severe cases. But the association between hypertension, diabetes, CVD, and severity of COVID-19 was declined by the increase of age. A significant elevation in cardiac TnI/TnT, the hepatic enzymes, and SCr and the reduction in lymphocytes with elevated CRPs are important markers for the severity. Specific attention should be given to the elderly male and obese patients and those with indications of severe immune injury in combination with bacterial infection and indication of multi-organ dysfunction or damages.

Introduction

In early December 2019, the coronavirus disease 2019 (COVID-19) broke out in Wuhan, China, and shortly reported over the world [1–4]. COVID-19 was caused by a previously unknown betacoronavirus, named 2019-nCoV or severe acute respiratory syndrome (SARS)-CoV-2 [5]. In this pandemic, the urban medical facilities...
in many countries have been overwhelmed with the treatment of severe cases [6]. Understanding the clinical characteristics and the risk factors of severe cases is critically important to improve the efficacy and outcome for the COVID-19 treatment. More and more studies have been published during the COVID-19 crisis. Here, we collected all relevant publications up to July 26, 2020, to reveal the clinical characteristics and the risk factors of severe COVID-19 to help identifying patients who are likely to develop to severe cases.

Methods

Protocol and Search Strategy

Our study followed PRISMA statement. We searched all relevant papers from PubMed, EMBASE, Web of Science, and CNKI with the following keywords: “2019-nCoV,” “COVID-19,” or “SARS-CoV-2” and “clinical characteristics,” “clinical finding,” “clinical feature,” “clinical study,” or “clinical case.” The search period was updated to July 26, 2020. Then 2 researchers did a further artificial selection to screen eligible papers independently.

The Inclusive and Exclusive Criteria

In this article, we focused on the clinical characteristics of severe patients with COVID-19 and the differences between the severe and non-severe COVID-19 patients. The studies on observation of clinical characteristics in severe and non-severe patients with COVID-19 were included, and studies without severe patients’ data or the comparison between the severe and non-severe patients or lack of clear diagnostic criteria were excluded.

The severe patients in our article included the patients hospitalized in intensive care unit and the severe/critical patients defined by the seventh guideline for the diagnosis and treatment of COVID-19 issued by the Chinese National Health Commission & State Administration of Traditional Chinese Medicine. Because of the difficulty of obtaining original data, the classification was achieved based on the authors’ statement presented in papers.

The severe illness of COVID-19 was defined if satisfying at least one of the following criteria: (a) breathing rate ≥30/min; (b) pulse oximeter oxygen saturation ≤93% at rest; or (c) ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ≤300 mm Hg (1 mm Hg = 0.133 kPa). Critical illness was defined if satisfying at least one of the following criteria: (a) respiratory failure with required mechanical ventilation; (b) shock; or (c) failure of other organs and received medical care in the intensive care unit.

The reference intervals of laboratory findings varied in different studies, which was presented in online supplementary Table S1 (see www.karger.com/doi/10.1159/000513400 for all online suppl. material).

Data Extraction

The papers we searched and screened were imported to EndNote (version 8) to remove all duplicates. We then screened the titles and abstracts of retrieved papers in the list. All useful data were extracted in a form after reading the full text. Due to the reality in clinical practice and ethical restrictions, all included studies were cross-sectional studies.

Results

Literature Summary

We retrieved a total of 637 papers. 292 repetitive papers were removed and 131 papers were excluded after screening the titles and abstracts. 182 articles were eliminated due to lack of a comparison between non-severe and severe COVID-19 patients, short of original data or diagnosis criteria. At the end, 30 papers were included in our meta-analysis [1], [7–35]. The screening process was shown in Figure 1. The detailed information about basic characteristics, underlying diseases, and laboratory findings was summarized in Tables 1 and 2 and online supplementary Tables S1 and S2.

Because of the reality in clinical practice and medical ethics, all included studies are case series studies. A total of 6,685 individuals were involved in our study with the sample size ranging from 41 to 1,099.

Meta-Analysis Results

The Clinical Characteristics of Severe COVID-19

A total of 1,457 severe COVID-19 patients were included in this meta-analysis. In the severe COVID-19 patients, 60% (95% CI = 56–64%) were male, 25% (95% CI = 21–29%) were over 65 years old, 34% (95% CI = 24–44%) were obese, and 55% (95% CI = 41–70%) had comorbidities. The most prevalent comorbidities were hypertension (34%, 95% CI = 25–44%), diabetes (20%, 95% CI = 15–25%), and cardiovascular disease (CVD; 12%, 95% CI = 9–16%). For laboratory findings, the prevalence of elevated C-reactive protein (CRP) was 87% (82–92%), decreased lymphocyte count was 68% (58–77%), and increased lactate dehydrogenase (LDH) was 69%
(95% CI = 57–81%). In addition, significant decrease in albumin (43%, 95% CI = 24–63%) and increase in aspartate aminotransferase (AST; 47%, 95% CI = 38–56%), alanine aminotransferase (ALT; 28%, 95% CI = 16–39%), troponin I/troponin T (TnI/TnT; 29%, 95% CI = 13–45%), and serum Cr (SCr; 10%, 95% CI = 5–15%) were observed (Table 3).

