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Review

The Severity of COVID-19 and Its Determinants: A Systematic Review and Meta-Analysis in China

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Abstract: To analyse the prevalence of severe and critical COVID-19 cases and its determinants, a systematic review and meta-analysis were conducted using Review Manager. Four English and two Chinese databases were used to identify and explore the relationships between the severity of COVID-19 and its determinants, with no restrictions on publication date. The odds ratio and 95% CI were combined to assess the influencing level of all factors. Twenty-three articles containing a total of 15,828 cases of COVID-19 were included in this systematic review. The prevalence of severe and critical COVID-19 cases was 17.84% and 4.9%, respectively. A total of 148 factors were identified, which included behavioural, symptom, comorbidity, laboratory, radiographic, exposure, and other factors. Among them, 35 factors could be included in the meta-analysis. Specifically, for example, the male (OR 1.55, 95% CI 1.42–1.69) and elderly (OR 1.06, 95% CI 1.03–1.10) populations tended to experience severe and critical illness. Patients with cough, dyspnea, fatigue, fever, and gastrointestinal symptoms could have severe and critical diseases. Regarding laboratory results, albumin, aspartate aminotransferase, creatinine, D-dimer, fibrinogen, neutrophils, procalcitonin, platelets, and respiratory rate were potential factors that could be used to predict the severity of COVID.

Keywords: systematic review; COVID-19; severity

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1. Introduction

Coronavirus disease 2019 (COVID-19), initially found in Wuhan, China in December 2019 [1] rapidly developed into a global pandemic. The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with symptoms such as cough, fever, dyspnea, fatigue and other respiratory-tract symptoms. According to COVID-19 data issued by The Johns Hopkins Coronavirus Resource Center (CRC), as of 26 January 2021, there were 99,655.985 confirmed infections and 2138.251 deaths [2]. In China, there were 100,291 confirmed cases and 4814 deaths according to data issued by the National Health Commission of the PRC.

An emergent public-health problem, especially under the circumstance of a completely novel pathogen, is to predict the severity of the disease for each patient. For medical treatment, this issue concerns the reputation of the clinician, the life of the patients, and the therapeutic effects, especially under the conditions of a novel disease and a lack of basic medical resources [3].

Disease prevention is related to crucial policy making. Specifically, the severity of disease in different regions could affect the distribution and redeployment of medical staff, equipment, and financial appropriation during the pandemic. In addition, it could need to be traded off against economic-, social-, and personal-freedom costs, such as wearing masks and maintaining social distancing, shutting down factories and schools, and imposing travel restrictions [3–5]. Above all, knowledge about the severity of COVID-19 affects every aspect of the community. According to the guidelines of the World Health Organisation (WHO) and the National Health Commission of the PRC [6,7], the severity of COVID-19 can be classified into four types on the basis of patients' symptoms, laboratory results, and imaging findings at admission: mild, moderate, severe, and critical [8].

Considering the severity of COVID-19, it is crucial to predict the progression of the illness on the basis of evaluable determinants. Previous studies explored and analysed the association between risk factors and the severity of COVID-19. The risk factors could be divided into several types: individual factors (such as gender [9], age [10], residential location [11], and occupation [11]), symptom factors (such as cough [12] and fever [13]), comorbidity factors (such as cancer [14], diabetes [15], psychiatric disorders [16], nephritis [17], and obesity [18]), laboratory factors [19–21], radiographic factors [22], exposure factors [18], treatment factors [23], environmental factors [24–27], social factors [28], and regional factors [29]. In the Chinese context, many empirical studies were conducted to discuss this association [12,30,31]. Among these studies, most reported clinical characteristics of confirmed COVID-19 cases on the basis of different regions, collecting individual, epidemiological, clinical, laboratory, computed-tomography-imaging, and outcome data. However, there is no systematic review or meta-analysis that summarises all results on the basis of an analytical framework. In addition, there is no comprehensive classification of all determinants. Therefore, on the basis of the above findings, this study aimed to examine the prevalence of severe COVID-19 and its relationship with other risk factors in China by conducting a systematic review and meta-analysis. This meta-analysis could provide a systemic classification of factors of determinants and most comprehensive results of this subject.

2. Materials and Methods

2.1. Literature Search

On the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we conducted a systematic search on 1 January 2021 of four English language databases, namely, PubMed, EMBASE, the Cochrane Library, and the Web of Science, and two Chinese language databases (CNKI and CBM). Studies with different languages and publication dates in these databases were included. The search strategy was based on the following syntax: (#1) ("China" OR "Chinese" (Title/Abstract)) AND (#2) ("COVID-19" OR "coronavirus disease 2019" OR "SARS-CoV-2" (Title/Abstract)) AND (#3) ("severity" OR "progression" OR "critical" (Title/Abstract)) AND (#4) ("determinants" OR "factors" OR "indicators" (Title/Abstract)). The full search strategy can be found in Table S1. Additionally, references of the retrieved papers were reviewed to identify additional relevant studies.

2.2. Study Eligibility

As inclusion criteria, each study had to: (1) be an original study conducted in China; (2) be published in Chinese or English; (3) report the relationship between at least one determinant and the severity of COVID-19; and (4) provide sufficient information that we could extract the OR and 95% CI of the factors from the study. Studies that met one of the following criteria were excluded: (1) having no original data such as reviews, editorials, or communications; (2) sample source or size was not clear; (3) reported insufficient information to allow for the extraction of the OR and 95% CI for the factors; (3) only studied specific populations such as students, older people, medical staff, or migrants; (4) only reported the mortality of COVID-19 and its determinants.

