Clinical Determinants of Severe COVID-19 Disease – A Systematic Review and Meta-Analysis

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Abstract

Background: A systematic review and meta-analysis of available studies was performed to investigate the clinical characteristics that can predict COVID-19 disease severity. Materials and Methods: Databases including PubMed, Embase, and Web of Science were searched from December 31, 2019, to May 24, 2020. Random-effects meta-analysis was used for summarizing the Pooled odds ratio (pOR) of individual clinical characteristics to describe their association with severe COVID-19 disease. Results: A total of 3895 articles were identified, and finally, 22 studies comprising 4380 patients were included. Severe disease was more common in males than females (pOR: 1.36, 95% confidence interval [CI]: 1.08–1.70). Clinical features that were associated with significantly higher odds of severe disease were abdominal pain (pOR: 6.58, 95% CI: 1.56–27.67), breathlessness (pOR: 3.94, 95% CI: 2.55–6.07), and hemoptysis (pOR: 3.35, 95% CI: 1.05–10.74). pOR was highest for chronic obstructive pulmonary disease (pOR: 2.92, 95% CI: 1.70–5.02), followed by obesity (pOR: 2.84, 95% CI: 1.19–6.77), malignancy (pOR: 2.38, 95% CI: 1.25–4.52), diabetes (pOR: 2.29, 95% CI: 1.56–3.39), hypertension (pOR: 1.72, 95% CI: 1.23–2.42), cardiovascular disease (pOR: 1.61, 95% CI: 1.31–1.98) and chronic kidney disease (pOR: 1.46, 95% CI: 1.06–2.02), for predicting severe COVID-19. Conclusion: Our analysis describes the association of specific symptoms and comorbidities with severe COVID-19 disease. Knowledge of these clinical determinants will assist the clinicians in the risk-stratification of these patients for better triage and clinical management.

Keywords: Clinical determinants, clinical predictors, COVID-19, meta-analysis, severe disease

Introduction

The novel coronavirus, named as severe acute respiratory syndrome coronavirus 2, was identified in Wuhan, China, in December 2019. The disease caused by the virus, COVID-19, has created havoc all over the world and has been declared pandemic by the World Health Organization (WHO). As of March 21, 2020, 11,183 patients have succumbed to this disease and with the rapid spread of the disease, these numbers might run into millions.[1]

The clinical spectrum of COVID-19 disease is wide, ranging from nonsevere (asymptomatic infection and mild respiratory tract infection) to severe disease (severe pneumonia and critical illness, including multiorgan dysfunction).[2] In a case series of 44,672 confirmed COVID-19 patients, 14% had severe, and 5% had critical disease.[2] However, most of the patients present with fever, dry cough, myalgia and have a favorable prognosis.[2] Older patients and those with comorbidities progress to severe disease and have worse outcomes.[3] With overwhelmed health-care systems and no proven treatment, it is important to identify the patients who could have a high likelihood of progression to severe disease. This will help the concerned physicians to allocate the resources judiciously. The goal of this investigation was to identify the clinical determinants which are associated with severe COVID-19 disease.

Materials and Methods

Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Review and
Meta-analysis (PRISMA). Databases including PubMed, Embase, and Web of Science were searched from December 31, 2019, to May 24, 2020. There were no restrictions in terms of country, publication language or publication date. Reference lists of all relevant articles and “related citation” search tool of PubMed were checked for any additional publications. The detailed search criteria used are available in Supplement.

**Selection criteria**

Study selection was performed by two independent investigators (A. S. and P. A.). We included studies that focused on individual symptoms and comorbidities of laboratory-confirmed COVID-19 patients and reported the data according to disease severity or ICU admission. Case reports, duplicate publications, reviews, editorials, letters, and family-based studies, studies with insufficient data on symptoms/comorbidities on admission in either severe or non-severe disease groups, and studies reporting exclusively on pediatric (<18 years age) or pregnant populations were excluded. Discrepancies between the reviewers were resolved in the presence of a third reviewer (J. N.).

**Data abstraction and quality assessment**

Data collected included: study characteristics – authors, publication date, study design, country, sample size; patient’s characteristics – median age with interquartile range, sex (% men); criteria for severe disease; total number of severe and non-severe patients; and clinical characteristics (clinical features and comorbidities) at admission – overall prevalence and prevalence among severe and non-severe patients. One reviewer extracted the data (A. S.) and second reviewer (S. S) verified the data independently. The methodological quality of the study was assessed with the Appraisal tool for Cross-Sectional Studies (AXIS) tool. Two authors (S. S, A. S.) performed the quality assessment separately, and disagreements were resolved by consensus in the presence of a third reviewer (P. A.). In the AXIS tool, for every correct answer, score of one was assigned to each of the twenty questions.

