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# SYSTEMATIC REVIEW

# **REVISED** Predictors of COVID-19 severity: a systematic review

# and meta-analysis [version 2; peer review: 2 approved]

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#### Abstract

**Background**: The unpredictability of the progression of coronavirus disease 2019 (COVID-19) may be attributed to the low precision of the tools used to predict the prognosis of this disease.

**Objective**: To identify the predictors associated with poor clinical outcomes in patients with COVID-19.

**Methods**: Relevant articles from PubMed, Embase, Cochrane, and Web of Science were searched as of April 5, 2020. The quality of the included papers was appraised using the Newcastle-Ottawa scale (NOS). Data of interest were collected and evaluated for their compatibility for the meta-analysis. Cumulative calculations to determine the correlation and effect estimates were performed using the Z test.

Results: In total, 19 papers recording 1,934 mild and 1,644 severe cases of COVID-19 were included. Based on the initial evaluation, 62 potential risk factors were identified for the meta-analysis. Several comorbidities, including chronic respiratory disease, cardiovascular disease, diabetes mellitus, and hypertension were observed more frequent among patients with severe COVID-19 than with the mild ones. Compared to the mild form, severe COVID-19 was associated with symptoms such as dyspnea, anorexia, fatigue, increased respiratory rate, and high systolic blood pressure. Lower levels of lymphocytes and hemoglobin; elevated levels of leukocytes, aspartate aminotransferase, alanine aminotransferase, blood creatinine, blood urea nitrogen, high-sensitivity troponin, creatine kinase, highsensitivity C-reactive protein, interleukin 6, D-dimer, ferritin, lactate dehydrogenase, and procalcitonin; and a high erythrocyte sedimentation rate were also associated with severe COVID-19. **Conclusion**: More than 30 risk factors are associated with a higher risk of severe COVID-19. These may serve as useful baseline parameters in the development of prediction tools for COVID-19 prognosis.

#### **Keywords**

SARS-CoV-2, COVID-19, prognosis, severity, clinical outcome



This article is included in the Disease Outbreaks gateway.



This article is included in the Coronavirus collection.



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Any reports and responses or comments on the article can be found at the end of the article.

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# **REVISED** Amendments from Version 1

In the revised version of our current article, we provided the revision of method, the limitation, and the clinical implication of our study.

Any further responses from the reviewers can be found at the end of the article

#### Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global crisis across health, economic, and educational dimensions<sup>1,2</sup>. The disease has spread rapidly, can cause severe illness, and is characterized by a high mortality rate in certain groups. Mortality is particularly high in the absence of proven effective standard management measures<sup>3</sup>. One of the problems with the management of this disease is the absence of standardized methods for diagnosis and the inability to estimate prognosis based on clinical features. Certain reports have shown that poor prognostic prediction has correlated with high mortality among patients with COVID-194,5. Among patients with similar clinical characteristics and with similar treatment regiments, there may be a diversity in clinical outcomes<sup>6</sup>. Therefore, the development and use of an accurate predictor for COVID-19 prognosis will be beneficial for the clinical management of patients with COVID-19, and will help reduce the mortality rate. Successful implementation of such a prediction mechanism could have a large public health impact. Better understanding of clinical progression could also improve public health messaging, particularly as many individuals may consider COVID-19 to not be severe.

Prognostic tools for the prediction of COVID-19 severity in patients have been in development since January 2020. At least nine studies proposed the use of prognostic tools for the prediction of COVID-19 severity<sup>7-15</sup>. However, a recent systematic review and critical appraisal study evaluated the accuracy of these tools using prediction model risk of bias assessment tool (PROBAST) and reported a high risk of bias<sup>16</sup>. The establishment of a prediction model for the estimation of disease prognosis may help health workers segregate patients according to prediction status. However, the high risk of bias in these prediction tools might lead to inaccurate prediction of COVID-19 severity. A comprehensive study of the identification of risk factors that might play a significant role in determining the severity of patients with COVID-19 is necessary. We performed a systematic review and meta-analysis to assess the risk factors associated with poor clinical outcomes among patients with COVID-19. To the best of our knowledge, this is the first meta-analysis to assess the comprehensive risk factors that might affect the severity of COVID-19 in patients. The results of our study might serve as preliminary data for the compilation or improvement of the scoring system in the prediction of COVID-19 severity.

# Methods

# Study design

We performed a systematic review and meta-analysis to evaluate potential risk factors that might influence the severity of COVID-19. These risk factors include comorbidities, clinical manifestations, and laboratory findings. Accordingly, we searched the relevant studies from major scientific websites and databases to collect the data of interest, and determined the association and effect estimates by calculating the combined odds ratio (OR) and 95% confidence intervals (95% CI). The protocols for the systematic review and meta-analysis were similar to those used in previous studies<sup>17–23</sup>, as well as to those recommended by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)<sup>24</sup>.

#### Eligibility criteria

Studies were included in this review if they met the following inclusion criteria: (1) assessed the clinical manifestations and laboratory findings of patients with mild to severe COVID-19; (2) provided adequate data for the calculation of OR and 95% CI (event per sample size or mean  $\pm$  SD in both case and control groups), (3) written in English. Review articles, articles with non-standard data presentation, and duplicate publications were excluded.

#### Search strategy and data extraction

Major scientific databases (PubMed, Embase, Cochrane, and Web of Science) were searched for articles as of April 5, 2020. Moreover, we also searched in google scholar for the additional database. A comprehensive initial search was performed to identify the potential predictors, and a final search was performed to identify the relevant papers that could be included in the meta-analysis. We used the keywords adapted from medical subject headings: ["COVID-19" or "Coronavirus disease-19" or "SARS-CoV-2"] and ["mild" or "severe" or "prognosis" or "clinical outcome"] and ["clinical manifestation" or "morbidity" or "laboratory findings"]. Only studies written in English were included. If a duplicate publication was found, the article with the larger sample size was included. We also searched for relevant studies from the reference lists in the articles. During data extraction, the following information of interest was extracted: (1) first author name; (2) publication year; (3) country of origin, (4) sample size of mild and severe cases, (5) clinical manifestations, (6) morbidities, and (7) laboratory findings. Data extraction was performed by two independent investigators (JKF and MI) using a pilot form. If the disagreement was found, we performed a discussion to resolve the disagreement.

#### Assessment of the methodological quality

Before inclusion in the meta-analysis, the methodological quality of the articles was assessed using the New Castle-Ottawa scale (NOS). NOS scores range from 0 to 9 and consider three items: selection of patients (4 points), comparability of the groups (2 points), and ascertainment of exposure (3 points). Each study was interpreted to be of low quality (for scores  $\leq$  4), moderate quality (for scores between 5–6), or high quality (for scores  $\geq$  7)<sup>25</sup>.

Articles with moderate to high quality were included in the analysis. The study assessment was conducted by two independent investigators (MI and YP) using a pilot form. The discrepancies between the findings of the two investigators were solved by consulting with another investigator (JKF).

#### Study measures

The outcome measure of the study was the severity of COVID-19 (mild vs. severe). The risk factors or predictors included three major groups: comorbidities, clinical manifestations, and laboratory parameters. Comorbid factors such as chronic kidney disease, chronic liver disease, chronic respiratory disease, cerebrovascular accident, cardiovascular disease, diabetes mellitus, hypertension, and malignancy were compatible with the analysis. For clinical manifestations, fever, cough, dry cough, expectoration, sore throat, dyspnea, diarrhea, myalgia, nasal congestion, anorexia, abdominal pain, fatigue, dizziness, headache, fever, heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure were included in this study. Among laboratory characteristics, the presence of leukocytosis, leukocytopenia, anemia, lymphocytopenia; the levels or the counts of white blood cell (WBC), hemoglobin, neutrophil, lymphocyte, monocyte, platelet, activated partial thromboplastin time (aPTT), partial thromboplastin time (PTT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, serum creatinine, blood urea nitrogen (BUN), high-sensitivity (Hs)-troponin I, creatine kinase, high-sensitivity C-reactive protein (Hs-CRP), C-reactive protein (CRP) >8 mg/L, interleukin 6 (IL-6), glucose, D-dimer, serum ferritin, sodium, potassium, lactate dehydrogenase, and procalcitonin, CD4 and CD8; erythrocyte sedimentation rate (ESR); elevated IL-16; and elevated ESR were all included.

#### Statistical analysis

The significant risk factors that might govern the severity of COVID-19 were determined by the calculation of a pooled OR and 95% CI. The significance of the pooled ORs was determined using the Z test (p<0.05 was considered statistically significant). Prior to identification of the significant risk factors, data were evaluated for heterogeneity and potential publication bias. The heterogeneity among included studies was evaluated using the Q test. If heterogeneity existed (p<0.10), a random effect model was adopted; if not, a fixed effect model was adopted. Egger's test and a funnel plot were used to assess the reporting or publication bias (p<0.05 was considered statistically significant). Furthermore, we performed a moderator analysis to identify the independent predictors of poor clinical outcomes among patients with COVID-19. The data were analyzed using Review Manager version 5.3 (Revman Cochrane, London, UK). To prevent analytical errors, statistical analysis was performed by two authors (JKF and MI). The cumulative calculation was presented in a forest plot.

#### Results

#### Eligible studies

Our searches yielded 6,209 potentially relevant studies, of which 6,170 studies were excluded after assessment of the titles

and abstracts. Subsequently, further review of the complete texts was performed for 39 potential studies. In the full text review, we excluded 20 studies because they were reviews articles (n = 9), inadequacy of data for the calculation of OR and 95% CI (n = 7), and poor quality (n = 4). Eventually, 19 papers were included in our meta-analysis<sup>26-42</sup> The paper selection process adopted in our study is summarized in Figure 1, and the characteristics of studies included in our analysis are outlined in Table 1.

#### Risk factors of severe COVID-19

We found that eight comorbidities, 19 clinical manifestations, and 35 laboratory parameters were available for the metaanalysis (Table 2 and Table 3). Among the comorbid factors, chronic respiratory disease (OR: 2.48; 95% CI: 1.44, 4.27), cardiovascular disease (OR: 1.70; 95% CI: 1.05, 2.78), diabetes mellitus (OR: 2.10; 95% CI: 1.33, 3.34), and hypertension (OR: 2.33; 95% CI: 1.42, 3.81) were associated with a greater risk of severe COVID-19 (Figure 2A–D).

Among the clinical manifestations, dyspnea (OR: 3.28; 95% CI: 2.09, 5.15), anorexia (OR: 1.83; 95% CI: 1.00, 3.34), fatigue (OR: 2.00; 95% CI: 1.25, 3.20), and dizziness (OR: 2.67; 95% CI: 1.18, 6.01) were associated with severe COVID-19 (Figure 3A–D). In addition, increased respiratory rate (OR: 2.85; 95% CI: 1.28, 6.33) and increased respiratory rate (OR: 1.84; 95% CI: 1.31, 2.60) were also associated with severe COVID-19 (Figure 4A and B). Compared to productive cough, dry cough was associated with a lower risk of severe COVID-19 (OR: 0.66; 95% CI: 0.44, 0.97).

Among laboratory characteristics, severe COVID-19 was associated with elevated WBC count (OR: 4.92; 95% CI: 2.12, 11.31), increased neutrophil count (OR: 5.45; 95% CI: 2.04, 14.54), lymphocytopenia (OR: 3.19; 95% CI: 1.14, 7.07), and decreased hemoglobin levels (OR: 0.76; 95%CI: 0.58, 1.00) (Figure 5A-D). Elevated levels of AST, ALT, and serum creatinine increased the risk for severe manifestations of COVID-19 (ORs 4.91, 3.23, and 2.14, respectively; Figure 6A-C). Elevated levels of BUN (OR: 6.15; 95% CI: 3.05, 12.37), Hs-troponin I (OR: 9.25; 95% CI: 3.51, 24.37), creatine kinase (OR: 2.44; 95% CI: 1.65, 3.62), Hs-CRP (OR: 14.27; 95% CI: 5.13, 39.71), IL-6 (OR: 6.68; 95% CI: 3.20, 13.94), D-dimer (OR: 6.19; 95% CI: 4.22, 9.08), ferritin (OR: 1.96; 95% CI: 1.06, 3.62), lactate dehydrogenase (OR: 8.28; 95% CI: 4.75, 14.46), procalcitonin (OR: 6.62; 95% CI: 3.32, 13.21), ESR (OR: 4.45; 95% CI: 2.56, 7.76), and CRP >8 (OR: 8.34; 95% CI: 1.85, 37.62) were also associated with severe COVID-19 (Figure 7-Figure 9). A low risk of severe COVID-19 was associated with low leukocyte levels (OR: 0.59; 95% CI: 0.41, 0.87) and elevated lymphocyte levels (OR: 0.34; 95% CI: 0.23, 0.50).