The Differences of Clinical Characteristics between Severe and Non-severe Groups
As shown in Table 4, male (OR = 1.383, 95% CI = 1.183–1.616), age over 65 years old (OR = 2.250, 95% CI = 1.677–3.017), and obesity (OR = 2.519, 95% CI = 1.498–4.235) were associated with increased severity of COVID-19. The prevalence of comorbidity, such as hypertension, CVD, and diabetes in the severe patients was significantly higher (OR = 2.661, 95% CI = 1.700–4.163; OR = 2.403, 95% CI = 1.389–2.483), LDH (OR = 1.744, 95% CI = 1.384–2.199), TnI/TnT (OR = 2.257, 95% CI = 1.562–3.262) and increased levels of CRP (OR = 1.495, 95% CI = 1.353–1.652), procalcitonin (OR = 2.403, 95% CI = 1.727–3.343), AST (OR = 2.356, 95% CI = 0.917–2.896), ALT (OR = 1.857, 95% CI = 1.389–2.483), LDH (OR = 1.744, 95% CI = 1.384–2.199), TnI/TnT (OR = 4.707, 95% CI = 2.234–9.917), and SCr (OR = 2.245, 95% CI = 1.474–3.421) was significantly higher in the severe patients.

The Result of Meta-regression
The meta-regression analysis with age as a covariate indicated that age declined the association between hypertension (p = 0.027), diabetes (p = 0.001), CVD (p = 0.003), and severity of COVID-19.

Heterogeneity Test, Sensitivity Analysis and Publication Bias
We observed significant heterogeneity (I²) varying from 52.1 to 96.2% in meta-analysis of the clinical characteristics of severe COVID-19 (Table 3). Significant publication bias (p < 0.05) was observed in the prevalence of CVD, increased white blood cells, increased CRP, and increased serum Cr (as shown in Table 3).