**Quantitative data synthesis**

Patient numbers were extracted across all the included studies for each group (severe and non-severe) according to the individual symptoms and comorbidities. The odds ratio (OR, 95% confidence intervals [CIs]) of individual clinical characteristics was used to describe their association with severe COVID-19 disease. These ORs were further pooled using random-effects meta-analysis. To assess the heterogeneity among studies, inconsistency statistics ($I^2$) were calculated. $I^2 > 50\%$ was considered as significant heterogeneity. Publication bias was visually analyzed from Funnel plots and Egger’s regression was also performed. $P$ value for Egger’s regression coefficient < 0.05 was considered as significant publication bias. All data were collected in Microsoft Excel Spreadsheet (MS Office – 2018). Random-effects analysis, generation of forest plot, assessment of heterogeneity, and publication bias were performed with the METAN platform for STATA (version-14.2), StataCorp, College Station, TX.

As the study design was a systematic review and meta-analysis, Institute Ethics Committee approval was not sought.

**Results**

**Search results and study characteristics**

The literature search flow diagram is summarized in PRISMA format [Figure 1]. Using our search criteria (available in supplement), we identified 3895 studies, of which 3645 were from PubMed, 50 were from EMBASE, and 200 were from Web of Science. A total of 209 records were screened after the removal of duplicates. A total of 87 full-text articles were assessed for eligibility and 65 articles were excluded due to various reasons, as shown in Figure 1. Finally, 22 studies were included in this meta-analysis.

**Characteristics of included studies**

A total of 22 studies, consisting of 4380 patients, were selected for this meta-analysis [Table 1]. Studies were published recently between January 24, 2020 and May 24, 2020. Individual study population size ranged between 12 and 1494 patients. Fifty-six percent of the study population were males. Median age of the patients in severe disease cohort varied from 45.2 to 67 years, whereas median age in non-severe disease cohort varied from 37 to 68.5 years. Individual symptoms studied were cough,[5-20] expectoration,[5-7,9,10,14,18,19,21] fever,[5-21] breathlessness,[5-11,13-21] hemoptysis,[5-6] sore throat,[5-7,9,10,15,16,18,21] fatigue,[5-6,9-11,13,14,16-18] myalgia,[5-7,9,10,12,16,18,19,21] headache,[5-10,12,16,18,21] nausea/vomiting,[5-9,11,12,16,18,21] diarrhea,[5-7,9,11,12,15-18,21] abdominal pain,[9-11] anorexia,[9,11] and anosmia.[16,18] The various comorbidities studied were chronic obstructive pulmonary disease (COPD)[5-7,9,11,12,16,18,21,26] diabetes[5-10,15,16,7,9,31-14,16-19,21-26] obesity[16,18,22] hypertension,[5-7,9,11-14,16-19,21-23,26] cardiovascular disease (CVD),[5-7,9,11-14,16-19,21,22,24,25] cerebrovascular accidents[5-9,11,16,18,19,21,24] chronic kidney disease (CKD)[5-9,11,12,16,18,21,24-26] chronic liver disease[6,9,11,19,21,24] malignancy,[5-6,9,16,17,19,21,23,26] and immunocompromised state.[5,18,24] Majority of the studies (13) were from China,[5-14,22,23,26] however, three studies were from the United States,[16,18,24] two from Italy[17,21] and one each from Singapore,[15] Norway,[20] South Korea[19] and Israel.[22] Each study was retrospective observational in design. The number of clinical characteristics including comorbidities reported in each study, varied from 3 in one study[20] to 21 in another study.[5]

Patients with severe disease were older compared to those with non-severe disease (59.8 years vs. 50.8 years, $P = 0.008$). According to the WHO-China joint mission,[23] severe disease was defined as tachypnea (> 30 breaths/min) or oxygen saturation ≤ 93% at rest, or ratio of arterial oxygen saturation and fraction of inspired oxygen < 300 mmHg, and critical disease was defined as respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires intensive care. Severe/critical disease were considered “Severe” in most of the studies.[5,7,8,10,12,16,25] Intensive care unit (ICU)
admission was considered as “Severe/critical disease” in six studies. Results of quality assessment of the included studies are summarized as AXIS scores in Table 1. Overall quality of studies was good, with thirteen out of twenty-two studies having scores above average (score ≥ 15).