#### Source of heterogeneity

Heterogeneity was detected in the data of chronic kidney disease, cerebrovascular disease, cardiovascular disease, diabetes mellitus, hypertension, and malignancy among the comorbid factors analyzed. Therefore, we used the random effect model



Figure 1. A flowchart of paper selection in our study.

to analyze the data. The fixed effect model was used to analyze the data on chronic liver disease and chronic respiratory disease, as there was no evidence of heterogeneity. For clinical manifestations, the data on fever, cough, sore throat, dyspnea, diarrhea, anorexia, fatigue, temperature  $>38^{\circ}$ C, respiratory rate, and diastolic blood pressure were analyzed using the random effect model while the rest of clinical manifestation data were analyzed using the fixed effect model.

Among laboratory parameters, evidence of heterogeneity was found in count of WBC, neutrophil, monocyte, lymphocyte, platelet, CD4, and CD8; the presence of lymphocytopenia and anemia; the levels of AST, ALT, total bilirubin, albumin, aPTT, PTT, serum creatinine, BUN, Hs-Troponin I, creatine kinase, IL-6, Hs-CRP, glucose, D-dimer, sodium, potassium, lactate dehydrogenase, and procalcitonin; elevated CRP; and ESR. Accordingly, the data were analyzed using the random effect model. The data for the remaining parameters were analyzed using the fixed effect model.

#### Potential publication bias

We used Egger's test to assess the potential publication bias. Our cumulative calculation revealed that reporting or publication bias (p<0.05) existed with respect to chronic liver disease, expectoration, myalgia, abdominal pain, heart rate, leukocytosis, elevated ESR, and elevated IL-6 levels.

#### Discussion

Our data suggest that comorbidities, such as chronic respiratory disease, cardiovascular disease, diabetes, and hypertension, were associated with a higher risk of severe COVID-19, among which, hypertension was the strongest risk factor. These

A	Author & year Country City		I to an it all	Sample	e size	0	NOC
Author & year	Country	City	Hospitai	Severe	Mild	Outcome measure	NUS
Bai <i>et al.</i> 2020 <sup>26</sup>	China	Wuhan	Jinyintan Hospital	91	36	Died vs. cured	7
Cai <i>et al.</i> 2020 <sup>27</sup>	China	Shenzen	Third people's Hospital	58	240	Severe vs. non severe	9
Chen <i>et al.</i> 2020 <sup>28</sup>	China	Wuhan	Tongji hospital	11	10	Severe vs. moderate	9
Chen <i>et al.</i> 2020 <sup>29</sup>	China	Mixed	Multicenter	50	241	Severe vs. mild-moderate	9
Chen <i>et al.</i> 2020 <sup>30</sup>	China	Wuhan	Zhongnan Hospital	14	11	Viral clearance vs. without viral clearance	9
Duan <i>et al.</i> 2020 <sup>31</sup>	China	Wuhan	Wuhan Pulmonary Hospital	44	72	Uncured vs. cured	9
Gao <i>et al.</i> 2020 <sup>32</sup>	China	Fuyang	Second People's Hospital	15	28	Severe vs. mild	7
Guan <i>et al.</i> 2020 <sup>33</sup>	China	Guangdong	National Health Commision of China	926	173	Severe vs. non-severe	7
Huang <i>et al.</i> 2020 <sup>34</sup>	China	Wuhan	Jinyintan hospital	13	28	ICU vs. non-ICU	9
Jian-Ya <i>et al.</i> 2020 <sup>35</sup>	China	Chongqing	Three Gorges Hospital	7	44	Severe vs. non severe	9
Liu <i>et al.</i> 2020 <sup>36</sup>	China	Wuhan	Union Hospital	69	69	Severe vs. non severe	7
Shi <i>et al.</i> 2020 <sup>37</sup>	China	Wuhan	Renmin Hospital	48	53	Died <3 d vs. >3 d	9
Wang <i>et al.</i> 2020 <sup>38</sup>	China	Mixed	Multicenter	50	115	CT imaging score >11 vs. <11	8
Wang <i>et al.</i> 2020 <sup>39</sup>	China	Wuhan	Wuhan First People's Hospital	22	283	Survivor vs. non-survivor	8
Wang <i>et al.</i> 2020 <sup>43</sup>	China	Wuhan	Zhongnan Hospital	36	102	ICU vs. non-ICU	9
Xu <i>et al.</i> 2020 <sup>40</sup>	China	Mixed	Multicenter	25	44	Severe vs. mild	8
Zhang <i>et al.</i> 2020 <sup>41</sup>	China	Wuhan	Zhongnan Hospital	55	166	Severe vs. non-severe	9
Zhang <i>et al.</i> 2020 <sup>44</sup>	China	Wuhan	Wuhan Seventh Hospital	56	82	Severe vs. non-severe	7
Zhou <i>et al.</i> 2020 <sup>42</sup>	China	Wuhan	Wuhan Pulmonary Hospital	54	137	Survivor vs. non-survivor	8

#### Table 1. Baseline characteristics of studies included in our analysis.

Note: ICU, intensive care unit; CT, computed tomography; NOS, Newcastle Ottawa Scale.

## Table 2. Clinical characteristics of Covid-19 patients and the risk of severity.

	NG		Va	lue	_				0.50/ 63
Clinical characteristics	NS	Model	Severe	Mild	рЕ	рнет	р	OR	95%CI
Comorbids									
Chronic kidney disease	6	Random	14 [3.94]	15 [1.68]	1.3430	0.0280	0.1910	2.56	0.63-10.45
Chronic liver disease	6	Fixed	16 [4.82]	26 [4.04]	<0.0001	0.3220	0.3220	1.45	0.70-3.01
Chronic respiratory disease	10	Fixed	31 [5.47]	31 [1.66]	0.7060	0.1020	0.0010	2.48	1.44-4.27
Cerebrovascular accident	5	Random	20 [5.54]	30 [2.09]	0.9110	0.0380	0.1850	2.02	0.71-5.70
Cardiovascular disease	13	Random	76 [10.45]	94 [4.95]	0.5400	0.0580	0.0310	1.70	1.05-2.78
Diabetes mellitus	17	Random	156 [19.24]	194 [8.40]	0.7040	<0.0001	0.0020	2.10	1.33-3.34
Hypertension	15	Random	269 [35.54]	369 [16.79]	0.7680	< 0.0001	0.0010	2.33	1.42-3.81
Malignancy	11	Fixed	29 [4.43]	40 [2.23]	0.6150	0.1430	0.5330	1.18	0.70-1.99

<b>Clinical share stanistics</b>	acteristics NS Model		Va				0.0	050/ 67		
Clinical characteristics	NS	Model	Severe	Mild	pE	рнет	р	OR	957001	
Symptoms										
Fever	16	Random	599 [79.34]	1932 [80.84]	0.9220	< 0.0001	0.1730	1.51	0.83-2.74	
Cough	12	Random	377 [64.33]	1120 [ 54.05]	0.9560	< 0.0001	0.1890	1.53	0.81-2.90	
Dry cough	4	Fixed	75 [44.38]	178 [55.97]	0.3130	0.1880	0.0360	0.66	0.44-0.97	
Expectoration	10	Fixed	136 [26.67]	438 [29.05]	< 0.0001	0.8370	0.4970	1.09	0.85-1.39	
Sore throat	10	Random	59 [10.57]	196 [10.96]	0.7860	0.0040	0.6350	1.18	0.59-2.37	
Dyspnea	13	Random	286 [42.56]	318 [16.51]	0.6340	<0.0001	< 0.0001	3.28	2.09-5.15	
Diarrhea	13	Random	65 [9.62]	134 [6.68]	0.5180	0.0690	0.8030	1.07	0.67-1.69	
Myalgia	11	Fixed	105 [17.89]	283 [15.70]	< 0.0001	0.7330	0.5160	1.10	0.831-1.44	
Nasal congestion	4	Fixed	15 [5.02]	53 [4.34]	0.9350	0.1000	0.7590	1.12	0.55-2.29	
Anorexia	9	Random	103 [25.37]	143 [15.10]	0.6960	0.0040	0.0490	1.83	1.00-3.34	
Abdominal pain	5	Fixed	15 [6.07]	6 [0.95]	< 0.0001	0.5650	0.0040	3.91	1.53-10.02	
Fatigue	13	Random	310 [46.48]	694 [34.49]	0.6790	< 0.0001	0.0040	2.00	1.25-3.20	
Dizziness	4	Fixed	13 [10.08]	24 [5.02]	0.6510	0.1950	0.0180	2.67	1.18-6.01	
Headache	11	Fixed	56 [10.45]	197 [11.58]	0.5070	0.1110	0.9950	1.00	0.71-1.41	
Signs										
Temperature >38°C	5	Random	200 [57.97]	738 [50.14]	0.6090	0.0020	0.2660	1.44	0.76-2.73	
Heart rate (x/min)	4	Fixed	269 ± 35.54	87.88 ± 13.30	< 0.0001	0.4070	0.0010	1.79	1.25-2.56	
Respiratory rate (x/min)	5	Random	22.6 ± 4.80	20.36 ± 2.00	0.8080	< 0.0001	0.0100	2.85	1.28-6.33	
SBP (mmHg)	5	Fixed	132.57 ± 23.16	123.88 ± 14.37	0.3340	0.1560	< 0.0001	1.84	1.31-2.60	
DBP (mmHg)	3	Random	76.50 ± 10.61	75.59 ± 9.89	0.5350	0.0260	0.7190	1.14	0.56-2.32	

Note, Value, data were presented in number [%] or mean ± SD; NS, number of studies; pE, p Egger; pHet, p heterogeneity; OR, odd ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure.

# Table 3. Laboratory findings and the risk of severity in Covid-19 patients.

Clinical			Val	ue	_				050/ 65
characteristics	NS	Model	Severe	Mild	рЕ	рнет	р	OR	95%CI
Complete Blood Count									
WBC (10^9/L)	14	Random	7.32 ± 3.84	5.17 ± 2.04	1.4980	<0.0001	< 0.0001	4.92	2.12-11.31
Leukocytosis	6	Fixed	62 [26.00]	40[6.03]	0.0000	0.5940	<0.0001	5.38	3.36-8.62
Leukopenia	6	Fixed	44 [18.00]	206 [31.07]	0.2890	0.2480	0.0160	0.59	0.41-0.87
Neutrophil count (10^9/L)	12	Random	5.96 ± 3.62	3.84 ± 2.12	1.6380	<0.0001	0.0010	5.45	2.04-14.54
Lymphocyte count (10^9/L)	15	Random	0.74 ± 0.36	1.03 ± 0.44	0.6440	<0.0001	<0.0001	0.34	0.23-0.50
Lymphocytopenia	6	Random	158 [59.00]	40 [6.03]	0.8270	<0.0001	<0.0001	3.19	1.14-7.07