Two investigators conducted eligibility assessment by screening and evaluating the titles, abstracts, and full texts of the studies retrieved by the search strategy according to the above-predetermined selection criteria. Two investigators cross-checked assessments. Disagreements on which studies should be included or excluded in this systematic review were subjected to discussion to achieve a group consensus.

2.3. Data Extraction

Referring to the checklist of items to consider in the data collection issued by the Cochrane Handbook for Systematic Reviews of Interventions, the following data were extracted from the included full-text studies: first author's name, publication year, region, sample size, patient admission status, severity rate (%), and critical rate (%). One author extracted all necessary data, and another author independently reviewed all information. The inter-rater reliability for title screening between the two authors was 95.55%; for abstract screening, it was 93.12%

2.4. Quality Assessment

The Newcastle–Ottawa Quality Assessment Scale [32], recommended by the Cochrane Collaboration [33], was applied to assess the quality of the included articles. The standard assessment scale considers patient selection (representativeness of the sample, sample size, nonrespondents and ascertainment of exposure), comparability of the groups (confounding factors are controlled), and outcomes (assessment of outcomes and statistical tests). The highest score is a 7. A score in the range of 5–7 represents a high-quality study, a score in the range of 3–4 means medium-quality research, and a score in the range of 1–2 indicates a poor-quality study. Only medium- and high-quality studies were included in this review. Two reviewers independently evaluated all studies, with disagreements resolved by discussion.

2.5. Data Synthesis and Statistical Analysis

In this study, two main outcomes were analysed, namely, severe and critical cases of COVID-19. In addition, the relationship between the severity of COVID-19 and various determinants was researched. Only those rick factors mentioned by at least three articles were included for meta-analysis (for example, gender was discussed by 13 papers, so we included gender in meta-analysis, while exercise was discussed by 2 papers, so it was not meta-analysed). The specific determinant-analysis framework could be formed through previous articles (Figure 1) [13,31,34–36]. Additionally, the reported variable values needed to be the same among selected factors to conduct meta-analysis. The risk-factor selection process is shown in Tables S2 and S3.

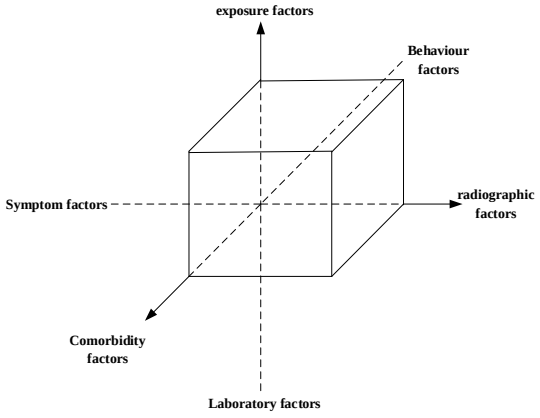

Figure 1. Determinant analysis framework.

In meta-analysis, the odds ratios (ORs) and 95% CIs were combined to assess the influencing level of all factors. Forest plots were drawn to visualise the data-analysis

results and to identify the strength of the relationship. The heterogeneity of the pooled results was determined by Cochrane's Q test and Higgins' I^2 test. Synthesis results with a p value above 1 or an I^2 beyond 50% were considered to be heterogeneous and analysed through a random-effects model. Otherwise, heterogeneity was ignored and analysed with a fixed-effects model.

All statistical analyses were performed by using Stata 13.0 (Stata Corp, College Station, TX, USA) and RevMan 5.3 (The Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Study Characteristics

A total of 2534 records were identified through our initial systematic search of the literature (PubMed: 435, EMBASE: 699, Cochrane: 5, CNKI: 96, Wang Fang: 363, Web of Science: 936). A total of 1986 unique records were screened on the basis of the title and abstract, and 1798 records were excluded after the removal of duplicate studies, leaving 188 articles for full-text assessment. Among these, nine articles were excluded due to a lack of original data. Seven records were eliminated for unclear samples. A total of 107 articles were removed because they did not report the OR and 95% CI of the factors of interest. The reviewers ruled out 12 studies because they targeted only a specific population. Thirty articles were excluded because they only studied the mortality of COVID-19 and its determinants. Ultimately, this study included 23 records. In addition, no other studies were included after checking all references of the retrieved articles. The study-selection process is shown in Figure 2.