Quantitative data synthesis results
ORs of severe disease were pooled for each of the individual symptoms and comorbidities. Forest plots of pOR and funnel plots for each of the clinical determinants are depicted in Supplementary Figures S1-S50. Table 2 and Figure 2 summarizes the pOR for each clinical determinant (clinical feature at admission and comorbidities). Severe disease was more common in males than females (pOR: 1.36, 95% CI: 1.08–1.70). Clinical features associated with significantly higher odds of disease severity were abdominal pain (pOR: 6.58, 95% CI: 1.56–27.67) and breathlessness (pOR: 3.94, 95% CI: 2.55–6.07). Fever (pOR: 1.48, 95% CI: 1.19–1.85) and hemoptysis (pOR: 3.35, 95% CI: 1.05–10.74) were also associated with severe disease, although their lower confidence levels were approaching near one. Patients with comorbidities were also at higher odds of presenting with severe COVID-19 disease. pOR was highest for COPD (pOR: 2.92, 95% CI: 1.70–5.02), followed by obesity (pOR: 2.84, 95% CI: 1.19–6.77), malignancy (pOR: 2.38, 95% CI: 1.25–4.52), diabetes (pOR: 2.29, 95% CI: 1.56–3.39), hypertension (pOR: 1.72, 95% CI: 1.23–2.42), CVD (pOR: 1.61, 95% CI: 1.31–1.98) and CKD (pOR: 1.46, 95% CI: 1.06–2.02). With the exception of the studies considered for breathlessness, nausea/vomiting, anorexia, and diabetes, none of the studies included in the meta-analysis for comorbidities had statistical heterogeneity ($I^2 < 50\%$). Funnel plot analyses [Supplementary Figures: S1-S50] and Egger’s regression [Table 2] demonstrated the evidence of publication bias in the meta-analysis of studies focussing on fever, COPD and CVD.

Discussion
COVID-19 is a rapidly progressing pandemic affecting millions of people worldwide. With the surge of cases, it is expected to overwhelm health-care systems, thereby making it important for physicians to identify clinical characteristics that could point toward progression-to-severe illness. In our meta-analysis of 4380 patients, we found that patients presenting with complaints of breathlessness, hemoptysis and/or abdominal pain, and comorbidities had significantly higher odds of having severe disease.

Multiple studies have shown that patients with breathlessness on arrival had a higher likelihood development of acute respiratory distress syndrome and ICU requirements. In studies conducted by Guan et al. and Huang et al., the incidence of hemoptysis was higher among patients with severe disease as compared to that of non-severe disease, although its proportion was lower in both the study groups. In a study by Zhang et al., few COVID-19 patients presented with atypical abdominal pain and were initially admitted to the surgical ward but subsequently required ICU. These patients were presumed to infect others during their hospital stay, and the newly infected patients also had abdominal pain at presentation. Hence, some authors have suggested the gastrointestinal tract as an alternative route for viral transmission. Hence, it is
# Table 1: Characteristics of the included studies