Clinical	NC	Medal	Val	ue	ъĘ	nllat			0504 61
characteristics	IN S	wodei	Severe	Mild	pe	рнес	Р	UK	95%CI
Complete Blood Count									
Monocyte count (10^9/L)	6	Random	0.38 ± 0.17	0.36 ± 0.15	0.5860	0.0100	0.5100	1.22	0.68-2.20
Hemoglobin (g/L)	9	Fixed	129.11 ± 16.98	132.02 ± 17.50	0.0900	0.4000	0.0460	0.76	0.58-1.00
Anaemia	2	Random	18 [17.00]	39 [10.32]	0.7640	0.0660	0.4730	1.58	0.45-5.56
Platelet count (10^9/L)	12	Random	172.58 ± 69.19	183.21 ± 62.50	0.5550	0.0010	0.8200	0.82	0.55-1.23
Physiological function									
AST (U/L)	11	Random	56.20 ± 35.83	28.67 ± 11.18	0.6930	< 0.0001	<0.0001	4.91	2.96-8.12
ALT (U/L)	12	Random	38.65 ± 22.90	25.60 ± 14.71	0.8060	<0.0001	<0.0001	3.23	1.90-5.52
Total bilirubin (µmol/L)	7	Random	15.80 ± 9.50	13.46 ± 4.62	1.6600	< 0.0001	0.5800	1.46	0.41-5.21
Albumin (g/L)	6	Random	32.39 ± 3.64	35.53 ± 3.71	2.3900	< 0.0001	0.0950	0.19	0.03-1.34
aPTT (s)	7	Random	31.23 ± 5.02	33.13 ± 3.66	1.1900	< 0.0001	0.3420	0.58	0.19-1.79
PTT (s)	11	Random	13.45 ± 1.86	12.53 ± 1.31	0.7700	< 0.0001	0.2430	0.56	0.21-1.48
Serum creatinine (µmol/L)	13	Random	82.04 ± 31.69	70.25 ± 20.87	0.6670	<0.0001	0.0010	2.14	1.37-3.33
BUN (mmol/L)	10	Random	6.71 ± 2.70	4.74 ± 1.38	1.0220	<0.0001	<0.0001	6.15	3.05-12.37
Hs-Troponin I (pg/ml)	6	Random	31.9 ± 61.55	3.55 ± 3.71	1.1290	< 0.0001	<0.0001	9.25	3.51-24.37
Creatine kinase (U/L)	10	Random	121.13 ± 115.63	77.47 ± 56.26	0.4860	0.0030	< 0.0001	2.44	1.65-3.62
Inflammation markers	5								
Hs-CRP (mg/L)	10	Random	73.25 ± 49.97	29.96 ± 24.40	1.5600	< 0.0001	< 0.0001	14.27	5.13-39.71
CRP >8 mg/L	3	Random	147 [83.10]	254 [52]	1.1590	0.0050	0.0060	8.34	1.85-37.62
ESR (mm/h)	4	Random	50.60 ± 27.25	29.19 ± 26.52	0.4200	0.0710	< 0.0001	4.45	2.56-7.76
Elevated ESR	2	Fixed	73 [68.00]	214 [44.49]	< 0.0001	0.8060	< 0.0001	2.80	1.78-4.39
IL-6 (pg/ml)	8	Random	30.45 ± 31.29	11.06 ± 10.89	0.9120	< 0.0001	< 0.0001	6.68	3.20-13.94
Elevated IL-6	2	Fixed	44 [66]	115 [46.56]	<0.0001	0.7160	0.0200	1.98	1.12-3.52
CD4 count(10^9/L)	3	Random	217.19 ± 118.56	337.87 ± 149.93	1.5920	0.0010	0.2760	0.34	0.05-2.39
CD8 count (10^9/L)	3	Random	178.80 ± 95.77	224.17 ± 76.36	1.4260	0.0030	0.1420	0.26	0.04-1.57
Others									
Glucose (mmol/L)	3	Random	7.04 ± 1.83	6.45 ± 1.33	0.9480	0.0030	0.3340	1.80	0.55-5.90
D-dimer (pg/mL)	15	Random	111.34 ± 145.12	38.88 ± 28.93	0.6070	<0.0001	<0.0001	6.19	4.22 - 9.08
Serum Ferritin (µg/L)	4	Fixed	1062.90 ± 868.19	600.67 ± 758.61	0.4310	0.1070	0.0310	1.96	1.06-3.62
Sodium (mmol/L)	3	Random	137.40 ± 3.13	92.39 ± 1.77	3.2770	<0.0001	0.2840	11.93	0.13-1109.37
Potassium (mmol/L)	3	Random	4.12 ± 0.61	4.00 ± 0.54	0.9630	0.0010	0.7470	1.21	0.32-0.75
Lactate dehydrogenase (U/L)	9	Random	381.85 ± 159.44	283. 03 ± 89.40	0.6840	<0.0001	<0.0001	8.28	4.75-14.46
Procalcitonin (ng/mL)	10	Random	0.40 ± 0.29	0.12 ± 0.07	0.9880	< 0.0001	< 0.0001	6.62	3.32-13.21

Note: Value, data were presented in number [%] or mean ± SD; NS, number of studies; pE, p Egger; pHet, p heterogeneity; OR, odd ratio; CI, confidence interval; CBC, complete blood count; WBC, white blood cells; AST, aspartate transaminase; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; PTT, partial thromboplastin time; BUN, blood urea nitrogen; Hs-CRP, high sensitivity C reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin.

A).	•
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			20/8								
A).	Study or Subgroup	Sevel Events	Total	mild Events	Total	Weight	Odds Ratio		Odd M.H. Fiv	s Ratio red 95% CI	
	Chen et al (2) 2020	5	50	5	241	8.8%	5 24 [1 46 18 86]		M-11, 114		
	Chen et al (3) 2020	0	11	ñ	14	0.070	Not estimable				
	Gao et al 2020	3	15	0	28	1.6%	15.96 (0.77, 332.61)			- · ·	
	Guan et al 2020	3	173	6	926	10.5%	2.71 [0.67, 10.92]				
	Huang et al 2020	4	54	5	111	17.2%	1.70 [0.44, 6.59]		_		
	Shi et al 2020	1	13	0	13	2.5%	3.24 [0.12, 87.13]		-		
	Wang et al (1) 2020	4	48	10	53	49.3%	0.39 [0.11, 1.34]			+	
	Zhang et al (1) 2020	3	36	1	102	2.7%	9.18 [0.92, 91.31]			100 M	
	Zhang et al (2) 2020 Zhou et al 2020	4	50	2	100	5.2%	0.43 [1.14, 30.14] 7 20 (0.24, 154, 06)		_		_
	Zhou et al 2020	2	20	U	02	2.370	7.30 [0.34, 154.90]			1.1	
	Total (95% CI)		513		1736	100.0%	2.31 [1.37, 3.89]			•	
	Total events	29		29							
	Heterogeneity: Chi <sup>2</sup> =	14.68, df=	: 8 (P =	0.07); 12:	= 45%			+	1	1	
	Test for overall effect:	Z = 3.15 (F	P = 0.0	02)				0.002	0.1	1 10	500
				- 20							
B)		sever	е	mild			Odds Ratio		Odd	Is Ratio	
2).	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Ran	dom, 95% Cl	
	Bai et al 2020	3	91	2	16	5.1%	0.24 [0.04, 1.56]	_			
	Chen et al (2) 2020	3	50	7	241	7.8%	2.13 [0.53, 8.55]		_	1.10	
	Chen et al (3) 2020	1	11	1	14	2.5%	1.30 [0.07, 23.43]				
	Gaulet al 2020 Guan et al 2020	10	172	17	026	3.2%	0.93 [0.08, 11.10]			_	
	Huang et al 2020	3	13	3	320	5 3 96	1.00.00.16.6.201		-		
	Liu et al 2020	6	69	0	11	24%	2 35 [0 12 44 72]			-	
	Shi et al 2020	9	48	15	53	11.8%	0.58 [0.23, 1.50]				
	Wang et al (1) 2020	9	36	11	102	11.4%	2.76 [1.03, 7.35]				
	Wang et al (2) 2020	12	54	22	111	13.5%	1.16 [0.52, 2.56]		-		
	Zhang et al (1) 2020	13	55	9	166	12.1%	5.40 [2.16, 13.49]				
	Zhang et al (2) 2020	4	58	3	82	6.8%	1.95 [0.42, 9.07]			· · ·	
	Zhou et al 2020	2	54	2	137	4.7%	2.60 [0.36, 18.91]				
	Total (95% CI)		727		1900	100.0%	1.71 [1.05, 2.78]			•	
	Total events	76		94							
	Heterogeneity: Tau <sup>2</sup> =	0.29; Chi <sup>2</sup>	= 20.6	1, df = 12	(P = 0.	06); l <sup>2</sup> = 4	12%	0.01	0.1	1 10	100
	Test for overall effect:	Z = 2.15 (F	' = 0.03	3)							
~	2	sever	e	mild			Odds Ratio		Odd	ls Ratio	
С).	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-H, Ran	dom, 95% Cl	
	Bai et al 2020	10	91	5	16	6.2%	0.27 [0.08, 0.94]			-	
	Chen et al (1) 2020	2	11	1	10	2.5%	2.00 [0.15, 26.19]		-	1	
	Chen et al (2) 2020	7	50	15	241	7.6%	2.45 [0.94, 6.37]				
	Chen et al (3) 2020	2	11	2	14	3.3%	1.33 [0.16, 11.36]				
	Gan et al 2020	6	44	1	29	2 1 96	19 00 [1 00 170 3/1			- <u> </u>	_
	Guan et al 2020	28	173	53	926	0.0%	3 1 9 11 95 5 1 91				
	Huang et al 2020	1	13	7	13	2.9%	0.07 [0.01, 0.72]	-		-	
	Jian-Ya et al 2020	4	7	0	44	1.8%	114.43 [5.06, 2585.61]				+
	Liu et al 2020	11	69	0	11	2.1%	4.52 [0.25, 82.27]				
	Shi et al 2020	9	48	13	53	7.5%	0.71 [0.27, 1.85]			•	
	Wang et al (1) 2020	8	36	6	102	6.6%	4.57 [1.46, 14.28]				
	Wang et al (2) 2020	12	54	12	111	7.9%	2.36 [0.98, 5.67]				
	Wang et al (3) 2020	6	22	25	283	7.2%	3.87 [1.39, 10.78]				
	Zhang et al (1) 2020	7	55	15	166	7.6%	1.47 [0.57, 3.81]				
	Zhang et al (2) 2020 Zhou et al 2020	10	58	10	127	0.70	1.30 [0.47, 3.59]		-		
	2nou et al 2020	19	54	19	137	8.7%	3.37 [1.01, 7.00]			-	
	Total (95% CI)		811		2309	100.0%	2.10 [1.32, 3.34]			•	
	Total events	156 0.50 Chił	- 12 21	194 df = 16	(P = 0)	0002\-12-	- 62%	L			
	Test for overall effect:	Z = 3.15 (P	= 0.00	12)	(1 - 0.1	00003/,1 -	- 05 %	0.001	0.1	1 10	1000
D).	Chult - Culture	sever	e	mild	T		Odds Ratio		Odd	Is Ratio	
	Study or Subgroup	Events	1 otal	Events	1000	2 6%	M-H, Kandom, 95% CI		M-H, Kan	dom, 95% CI	
	Chen et al (1) 2020	4	11	2	10	3.8%	2 29 [0.32 16 51]		_		
	Chen et al (2) 2020	19	50	20	241	8 4 %	6 77 [3 26 14 08]				
	Chen et al (3) 2020	3	11	0	14	2.0%	11.94 [0.55, 260,28]		-		-
	Duan et al 2020	21	44	24	72	8.2%	1.83 [0.85, 3.94]				
	Gao et al 2020	6	15	7	28	5.8%	2.00 [0.52, 7.65]			· · · ·	
	Guan et al 2020	41	173	124	926	9.7%	2.01 [1.35, 2.99]			-	
	Livena et al 2020	2	13	4	13	4.0%	0.41 [0.06, 2.77]				
	Huang et al 2020	1	7	3	44	2.9%	2.28 [0.20, 25.61]				
	Jian-Ya et al 2020			0	11	2.2%	6.01 [0.33, 108.10]				- 1
	Jian-Ya et al 2020 Liu et al 2020	14	69	U							
	Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020	14 26	69 48	33	53	8.1%	0.72 [0.32, 1.58]		1	-	
	Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020	14 26 21	48 36	33 22	53 102	8.1% 8.0%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48]		-		
	Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (3) 2020	14 26 21 10	69 48 36 22	33 22 35	53 102 283	8.1% 8.0% 7.6%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68]		7	-	
	Jian-Ya et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (3) 2020 Zhang et al (1) 2020 Zhang et al (2) 2020	14 26 21 10 26	69 48 36 22 55	33 22 35 28	53 102 283 166	8.1% 8.0% 7.6% 8.7%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68] 4.42 [2.27, 8.61]		_	=	
	Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (3) 2020 Zhang et al (1) 2020 Zhang et al (2) 2020 Zhou et al 2020	14 26 21 10 26 22 32	69 48 36 22 55 58 58	33 22 35 28 20 32	53 102 283 166 82 137	8.1% 8.0% 7.6% 8.7% 8.4% 8.6%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68] 4.42 [2.27, 8.61] 1.89 [0.91, 3.94] 4.77 [2.44 9.34]		-		
	Huang et al 2020 Jian-Ya et al 2020 Eliu et al 2020 Wang et al (2) 2020 Wang et al (3) 2020 Zhang et al (2) 2020 Zhou et al 2020	14 26 21 10 26 22 32	69 48 36 22 55 58 58 54	33 22 35 28 20 32	53 102 283 166 82 137	8.1% 8.0% 7.6% 8.7% 8.4% 8.6%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68] 4.42 [2.27, 8.61] 1.89 [0.91, 3.94] 4.77 [2.44, 9.34]		-		
	All angle et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (2) 2020 Wang et al (3) 2020 Zhang et al (2) 2020 Zhang et al (2) 2020 Zhou et al 2020 Total (95% CI) Total exercto	14 26 21 10 26 22 32	69 48 36 22 55 58 58 54 <b>757</b>	33 22 35 28 20 32	53 102 283 166 82 137 2198	8.1% 8.0% 7.6% 8.7% 8.4% 8.6% <b>100.0%</b>	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68] 4.42 [2.27, 8.61] 1.89 [0.91, 3.94] 4.77 [2.44, 9.34] <b>2.32 [1.43, 3.78]</b>		-	• • •	
	Jian-Ya et al 2020           Jian-Ya et al 2020           Liu et al 2020           Shi et al 2020           Wang et al (1) 2020           Wang et al (3) 2020           Zhang et al (1) 2020           Zhang et al (2) 2020           Zhang et al (2) 2020           Zhou et al 2020           Total (95% CI)           Total events           Heterogeneity: Tau <sup>2</sup> =	14 26 21 10 26 22 32 32 269 0.60; Chi <sup>2</sup>	69 48 36 22 55 58 54 757 = 59.2	33 22 35 28 20 32 369 7, df = 15	53 102 283 166 82 137 2198 (P < 0	8.1% 8.0% 7.6% 8.7% 8.4% 8.6% 100.0%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68] 4.42 [2.27, 8.61] 1.89 [0.91, 3.94] 4.77 [2.44, 9.34] <b>2.32 [1.43, 3.78]</b> = 75%	1			
	Jian-Ya et al 2020 Jian-Ya et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (1) 2020 Zhang et al (1) 2020 Zhang et al (2) 2020 Zhou et al 2020 <b>Total (95% Cl)</b> Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	14 26 21 10 26 22 32 269 0.60; Chi <sup>2</sup> Z = 3.39 (F	69 48 36 22 55 58 54 <b>757</b> = 59.2 2 = 0.00	33 22 35 28 20 32 369 7, df = 15 107)	53 102 283 166 82 137 <b>2198</b> (P < 0.	8.1% 8.0% 7.6% 8.7% 8.4% 8.6% 100.0%	0.72 [0.32, 1.58] 5.09 [2.26, 11.48] 5.90 [2.37, 14.68] 4.42 [2.27, 8.61] 1.89 [0.91, 3.94] 4.77 [2.44, 9.34] <b>2.32 [1.43, 3.78]</b> <sup>2</sup> = 75%	1 0.002	0.1	• • • • •	500