As for meta-analysis of the differences between severe and non-severe patients, heterogeneity varied from 0.0 to...
| Studies         | Disease severity | Sex (male) |
|-----------------|------------------|------------|
|                 | Patients, n      | Age, n (%) |
|                 | >50 yr           | >60 yr     | >65 yr     |
| Guan, Weijie    | Severe           | 173        | 926        |
|                 | Non-severe       | 44/163 (27.0) | 109/848 (12.9) |
|                 | 100 (57.8)       | 67 (38.7)  | 41 (23.7)  | 28 (16.2)  |
|                 | 540 (58.3)       | 194 (21.0) | 124 (13.4) | 53 (5.7)   |
| Huang, Chaolin  | Severe           | 13         | 28         |
|                 | Non-severe       | 11 (84.6)  | 19 (67.9)  | 3 (15%)    |
|                 |                  | 5 (38%)    | 8 (29%)    | 2 (14%)    |
|                 |                  | 2 (15%)    | 4 (17%)    | 1 (8%)     |
|                 |                  | 8 (29%)    | 17 (25%)   | 3 (23%)    |
| Zhang, Jinjin   | Severe           | 58         | 82         |
|                 | Non-severe       | 48 (82.8)  | 50 (61.0)  |
|                 |                  | 33 (56.9)  | 38 (46.3)  |
|                 |                  | 46 (79.3)  | 44 (53.7)  |
|                 |                  | 22 (37.9)  | 20 (24.4)  |
|                 |                  | 8 (13.8)   | 9 (11.0)   |
| Xu, Yuhuan      | Severe           | 13         | 37         |
|                 | Non-severe       | 5 (38.5)   | 10 (27.0)  |
|                 |                  | 7 (53.8)   | 22 (59.5)  |
| Li, Kunhua      | Severe           | 25         | 58         |
|                 | Non-severe       | 15 (60)    | 29 (50)    |
|                 |                  | 11 (44.0)  | 4 (6.9)    |
|                 |                  | 2 (8.0)    | 3 (5.2)    |
|                 |                  | 7 (28.0)   | 0 (0.0)    |
| Wan, Suxin      | Severe           | 40         | 95         |
|                 | Non-severe       | 21 (52.5)  | 52 (54.7)  |
|                 |                  | 28 (70)    | 15 (16.3)  |
|                 |                  | 4 (10)     | 9 (9.4)    |
|                 |                  | 9 (22.5)   | 3 (3.1)    |
| Cai, Qingxian   | Severe           | 58         | 240        |
|                 | Non-severe       | 50 (86.21) | 88 (36.67) |
|                 |                  | 39 (67.24) | 106 (44.17) |
|                 |                  | 22 (37.9)  | 25 (10.4)  |
|                 |                  | 8 (13.79)  | 13 (22.41) |
|                 |                  | 12 (5.0)   |
| Zhang, Gemin    | Severe           | 32         | 63         |
|                 | Non-severe       | 7 (21.9)   | 10 (15.9)  |
|                 |                  | 21 (65.6)  | 32 (50.8)  |
| Zheng, F.       | Severe           | 30         | 131        |
|                 | Non-severe       | 14 (46.7)  | 66 (50.4)  |
|                 |                  | 12 (40)    | 10 (7.6)   |
|                 |                  | 2 (6.7)    | 5 (3.8)    |
|                 |                  | 2 (6.7)    | 2 (1.5)    |
| Cheng, Kebing   | Severe           | 181        | 282        |
|                 | Non-severe       | 42 (23.2)  | 36 (12.77) |
|                 |                  | 99 (54.7)  | 145 (51.42) |
|                 |                  | 53 (29.28) | 54 (19.15) |
|                 |                  | 20 (11.05) | 20 (7.09)  |
|                 |                  | 16 (8.84)  | 12 (4.26)  |
| Xiao, Kaihu     | Severe           | 36         | 107        |
|                 | Non-severe       | 20 (55.6)  | 52 (48.6)  |
|                 |                  | 17 (47.2)  | 29 (27.1)  |
|                 |                  | 5 (13.9)   | 12 (11.2)  |
|                 |                  | 5 (13.9)   | 4 (7.4)    |
|                 |                  | 2 (5.6)    | 3 (2.8)    |
| Yuan, Jing      | Severe           | 31         | 192        |
|                 | Non-severe       | 18 (58.1)  | 88 (45.8)  |
|                 |                  | 14 (45.2)  | 40 (20.8)  |
|                 |                  | 4 (12.9)   | 21 (10.9)  |
|                 |                  | 8 (25.8)   | 10 (5.2)   |
|                 |                  | 0 (0)      | 1 (0.5)    |
| He, Xingwei     | Severe           | 54         | 54         |
|                 |                  | 34 (63.0)  | 24 (44.4)  |
|                 |                  | 24 (44.4)  | 13 (24.1)  |
|                 |                  | 5 (9.3)    |
| Deng, Qing      | Severe           | 67         | 45         |
|                 | Non-severe       | 38 (56.7)  | 19 (42.2)  |
|                 |                  | 28 (41.8)  | 13 (28.9)  |
|                 |                  | 13 (52.0)  | 13 (52.0)  |
|                 |                  | 9 (36.0)   | 7 (8.4)    |
|                 |                  | 3 (12.0)   | 2 (2.4)    |
|                 |                  | 2 (8.0)    | 2 (2.4)    |
| Yao, Qingchun   | Severe           | 25         | 83         |
|                 | Non-severe       | 9/25 (36.0)| 8/83 (9.6) |
|                 |                  | 13 (52.0)  | 30 (36.1)  |
|                 |                  | 13 (52.0)  | 12 (14.5)  |
|                 |                  | 9 (36.0)   | 7 (8.4)    |
|                 |                  | 3 (12.0)   | 2 (2.4)    |
| Xu, Jing        | Severe           | 30         | 125        |
|                 | Non-severe       | 20 (66.7)  | 67 (53.6)  |
|                 |                  | 12 (40.0)  | 16 (12.8)  |
| Asghar, M.S.    | ICU              | 33         | 67         |
|                 | Ward             | –          | –          |
| Cao, Zhenhuan   | Severe           | 27         | 53         |
|                 | Non-severe       | 16 (59.3)  | 22 (41.5)  |
|                 |                  | 4 (14.8)   | 16 (30.2)  |
|                 |                  | 3 (11.1)   | 5 (18.5)   |
|                 |                  | 5 (9.4)    |
### Table 1 (continued)