| Author          | Publication date | Country       | Sample size | Age (median, IQR) | Male (%) | Clinical characteristics included | Definition of severity | Quality of study (score out of 20)** |
|-----------------|------------------|---------------|-------------|-------------------|----------|-----------------------------------|-----------------------|-----------------------------------|
| Huang C         | January 24, 2020 | China         | 41          | 49 (41-61)        | 85       | a, b, c, d, e, g, i, n, o, p, q, t, v | Requiring ICU care    | 16                                |
| Wang D          | February 07, 2020| China         | 138         | 66 (57-78)        | 61.1     | a, b, c, d, f, g, h, t, t, v       | Requiring ICU care    | 16                                |
| Liu Y           | February 09, 2020| China         | 12          | 64                | 50       | a, c, h, i, j, k, n, o, p, q, s    | Severe and critical disease | 12                                |
| Zhang J         | February 18, 2020| China         | 140         | 64 (25-87)        | 56.9     | a, c, d, g, j, k, l, m, n-t        | Severe and critical disease | 15                                |
| Xu Y            | February 21, 2020| China         | 50          | NA                | 54       | a, b, c, d, f, g, h, i             | Severe and critical disease | 14                                |
| Tian S          | February 27, 2020| China         | 262         | 61.4 (1-94)       | 56.5     | a, c, d, i                         | Severe and critical disease | 16                                |
| Guan W          | February 28, 2020| China         | 1099        | 52 (40-65)        | 57.8     | a - s, v, w                        | Severe and critical disease | 16                                |
| Liu F           | February 28, 2020| China         | 78          | 66 (51-70)        | 63.6     | n, o, p, v                         | Clinical deterioration to severe or critical disease or death | 16                                |
| Li K            | February 29, 2020| China         | 83          | 53.7 (12.3)       | 60       | a, b, c, d, f, h, i, k, n, o, p, q | Severe and critical disease | 16                                |
| Yudong P        | March 02, 2020   | China         | 112         | 57.5 (54-63)      | 56.25    | a, c, d, g, o, p, q                | Critical disease       | 15                                |
| Young B         | March 03, 2020   | Singapore     | 18          | 56 (47-73)        | 33       | a, c, d, f, k                      | Requiring supplemental oxygen | 12                                |
| Wu C            | March 13, 2020   | China         | 201         | 58.5 (50-69)      | 71.4     | a, b, c, d, g, o, p, q             | Acute respiratory distress syndrome | 17                                |
| Gao Y           | March 17, 2020   | China         | 43          | 45.2 (7.68)       | 60       | n, o, p, q, u                      | Not clear              | 14                                |
| Chow N (CDC US) | March 31, 2020   | US            | 1494        | NA                | 60       | n, o, q, r, s, t, w                | Requiring ICU care     | 15                                |
| Ihle-hansen H   | April 10, 2020   | Norway        | 42          | 71.8              | 33       | a, c, d                            | Requiring ICU care     | 17                                |
| Colaneri M      | April 23, 2020   | Italy         | 44          | 76.5              | 10       | a, c, d, g, k, n-q, v              | Requirement for highflow oxygen | 17                                |
| Hong K          | April 24, 2020   | South Korea   | 98          | NA                | 46.2     | a-d, h, n-r, t, v                  | Requiring ICU care     | 16                                |
| Aggarwal S      | April 29, 2020   | US            | 16          | 67 (38-70)        | 63       | a-b, d, F-k, X, n-s, u, v          | Critical disease       | 14                                |
| Zhao X          | April 29, 2020   | China         | 91          | NA                | 46.7     | n-q, s, v                          | Not clear              | 15                                |
| Lagi F          | April 30, 2020   | Italy         | 84          | 67 (58-71)        | 87.5     | a-d, f, h-k, n-t, v                | Requiring ICU care     | 18                                |
| Itelman E       | May 01, 2020     | Israel        | 162         | NA                | 80.8     | n-q, s                            | Requiring ICU care     | 17                                |
| Ferguson J      | May 14, 2020     | US            | 72          | 57.6 (42.2-70.1)  | 61.9     | a-d, f-k, X, n-s, u, w             | Requiring ICU care     | 19                                |

*Clinical characteristics: Clinical symptoms - a: Cough, b: Expectoration, c: Fever, d: Dyspnea, e: Hemoptyis, f: Sore throat, g: Fatigue, h: Myalgia, i: Headache, j: Nausea or vomiting, k: Diarrhea, l: Abdominal pain, m: Anorexia, n: Chronic obstructive pulmonary disease, o: Diabetes, p: Hypertension, q: Cardiovascular diseases, r: Cerebrovascular accidents, s: Chronic kidney disease, t: Chronic liver disease, u: Obesity, v: Malignancy, w: Immune deficiency, x: Anosmia. **Severe disease (any of the following conditions): I. respiratory distress, RR ≥30 breaths/min; II. oxygen saturation ≥93% at rest; III. $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (1 mmHg=0.133 kPa); AND critical disease (any of the following conditions): I. respiratory failure and a requirement for mechanical ventilation; II. shock; III. concomitant failure of other organs and requirement for ICU monitoring and treatment[7]. **Scores for each study in AXIS tool: RR: Respiratory rate, $\text{PaO}_2/\text{FiO}_2$: Partial pressure of oxygen/fraction of inspired oxygen, ICU: Intensive care unit, AXIS: Appraisal tool for Cross-Sectional Studies, IQR: Interquartile range, NA: Not available
necessity to not miss abdominal pain as a rare but important predictor of severe disease. Therefore, any patient presenting with SARI with suspicion of COVID-19 and complaints of breathlessness, hemoptysis and/or abdominal pain should be admitted and evaluated further before deciding further course of treatment. These symptoms, along with fever and cough, might act as warning signs of severe disease.

In most of the included studies, the patients in the severe group had a higher median age when compared to the non-severe group, which was consistent with previous reports.\(^{[14,23]}\) Our meta-analysis showed that patients with COPD had the highest risk of the development of severe disease, followed by obesity, malignancy, diabetes, hypertension, CVD, and CKD. A previous meta-analysis of eight studies had shown CVD, respiratory illness, and hypertension as significant predictors of severe disease.\(^{[28]}\) The study differs in terms of the inclusion of a greater number of studies and comorbidities. A weaker immune system might explain the higher likelihood of the development of severe disease among older patients with comorbidities.