Figure 2. A forest plot of the association between comorbid factors and the risk of severe COVID-19. A) Chronic respiratory disease; B) Cardiovascular diease; C) Diabetes mellitus; D) Hypertension.

		6010		mild			Odde Patio	Odde Patio
A).	Study or Subgroup	Evente	Total	Evente	Total	Mojaht	M Ll Pandom 05% CL	M H Bandom 05% Cl
	Dei et el 2020	LVCIRS	10101	LVCIRS	10(a)	o and	4.001046.44.04	
	Ballet al 2020	22	36	22	91	9.2%	4.93 [2.16, 11.24]	
	Chen et al (2) 2020	18	50	19	241	9.7%	6.57 [3.12, 13.82]	
	Chen et al (3) 2020	3	11	4	14	4.4%	0.94 [0.16, 5.46]	
	Duan et al 2020	3	44	4	72	5.2%	1.24 [0.26, 5.84]	
	Guan et al 2020	65	173	140	926	12.2%	3.38 [2.37, 4.83]	
	Huang et al 2020	12	13	10	28	3.2%	21.60 [2.44, 191.38]	· · · · · · · · · · · · · · · · · · ·
	Liu et al 2020	40	69	4	11	6.2%	2.41 [0.65, 9.02]	
	Shi et al 2020	28	53	31	53	9.6%	0.79 [0.37, 1.71]	
	Wang et al (1) 2020	23	36	20	102	9.1%	7.25 [3.14, 16.76]	
	Wang et al (2) 2020	4	54	7	111	6.4%	1.19 [0.33, 4.25]	
	Xu et al 2020	9	25	2	44	4.8%	11.81 [2.30, 60.70]	
	Zhang et al (1) 2020	35	55	35	166	10.3%	6.55 [3.37, 12.72]	
	Zhang et al (2) 2020	24	53	20	67	9.7%	1.94 [0.92, 4.13]	
	Total (95% CI)		672		1926	100.0%	3.28 [2.09, 5.15]	•
	Total events	286		318				
	Heterogeneity: Tau <sup>2</sup> =	0.40 Chi <sup>2</sup>	= 38.1	4 df = 12	(P = 0)	0001): 12	= 69%	
	Test for overall effect	7 = 5 15 (		0001	ų o.			0.005 0.1 1 10 200
			0.01					
		000	10	mild			Odde Patia	Odde Datia
<b>B</b> ).	Study or Subgroup	Evente	Total	Evente	Total	Moight	M H Random 95% CL	M H Bandom 95% Cl
	Bei et al 2020	Lveins	Total	LVCING	10(a)	2 201	M-H, Kandoni, 35% Cl	M-n, Random, 55% Cl
	Ballet al 2020	0	36	2	91	3.2%	0.49 [0.02, 10.47]	
	Chen et al (2) 2020	2	50	15	241	8.8%	0.03 [0.14, 2.84]	
	Duan et al 2020	8	44	11	72	12.6%	1.23 [0.45, 3.35]	
	Shi et al 2020	4	53	3	53	8.5%	1.36 [0.29, 6.40]	
	Wang et al (1) 2020	24	36	31	102	14.4%	4.58 [2.04, 10.31]	
	Wang et al (2) 2020	19	54	34	111	15.5%	1.23 [0.62, 2.45]	
	Xu et al 2020	4	25	4	44	8.9%	1.90 [0.43, 8.39]	
	Zhang et al (1) 2020	34	55	34	166	15.7%	6.29 [3.24, 12.18]	
	Zhang et al (2) 2020	8	53	9	67	12.4%	1.15 [0.41, 3.21]	
	T-A-LIDEN CD		100		0.47	400.00	4 00 14 00 0 04	
	Total (95% CI)		406		947	100.0%	1.83 [1.00, 3.34]	-
	I otal events	103		143				
	Heterogeneity: 1 au-=	0.49; Chi	- 22.3	9, ai = 8 (	P = 0.0	(04); 1-= 6	14 %	0.01 0.1 1 10 100
	Test for overall effect.	2 = 1.96 (1	- = 0.0	5)				
		6010		mild			Odde Datio	Odde Patio
C).	Study or Subgroup	Events	Total	Events	Total	Weight	M H Random 95% CL	MH Bandom 95% Cl
	Study of Subgroup	Lycins	10101	LVCIRG	01	2.4%	0.40 0.06 4.261	M-1, Nandoli, 55% Ci
	Pointal 2020	1					0.4310.00.4.301	
	Bailet al 2020 Chap et al (2) 2020	1	30	C 0	241	10.20	2 07 14 54 5 261	
	Bai et al 2020 Chen et al (2) 2020 Ohan et al (2) 2020	1 26	36 50	5 66	241	10.2%	2.87 [1.54, 5.36]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duran et al 2020	1 26 9	36 50 11	5 66 11	241 14	10.2%	2.87 [1.54, 5.36] 1.23 [0.17, 9.02]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020	1 26 9 21	36 50 11 44	5 66 11 41	241 14 72	10.2% 3.9% 9.5%	2.87 [1.54, 5.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020	1 26 9 21 69	36 50 11 44 173	5 66 11 41 350	241 14 72 926	10.2% 3.9% 9.5% 11.8%	2.87 [1.54, 5.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020	1 26 9 21 69 6	36 50 11 44 173 7	5 66 11 41 350 16	91 241 14 72 926 44	10.2% 3.9% 9.5% 11.8% 3.3%	2.87 [1.54, 5.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020	1 26 9 21 69 65	36 50 11 44 173 7 69	5 66 11 41 350 16 1	91 241 14 72 926 44 11	10.2% 3.9% 9.5% 11.8% 3.3% 3.6%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020	1 26 9 21 69 6 35 19	36 50 11 44 173 7 69 53	5 66 11 350 16 17	91 241 72 926 44 11 53	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020	1 26 9 21 69 6 35 19 29	36 50 11 44 173 7 69 53 36	5 66 11 350 16 17 67	91 241 14 72 926 44 11 53 102	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 8.4%	2.87 [1.54, 5.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020	1 26 9 21 69 6 35 19 29 20	36 50 11 44 173 7 69 53 36 54	5 66 11 41 350 16 17 67 27	91 241 14 72 926 44 11 53 102 111	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 8.4% 9.8%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020	1 26 9 21 69 6 35 19 29 20 18	36 50 11 44 173 7 69 53 36 54 25	5 66 11 350 16 17 67 27 22	91 241 14 72 926 44 11 53 102 111 44	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 8.4% 9.8% 7.7%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhang et al (1) 2020	1 26 9 21 69 6 35 19 29 20 18 42	36 50 11 44 173 7 69 53 36 54 25 55	5 66 11 350 16 17 67 27 22 42	91 241 14 72 926 44 11 53 102 111 44 166	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 8.4% 9.8% 7.7% 9.7%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47]	
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	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Zhang et al (1) 2020 Zhou et al 2020	1 26 9 21 69 6 35 19 20 20 18 42 15	36 50 11 44 173 7 69 53 36 54 25 55 55 54	5 66 11 41 350 16 1 17 67 27 22 42 29	91 241 14 72 926 44 11 53 102 111 44 166 137	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 8.4% 9.8% 7.7% 9.6%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95]	
	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (1) 2020 Zhang et al (1) 2020 Zhou et al 2020 <b>Total (95% CI)</b>	1 26 9 21 69 65 19 29 20 18 42 15	36 50 11 44 173 7 69 53 36 54 25 55 55 54 <b>667</b>	5 66 11 350 16 1 17 67 27 22 42 29	91 241 14 72 926 44 11 53 102 111 44 166 137 <b>2012</b>	10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 8.4% 9.8% 7.7% 9.6% 100.0%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] <b>2.00 [1.25, 3.21]</b>	
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	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect :	1 26 9 21 69 6 35 19 20 18 42 15 310 0.46; Chi <sup>2</sup> Z = 2.89 (I	36 50 11 44 173 7 69 53 36 54 25 55 54 667 *= 46.2 ° = 0.00	5 66 111 350 16 1 7 7 27 22 42 29 694 0, df = 12 04)	91 241 14 72 926 44 11 53 102 111 44 166 137 <b>2012</b> (P < 0.	0.2% 10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.8% 9.8% 9.7% 9.6% 100.0% 000001);1	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] <b>2.00 [1.25, 3.21]</b> <sup>2</sup> = 74%	
D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect .	1 26 9 21 69 6 35 19 29 20 18 42 15 310 0.46; Chi <sup>2</sup> Z = 2.89 (I Seve	36 50 11 44 173 7 69 53 36 54 25 55 54 667 8 = 46.2 9 = 0.00	5 66 111 350 16 1 17 67 27 22 42 29 694 42 29 694 42 29 694 mile	91 241 14 72 926 44 11 53 102 111 44 166 137 <b>2012</b> (P < 0.	0.2% 10.2% 3.9% 9.5% 11.8% 3.6% 9.1% 8.4% 9.8% 7.7% 9.6% 100.0% 000001); 1	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] = 74% Odds Ratio	
D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect.	1 26 9 21 69 6 35 19 29 20 18 42 15 310 0.46; Chi <sup>2</sup> Z = 2.89 (I Seve Events	36 50 11 44 173 7 69 53 36 54 25 55 54 667 e = 0.00 re Total	5 66 11 41 350 16 1 17 67 27 22 42 29 694 0, df = 12 04) mili Events	91 241 12 72 926 44 11 53 102 111 44 166 137 <b>2012</b> (P < 0.	0.2% 10.2% 3.9% 9.5% 11.8% 3.6% 9.1% 8.4% 9.8% 9.7% 9.6% 9.6% 000001); 1 Weight	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] * = 74% Odds Ratio t M-H, Fixed, 95% Cl	0.01 0.1 10 100 Odds Ratio M-H, Fixed, 95% Cl
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D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhou et al 2020 Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Study or Subgroup Bai et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020	1 26 9 21 69 6 35 19 29 20 29 20 18 42 15 310 0.46; Chi <sup>a</sup> Z = 2.89 (I <b>Events</b> 2 2 1 2 2 310 0.46; Chi <sup>a</sup> Z = 2.89 (I 2 2 310 0.46; Chi <sup>a</sup> 2 2 3 2 3 2 3 2 3 2 3 3 1 3 3 1 3 3 1 3 3 1 3 3 1 3 3 1 3 3 1 3	30 500 111 44 173 7 69 53 36 54 25 55 54 667 re Total 36 50 7 7	5 66 111 350 16 1 1 7 7 27 22 42 29 694 0, df = 12 04) 694 0, df = 12 04) 8 8 9 8 9 4 2 9 3 11 1 5	91 241 14 72 926 44 41 15 53 102 111 44 166 137 <b>2012</b> (P < 0. <b>1</b> <b>Total</b> 91 241 241		2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] <sup>2</sup> = 74% Odds Ratio M-H, Fixed, 95% CI 1.73 [0.28, 10.78] 0.43 [0.05, 3.38] 3.12 [0.47, 20.56]	