| Studies                        | Disease severity | Patients, | Age, n (%) | Sex (male) | Obesity* | Comorbidity | Hypertension | Diabetes | CVD n (%) | Ref. |
|--------------------------------|------------------|-----------|------------|------------|----------|-------------|--------------|----------|-----------|------|
| Pellaud, Charlotte             | ICU              | 49        | –          | >50 y 34 (70.0) | 30 (61.0) | 28 (19) | 40 (82.0) | 27 (55) | 11 (22) | 6 (12) [24] |
| Ward                           |                  | 147       | 114 (77.0) |            | 89 (60.0) | 13 (27) | 122 (83.0) | 91 (62) | 41 (28) | 20 (14) |
| Chen, Qingqing                 | Severe           | 43        | –          | >50 y 34 (70.0) | 23 (53.5) | 9 (20.9) | 7 (16.3) |          |          |       [25] |
| Non-severe                     |                  | 102       | 114 (77.0) |            | 56 (54.9) | 13 (12.7) | 7 (6.9) |          |          |       |
| Liu, Changquan                 | Severe           | 42        |            | >50 y 28 (66.7) | 102 (43.2) |          |          |          |          |       [26] |
| Non-severe                     |                  | 236       |            | >60 y 41 (97.6) | 197 (83.5) |          |          |          |          |       |
| Ebinger, Joseph E.             | ICU              | 77        |            | >50 y 57 (74.0) | 78 (56.9) | 17 (22.1) | 49 (63.6) | 40 (29.2) | 18 (23.4) | 27 (19.7) [27] |
| Ward                           |                  | 137       |            | >60 y 57 (74.0) | 78 (56.9) | 17 (22.1) | 49 (63.6) | 40 (29.2) | 18 (23.4) | 27 (19.7) |
| Hong, Kyung Soo                | ICU              | 13        |            | >50 y 6 (46.2) | 23 (27.1) | 6 (46.2) | 5 (38.5) | 3 (23.1) | 0 (0) | [28] |
| Not-ICU                        |                  | 85        |            | >60 y 5 (38.5) | 33 (38.8) | 25 (29.4) | 6 (7.1) | 11 (12.9) |          |       |
| Huang, Rui                     | Severe           | 23        |            | >50 y 17 (73.9) | 99 (55.3) | 8 (44.4) | 9 (39.1) | 8 (34.8) | 1 (4.3) | 6 (3.3) [29] |
| Non-severe                     |                  | 179       |            | >60 y 21 (11.7) |          | 16 (10.4) | 46 (25.7) | 11 (6.1) |          |       |
| Liu, Fang                      | Severe           | 33        |            | >50 y 8 (24.2) | 41 (38.3) |          | 22 (66.7) | 12 (36.4) | 13 (39.4) |          [30] |
| Non-severe                     |                  | 107       |            | >60 y 22 (66.7) | 41 (38.3) |          | 22 (66.7) | 12 (36.4) | 13 (39.4) |          |
| Shahntarirad, Reza             | ICU              | 11        |            | >50 y 7 (63.6) | 64 (62.7) |          | 5 (45.5) | 3 (27.3) | 4 (36.4) |          [31] |
| Not-ICU                        |                  | 102       |            | >60 y 7 (63.6) | 64 (62.7) |          | 5 (45.5) | 3 (27.3) | 4 (36.4) |          |
| Geehan, Suleyman               | ICU              | 141       |            | >50 y 80 (56.7) | 111 (78.7) | 37 (26.2) | 73 (51.8) | 26 (18.4) |          |       [32] |
| Not-ICU                        |                  | 214       |            | >60 y 80 (56.7) | 111 (78.7) | 37 (26.2) | 73 (51.8) | 26 (18.4) |          |       |
| Zheng, Yufen                   | Severe           | 29        |            | >50 y 16 (55.2) | 11 (37.9) |          |          |          |          |       [33] |
| Non-severe                     |                  | 112       |            | >60 y 58 (51.7) | 58 (51.8) |          |          |          |          |       |
| Almazeedi, Sulaiman            | ICU              | 42        |            | >50 y 32 (76.2) | 856 (81.2) |          | 17 (40.5) | 137 (13.0) | 8 (19.0) | 33 (3.1) [34] |
| Not-ICU                        |                  | 1,054     |            | >60 y 17 (40.5) | 160 (15.2) |          | 18 (42.9) |          |          |       |
| Cao, Min                       | ICU              | 19        |            | >50 y 15 (78.9) | 17 (89.5) |          | 6 (31.6) | 2 (10.5) | 5 (26.3) | [35] |
| Not-ICU                        |                  | 179       |            | >60 y 54 (30.1) | 84 (46.9) |          | 36 (20.1) | 13 (7.3) | 7 (3.9) |       |

COVID-19, coronavirus disease 2019; ICU, intensive care unit. *Obesity: BMI >30 or 28 kg/m² (China).
Table 2. The laboratory findings in patients with COVID-19