There are certain limitations of this meta-analysis. The studies included are retrospective in nature with considerable heterogeneity. Further, 13 out of 22 of the studies are from a single country. The criteria of severe disease were also not similar across all the included studies, thereby limiting the strength of our observations. We have also not included the studies exclusively reporting predictors of mortality in COVID-19 patients. Finally, it is possible that newer studies might have been published between the completion of this literature review and its publication.

### Table 2: Summary of meta-analyses for each of the clinical symptoms and comorbidities that are associated with severe COVID-19 infection

| Clinical characteristics | Odds ratio | Lower CL | Upper CL | Number of studies | Total patients included in meta-analysis (n/N) | Prevalence of characteristics in severe disease (n/N) | Prevalence of characteristics in mild disease (n'/N') | P (%) | Publication bias (Egger's P value) |
|--------------------------|------------|----------|----------|-------------------|-----------------------------------------------|-----------------------------------------------------|-----------------------------------------------|-------|-------------------------------|
| Demographic characteristics |            |          |          |                   |                                               |                                                     |                                               |       |                               |
| Male gender              | 1.36       | 1.08     | 1.70     | 20                | 2844                                          |                                                     |                                               | 13.4  | 0.16                          |
| Clinical characteristics |            |          |          |                   |                                               |                                                     |                                               |       |                               |
| Cough                    | 1.24       | 0.98     | 1.56     | 17                | 2512                                          | 392/560                                             | 1242/1952                                     | 5.0   | 0.26                          |
| Expectoration            | 1.15       | 0.73     | 1.82     | 9                 | 1866                                          | 132/394                                             | 454/1472                                     | 47.8  | 0.65                          |
| Fever                    | 1.48       | 1.19     | 1.85     | 17                | 2512                                          | 369/560                                             | 1055/1952                                     | 0.0   | 0.03                          |
| Dyspnea                  | 3.94       | 2.55     | 6.07     | 16                | 2500                                          | 251/554                                             | 339/1946                                     | 56.1  | 0.12                          |
| Hemoptysis               | 3.35       | 1.05     | 10.74    | 2                 | 1140                                          | 5/186                                               | 7/954                                        | 0.0   | NA                            |
| Sore throat              | 1.39       | 0.77     | 2.49     | 8                 | 1560                                          | 47/298                                              | 168/1262                                     | 29.6  | 0.79                          |
| Fatigue                  | 1.22       | 0.83     | 1.81     | 10                | 1913                                          | 196/439                                             | 607/1474                                     | 41.6  | 0.23                          |
| Myalgia                  | 1.25       | 0.87     | 1.79     | 9                 | 1652                                          | 73/311                                              | 249/1341                                     | 8.0   | 0.34                          |
| Headache                 | 1.15       | 0.80     | 1.64     | 9                 | 1857                                          | 44/357                                              | 174/1500                                     | 0.0   | 0.89                          |
| Nausea/vomiting          | 0.68       | 0.30     | 1.51     | 7                 | 1561                                          | 29/318                                              | 104/1243                                     | 55.6  | 0.31                          |
| Diarrhea                 | 1.43       | 0.93     | 2.21     | 10                | 1706                                          | 36/366                                              | 88/1340                                     | 0.0   | 0.74                          |
| Abdominal pain           | 6.58       | 1.56     | 27.67    | 2                 | 278                                           | 9/94                                                | 2/184                                       | 0.0   | NA                            |
| Anorexia                 | 2.54       | 0.74     | 8.70     | 2                 | 278                                           | 32/94                                               | 40/184                                      | 72.3  | NA                            |
| Anosmia                  | 0.61       | 0.11     | 3.48     | 2                 | 88                                            | 2/29                                                | 5/59                                        | 0.0   | NA                            |
| Comorbid illness         |            |          |          |                   |                                               |                                                     |                                               |       |                               |
| Chronic obstructive pulmonary disease | 2.92       | 1.70     | 5.02     | 16                | 3695                                          | 124/925                                             | 177/2770                                    | 23.3  | <0.01                         |
| Diabetes                 | 2.29       | 1.56     | 3.39     | 18                | 4008                                          | 258/1025                                            | 413/2983                                    | 50.5  | 0.08                          |
| Obesity                  | 2.84       | 1.19     | 6.77     | 3                 | 131                                           | 18/44                                               | 18/87                                       | 0.0   | 0.43                          |
| Hypertension             | 1.72       | 1.23     | 2.42     | 17                | 2514                                          | 182/568                                             | 412/1946                                    | 41.6  | 0.41                          |
| Cardiovascular disease   | 1.61       | 1.31     | 1.98     | 16                | 3839                                          | 199/984                                             | 372/2855                                    | 0.0   | 0.01                          |
| Cerebrovascular accidents | 1.68       | 0.73     | 3.84     | 8                 | 3141                                          | 21/782                                              | 44/2359                                     | 32.1  | 0.45                          |
| Chronic kidney disease   | 1.46       | 1.06     | 2.02     | 10                | 3308                                          | 70/831                                              | 112/2477                                    | 0.0   | 0.16                          |
| Chronic liver disease    | 1.55       | 0.75     | 3.18     | 6                 | 1995                                          | 12/593                                             | 20/1402                                    | 0.0   | 0.90                          |
| Malignancy               | 2.38       | 1.25     | 4.52     | 9                 | 1689                                          | 19/317                                             | 29/1372                                    | 0.0   | 0.81                          |
| Immuno-compromised state | 1.46       | 0.98     | 2.17     | 3                 | 2665                                          | 42/651                                             | 70/2014                                    | 0.0   | 0.33                          |