D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhou et al 2020 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Study or Subgroup Bai et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020 Wang et al (1) 2020	1 26 9 21 69 6 35 19 20 18 42 15 310 0.46; Chi <sup>2</sup> Z = 2.89 (I <b>Seve</b> <b>Events</b> 2 1 2 2 8	36 50 11 44 173 7 89 53 36 54 25 55 54 667 7 2 = 46.2 2 = 0.00 Total 36 50 7 36 50 7 36 50 7 36 50 50 50 50 50 50 50 50 50 50	5 66 111 350 16 1 7 7 27 22 42 29 694 0, df = 12 04) 694 8 42 29 694 3 11 5 5 5 5	91 241 14 72 926 44 11 13 102 111 44 166 137 <b>2012</b> (P < 0. (P < 0. (P < 0. (P < 0. (P < 0. (P < 0. (P < 0. ) (P < 0. ) (P < 0.) (P < 0.)		2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] * = 74% Odds Ratio M-H, Fixed, 95% Cl 0.13 [0.28, 10.78] 0.43 [0.05, 3.38] 0.54 [1.68, 18.29]	Odds Ratio
D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhou et al 2020 <b>Total (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect. <b>Study or Subgroup</b> Bai et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020 Wang et al (1) 2020	1 26 9 21 69 6 35 19 29 20 18 42 15 310 0.46; Chi <sup>2</sup> Z = 2.89 (I <b>seve</b> <b>Events</b> 2 1 2 3 3 3 3 1 2 3 1 2 3 3 1 2 3 1 3 1	30 50 11 44 173 7 69 53 36 54 25 54 667 54 667 54 667 54 667 7 36 50 7 36	5 66 11 41 350 16 1 17 67 27 22 42 29 694 0, df = 12 04) 694 0, df = 12 04) <b>mili</b> <b>Events</b> 3 11 5 5	91 241 14 72 926 44 41 153 102 111 44 166 137 <b>2012</b> (P < 0. <b>1</b> <b>Total</b> 91 241 241 44 102	0.2% 10.2% 3.9% 9.5% 11.8% 3.6% 9.1% 8.4% 9.8% 7.7% 9.6% 100.0% 000001); 1 Weight 19.3% 44.5% 11.8% 24.4%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] 2 = 74% Odds Ratio M-H, Fixed, 95% CI 1.73 [0.28, 10.78] 0.43 [0.05, 3.38] 3.12 [0.47, 20.56] 5.54 [1.68, 18.29]	Odds Ratio M-H, Fixed, 95% CI
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D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhang et al (1) 2020 Zhou et al 2020 Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Study or Subgroup Bai et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020 Wang et al (1) 2020 Total (95% CI) Total events	1 26 9 21 69 6 35 19 29 20 18 42 15 310 0.46; Chi <sup>3</sup> Z = 2.89 (I <b>Seve</b> <b>Events</b> 2 2 2 2 1 2 3 10 0.46; Shi <sup>3</sup> 2 8 8 8 8 8 13	30 500 11 44 173 7 69 53 36 54 25 55 54 667 7 2 = 46.2 25 55 54 667 7 36 50 7 36 50 7 36	5 66 11 41 350 16 1 7 7 27 22 42 29 694 40, df = 12 04) 694 80, df = 12 04) <b>mild</b> <b>Events</b> 3 11 5 5	91 241 14 72 926 44 11 53 102 111 44 166 137 <b>2012</b> (P < 0. (P < 0. <b>1</b> <b>1</b> <b>1</b> <b>2</b> <b>1</b> <b>1</b> 4 4 102 (P < 0. <b>1</b> <b>1</b> 4 4 112 102 111 4 4 102 102 111 4 4 102 102 111 4 4 102 102 102 102 102 102 102 102 102 102	10.2% 10.2% 3.9% 9.5% 11.8% 3.3% 3.3% 9.1% 9.1% 9.7% 9.6% 100.0% 00001); 1 Weight 19.3% 44.5% 11.8% 24.4% 100.0%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] <sup>2</sup> = 74% <sup>2</sup> = 74% <sup>3</sup> = 74% <sup>3</sup> = 74%	Odds Ratio M-H, Fixed, 95% Cl
D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect. Study or Subgroup Bai et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020 Wang et al (1) 2020 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> =	1 26 9 21 69 6 35 19 29 20 18 42 15 310 0.46; Chi <sup>a</sup> Z = 2.89 (f <b>Seve</b> <b>Events</b> 2 1 2 2 1 2 8 3 13 4.87, df =	30 500 111 44 173 7 693 533 667 54 667 7 7 667 7 7 667 7 7 7 7 693 53 667 7 7 7 7 7 7 8 9 9 53 36 54 25 55 54 667 7 7 7 7 7 8 9 9 53 667 7 7 7 7 7 8 9 9 53 56 54 667 7 7 7 7 7 7 7 7 7 7 7 7 7	5 66 111 41 3500 16 1 1 7 7 27 22 42 29 694 40, df = 12 04)	91 241 14 72 926 44 11 53 102 111 44 166 137 <b>2012</b> (P < 0. <b>1</b> <b>Total</b> 91 241 44 102 478 = 38%	0.2% 10.2% 3.9% 9.5% 11.8% 3.3% 3.3% 9.1% 9.1% 9.8% 7.7% 9.6% 100.0% 00001);1 Weight 19.3% 44.5% 11.8% 24.4% 100.0%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] <sup>2</sup> = 74% <sup>2</sup> = 74% <sup>3</sup> Odds Ratio <b>M-H, Fixed, 95% CI</b> 1.73 [0.28, 10.78] 0.43 [0.05, 3.38] 3.12 [0.47, 20.56] 5.54 [1.68, 18.29] 2.24 [1.08, 4.65]	Odds Ratio M-H, Fixed, 95% Cl
D).	Bai et al 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Guan et al 2020 Jian-Ya et al 2020 Liu et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Xu et al 2020 Zhou et al 2020 Total (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Bai et al 2020 Chen et al (2) 2020 Jian-Ya et al 2020 United the state of	1 26 9 21 69 6 35 19 29 20 18 42 15 310 0.46; Chi <sup>2</sup> Z = 2.89 (f <b>Events</b> 2 1 2 8 <b>seve</b> <b>Events</b> 2 1 2 8 310 0.46; Chi <sup>2</sup> Z = 2.89 (f 2 310 0.46; Chi <sup>2</sup> Z = 2.89 (f 2 2 310 0.46; Chi <sup>2</sup> Z = 2.89 (f 2 310 0.46; Chi <sup>2</sup> Z = 2.89 (f 2 310 2 32 2 32 310 2 32 32 32 32 34 32 32 32 32 32 32 32 32 32 32 32 32 32	30 500 111 44 173 7 89 53 36 54 25 55 54 667 7 36 50 7 36 50 7 36 50 7 36 50 11 14 4 17 36 54 25 55 54 667 7 8 9 9 53 36 54 25 55 54 667 7 8 9 9 53 54 25 55 54 667 7 8 9 9 53 54 25 55 54 667 7 8 9 9 53 54 25 55 54 667 7 8 9 9 53 54 25 55 54 667 7 8 9 9 53 54 25 55 54 667 7 8 9 9 53 54 25 55 54 8 667 7 8 9 9 53 54 54 667 7 8 9 9 53 54 55 55 54 7 7 8 9 9 7 7 8 9 9 53 54 55 55 54 7 8 10 10 10 10 10 10 10 10 10 10	5 66 11 41 350 16 1 7 7 27 22 42 29 694 0, df = 12 04) <b>Events</b> 3 3 11 5 5 5 24 0.18);  ₹= 03)	91 241 14 72 926 44 11 53 102 111 44 166 137 <b>2012</b> (P < 0. <b>1</b> <b>Total</b> 91 241 241 44 102 <b>478</b>	0.2% 10.2% 3.9% 9.5% 11.8% 3.3% 3.6% 9.1% 9.8% 9.7% 9.6% 100.0% 00001); 1 Weight 19.3% 44.5% 11.8% 24.4% 100.0%	2.87 [1.54, 6.36] 1.23 [0.17, 9.02] 0.69 [0.33, 1.47] 1.09 [0.78, 1.52] 10.50 [1.16, 95.17] 10.29 [1.25, 84.83] 1.18 [0.53, 2.65] 2.16 [0.86, 5.44] 1.83 [0.91, 3.69] 2.57 [0.90, 7.38] 9.54 [4.67, 19.47] 1.43 [0.70, 2.95] 2.00 [1.25, 3.21] <sup>2</sup> = 74% Odds Ratio M-H, Fixed, 95% CI 9.1.73 [0.28, 10.78] 9.3.12 [0.47, 20.56] 5.54 [1.68, 18.29] 2.24 [1.08, 4.65]	Odds Ratio M-H, Fixed, 95% CI

**Figure 3. A forest plot of the association between clinical manifestations and the risk of severe COVID-19. A**) Dyspnea; **B**) Anorexia; **C**) Fatique; **D**) Dizziness.

severe mild Std. Mean Difference Std. Mean Difference A). IV, Random, 95% CI Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI 0.75 Bai et al 2020 36 20.8% 1.19 [0.78, 1.61] 26 6.18 22 91 Chen et al (2) 2020 0.83 [0.51, 1.14] 20.67 1.53 50 19.45 1.46 241 22.6% Chen et al (3) 2020 2.54 11 20.33 247 13.9% 0.00 [-0.79, 0.79] 20.33 14 Duan et al 2020 21.5% 0.00 [-0.38, 0.38] 19 1.53 44 19 1.51 72 0.66 [0.27, 1.05] Shi et al 2020 27 12 23 53 21 3.81 53 21.2% Total (95% CI) 194 471 100.0% 0.57 [0.14, 1.01] Heterogeneity: Tau<sup>2</sup> = 0.20; Chi<sup>2</sup> = 21.95, df = 4 (P = 0.0002); l<sup>2</sup> = 82% Test for overall effect: Z = 2.57 (P = 0.01) mild Std. Mean Difference Std. Mean Difference severe B). Study or Subgroup SD Total SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI Mean Mean Bai et al 2020 134.67 16.21 36 126.67 14.31 91 23.3% 0.53 [0.14, 0.93] 0.12 [-0.19, 0.42] Chen et al (2) 2020 50 38.5% 124 15.27 122.28 241 14.27 Chen et al (3) 2020 134.2 27.1 11 126.8 22.6 14 5.7% 0.29 [-0.50, 1.08] 125 20.69 0.29 [-0.09, 0.67] Duan et al 2020 44 120.33 121 72 25.2% Huang et al 2020 145 36.54 0.99 [0.29, 1.68] 13 123.33 8 59 74% 28 Total (95% CI) 154 446 100.0% 0.33 [0.14, 0.52] Heterogeneity: Chi<sup>2</sup> = 6.39, df = 4 (P = 0.17); I<sup>2</sup> = 37% Test for overall effect: Z = 3.46 (P = 0.0005)

Figure 4. A forest plot of the association between clinical manifestation and the risk of severe COVID-19. A) Respiratory rate; B) Systolic blood pressure.

results are consistent with those of previous meta-analyses<sup>43,44</sup> that indicated that chronic respiratory disease, cardiovascular disease, diabetes, and hypertension are significantly associated with higher COVID-19 mortality. Hypertension and diabetes are also associated with higher mortality among patients with dengue fever, West Nile virus infection, Zika virus infection, and yellow fever<sup>45</sup>. To date, no study has reported details of the primary mechanism underlying the association between severe COVID-19 and comorbid factors. However, immune responses might be the most crucial factor underlying this association. Patients with comorbidities such as cardiovascular disease, chronic respiratory disease, hypertension, and diabetes were observed to have a lower immunity status than healthy individuals<sup>46–48</sup>. Since COVID-19 primarily affects the respiratory tract<sup>49</sup>, patients with chronic respiratory diseases might be at a higher risk of contracting severe COVID-19. In addition, endothelial dysfunction might also play a pivotal role<sup>50</sup>.