| Studies          | Disease     | Patients, N (%) | N (%) | ICU | Not-ICU | ICU | Not-ICU |
|------------------|-------------|-----------------|-------|-----|---------|-----|---------|
| Guan, Weijie     | Severe      | 19/167 (11.4)   | 167   | 11.4| 167     | 1.0 | 167     |
|                  | Non-severe  | 39/811 (28.1)   | 811   | 28.1| 811     | 1.0 | 811     |
| Wang, Jinjin     | Severe      | 58/137 (42.0)   | 137   | 42.0| 137     | 1.0 | 137     |
|                  | Non-severe  | 13/27 (48.1)    | 27    | 48.1| 27      | 1.0 | 27      |
| Xu, Tuanan       | Severe      | 52/193 (27.0)   | 193   | 27.0| 193     | 1.0 | 193     |
|                  | Non-severe  | 5/27 (19)       | 27    | 19  | 27      | 1.0 | 27      |
| Li, Kaibin       | Severe      | 40/103 (38.8)   | 103   | 38.8| 103     | 1.0 | 103     |
|                  | Non-severe  | 10/27 (37.0)    | 27    | 37.0| 27      | 1.0 | 27      |
| Chen, Jialei     | Severe      | 40/125 (32.0)   | 125   | 32.0| 125     | 1.0 | 125     |
|                  | Non-severe  | 6/27 (22.2)     | 27    | 22.2| 27      | 1.0 | 27      |
| Wang, Song       | Severe      | 31/75 (41.3)    | 75    | 41.3| 75      | 1.0 | 75      |
|                  | Non-severe  | 6/27 (22.2)     | 27    | 22.2| 27      | 1.0 | 27      |
| Cai, Qingxian    | Severe      | 58/157 (37.0)   | 157   | 37.0| 157     | 1.0 | 157     |
|                  | Non-severe  | 75/235 (31.9)   | 235   | 31.9| 235     | 1.0 | 235     |
| Li, Kunhua       | Severe      | 25               | 67    | 37.3| 67      | 0.5 | 67      |
|                  | Non-severe  | 85               | 214   | 39.5| 214     | 1.2 | 214     |
| Cao, Min         | Severe      | 33               | 179   | 18.7| 179     | 1.0 | 179     |
|                  | Non-severe  | 102              | 214   | 47.9| 214     | 1.2 | 214     |
| Asghar, M.S.     | Severe      | 33               | 179   | 18.7| 179     | 1.0 | 179     |
|                  | Non-severe  | 107              | 214   | 47.9| 214     | 1.2 | 214     |
| Shahriarirad, R. | Severe      | 11               | 65    | 16.9| 65      | 1.6 | 65      |
|                  | Non-severe  | 92               | 554   | 16.7| 554     | 2.0 | 554     |
| Gorham, Shyam    | Severe      | 13               | 79    | 16.4| 79      | 1.6 | 79      |
|                  | Non-severe  | 79               | 425   | 18.6| 425     | 4.6 | 425     |

**Legend:**
- **WBC:** white blood cell
- **CRP:** C-reactive protein
- **PCT:** procalcitonin
- **ALT:** alanine aminotransferase
- **AST:** aspartate aminotransferase
- **LDH:** lactate dehydrogenase
- **TnI/TnT:** troponin I/troponin T
- **SCr:** serum Cr

**Notes:**
1. Increased means over the upper limit of the reference range.
2. Decreased means below the lower limit of the reference range.