CL: Confidence limits, n: Number of patients with the clinical determinant among patients with severe disease, N: Total number of patients with severe disease, n': Number of patients with the clinical determinant among patients with mild disease, N': Total number of patients with severe disease, F: Heterogeneity statistics, Egger’s P<0.05: Publication bias present.
were also significant risk factors for severe disease, which is in line with previous studies. Knowledge of these clinical determinants will assist the clinicians in the risk-stratification of the patients for better triage and clinical management.

What is already known on the subject
- Patients with COVID-19 present with a wide spectrum of clinical manifestations, i.e., asymptomatic, mild upper respiratory tract symptoms, severe disease, and critical disease
- It is difficult to predict the disease progression early in the course of illness
- Multiple laboratory parameters, comorbid illness, and advanced age have been shown to predict the disease prognosis.

Study’s main messages
- This updated meta-analysis consisted of 22 studies comprising 4380 patients
- Severe disease was more common in males than females
- Clinical features that were associated with significantly higher odds of severe disease were abdominal pain, breathlessness, and hemoptysis
- pOR was highest for chronic obstructive pulmonary disease, followed by obesity, malignancy, diabetes, hypertension, CVD, and CKD, for predicting severe COVID-19
- Knowledge of these clinical determinants will help the clinician to triage and manage the patients carefully, and appropriately allocate the resources in this resource-constraining pandemic.

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Conflicts of interest
There are no conflicts of interest.

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| Study |
|-------|
| ID    |
| Events |
| Events |
| %     |
| OR (95% CI) |
| Treatment |
| Control |
| Weight |
| Qian W | 3.36 (2.27, 4.34) | 50 (73) | 140 (26) | 13.50 |
| Huang C | 21.60 (2.44, 191.32) | 192 | 1528 | 3.11 |
| Li K | 16.88 (2.07, 72.20) | 25 | 158 | 4.68 |
| Tyan S | 34.35 (6.40, 128.33) | 124 | 3215 | 6.34 |
| Wang G | 7.25 (3.14, 16.76) | 2536 | 20102 | 9.45 |
| Xu Y | 35.02 (1.76, 71.78) | 737 | 1.62 |
| Zheng | 2.19 (1.05, 4.52) | 2445 | 2582 | 10.26 |
| Yudong P | 1.98 (0.48, 8.49) | 358 | 1588 | 5.71 |
| Wu C | 4.26 (2.34, 7.78) | 1064 | 30117 | 11.40 |
| Young C | 2.20 (0.11, 0.73) | 14 | 112 | 1.86 |
| Appavu P | 2.39 (0.37, 2.02) | 19 | 61 | 2.28 |
| Colerant M | 1.08 (0.25, 4.35) | 417 | 627 | 5.59 |
| Ferguson J | 1.01 (0.84, 1.20) | 1221 | 2561 | 6.53 |
| Hong R | 4.07 (1.21, 13.86) | 913 | 2462 | 6.62 |
| Ilie-hanes I | 12.51 (1.67, 233.39) | 2033 | 1.91 |
| Log F | 2.16 (0.75, 6.06) | 716 | 1865 | 7.36 |
| Overall (I-squared = 96.1%, p = 0.022) | 3.94 (2.25, 6.97) | 355169 | 539646 | 102.35 |

NOTE: Weights are from random effects analysis.