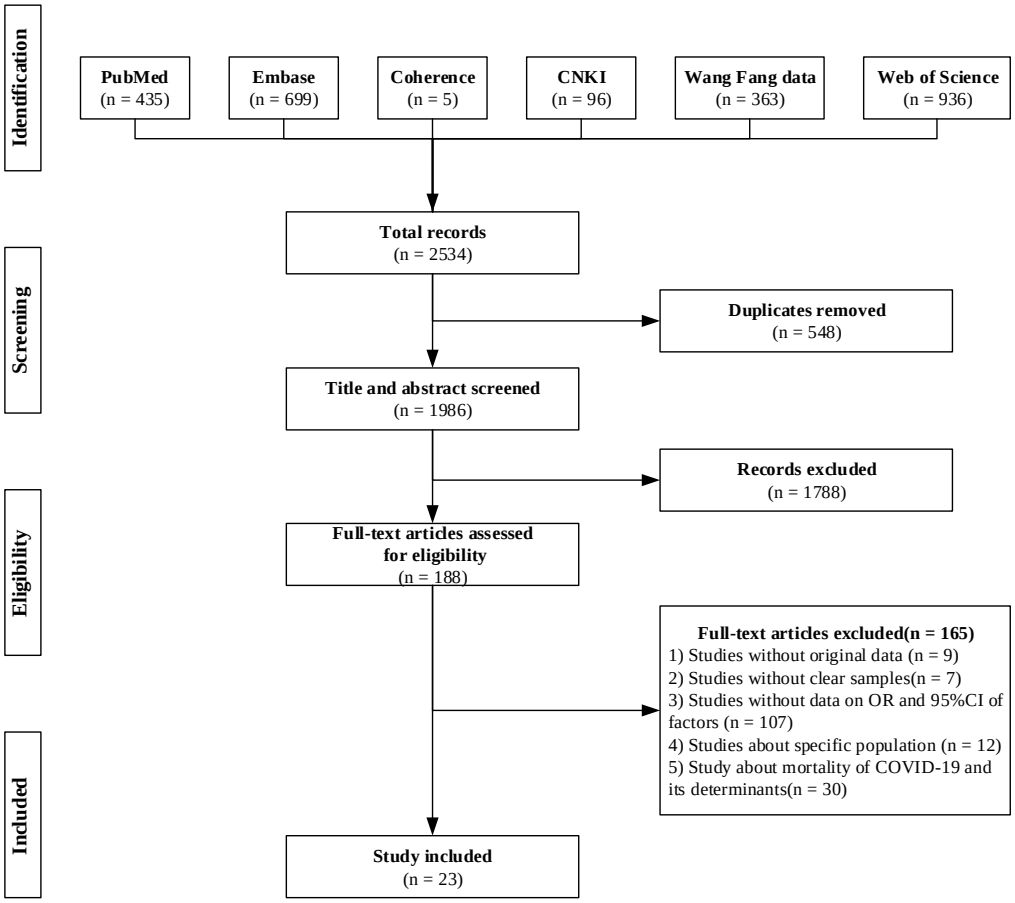

Figure 2. Flow diagram of study selection.

Table 1 presents the main characteristics of all 23 identified studies. These studies were performed in 18 provinces of China in 2020. The included articles contained

15,828 cases with a median sample size of 333 (range 63–7276). Eleven studies were conducted in Wuhan, Hubei, and 17 in other provinces. In addition, the patient admission time of the included research ranged from 12 December 2019 to 2 April 2020. Twenty-one studies reported the prevalence of severe cases or critical cases, while the two other studies used the progression of COVID-19 as their research object.

Table 1. Characteristics of 23 identified studies.

Study	Publication Year	Region	Sample Size	Patient Admission	Severity (%)	Critical (%)
Liu [37]	November 2020	Wuhan	78	2019.12.30–2020.01.15	11 (14.1%)	-
Xu [38]	July 2020	Shanghai\Hubei\Anhui	598	2020.01.01–2020.03.08	85 (14.21)	113 (18.90)
Sun [12]	April 2020	Beijing	63	-	10 (15.9%)	9 (14.3%)
Hu [36]	September 2020	Changsha\Xiangtan	213	2020.01.24–2020.02.16	38 (17.84%)	
Liu [37]	August 2020	Jiangsu	625	2020.01.10–2020.03.15	64 (10.2%)	
Zhang [31]	July 2020	Zhejiang	788	2020.01.17–2020.02.12	61 (7.2%)	17 (2.2%)
Wang [30]	May 2020	Tianjin	131	Before 2020.02.20	22 (16.79%)	-
Zhou [38]	September 2020	Eighteen provinces	7276	2020.01.21–2020.03.02	-	-
Lian [39]	May 2020	Zhejiang	465	2020.01.17–2020.01–31	49 (10.54%)	
Bi [5]	April 2020	Shenzhen	391	2020.01.14–2020.02-12	35 (9%)	-
Hu [40]	August 2020	Hunan	1178	2020.01.16–2020.04.02	119 (11.7%)	31 (3.0%)
Huang [41]	December 2020	Henan\Shandong\Hubei	367	2020.02.10–2020.03.28	46 (12.53%)	-
Cai [42]	July 2020	Shenzhen	383	2020.01.11–2020.03.26	91 (23.8%)	-
Zhou [43]	June 2020	Wuhan	123	2020.01.01–2020.03.31	28 (22.76%)	-
Hu [44]	May 2020	Wuhan	323	2020.01.08–2020.02.20	146 (45.20%)	26 (8.05%)
Cen [45]	June 2020	Wuhan	1007	2020.02.10–2020.03.10	222 (22.05%)	22 (2.18%)
He [46]	August 2020	Guangzhou	288	2020.01.15–2020.03.10	30 (10.4%)	-
Wei [47]	August 2020	Anhui	167	Before 2020.03.20	30 (17.9%)	-
Li [48]	April 2020	Wuhan	548	2020.01.26–2020.02.05	269 (49.1%)	-
Cheng [49]	October 2020	Jiangxi\Hubei\Guangdong	252	2020.01.19–2020.03.06	-	52 (20.6%)
Shao [50]	September 2020	Wuhan\Zhoukou	126	2020.01.23–2020.03.23	36 (28.67%)	-
Gao [51]	November 2020	Wuhan	105	2020.02.10–2020.03.01	-	-
Wang [52]	July 2020	Shenzhen	333	2020.01.10–2020.02.10	70 (21.0%)	-

A total of 148 factors were extracted from 23 identified studies (Table S3). All were divided into seven categories: 28 behavioural factors, 28 symptom factors, 13 comorbidity factors, 56 laboratory factors, 9 radiographic factors, 7 exposure factors, and 7 other factors. According to the modified Newcastle–Ottawa Scale, the quality scores of all included studies are presented in Table S4. None of the identified studies was excluded due to quality issues.

3.2. Severe and Critical Cases of COVID-19

Table 1 shows the percentage of severe and critical cases of COVID-19. On the basis of studies reporting severe cases, 1462 out of 8195 (17.84%) severe cases were found. The highest proportion of severe cases was reported by Li (49.1%), while the lowest was 7.2%. According to research presenting critical cases, the pooled prevalence of critical cases was 4.9% (270/5512). Cheng found the highest percentage of critical cases, 20.6%, whereas 2.18% was the lowest reported. All studies reported ORs and 95% CIs of the factors, and examined their relationship with COVID-19. In addition, among all 148 determinants, 35 factors could be included in meta-analysis.