**COVID-19:** coronavirus disease 2019.
Table 3. The clinical characteristics of severe patients with COVID-19

| Clinical characteristic | Studies, n | Subgroup | Prevalence | 95% CI | Quantifying heterogeneity, % | Egger test |
|-------------------------|------------|----------|------------|--------|-------------------------------|-----------|
| Male                    | 29         | Total    | 0.60       | [0.56; 0.64] | 52.1                          | 0.9551    |
|                         |            | Severe   | 0.58       | [0.55; 0.61] | 45.9                          |           |
|                         |            | ICU      | 0.65       | [0.60; 0.70] | 59.1                          |           |
| Age                     | 3          | >50 yr   | 0.74       | [0.57; 0.92] | 82.3                          | 0.7839    |
|                         | 5          | >60 yr   | 0.52       | [0.30; 0.73] | 92.5                          |           |
|                         | 4          | >65 yr   | 0.25       | [0.21; 0.29] | 0.0                           |           |
| Obesity                 | 6          | Total    | 0.34       | [0.24; 0.44] | 77.7                          | 0.1885    |
|                         |            | Severe   | 0.35       | [0.26; 0.44] | 19.5                          |           |
|                         |            | ICU      | 0.34       | [0.17; 0.52] | 89.2                          |           |
| Comorbidity             | 15         | Total    | 0.55       | [0.41; 0.70] | 95.1                          | 0.4874    |
|                         |            | Severe   | 0.54       | [0.37; 0.72] | 95.9                          |           |
|                         |            | ICU      | 0.60       | [0.32; 0.87] | 83.4                          |           |
| Hypertension            | 24         | Total    | 0.34       | [0.25; 0.44] | 93.2                          | 0.0963    |
|                         |            | Severe   | 0.28       | [0.21; 0.34] | 82.6                          |           |
|                         |            | ICU      | 0.52       | [0.38; 0.67] | 86.3                          |           |
| Diabetes                | 26         | Total    | 0.20       | [0.15; 0.25] | 81.8                          | 0.0523    |
|                         |            | Severe   | 0.15       | [0.12; 0.19] | 52.2                          |           |
|                         |            | ICU      | 0.31       | [0.19; 0.43] | 82.8                          |           |
| CVD                     | 24         | Total    | 0.12       | [0.09; 0.16] | 74.8                          | 0.0017    |
|                         |            | Severe   | 0.11       | [0.07; 0.14] | 72.3                          |           |
|                         |            | ICU      | 0.17       | [0.10; 0.24] | 65.1                          |           |
| WBC increased           | 17         | Total    | 0.22       | [0.15; 0.30] | 90.5                          | 0.0134    |
|                         |            | Severe   | 0.20       | [0.12; 0.28] | 91.4                          |           |
|                         |            | ICU      | 0.30       | [0.10; 0.50] | 74.8                          |           |
| Lymphocyte decreased    | 20         | Total    | 0.68       | [0.58; 0.77] | 92.2                          | 0.269     |
|                         |            | Severe   | 0.65       | [0.54; 0.77] | 93.5                          |           |
|                         |            | ICU      | 0.78       | [0.60; 0.95] | 76.3                          |           |
| Platelet decreased      | 14         | Total    | 0.20       | [0.11; 0.30] | 89.0                          | 0.0789    |
|                         |            | Severe   | 0.19       | [0.08; 0.31] | 92.3                          |           |
|                         |            | ICU      | 0.23       | [0.14; 0.33] | 76.3                          |           |
| CRP increased           | 18         | Total    | 0.87       | [0.82; 0.92] | 82.0                          | 0.0055    |
|                         |            | Severe   | 0.87       | [0.81; 0.92] | 86.0                          |           |
|                         |            | ICU      | 0.92       | [0.86; 0.98] | 0.0                           |           |
| PCT increased           | 12         | Total    | 0.32       | [0.19; 0.44] | 93.1                          | 0.1314    |
|                         |            | Severe   | 0.34       | [0.15; 0.53] | 95.5                          |           |
|                         |            | ICU      | 0.24       | [0.18; 0.30] | 0.0                           |           |
| LDH increased           | 11         | Total    | 0.69       | [0.57; 0.81] | 91.8                          | 0.1586    |
|                         |            | Severe   | 0.67       | [0.53; 0.81] | 93.0                          |           |
|                         |            | ICU      | 0.78       | [0.50; 1.00] | 84.8                          |           |
| Albumin decreased       | 5          | Total    | 0.43       | [0.24; 0.63] | 91.5                          | 1         |
|                         |            | Severe   | 0.50       | [0.01; 1] | 96.4                          |           |
|                         |            | ICU      | 0.38       | [0.23; 0.53] | 81.1                          |           |
| AST increased           | 10         | Total    | 0.47       | [0.38; 0.56] | 66.9                          | 0.0892    |
|                         |            | Severe   | 0.43       | [0.35; 0.50] | 40.0                          |           |
|                         |            | ICU      | 0.56       | [0.29; 0.84] | 83.6                          |           |
| ALT increased           | 9          | Total    | 0.28       | [0.16; 0.39] | 86.1                          | 0.8348    |
|                         |            | Severe   | 0.31       | [0.15; 0.45] | 91.0                          |           |
|                         |            | ICU      | 0.21       | [0.11; 0.31] | 0.0                           |           |
| TnI/TnT increased       | 7          | Total    | 0.29       | [0.13; 0.45] | 96.2                          | 0.2931    |
|                         |            | Severe   | 0.23       | [0.06; 0.40] | 95.6                          |           |
|                         |            | ICU      | 0.42       | [0.34; 0.49] | 0.0                           |           |
| SCr increased           | 10         | Total    | 0.10       | [0.05; 0.15] | 70.6                          | 0.0095    |
|                         |            | Severe   | 0.06       | [0.03; 0.08] | 31.1                          |           |
|                         |            | ICU      | 0.29       | [0.13; 0.46] | 52.8                          |           |

COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TnI/TnT, troponin I/troponin T; SCr, serum Cr.
Table 4. The association of different patients’ characteristics and clinical manifestations with increased severity of COVID-19