COVID-19 is a novel disease, and the immune response of this disease is not completely understood. Our data suggest that elevated leukocyte and neutrophil levels and reduced lymphocyte levels are associated with severe COVID-19. In other viral infections, such as influenza, elevated leukocyte and neutrophil levels serve as important predictors of disease severity<sup>51</sup>. The role of leukocytes in the pathogenesis of COVID-19 is conflicting. In most cases, viral infections have been observed to cause leukopenia<sup>52</sup>. Furthermore, a study also reported that leukopenia was observed at a significantly higher frequency among COVID-19 patients than among non-COVID-19 patients<sup>53</sup>. However, in our present study, we did not compare COVID-19 and non-COVID-19 patients. The major factor that seemed to affect our findings was the occurrence of cytokine storm in patients. In COVID-19, there is an immune system overreaction, which

results in a cytokine storm. In this condition, leukocytes might be over-activated, which might lead to the release of high levels of cytokines<sup>54</sup>. Consistent with our data, a study has confirmed that cytokine storm is significantly associated with severe COVID-19<sup>55</sup>. The theory underlying the role of neutrophils in COVID-19, as reported in our study, remains unclear. The speculations might be attributed to the involvement of neutrophil extracellular traps (NETs). While no study has assessed the precise role of NETs in COVID-19 pathogenesis, certain researchers speculate that SARS-CoV-2 might stimulate neutrophils to produce NETs, similar to several other viral pathogens<sup>56</sup>. Furthermore, this might lead to neutrophil infiltration in pulmonary capillaries, organ damage, and the development of acute respiratory distress syndrome<sup>57</sup>.

Low lymphocyte levels were observed in patients with severe COVID-19 compared with those with mild COVID-19. In the context of the immunological mechanism, our results might be contradictory. Lymphocyte subsets are known to play an important role in the action against bacterial, viral, fungal, and parasitic infections<sup>58</sup>; therefore, the levels of circulating lymphocytes should increase. The immunological response in COVID-19 is unique and remains unclear. However, certain propositions might help describe our findings. First, coronaviruses infect human cells through ACE2 receptors<sup>59</sup>. Since ACE2 receptors are also expressed by lymphocytes<sup>60</sup>, the coronaviruses may enter lymphocytes and induce apoptosis. Second, the feedback mechanism between pro-inflammatory cytokines (such as IL-6) and lymphocytes might also explain our results. A study revealed that elevation in the levels of pro-inflammatory cytokines correlated with reduction in the levels of lymphocytes<sup>61</sup>. Moreover, our findings also confirmed the significant elevation in the levels of IL-6. Third, ACE2 receptors

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A).	Study or Subgroup	Mean	SD	Total	Mean	SD 1	fotal V	: Neiaht	IV. Random, 95% Cl	N. Random, 95% Cl
	Chen et al (1) 2020	9.2	3.6	11	4 7	1.5	10	6 4 %	1 54 [0 54 2 54]	
	Chen et al (2) 2020	4 62	2.06	50	4 67	1.32	241	8 4 %	-0.03 (-0.34, 0.27)	+
	Chen et al (3) 2020	4.5	2.2	11	4.5	1.7	14	7.1%	0.00[-0.79]0.79]	
	Duan et al 2020	8.9	6.44	44	6.43	3.56	72	8.2%	0.51 [0.12, 0.89]	+
	Huang et al 2020	4.26	1.64	15	4 96	1.85	28	7.6%	-0.39 (-1.02, 0.25)	
	Jian-Ya et al 2020	8.1	4 99	22	4 87	2.31	283	8.1%	1,25 (0,80, 1,69)	+
	Shi et al 2020	6.63	6.61	7	5.63	2.68	44	7.0%	0.29 (-0.51, 1.09)	
	Wang et al (1) 2020	12.36	1.25	48	7.72	0.51	53	7.1%	4.91 [4.12, 5.71]	
	Wang et al (3) 2020	9.73	5.23	13	5.47	3.52	28	7.4%	1.01 [0.32, 1.71]	
	Xu et al 2020	6.67	4.79	36	4.33	1.58	102	8.2%	0.84 [0.44, 1.23]	+
	Zhang et al (1) 2020	4.6	1.73	25	4.47	1.69	44	8.0%	0.08 [-0.42, 0.57]	+
	Zhang et al (2) 2020	6.57	4.03	55	4.33	2.02	166	8.4%	0.84 [0.52, 1.15]	+
	Zhou et al 2020	6.1	3.8	56	4.63	1.81	82	8.3%	0.52 [0.18, 0.87]	+
	T-4-1 (05%) ON			202				00.00	0.0440.05 4.001	•
	Total (95% CI)	0.72.06	iz - 10	393 1 20 4	(- 10 /D	~ 0.00	0043-12	- 0.20%	0.84 [0.35, 1.33]	<b>▼</b> 1 1 1
	Test for overall effect	7 = 3.36	(P = 0)	3.20, u 0008)	1 = 12 (F	~ 0.00	001), 1	- 93%		-10 -5 0 5 10
	rootion ovorall oncor.	2 0.00	() – <u>0</u> .	0000,						
D)		S	evere		n	nild			Std. Mean Difference	Std. Mean Difference
Б).	Study or Subgroup	Mean	SD	Total	Mean	SD 1	Total V	Veight	IV, Random, 95% Cl	IV, Random, 95% Cl
	Chen et al (1) 2020	8	3.7	11	3.1	1.3	10	7.0%	1.66 [0.64, 2.68]	
	Chen et al (2) 2020	3.23	1.53	50	2.92	1.17	241	9.1%	0.25 [-0.06, 0.55]	-
	Chen et al (3) 2020	2.73	2.54	11	3.17	2.64	14	7.8%	-0.16 [-0.96, 0.63]	
	Duan et al 2020	8	6.28	44	5.2	3.71	72	8.9%	0.57 [0.19, 0.96]	+
	Gao et al 2020	2.65	1.49	15	3.43	1.63	28	8.3%	-0.48 [-1.12, 0.15]	
	Huang et al 2020	9.13	5.65	13	4.17	3.2	28	8.0%	1.18 [0.47, 1.89]	
	Jian-Ya et al 2020	6.1	6.15	7	3.83	2.45	44	7.7%	0.71 [-0.10, 1.52]	
	Shi et al 2020	11.23	1.24	48	6.48	0.48	53	1.1%	5.11 [4.29, 5.93]	
	Wang et al (1) 2020	5.03	4.09	30	2.83	1.5	102	8.9%	0.89 [0.50, 1.29]	-
	Vialigieral (3) 2020 Vicet al 2020	0.0	4.70	22	2.46	4.47	203	0.0%	0.25 [-0.16, 0.09]	-
	Zhang et al (1) 2020	5.33	4.26	55	2.40	1.79	166	9.1%	0.86 [0.16, 1.16]	+
	Total (95% CI)			337			1085 1	00.0%	0.92 [0.39, 1.45]	•
	Heterogeneity: Tau <sup>2</sup> =	0.79; Ch	i <sup>z</sup> = 15	1.21, d	f= 11 (P	< 0.00	001); I²	= 93%		-10 $-5$ $0$ $-5$ $10$
	Test for overall effect:	Z = 3.39	(P = 0.	0007)						
									o.u. p.::	
C).	Study or Subgroup	Se	evere	atal E	mild	Total	Mojak	4 M U	Odds Ratio	Odds Ratio
	Study of Subgroup	Ever			vents	TOLAL	vveigr	it IVI-F1,	, Random, 95% CI	M-H, Random, 95% Ci
	Callet al 2020		39	58	/5	240	21.19	Xo 	4.52 [2.45, 8.33]	
	Chen et al (1) 2020		8	11	1	10	7.39	\$6 24	.00 [2.06, 279.62]	
	Chen et al (2) 2020		24	50	42	241	20.89	80	4.37 [2.29, 8.35]	
	Huang et al 2020		11	13	15	28	11.69	Xo .	4.77 [0.89, 25.57]	
	Zhang et al (1) 2020		18	55	21	166	20.19	Xo	3.36 [1.63, 6.94]	
	Zhang et al (2) 2020		58	82	46	56	19.19	8	0.53 [0.23, 1.21]	-7.1
	Total (05% CI)			260		744	100.00	4	3 10 [1 14 7 00]	
	Total (95% CI)		c 0	209	200	741	100.0	70	5.19[1.44,7.09]	-
	Total events	0.00.	58		200		0000.13	700	1	
	Test for overall offer	= 0.69, ( + 7 - 2 0	5 /P -	23.04,	ui= 5 (f	<sup>2</sup> = 0.0	003), 1	= / 8%	0.0	02 0.1 1 10 500
	restion overall ellec	1. 2 - 2.0	io (r -	0.004	,					
			moro			mild			Std Mean Difference	Std Mean Difference
D).	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weigh	t IV. Fixed. 95% C	IV. Fixed, 95% Cl
	Chen et al (1) 2020	138.1	15.9	11	135.8	18.4	10	3.09	6 0.131-0.73.0.99	
	Chen et al (2) 2020	131.17	17.94	50	130.83	16.61	241	24.09	6 0.02 (-0.28, 0.32	-
	Duan et al 2020	129.33	13.79	44	129.1	16.28	72	15.89	6 0.01 [-0.36, 0.39	_ <b>_</b>
	Huang et al 2020	119.67	14.12	13	130.17	15.62	28	4.99	6 -0.68 [-1.35, -0.00	
	Jian-Ya et al 2020	135	28.47	7	137	22.22	44	3.5%	-0.09 [-0.88, 0.71	
		100 7	7.00	60	127.8	16.13	11	5.49	% -0.54 [-1.18, 0.10	
	Liu et al 2020	122.7	1.82	03	121.0					
	Liu et al 2020 Wang et al (3) 2020	122.7	20.7	22	129.2	18	283	11.89	6 -0.44 [-0.87, -0.00	
	Liu et al 2020 Wang et al (3) 2020 Xu et al 2020	122.7 121.2 138.5	20.7	22	129.2	18 19.31	283 44	11.89 9.29	% -0.44 [-0.87, -0.00 % -0.03 [-0.52, 0.47	
	Liu et al 2020 Wang et al (3) 2020 Xu et al 2020 Zhou et al 2020	122.7 121.2 138.5 126.33	7.82 20.7 16.59 17.52	22 25 54	129.2 138.97 129.33	18 19.31 14.98	283 44 137	11.89 9.29 22.49	% -0.44 [-0.87, -0.00 % -0.03 [-0.52, 0.47 % -0.19 [-0.51, 0.13	
	Liu et al 2020 Wang et al (3) 2020 Xu et al 2020 Zhou et al 2020 Total (95% CI)	122.7 121.2 138.5 126.33	7.82 20.7 16.59 17.52	22 25 54 295	129.2 138.97 129.33	18 19.31 14.98	283 44 137 870	11.89 9.29 22.49 <b>100.0</b> 9	<ul> <li>-0.44 [-0.87, -0.00</li> <li>-0.03 [-0.52, 0.47</li> <li>-0.19 [-0.51, 0.13</li> <li>-0.15 [-0.30, -0.00</li> </ul>	
	Liu et al 2020 Wang et al (3) 2020 Xu et al 2020 Zhou et al 2020 <b>Total (95% CI)</b> Heterogeneity: Chi <sup>2</sup> = 8	122.7 121.2 138.5 126.33 3.16, df =	20.7 20.7 16.59 17.52 8 (P =	22 25 54 <b>295</b> 0.42): P	129.2 138.97 129.33	18 19.31 14.98	283 44 137 <b>870</b>	11.89 9.29 22.49 <b>100.0</b> 9	<ul> <li>6.44 [-0.87, -0.00</li> <li>6.03 [-0.52, 0.47</li> <li>6.19 [-0.51, 0.13</li> <li>6.15 [-0.30, -0.00</li> </ul>	

Figure 5. A forest of the association between complete blood count and the risk of severe COVID-19. A) White blood cells; B) Neutrophil count; C) Lymphocytopenia; D) Hemoglobin.