3.3. Behavioural, Radiographic, and Exposure Factors, and COVID-19 Severity

Among 28 behavioural factors, sex, age, and smoking history could be included in meta-analysis. In this study, the quantitative synthesis of age and gender were presented by two figures according to the different classification of variables ($\leq$65 as reference versus >65; younger age as reference versus younger age) (female as reference versus male; male as reference versus female). In addition, no history of smoking was the reference group. Figure 3 shows that the results of related variables apart from gender, with females as a reference (I^2 = 36%, p = 0.12) showing obvious heterogeneity (I^2 > 50%, p < 0.1). Therefore, random-effects analysis was used; age $\leq$65 as a reference (Z = 4.32, p < 0.0001), younger age as a reference (Z = 3.97, p < 0.0001), and gender with female as a reference

(Z = 9.69, $p < 0.00001$) were associated with the severity of COVID-19. Specifically, the population aged > 65 (OR 3.06, 95% CI 1.84–5.09), the elderly population (OR 1.06, 95% CI 1.03–1.10), and men (OR 1.55, 95% CI 1.42–1.69) showed a higher probability of having severe disease than that of the younger generation and women. In addition, the *p* value of sex with the male group as the reference and a history of smoking were not significant.

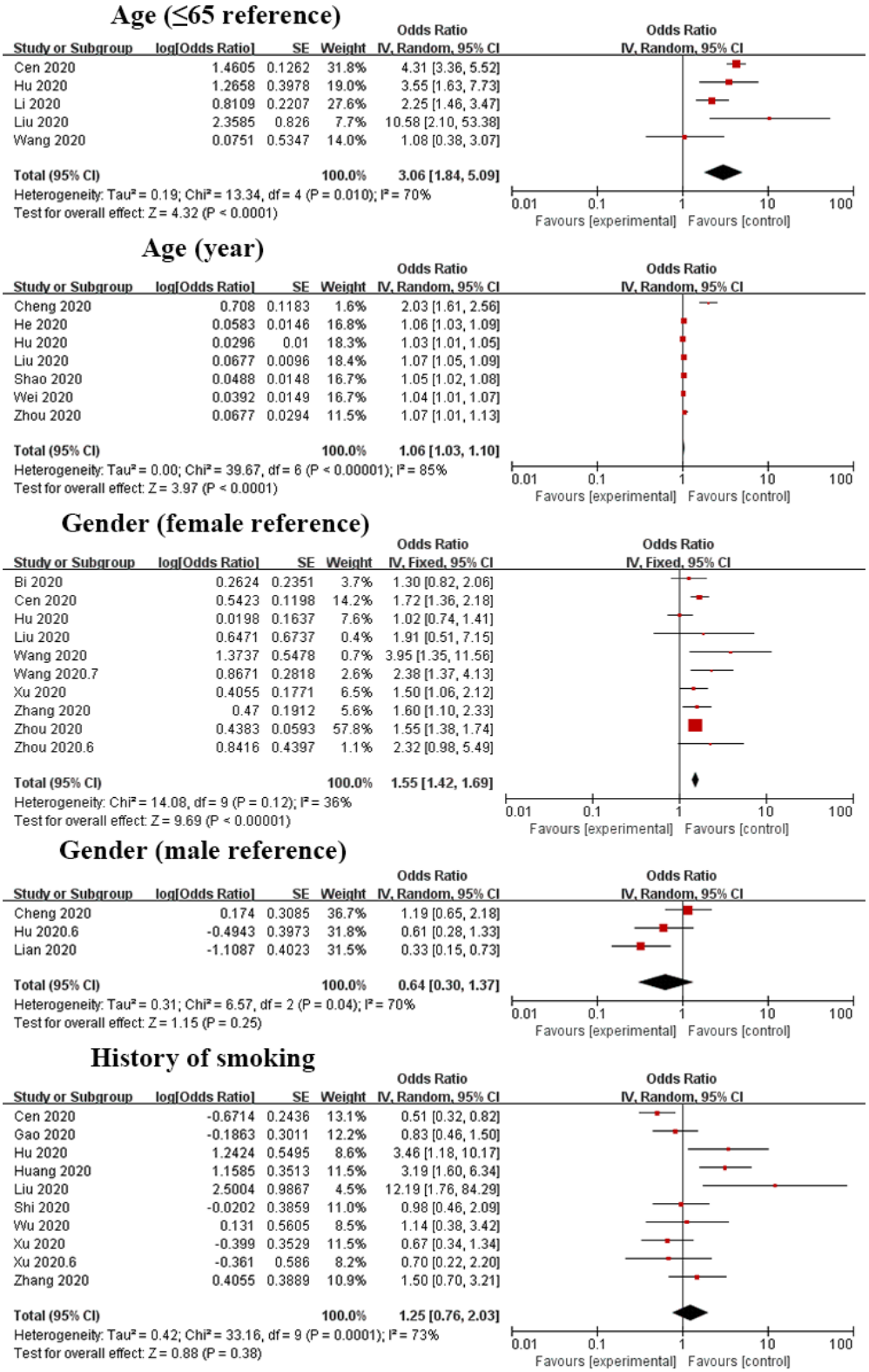

Figure 3. Forest plot of behavioural, radiographic, and exposure factors.