| Clinical characteristic | Subgroup | Pooled OR | 95% CI         | \( I^2, \% \) | \( p \) value | Egger test |
|-------------------------|----------|-----------|----------------|----------------|--------------|------------|
| Male                    | Total    | 1.383     | 1.183; 1.616   | 22.3           | 0.000        | 0.385      |
|                         | Severe   | 1.306     | 1.144; 1.618   | 18.7           | 0.001        |            |
|                         | ICU      | 1.405     | 0.964; 2.047   | 39.0           | 0.077        |            |
| Age                     | >50 yr   | 4.153     | 1.426; 12.090  | 73.8           | 0.009        | 0.650      |
|                         | >60 yr   | 1.841     | 0.905; 3.746   | 72.8           | 0.092        | 0.442      |
|                         | >65 yr   | 2.250     | 1.677; 3.017   | 0.0            | 0.000        | 0.343      |
| Obesity                 | Total    | 2.519     | 1.498; 4.235   | 81.7           | 0.000        | 0.198      |
|                         | Severe   | 2.380     | 0.995; 5.695   | 71.6           | 0.051        |            |
|                         | ICU      | 1.267     | 0.706; 2.276   | 89.8           | 0.000        |            |
| Comorbidity             | Total    | 2.661     | 1.700; 4.163   | 71.5           | 0.000        | 0.289      |
|                         | Severe   | 3.258     | 1.955; 5.428   | 72.8           | 0.000        |            |
|                         | ICU      | 1.267     | 0.706; 2.276   | 8.2            | 0.427        |            |
| Hypertension            | Total    | 2.041     | 1.591; 2.619   | 50.1           | 0.000        | 0.545      |
|                         | Severe   | 2.170     | 1.586; 2.970   | 48.1           | 0.000        |            |
|                         | ICU      | 1.835     | 1.188; 2.833   | 56.8           | 0.006        |            |
| CVD                     | Total    | 2.264     | 1.705; 3.007   | 44.4           | 0.000        | 0.148      |
|                         | Severe   | 2.353     | 1.815; 3.051   | 79.1           | 0.000        |            |
|                         | ICU      | 2.056     | 1.001; 3.983   | 0.0            | 0.033        |            |
| Diabetes                | Total    | 2.156     | 1.651; 2.815   | 63.7           | 0.000        | 0.030      |
|                         | Severe   | 2.569     | 1.906; 3.463   | 36.1           | 0.000        |            |
|                         | ICU      | 1.608     | 1.043; 1.043   | 76.8           | 0.032        |            |
| WBC increased           | Total    | 2.784     | 1.878; 4.125   | 55.2           | 0.000        | 0.069      |
|                         | Severe   | 2.530     | 1.546; 4.142   | 61.4           | 0.000        |            |
|                         | ICU      | 3.573     | 2.201; 5.800   | 0.1            | 0.000        |            |
| Lymphocyte decreased    | Total    | 2.054     | 1.641; 2.571   | 91.7           | 0.000        | 0.094      |
|                         | Severe   | 1.851     | 1.496; 2.289   | 89.9           | 0.000        |            |
|                         | ICU      | 4.262     | 1.817; 9.997   | 88.2           | 0.001        |            |
| Platelet decreased      | Total    | 1.852     | 1.602; 2.142   | 0.0            | 0.000        | 0.635      |
|                         | Severe   | 1.871     | 1.607; 2.178   | 0.0            | 0.000        |            |
|                         | ICU      | 1.680     | 1.037; 2.720   | 0.0            | 0.035        |            |
| CRP increased           | Total    | 1.495     | 1.353; 1.652   | 79.3           | 0.000        | 0.009      |
|                         | Severe   | 1.493     | 1.345; 1.658   | 77.8           | 0.000        |            |
|                         | ICU      | 1.523     | 1.087; 2.132   | 87.4           | 0.014        |            |
| PCT increased           | Total    | 2.403     | 1.727; 3.343   | 54.7           | 0.000        | 0.002      |
|                         | Severe   | 2.613     | 1.753; 3.894   | 57.2           | 0.000        |            |
|                         | ICU      | 2.151     | 0.930; 4.973   | 68.3           | 0.073        |            |
| Albumin decreased       | Total    | 2.257     | 1.562; 3.262   | 69.9           | 0.000        | 0.585      |
|                         | Severe   | 2.555     | 1.501; 4.350   | 77.2           | 0.001        |            |
|                         | ICU      | 1.352     | 0.260; 7.029   | 83.5           | 0.720        |            |
| ALT increased           | Total    | 1.857     | 1.389; 2.483   | 41.1           | 0.000        | 0.645      |
|                         | Severe   | 2.057     | 1.396; 3.032   | 60.6           | 0.000        |            |
|                         | ICU      | 1.407     | 0.830; 2.384   | 0.0            | 0.205        |            |
| AST increased           | Total    | 2.356     | 1.917; 2.896   | 39.1           | 0.000        | 0.087      |
|                         | Severe   | 2.468     | 1.810; 3.363   | 56.6           | 0.000        |            |
|                         | ICU      | 2.292     | 1.756; 2.990   | 0.0            | 0.000        |            |
| LDH increased           | Total    | 1.744     | 1.384; 2.199   | 86.2           | 0.000        | 0.243      |
|                         | Severe   | 1.860     | 1.487; 2.326   | 81.5           | 0.000        |            |
|                         | ICU      | 1.315     | 0.443; 3.901   | 96.3           | 0.622        |            |
| SCr increased           | Total    | 2.245     | 1.474; 3.421   | 21.2           | 0.000        | 0.534      |
|                         | Severe   | 2.003     | 1.247; 3.217   | 0.0            | 0.000        |            |
|                         | ICU      | 2.568     | 0.971; 6.792   | 66.8           | 0.057        |            |
| TnI/TnT increased       | Total    | 4.707     | 2.234; 9.917   | 77.2           | 0.000        | 0.154      |
|                         | Severe   | 6.034     | 2.758; 13.201  | 40.5           | 0.000        |            |
|                         | ICU      | 3.357     | 0.978; 11.520  | 90.2           | 0.054        |            |

COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TnI/TnT, troponin I/troponin T; SCr, serum Cr.
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et al. [48] concluded that there was a significant association between COVID-19 mortality and cardiac injury. A study found that ACE2 activity is increased in patients with type 1 diabetes with vascular complications [49]. It is known that the ACE2 expression and activity are connected with Angiotsin-converting enzyme inhibitor (ACEI). ACE1 is the drug for treating hypertension and heart failure by regulating blood pressure and prevention of ventricular remodeling via suppressing the elevated activity of renin-angiotensin-aldosterone system. During ACEI application, ACE2 activity is not inhibited. Instead, the upregulation of ACE2 expression and increased activity were observed [50, 51]. However, latest studies found that ACE1 or ARB use was not associated with more severe COVID-19 disease [52], but the use of ARBs increased the risk of SARS-CoV-2 infection in younger patients [53].