Church a new Cash same	S	severe			mild	1.1 <u>1</u> 1.11		Std. Mean Difference	St	d. Mean Diffe	erence
Study of Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	N	/, Random, 9	5% CI
Chen et al (1) 2020	51	28.3	11	24.2	4.1	10	6.3%	1.24 [0.29, 2.19]			
Chen et al (3) 2020	33.97	15.88	50	24.04	7.88	241	12.8%	1.02 [0.70, 1.34]			-
Duan et al 2020	29	5.94	11	24.93	14.66	14	7.6%	0.34 [-0.46, 1.13]			
Gao et al 2020	43.17	28.74	44	29.33	18.16	72	12.1%	0.60 [0.22, 0.99]			
Huang et al 2020	37	19.08	50	21	7.5	115	12.3%	1.31 (0.94, 1.67)			
Jian-Ya et al 2020	48	33	13	32.83	12.89	28	8.8%	0 70 10 02 1 381		-	
Shi et al 2020	25.67	18 37	7	22	9.96	44	7.6%	0 32 60 48 1 1 21		_	
Wang et al (1) 2020	210.07	165.2	48	46 15	13	53	11 496	1 51 [1 06 1 95]			
Wang et al (1) 2020	213.2	11 42	40	40.15	4.3	20	0.200	0.01 [1.00, 1.93]			
Wang et al (2) 2020	21.0	11.42	10	33.21	10.24	100	9.370	-0.33 [-0.96, 0.30]			
Zhang et al (1) 2020	50.67	30.89	30	29.33	12.78	102	11.9%	1.11 [0.71, 1.51]			
Total (95% CI)			285			707	100.0%	0.83 [0.51, 1.14]		<	•
Heterogeneity: Tau <sup>2</sup> =	0.18; Ch	i <sup>2</sup> = 34.9	93, df =	9 (P < (	0.0001);	<sup>2</sup> = 74	%		+ +		1
Test for overall effect: 2	Z= 5.14	(P < 0.0	0001)						-4 -2	0	2
	S	severe			mild			Std. Mean Difference	St	d. Mean Diffe	erence
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	n	/, Random, 9	5% CI
Chen et al (1) 2020	41.4	14.9	11	17.6	5.8	10	4.4%	1.98 [0.90, 3.07]			
Chen et al (2) 2020	24.4	12.67	50	21.45	11.09	241	10.2%	0.26 [-0.05, 0.56]			
Chen et al (3) 2020	27	11.88	11	30.17	25.95	14	6.2%	-0.15 [-0.94, 0.65]			
Duan et al 2020	30.33	21.84	44	27.33	22.69	72	9.7%	0.13 [-0.24, 0.51]			
Gao et al 2020	29.67	16.36	15	26	17.19	28	7.5%	0.21 [-0.42, 0.84]			-
Huang et al 2020	48	33	13	32.83	12.89	28	7.1%	0.70 (0.02, 1.38)		-	
Jian-Ya et al 2020	22	18 37	7	21.33	13.79	44	6.2%	0.05 [-0.75, 0.84]			-
Shi et al 2020	88.64	46.39	49	34.15	A 1A	53	Q 196	1 68 [1 23 2 1 4]			_
Wang at al (1) 2020	00.04	20.33	26	24.13	15 70	102	0.606	0.64 (0.22, 0.00)		_	_
Wang et al (1) 2020	37	28.34	50	24.07	14.26	115	9.0%	1.07 (0.22, 0.99)			-
Wang et al (2) 2020	40	22.9	50	21.33	14.20	115	9.9%	1.07 [0.72, 1.43]			
Zhang et al (1) 2020	37	20.04	55	23	14.21	100	10.2%	0.77 [0.46, 1.08]			
Zhou et al 2020	38.33	20.56	54	27.33	18.73	137	10.1%	0.57 [0.25, 0.89]		1.0	
			394			1010	100.0%	0.64 [0.35, 0.93]		•	•
Total (95% CI)				11/0 -	0.0000	1);  = '	79%		+		1
Total (95% Cl) Heterogeneity: Tau <sup>2</sup> =	0.19; Ch	i <sup>2</sup> = 53.3	36, df =	11 (F ~					-4 -2	0	2
<b>Total (95% CI)</b> Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2	0.19; Ch Z= 4.31	i² = 53.: (P < 0.0	36, df = 1001)	II (F s							
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2	0.19; Ch Z = 4.31 S	i <sup>z</sup> = 53.: (P < 0.0 Severe	36, df = 1001)	11 (F \$	mild			Std. Mean Difference	St	d. Mean Diffe	erence
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup	0.19; Ch Z = 4.31 S Mean	i <sup>2</sup> = 53.3 (P < 0.0 Severe SD	36, df = 1001) Total	Mean	mild SD	Total	Weight	Std. Mean Difference IV, Random, 95% Cl	St	d. Mean Diffe /, Random, 9	erence 5% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020	0.19; Ch Z = 4.31 S <u>Mean</u> 90.7	i <sup>2</sup> = 53.3 (P < 0.0 Severe SD 38.5	36, df= 1001) Total 11	Mean 73.3	mild SD 11.6	Total 10	Weight 4.6%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45]	St	d. Mean Diffe /, Random, 9	erence 5% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020	0.19; Ch Z = 4.31 <b>S</b> <u>Mean</u> 90.7 54.43	i <sup>2</sup> = 53.: (P < 0.0 Severe SD 38.5 18.09	36, df = 1001) Total 11 50	Mean 73.3 53.07	mild SD 11.6 19.04	<b>Total</b> 10 241	Weight 4.6% 9.9%	Std. Mean Difference IV, Random, 95% Cl 0.58 (-0.30, 1.45) 0.07 (-0.23, 0.38)	St	d. Mean Diffe /, Random, 9	srence 5% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (3) 2020	0.19; Ch Z = 4.31 <u>S</u> Mean 90.7 54.43 67	i <sup>2</sup> = 53. (P < 0.0 Severe SD 38.5 18.09 15.6	36, df = 1001) Total 11 50 11	Mean 73.3 53.07 64.3	mild SD 11.6 19.04 14.3	<b>Total</b> 10 241 14	Weight 4.6% 9.9% 5.2%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97]	Sto N	d. Mean Diffe	erence 5% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020	0.19; Ch Z = 4.31 <b>S</b> Mean 90.7 54.43 67 106.7	iř = 53.3 (P < 0.0 Severe SD 38.5 18.09 15.6 85.6	36, df = 1001) Total 11 50 11 44	Mean 73.3 53.07 64.3 76.8	mild SD 11.6 19.04 14.3 69.98	Total 10 241 14 72	Weight 4.6% 9.9% 5.2% 9.1%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77]	Str N	d. Mean Diffe	erence 5% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Gao et al 2020	0.19; Ch Z = 4.31 <b>S</b> Mean 90.7 54.43 67 106.7 65.33	i <sup>2</sup> = 53.3 (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55	36, df = 1001) Total 11 50 11 44 15	Mean 73.3 53.07 64.3 76.8 66.96	mild SD 11.6 19.04 14.3 69.98 13.38	Total 10 241 14 72 28	Weight 4.6% 9.9% 5.2% 9.1% 6.6%	Std. Mean Difference IV, Random, 95% Cl 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51]	St N	d. Mean Diffe	erence 5% Cl 
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Gao et al 2020 Huang et al 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93	i <sup>P</sup> = 53. (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89	36, df = 1001) 11 11 50 11 44 15 13	Mean 73.3 53.07 64.3 76.8 66.96 71.8	mild SD 11.6 19.04 14.3 69.98 13.38 21.25	Total 10 241 14 72 28 28	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3%	Std. Mean Difference IV, Random, 95% Cl 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78]	St N	d. Mean Diffe	erence 5% Cl 
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Gao et al 2020 Huang et al 2020 Jian-Ya et al 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67	i <sup>P</sup> = 53. (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53	36, df = 1001) 11 11 50 11 44 15 13 7	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56	Total 10 241 14 72 28 28 28 44	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.44 [-1.29, 0.32]	Str N	d. Mean Diffe	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Chen et al (3) 2020 Duan et al 2020 Gao et al 2020 Huang et al 2020 Jian-Ya et al 2020 Shi et al 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67 1725	i <sup>P</sup> = 53.: (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75	36, df = 1001) 11 11 50 11 44 15 13 7 49	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.62	<b>Total</b> 10 241 14 72 28 28 28 44	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [112, 2, 02]	Str N	d. Mean Diffe	erence 5% Cl 
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect : Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Gao et al 2020 Huang et al 2020 Jian-Ya et al 2020 Shi et al 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5	i <sup>P</sup> = 53.: (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75	36, df = 1001) <b>Total</b> 11 50 11 44 15 13 7 8 26	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 24	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.63 21.63	Total 10 241 14 72 28 28 28 44 53	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [1.14, 0.05]	Str N	d. Mean Diffe	
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Chen et al 2020 Gao et al 2020 Huang et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (1) 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5 84 7	i <sup>P</sup> = 53. (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75 30.88	36, df = 1001) <b>Total</b> 11 50 11 44 15 13 7 48 36 50	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 71 71	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.63 19.55 14.55	Total 10 241 14 72 28 28 44 53 102	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4% 9.0%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.95] 0.47 [-1.20, 0.22]	Str N	d. Mean Diffe /, Random, 9	erence 5% Cl 
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Gao et al 2020 Huang et al 2020 Jian-Ya et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020	0.19; Ch Z = 4.31 ( 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5 84 70.43	i <sup>P</sup> = 53. (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75 30.88 18.62	36, df = 1001) <b>Total</b> 11 50 11 44 15 13 7 48 36 50	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 71 63.27	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.63 19.55 13.59	Total 10 241 14 72 28 28 44 53 102 115	Weight 4.6% 9.9% 5.2% 6.6% 6.3% 5.1% 8.4% 9.0% 9.6%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.95] 0.47 [0.13, 0.80] 0.47 [0.13, 0.80] 0.47 [0.13, 0.80] 0.47 [0.10, 0.87] 0.47 [0.10, 0.87] 0	St N	d. Mean Diffe /, Random, 9	erence 5% Cl 
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 3 Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Huang et al 2020 Huang et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Wang et al (3) 2020	0.19; Ch Z = 4.31 ( 90.7 54.43 67 106.7 65.33 61.67 172.5 84 70.43 71.7	i <sup>P</sup> = 53.: (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75 30.88 18.62 38.35	36, df = 1001) 11 11 50 11 44 15 13 7 48 36 50 22	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 71 63.27 62.6	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.63 19.55 13.59 17.5	Total 10 241 14 72 28 28 44 53 102 115 283	Weight 4.6% 9.9% 5.2% 6.6% 6.3% 5.1% 8.4% 9.0% 9.6% 8.5%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.95] 0.47 [0.13, 0.80] 0.46 [0.03, 0.90]	Str N	d. Mean Diffe	erence 5% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Gao et al 2020 Huang et al 2020 Jian-Ya et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Wang et al (3) 2020 Xu et al 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5 84 70.43 71.7 64.77	i <sup>P</sup> = 53.: (P < 0.0 <b>Severe</b> <b>SD</b> 38.5 18.09 15.6 85.6 15.55 32.89 16.53 32.89 16.53 32.89 16.53 32.89 16.53 32.89 18.62 38.35 22.17	36, df = 1001) 11 11 50 11 44 15 13 7 48 36 50 22 25	Mean 73.3 53.07 64.3 76.8 66.9 71.8 69 116.5 71 63.27 62.6 57.6	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.63 19.55 13.59 17.5 16.94	Total 10 241 14 72 28 28 44 53 102 115 283 44	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4% 9.6% 8.5% 7.9%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.93] 0.47 [0.13, 0.80] 0.46 [0.03, 0.90] 0.37 [-0.12, 0.87]	Str N	d. Mean Diffe /, Random, 9	erence 5% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: J Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Duan et al 2020 Huang et al 2020 Huang et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Wang et al (3) 2020 Xu et al 2020 Zhang et al (1) 2020	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5 84 70.43 71.7 64.77 82.33	i <sup>p</sup> = 53. (P < 0.0 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75 30.88 18.62 38.35 22.17 33.5	36, df = 1001) 11 50 11 44 15 13 7 48 36 50 22 25 55	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 71 63.27 62.6 57.6 67	mild SD 11.6 19.04 14.3 69.98 13.38 21.25 14.56 21.63 19.55 13.59 17.5 16.94 17.95	Total 10 241 14 72 28 28 44 53 102 115 283 44 166	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4% 9.0% 9.6% 8.5% 7.9% 9.8%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.95] 0.47 [0.13, 0.80] 0.46 [0.03, 0.90] 0.37 [-0.12, 0.87] 0.67 [0.36, 0.98]	Str N	d. Mean Diffe /, Random, 9	erence 5% CI
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Chen et al 2020 Gao et al 2020 Gao et al 2020 Jian-Ya et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (3) 2020 Xu et al 2020 Zhang et al (1) 2020 Xu et al 2020 Zhang et al (1) 2020 Total (95% CI)	0.19; Ch Z = 4.31 ( 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5 84 70.43 71.7 64.77 82.33	i <sup>p</sup> = 53.3 (P < 0.0 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75 30.88 18.62 38.35 22.17 33.5	36, df = 1001) Total 11 50 11 44 15 13 7 48 36 50 22 25 55 387	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 71 63.27 62.6 57.6 67	mild SD 11.6 19.04 13.38 21.25 14.56 21.63 19.55 13.59 17.5 16.94 17.95	Total 10 241 72 28 28 44 53 102 115 283 44 166 1200	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4% 9.0% 9.6% 8.5% 7.9% 9.8% <b>100.0%</b>	Std. Mean Difference IV, Random, 95% Cl 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.51] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.95] 0.47 [0.13, 0.80] 0.46 [0.03, 0.90] 0.37 [-0.12, 0.87] 0.67 [0.36, 0.98] 0.42 [0.17, 0.66]	Str N	d. Mean Diffe	erence 5% Cl
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: : Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Chen et al (2) 2020 Gao et al 2020 Huang et al 2020 Huang et al 2020 Shi et al 2020 Wang et al (1) 2020 Wang et al (2) 2020 Wang et al (3) 2020 Xu et al 2020 Zhang et al (1) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	0.19; Ch Z = 4.31 90.7 54.43 67 106.7 65.33 74.93 61.67 172.5 84 70.43 71.7 64.77 82.33 0.13; Ch	i <sup>p</sup> = 53.3 (P < 0.0 38.5 18.09 15.6 85.6 15.55 32.89 16.53 45.75 30.88 18.62 38.35 22.17 33.5	36, df = 1001) 11 50 11 44 15 13 7 48 36 50 22 25 55 55 <b>387</b> 43, df =	Mean 73.3 53.07 64.3 76.8 66.96 71.8 69 116.5 71 63.27 62.6 57.6 67 12 (P <	mild SD 11.6 19.04 13.38 21.25 14.56 21.63 19.55 13.59 17.5 16.94 17.95	Total 10 241 14 72 28 28 44 53 102 115 283 44 166 <b>1200</b> ); I <sup>2</sup> = 7;	Weight 4.6% 9.9% 5.2% 9.1% 6.6% 6.3% 5.1% 8.4% 9.0% 9.6% 8.5% 7.9% 9.8% <b>100.0%</b> 2%	Std. Mean Difference IV, Random, 95% CI 0.58 [-0.30, 1.45] 0.07 [-0.23, 0.38] 0.18 [-0.62, 0.97] 0.39 [0.01, 0.77] -0.11 [-0.74, 0.61] 0.12 [-0.54, 0.78] -0.49 [-1.29, 0.32] 1.58 [1.13, 2.03] 0.56 [0.18, 0.95] 0.47 [0.13, 0.80] 0.46 [0.03, 0.90] 0.37 [-0.12, 0.87] 0.67 [0.36, 0.98] 0.42 [0.17, 0.66]	Str N	d. Mean Diffe	erence 5% CI 