According to Figure 3, among all of these factors, only bilateral lung involvement and exposure history could be included in meta-analysis. Bilateral lung involvement (I^2 = 10%, p = 0.34) was conducted through fixed-effects analysis, and bilateral lung involvement in COVID-19 indicates a more severe disease (OR 1.78, 95% CI 1.29–2.46), while there was no significant relationship between exposure history and the severity of COVID-19.

3.4. Symptom Factors and Severity of COVID-19

Cough, dyspnoea, fatigue, fever, headache, muscle or joint pain, sore throat, and gastrointestinal symptoms could be extracted to conduct meta-analysis of all 28 symptom factors. No particular symptom was the reference group of all variables. As shown in Figure 4, all results of the symptom variables except dyspnoea (I^2 = 0%, p = 0.56), sore throat (I^2 = 44%, p = 0.15), and headache (I^2 = 46%, p = 0.14) had large heterogeneity. Above all, cough (Z = 2.22, p = 0.03), dyspnoea (Z = 10.22, p < 0.00001), fatigue (Z = 2.31, p = 0.02), fever (Z = 2.31, p = 0.02), and gastrointestinal symptoms (Z = 2.95, p = 0.003) had a significant relationship with the severity of COVID-19, while no significant association was found between headache (Z = 0.54, p = 0.59), muscle or joint pain (Z = 1.11, p = 0.27), and sore throat (Z = 0.14, p = 0.89). In other words, patients with a cough (OR 1.87, 95% CI 1.08–3.26), dyspnoea (OR 2.86, 95% CI 2.34–3.50), fatigue (OR 2.86, 95% CI 1.08–2.52), fever (OR 1.94, 95% CI 1.11–3.41), and gastrointestinal symptoms (OR 2.33, 95% CI 1.33–4.07) tended to suffer from more serious disease.

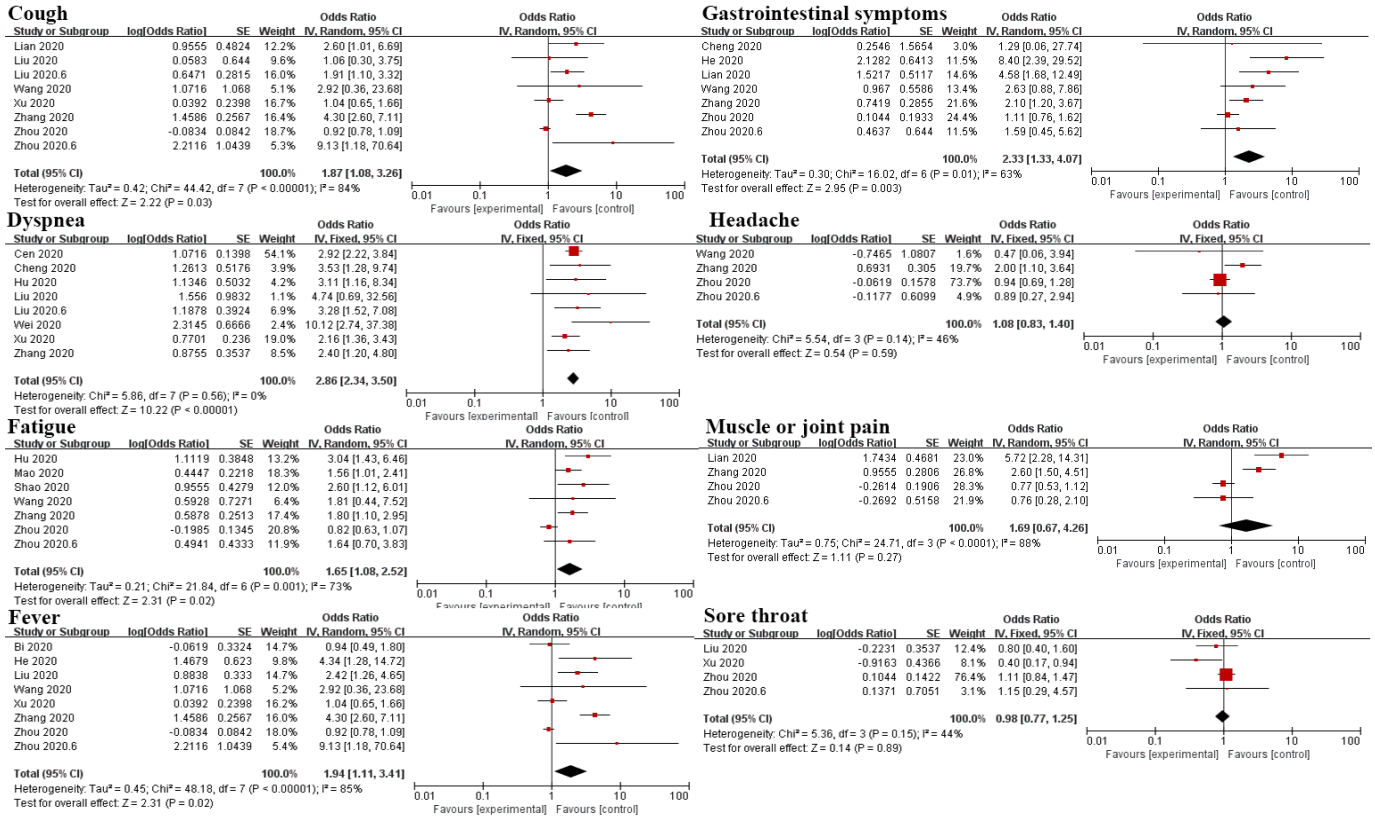

Figure 4. Forest plot of symptom factors.