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**Figure S8:** Forest plot of odds ratio for dyspnea as a predictor of disease severity

**Figure S10:** Funnel plot of odds ratio for hemoptysis as a predictor of disease severity

**Figure S12:** Funnel plot of odds ratio for sore throat as a predictor of disease severity
Figure S13: Forest plot of odds ratio for fatigue as a predictor of disease severity

Figure S14: Funnel plot of odds ratio for fatigue as a predictor of disease severity

Figure S15: Forest plot of odds ratio for myalgia as a predictor of disease severity

Figure S16: Funnel plot of odds ratio for myalgia as a predictor of disease severity

Figure S17: Forest plot of odds ratio for headache as a predictor of disease severity

Figure S18: Funnel plot of odds ratio for headache as a predictor of disease severity
Figure S19: Forest plot of odds ratio for nausea/vomiting as a predictor of disease severity

Figure S20: Funnel plot of odds ratio for nausea/vomiting as a predictor of disease severity

Figure S21: Forest plot of odds ratio for diarrhea as a predictor of disease severity

Figure S22: Funnel plot of odds ratio for diarrhea as a predictor of disease severity

Figure S23: Forest plot of odds ratio for abdominal pain as a predictor of disease severity

Figure S24: Funnel plot of odds ratio for abdominal pain as a predictor of disease severity
Figure S25: Forest plot of odds ratio for anorexia as a predictor of disease severity

Figure S26: Funnel plot of odds ratio for anorexia as a predictor of disease severity

Figure S27: Forest plot of odds ratio for anosmia as a predictor of disease severity

Figure S28: Funnel plot of odds ratio for anosmia as a predictor of disease severity

Figure S29: Forest plot of odds ratio for COPD as a predictor of disease severity

Figure S30: Funnel plot of odds ratio for COPD as a predictor of disease severity
**Figure S31:** Forest plot of odds ratio for diabetes as a predictor of disease severity

**Figure S32:** Funnel plot of odds ratio for diabetes as a predictor of disease severity

**Figure S33:** Forest plot of odds ratio for obesity as a predictor of disease severity

**Figure S34:** Funnel plot of odds ratio for obesity as a predictor of disease severity

**Figure S35:** Forest plot of odds ratio for hypertension as a predictor of disease severity

**Figure S36:** Funnel plot of odds ratio for hypertension as a predictor of disease severity
**Figure S37:** Forest plot of odds ratio for cardiovascular diseases as a predictor of disease severity

| Study | Events | Events | ID | OR (95% CI) | Treatment | Control | Weight |
|-------|--------|--------|----|-------------|-----------|---------|--------|
| Quan W | 3.28 (1.49, 7.26) | 10/73 | 1/102 | 0.93 |
| Huang C | 2.30 (0.43, 1.44) | 3/13 | 3/3 | 1.36 |
| Li K | 7.14 (0.38, 162.99) | 598 | 4.60 | 0.40 |
| Wang D | 2.74 (1.53, 4.90) | 10/30 | 10/52 | 0.39 |
| Zhang | 2.35 (0.61, 9.39) | 6/6 | 4/2 | 2.44 |
| Gao Y | 5.93 (0.08, 41.42) | 1/15 | 1/102 | 0.68 |
| Liu Y | 8.69 (0.34, 72.71) | 3/16 | 3/16 | 0.59 |
| Yudong P | 1.41 (0.47, 4.19) | 10/16 | 10/16 | 3.55 |
| Wu C | 2.41 (0.56, 10.53) | 3/9 | 3/9 | 1.58 |
| Agarwal S | 2.33 (0.17, 32.68) | 1/10 | 1/10 | 0.81 |
| Chown H (ESCUR) | 1.33 (0.84, 2.07) | 133/169 | 133/169 | 3.02 |
| Colombari M | 2.40 (0.93, 6.34) | 6/17 | 6/17 | 2.18 |
| Ferguson J | 5.87 (0.57, 54.43) | 3/21 | 3/21 | 1.42 |
| Hong K | 2.64 (0.87, 8.12) | 4/13 | 4/13 | 0.93 |
| Bollman E | 2.91 (0.81, 10.49) | 4/28 | 4/28 | 2.90 |
| Log F | 3.96 (0.29, 54.92) | 14/172 | 14/172 | 2.43 |

**NOTE:** Weights are from random effects analysis.

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**Figure S38:** Funnel plot of odds ratio for cardiovascular diseases as a predictor of disease severity