Our study found that patients with hypertension, diabetes, and CVD are more sensitive to SARS-CoV-2 infection and transition to severity. However, the association between hypertension, diabetes, and CVD and severity of COVID-19 was decreased by age. It is likely that age itself is closely related with the propensity of comorbidities which contributes somewhat to the severity transition. Also, male patients are more sensitive to the infection of bacteria, virus, parasite, and fungi [54]. This may be linked to their living habits. For instance, there are much more smokers in men than in women. In a recent meta-analysis study [55], Vardavas and Nikitara [55] reported that the smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to be admitted to an intensive care unit, need mechanical ventilation, or die compared to nonsmokers. This may be linked to an increased ACE2 gene expression in the smokers. From another point of view, in the smokers, unlikely to wear a mask and frequent hand-to-mouth contact may also increase the risk of SARS-CoV-2 infection. Given these, the male seems more easily to be attacked by SARS-CoV-2 and more likely to transit into severe cases.

In addition, obesity is a main risk factor of comorbidities such as hypertension, diabetes mellitus, and CVD [56]. Meanwhile, ACE2 abundantly expressed in adipose tissue. These may cause obese people vulnerable to SARS-CoV-2 as well [57].

COVID-19 patients were in some cases complicated with myocarditis. However, the diagnosis of myocarditis was largely based on troponin elevation. Actually, the myocardial injury could be likely caused by the viral infection-triggered inflammatory response, rather than the direct viral attack, and there was no SARS-CoV-2 observed in the heart tissue [58–61].
In terms of nervous injury, most publications included in our study only observed nonspecific neurological symptoms, such as headache, dizziness, and agitation. More specific manifestations like delirium were not generally reported. Mao et al. [62] and Julie Helms et al. [63] found delirium and/or neurological symptoms appeared more frequent in severe COVID-19 patients and were associated with worse prognosis. However, the direct evidence of COVID-19 invasion to nervous system is still limited. The RT-PCR test of SARS-CoV-2 was negative in cerebrospinal fluid and there was not remarkable pathological observation in the brain [61, 63].

Hypoalbuminemia in critically ill patients was statistically significant and associated with longer hospitalization and higher mortality [64]. Decreased albumin levels in severe COVID-19 patients could be the results of liver dysfunction or malnutrition due to gastrointestinal symptoms [65]. But hypoalbuminemia is a predictor of transition to the severity independent of age and comorbidity [66].

Comparing COVID-19 with SARS or Middle East Respiratory Syndrome, age, male gender, and comorbidities such as diabetes and hypertension were the mortality risk factors in common [67, 68]. Besides, laboratory findings including decreased lymphocytes, platelet count, and albumin level and increased AST, LDH, and CRP levels in patients diagnosed with COVID-19 were not remarkably different from those of patients diagnosed with SARS or Middle East respiratory syndrome [69].

We have to notice that the abnormal laboratory variants were obtained at the time of hospitalization but not always collected prior to the patient transition to the severe cases. In some cases, the results may be collected in patients who had already become a severe case at the time of hospital admission. Under this circumstance, we cannot rule out the possibility that these abnormalities were secondary to the disease development (present in online suppl. Tables S1, S2).

In summary, our study revealed that the elderly, male, obese people, and patients with any comorbidities, especially those with hypertension, CVD, or diabetes are more likely to develop to severe cases. A progressive elevation in cardiac TnI/TnT, the hepatic enzymes, and serum Cr and the advanced lymphocytopenia and leukocytosis are important alerting markers of mild to severe case transition.

A total of 30 papers were included in this meta-analysis. Although the literatures included in this study have good quality, some limitations remain. First, due to the inconsistency of the observation time of each study, heterogeneity and bias are inevitable. Second, all studies included in this meta-analysis are retrospective studies, and all the study objects were inpatients diagnosed with SARS-CoV-2 infection. Therefore, many patients who did not go to hospital were not included. A more solid conclusion can be achieved when more well-designed large-scale clinical trial studies become available.

**Statement of Ethics**

This study is exempt from Ethical Committee Approval since all human data were collected from the published sources.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

**Funding Sources**

This work was supported by grants awarded to Yanggan Wang from the National Natural Science Foundation of China (NSFC, Grant Nos. 81873507 and 81420108004).

**Author Contributions**

The research idea and study design were guided by Yanggan Wang. The data extraction and analysis were done by Jianhua Hu. The manuscript was written by Jianhua Hu and modified by Yanggan Wang.

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