3.5. Comorbidity Factors and COVID-19 Severity

Cancer, cardiovascular diseases, chronic obstructive pulmonary disorder (COPD), diabetes, hypertension, and any other coexisting diseases were identified to conduct meta-analysis. No comorbidity was the reference of all variables. According to Figure 5, only COPD presented distinct heterogeneity, with a 66% I^2 value and a 0.01 p value. Thus, random-effects analysis was adopted. Interestingly, all comorbidities

were significantly associated with the severity of COVID-19, namely, cancer (Z = 3.42, $p = 0.0006$), cardiovascular diseases (Z = 4.80, $p < 0.00001$), COPD (Z = 2.13, $p = 0.03$), diabetes (Z = 10.22, $p < 0.00001$), and hypertension (Z = 16.66, $p < 0.00001$). The possibility of patients with comorbidities to have severe COVID-19 was 3.33 times (cancer, 95% CI 1.67–6.65), 2.07 times (cardiovascular diseases, 95% CI 1.54–2.79), 2.69 times (COPD, 95% CI 1.08–6.70), 2.86 times (diabetes, 95% CI 2.34–3.50), 3.15 times (hypertension, 95% CI: 2.75–3.60), and 3.73 times (any other coexisting diseases, 95% CI: 2.83–4.91) higher than that for patients without comorbidities.

3.6. Laboratory Factors and COVID-19 Severity

Among all 56 laboratory factors, 16 factors could be analysed by meta-analysis. According to Figure 6, in this study, the results of the influence of albumin (<40 g/L versus ≥40 g/L as the reference; low value as reference versus high value), D-dimer (≤1 mg/ML as reference versus >1 mg/ML; low value as reference versus high value), lymphocytes (≤1.1 × 109/L as reference versus >1.1 × 109/L; low value as reference versus high value) and procalcitonin (PCT) (≤0.05 μ/L as reference versus >0.05 μ/L; low values as reference versus high value) were divided into two parts on the basis of classification. The reference groups of the other variables were the low-value group. In consideration of heterogeneity, apart from albumin with ≥40 g/L as a reference ($I^2 = 0\%$, $p = 0.42$), D-dimer with ≤1 mg/ML as a reference ($I^2 = 0\%$, $p = 0.44$), fibrinogen ($I^2 = 0\%$, $p = 0.39$), procalcitonin (PCT) ($I^2 = 0\%$, $p = 0.39$), and platelets ($I^2 = 0\%$, $p = 0.85$), all of the other variables were analysed by random effects.

Albumin ≥40 g/L as a reference (Z = 9.25, $p < 0.000001$), albumin (Z = 5.44, $p < 0.000001$), aspartate aminotransferase (AST) (Z = 2.09, $p = 0.04$), creatinine (Z = 1.95, $p = 0.05$), d-dimer with ≤1 mg/ML as a reference (Z = 7.73, $p < 0.00001$), fibrinogen (Z = 6.85, $p < 0.00001$), neutrophils (Z = 2.07, $p = 0.04$), procalcitonin (PCT) with ≤0.05 μ/L as a reference (Z = 5.67, $p < 0.00001$), platelets (Z = 3.66, $p = 0.0003$) and respiratory rate (Z = 2.53, $p = 0.01$) had a significant relationship with the severity of COVID-19. Apart from lymphocytes and platelet counts, the higher the other factors were, the more severe a patient's condition was.