**Figure S39:** Forest plot of odds ratio for cerebrovascular accidents as a predictor of disease severity

| Study | Events | Events | ID | OR (95% CI) | Treatment | Control | Weight |
|-------|--------|--------|----|-------------|-----------|---------|--------|
| Quan W | 27.01 (12.90, 59.90) | 3/173 | 1/173 | 1.12 |
| Wang D | 2.94 (0.48, 16.69) | 20/26 | 20/26 | 2.09 |
| Zhang | 7.72 (0.36, 16.94) | 309 | 309 | 1.11 |
| Liu Y | 1.39 (0.43, 4.64) | 18 | 18 | 1.12 |
| Agarwal S | 1.38 (0.43, 4.66) | 3/21 | 3/21 | 2.09 |
| Chown H (ESCUR) | 1.33 (0.17, 32.68) | 133/169 | 133/169 | 3.02 |
| Gregorio L | 0.48 (0.13, 1.74) | 54/210 | 54/210 | 0.30 |
| Hashem E | 3.46 (0.03, 33.32) | 126 | 126 | 1.23 |
| Log F | 3.96 (0.29, 54.92) | 14/172 | 14/172 | 2.43 |
| Zhou H | 2.96 (0.48, 16.94) | 18 | 18 | 1.12 |

**NOTE:** Weights are from random effects analysis.

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**Figure S40:** Funnel plot of odds ratio for cerebrovascular accidents as a predictor of disease severity

**Figure S41:** Forest plot of odds ratio for CKD as a predictor of disease severity

**Figure S42:** Funnel plot of odds ratio for CKD as a predictor of disease severity
**Figure S43**: Forest plot of odds ratio for chronic liver disease as a predictor of disease severity

**Figure S44**: Funnel plot of odds ratio for chronic liver disease as a predictor of disease severity

**Figure S45**: Forest plot of odds ratio for malignancy as a predictor of disease severity

**Figure S46**: Funnel plot of odds ratio for chronic liver disease as a predictor of disease severity

**Figure S47**: Forest plot of odds ratio for immunocompromised state as a predictor of disease severity

**Figure S48**: Funnel plot of odds ratio for immunocompromised state as a predictor of disease severity
Figure S49: Forest plot of odds ratio of gender for disease severity

| Study   | Events | Events | % Treatment | Control | OR (95% CI) | Weight |
|---------|--------|--------|-------------|---------|-------------|--------|
| Guan Y  | 0.98   | 0.70   | 1.309/0.173 | 54/952  | 21.93       |        |
| Huang C | 2.61   | 4.47   | 14.385/13   | 19/28   | 1.08        |        |
| Li X    | 1.70   | 3.06   | 3.65/15.25  | 28/58   | 4.08        |        |
| Tian S  | 1.48   | 0.78   | 2.813/0.46  | 101/128 | 0.34        |        |
| Wang D  | 1.45   | 0.67   | 3.13/2236   | 53/102  | 0.31        |        |
| Xu Y    | 0.70   | 0.22   | 2.95/0.12   | 22/37   | 0.47        |        |
| Zhang   | 1.53   | 0.78   | 3.013/0.58  | 38/53   | 5.29        |        |
| Gao Y   | 0.37   | 0.27   | 3.098/1.11  | 11/38   | 2.83        |        |
| Liu Y   | 1.91   | 0.51   | 1.95/1.11   | 32/87   | 2.69        |        |
| Liu Y   | 0.30   | 0.61   | 2.91/0.35   | 5/6     | 0.69        |        |
| Yu Long | 1.52   | 0.55   | 4.15/0.16   | 44/98   | 5.97        |        |
| Wu C    | 1.96   | 0.66   | 3.28/0.84   | 69/117  | 10.35       |        |
| Young B | 0.36   | 0.65   | 2.77/0.5    | 7/12    | 1.16        |        |
| Co Ier M | 3.60 | 0.87 | 15.89/0.17 | 15/27 | 2.96 |        |
| Hong X  | 1.42   | 0.44   | 4.65/0.13   | 33/85   | 3.32        |        |
| Aggarwal | 0.24 | 0.62 | 2.01/0.34 | 7/8 | 0.76 |        |
| Zhao X  | 0.65   | 0.37   | 1.05/0.13   | 35/61   | 5.68        |        |
| Li J et al | 0.65 | 0.37 | 1.05/0.13 | 35/61 | 5.68 |        |
| Jin J   | 3.95   | 1.37   | 10.78/0.26  | 71/136  | 4.21        |        |
| Ferguson | 1.99   | 0.40   | 4.77/0.21   | 29/51   | 4.17        |        |
| Overall  | 1.96   | 0.66   | 1.703/0.88  | 131/211 | 108.30      |        |

NOTE: Weights are from random effects analysis

Figure S50: Funnel plot of odds ratio of gender for disease severity