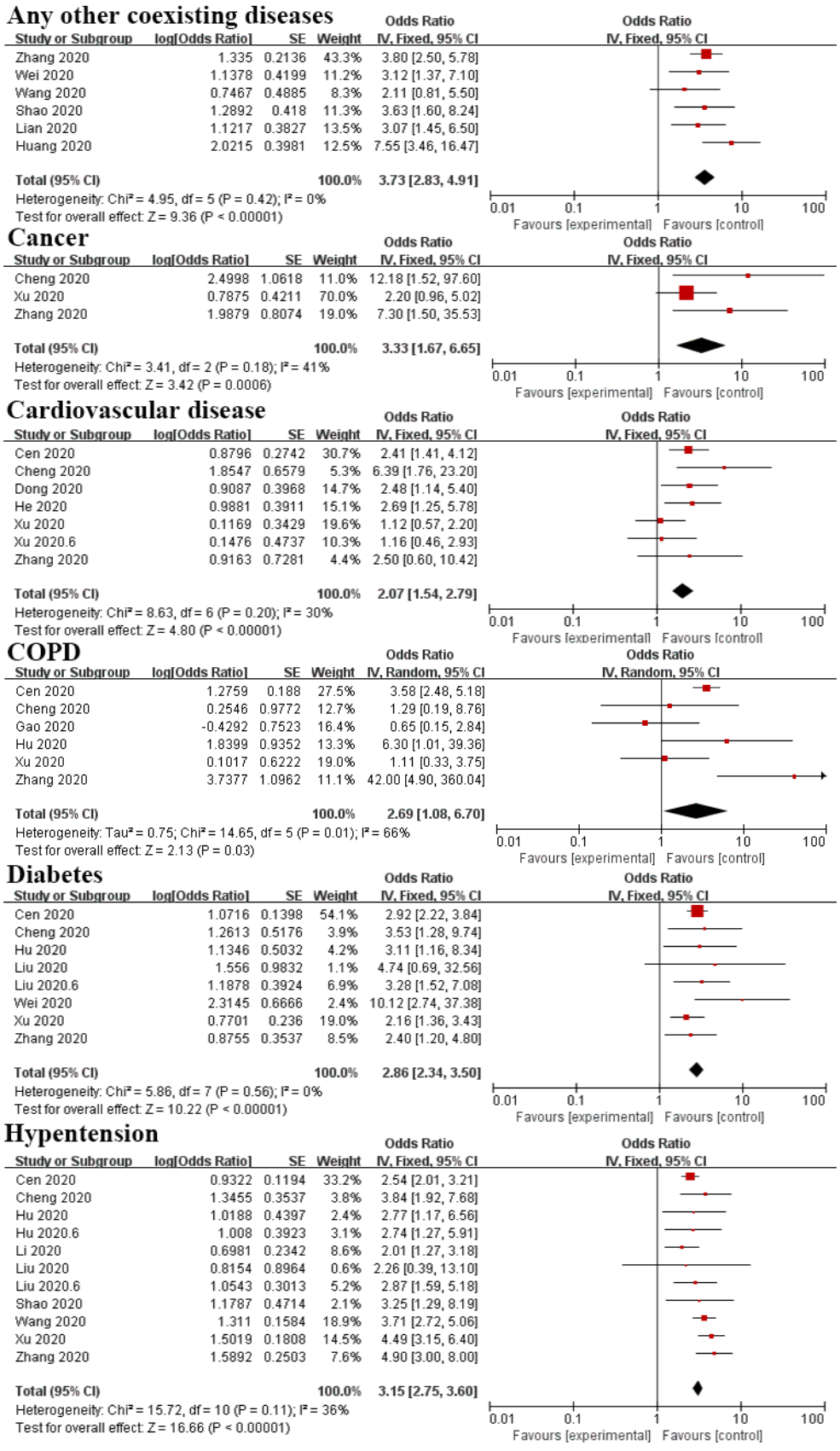

Figure 5. Forest plot of comorbidity factors.

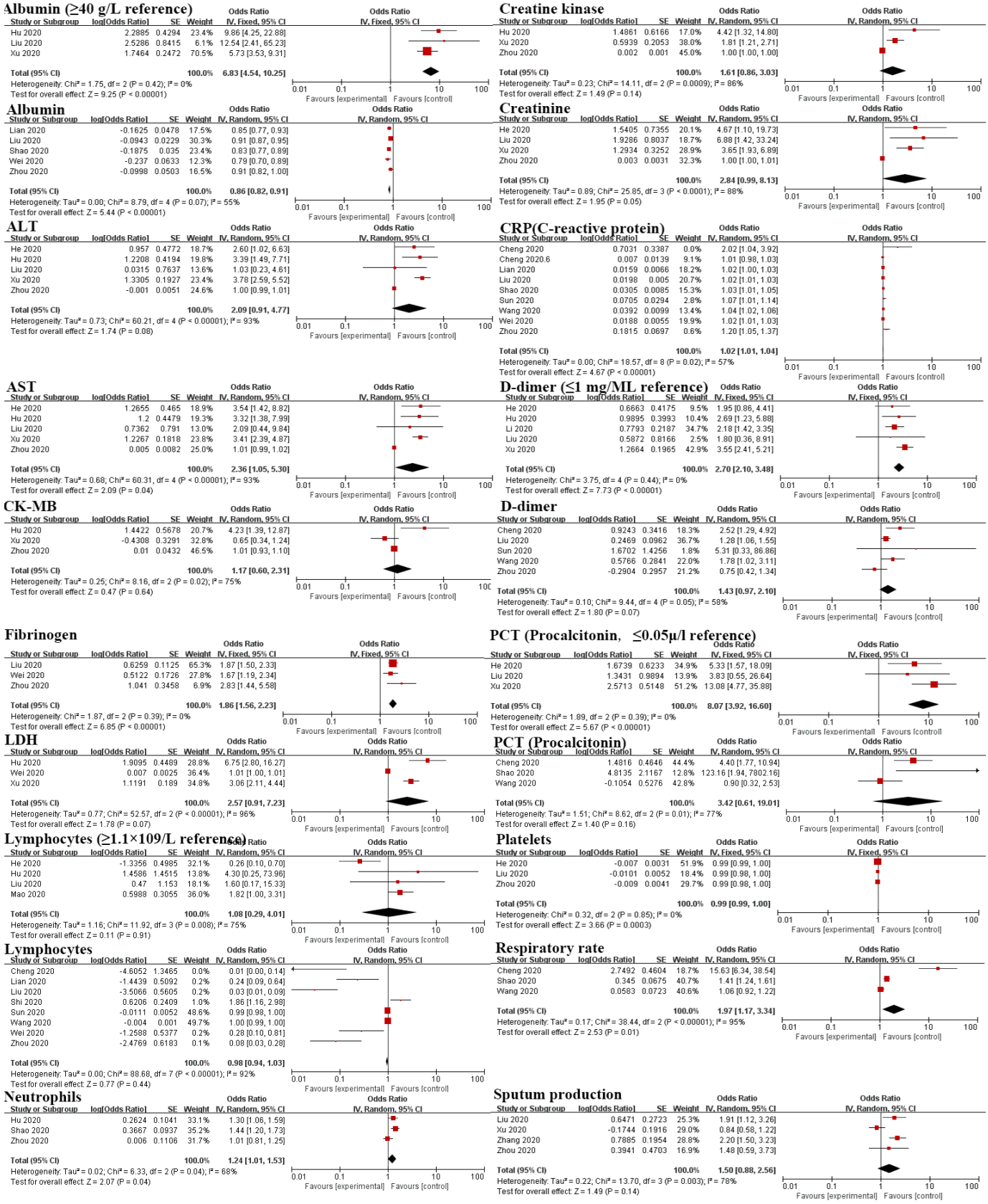

Figure 6. Forest plot of laboratory factors.

4. Discussion

To our knowledge, this is the most up-to-date and complete epidemiological and clinical assessment of determinants for the severity of COVID-19.

This systematic review found that 17.84% of all cases in China were reported to be severe, and 4.9% were critical. A study conducted in Europe from 22 March to 3 June 2020 reported 10.4% (269/2579 cases) severe-to-critical patients [53]. A total of 41 patients (4.9%) experienced severe or critical diseases in the Silicon Valley region, USA [54]. Apart from that, COVID-19 severity was found to be 51.6% in Egypt [55]. South Korea reported 11.96% of cases as severe [56]. It seems that the severity of COVID-19 is related to the economic-development level of countries.

In this review, individuals over 65 years tended to require intensive medical care, and men were more susceptible to severe disease than women were. The same results were also reported by other studies [57–62]. The age difference could be explained by immunological factors; young children are more adept at fighting off novel diseases, whereas the older population is more accustomed to having immune memory responses acquired over a lifetime [63]. Differences in the immune system could also explain why severe COVID-19 is much more common in men than in women [64,65]. A history of smoking was not related to the severity of COVID-19, and the same results were also found in a study conducted with a total of 7162 patients, suggesting that smoking is not significantly associated with the severity and mortality of COVID-19. The reasons behind the discrepancy may be linked to the lack of high-quality data and studies about the relationship between smoking and the severity of COVID-19 [66], since some researchers found a positive relationship [67–71]. In addition, there are currently no clinical or laboratory results about the influence of smoking on the disease.

In consideration of symptom factors, cough [31,39,55,72], dyspnoea [22,73,74], fatigue [73–75], and fever [30,31,39,72] were the main symptoms of severe COVID-19. Unsurprisingly, the existence of these symptoms could lead to severe illness. Cough and fever were globally regarded as main factors in previous studies [76,77]. The symptoms could be found in children, adolescents, and adults [78] in research on Europe [79], the UK [80], the United States [81], and other countries. Considering dyspnoea, infection with COVID-19 could result in severe outcomes and death from pneumonia with severe symptoms [82–84]. Fatigue could even be found in the post-COVID-19 period [85,86].

With regard to comorbidities, cancer, cardiovascular diseases, chronic obstructive pulmonary disorder (COPD), diabetes, hypertension, and any other coexisting diseases were related with severity of COVID-19. In the USA, patients with Type I diabetes have a higher possibility of hospitalisation and greater illness severity [87]. Some research suggested that diabetic patients' cytokine responses may be related to the severity of COVID-19 [87,88]. Meta-analysis found that pre-existing COPD was significantly associated with disease severity [89]. However, there are no clinical or laboratory results to explain the relationship between comorbidities and the outcomes of COVID-19. Some research proposed that a lack of respiratory support may cause this situation [90]. In addition, patients with diarrhoea were more likely to have severe disease; to some extent, faecal–oral transmission may result in an increasingly heavy load of the virus that exacerbates the symptoms of the illness [91]. Aggarwal et al. found that pre-existing cardiovascular diseases were associated with worse outcomes among patients with COVID-19. The pathologies of cardiovascular diseases could lead to critical pathomechanisms [92]. Raymond et al. found that hypertension could affect disease progression [93]. Some researchers believe that hypertension and its associated conditions are associated with the pathogenesis of COVID-19 [93], but some studies found no adequate evidence identifying hypertension as a risk factor [94]. In addition, there are different opinions about the effects of cancer on disease severity. Brar found that patients with COVID-19 and cancer showed similar symptoms and severity levels as those of patients without cancer [95]. Lee reported that the outcome of COVID-19 was much worse in patients with cancer [96].

In consideration of laboratory factors, higher D-dimer levels were strongly correlated with more severe COVID-19. Other researchers also found that D-dimer levels were higher in severe patients [97]. Additionally, PCT could be a risk factor to predict the severity of COVID-19 [98]. AST [99–101], creatinine [102–104], fibrinogen [105–107], neutrophils [108,109], and respiratory rate [14,110] were reported to be positively related to the severity of COVID-19. Murat et al. found that lymphocyte and platelet levels were higher in positive COVID-19 patients, while C-reactive protein (CRP) was higher in COVID-19-negative patients [111]. Wang also found that lower lymphocyte counts and elevated CRP were risk factors for severity [112]. The severity of the disease was related to the presence of opacity in one or more than one lobe [113]. Decreased albumin could be attributed to the severity of COVID-19, and the same results were found by Zhang [8]. In summary, apart from albumin, CRP, lymphocyte counts, and platelet levels, other laboratory factors examined in this review were not associated with the severity of COVID-19.

5. Conclusions

In summary, this paper reported the percentages of severe and critical cases of COVID-19 (17.84% and 4.9%, respectively). Furthermore, men, older people, and populations with coexisting diseases were more susceptible to severe disease than their counterparts were. Additionally, patients with cough, dyspnoea, fatigue, fever, and gastrointestinal symptoms tended to experience severe disease. Considering the laboratory results, albumin, AST, creatinine, D-dimer, fibrinogen, neutrophils, procalcitonin, platelets, and respiratory rate were potential factors that could be used to predict the severity of COVID-19. In the future, healthcare workers could use information about these risk factors to take necessary and effective measures to address patients who are likely to progress to severe and critical illness. Other countries could also learn from China's experience.

To our knowledge, this is the first systematic review on determinants of the severity of COVID-19 in China, and the findings provide comprehensive evidence for epidemiological research into this disease. One strength of this review is that it is based on a large sample size: a total of 15,828 cases diagnosed in 18 provinces in China. Another strength is that 148 risk factors were analysed in this review. Behavioural, symptom, comorbidity, laboratory, radiographic, exposure, and other factors were extracted from the included studies. However, there were several limitations of this study. Heterogeneity was quite common, perhaps due to differences among geographic regions and research sites.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/su13095305/s1. Table S1: search strategy; Table S2: extracted determinants; Table S3: extracted determinants; Table S4: quality scores assessing risk of bias using a modified Newcastle–Ottawa scale.

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