Figure 6. A forest plot of the association between the risk of severe COVID-19 and the levels of AST (A), ALT (B), and serum creatinine (C).

are expressed by cells from various organs, including the thymus and spleen<sup>62</sup>. As coronaviruses infect human cells through the ACE2 receptors, the spleen and thymus might also be damaged in patients with COVID-19, which would lead to lower levels of lymphocyte production. Fourth, lymphocyte proliferation requires a balanced metabolism, and metabolic disorders such as hyperlactic acidemia have been reported

to disturb lymphocyte proliferation<sup>63</sup>. Hyperlactic acidemia has been observed in patients with severe COVID-19<sup>64</sup>.

The studies included in this systematic review also suggest that the levels of D-dimer were significantly higher in patients with severe COVID-19. Coagulation in patients with COVID-19 has been a major concern, and the lack of reliable

	Se	evere		n	nild		5	Std. Mean Difference		Std. M	Mean Difference	
Study or Subgroup	Mean	SD T	otal	Mean	SD	Total	Weight	IV, Random, 95% Cl		IV, R	tandom, 95% Cl	
Chen et al (1) 2020	7.7	4.37	11	4.2	1.3	10	7.2%	1.02 [0.10, 1.94]				
Chen et al (2) 2020	4.56	1.79	50	3.83	1.02	241	11.4%	0.61 [0.31, 0.92]			-	
Duan et al 2020	7.63	2.07	44	5.23	1.97	72	10.8%	1.19 [0.78, 1.59]				
Gao et al 2020	4.51	1.76	15	4.09	1.29	28	9.2%	0.28 [-0.35, 0.91]				
Jian-Ya et al 2020	4.97	2.57	7	4.27	1.92	44	8.0%	0.34 [-0.46, 1.14]				
Shi et al 2020	15.2	2.37	48	10.08	1.01	53	9.7%	2.84 [2.28, 3.40]				-
Wang et al (1) 2020	6.6	4.09	36	4.07	1.5	102	10.8%	1.03 [0.63, 1.43]				
Wang et al (2) 2020	4.1	1.67	50	3.5	1.13	115	11.2%	0.45 [0.12, 0.79]				
Wang et al (3) 2020	5.63	3.09	22	4	1.4	283	10.5%	1.03 [0.59, 1.47]				
Zhang et al (1) 2020	6.2	3.2	55	4.1	1.29	166	11.3%	1.08 [0.76, 1.40]			+	
Total (95% CI)			338			1114	100.0%	0.99 [0.61, 1.37]			•	
Heterogeneity: Tau <sup>2</sup> =	0.31; Ch	i <sup>2</sup> = 65.5	9, df=	9 (P <	0.0000	01); F=	86%		<del>.</del>	-		
Test for overall effect:	Z = 5.09	(P < 0.0)	0001)						-4	-2	0 2	
1.1999/92732.4944 and 1.4944 and 1.4944 and 1.4944 and 1.4944												
	S	evere			mild			Std. Mean Difference		Std. I	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Tota	Weight	IV, Random, 95% Cl		IV, F	Random, 95% Cl	
Huang et al 2020	56.43	132.43	13	3.2	3.67	28	14.6%	0.71 [0.03, 1.39]			-	
Shi et al 2020	1.98	0.87	48	0.2	0.1	53	15.8%	2.93 [2.36, 3.49]				
Wang et al (1) 2020	14.33	16.06	36	5.67	5.79	102	2 17.4%	0.90 [0.51, 1.30]				
Yu et al 2020	55 97	124.05	25	2 27	2.76	2 4/	16 /06	0 70 10 00 4 041				
Au et al 2020	33.37	124.05	25	3.27	3.70	,	10.4%	0.70 [0.20, 1.21]				
Zhang et al (1) 2020	25.7	36.85	55	5.77	5.61	168	i 18.0%	1.05 [0.73, 1.37]			-	
Zhang et al (1) 2020 Zhou et al 2020	25.7 36.97	36.85 59.03	55 54	5.77 3.2	5.61	168	6 18.0% 7 17.9%	1.05 [0.73, 1.37] 1.07 [0.74, 1.40]			-	
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI)	25.7 36.97	36.85 59.03	55 54 231	5.77 3.2	5.61 3.3	168 137 530	10.4% 18.0% 17.9%	1.05 [0.73, 1.37] 1.07 [0.74, 1.40] 1.22 [0.69, 1.74]			÷	
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1	25.7 36.97 0.38; Chi <sup>a</sup>	36.85 59.03 <sup>2</sup> = 44.38	25 55 54 <b>231</b> 3, df = 1	5.77 3.2 5 (P < 0	5.61 3.3	166 137 530 1); F= 1	10.4% 18.0% 17.9% 17.9%	1.05 [0.20, 1.21] 1.05 [0.73, 1.37] 1.07 [0.74, 1.40] 1.22 [0.69, 1.74]	ī	- <u>L</u>	÷.	Į
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2	25.7 36.97 0.38; Chř Z= 4.51 (j	36.85 59.03 <sup>2</sup> = 44.36 P < 0.00	23 55 54 <b>231</b> 3, df = 9 001)	5.77 3.2 5 (P < 0	5.61 3.3	, 4. 16( 3 137 <b>530</b> 1);  ² = 1	10.4% 18.0% 17.9% 100.0%	1.05 [0.73, 1.37] 1.07 [0.74, 1.40] <b>1.22 [0.69, 1.74]</b>	<del> </del> -4	-2	+ + •	12
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2	25.7 36.97 0.38; Chi <sup>*</sup> Z = 4.51 (	36.85 59.03 <sup>2</sup> = 44.30 P < 0.00	23 55 54 <b>231</b> 3, df = 1 001)	5.77 3.2 5 (P < 0	5.61 5.61 3.3	168 137 530 1); I <sup>2</sup> = 1	10.4% 18.0% 17.9% 17.9%	1.05 [0.73, 1.37] 1.07 [0.74, 1.40] 1.22 [0.69, 1.74]	+ -4	-2		2
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Study or Subgroup	25.7 36.97 0.38; Chř Z = 4.51 () s 	36.85 59.03 <sup>2</sup> = 44.3€ P < 0.00 evereSD	23 55 54 <b>231</b> 3, df = 1 001)	5.77 3.2 5 (P < 0	5.61 5.61 3.3 .00000 mile an	1 16( } 137 530 1);  ² = 1 1 <u>\$D_</u> T(	10.4% 18.0% 17.9% 100.0%	1.05 [0.73, 1.37] 1.07 [0.74, 1.40] 1.22 [0.69, 1.74] Std. Mean Difference	+ -4 	-2 StdV,	Mean Difference Random, 95% Cl	2
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Study or Subgroup Chen et al (1) 2020	25.7 36.97 0.38; Chř Z = 4.51 (j <u>Mean</u> 208.3	<sup>2</sup> = 44.36 P < 0.00 evere 122.4	23 55 54 <b>231</b> 6, df = 001) <b>Tota</b>	5.27 5.77 3.2 5 (P < 0 <u>I Mea</u> 1 108	5.61 5.61 00000 mik an i.9 10	1 16€ 3 137 530 1); I² = d <u>SD T(</u> 12.8	10.4% 18.0% 17.9% 100.0% 89%	1.05 [0.73, 1.37]     1.07 [0.74, 1.40]     1.22 [0.69, 1.74]     Std. Mean Difference int IV, Random, 95% (     0.86 [-0.05, 1.7]	-4 -1 21 5]	-2 Std. IV,	Mean Difference	2
Zhang et al (1) 2020 Zhou et al 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: 2 Study or Subgroup Chen et al (1) 2020 Chen et al (2) 2020	25.7 36.97 0.38; Chř Z = 4.51 (j <u>Mean</u> 208.3 98.67	36.85 59.03 <sup>2</sup> = 44.36 P < 0.00 ievere SD 122.4 69.61	23 55 54 231 6, df = 1 001) Tota 1 50	5.27 5.77 3.2 5 (P < 0 1 106 0 71.3	.00000 mile an i.9 10 57 49	d 10: 13: 53( 1); 1² = d <u>SD</u> T( 12:8 1.02 :	10.4% 18.0% 17.9% 100.0% 89% 5tal Weig 10 4.3 241 12.8	0.70 [0.20, 1.21]           1.05 [0.73, 1.37]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           Jht           V, Random, 95% (           3%         0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]	-4 -1 21 5] 2]	-2 Std. IV,	. Mean Difference Random, 95% Cl	2
Zhang et al (1) 2020           Zhou et al 2020           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 1           Test for overall effect: 2           Study or Subgroup           Chen et al (1) 2020           Chen et al (2) 2020           Duan et al 2020	25.7 36.97 0.38; Chi <sup>-</sup> Z = 4.51 ( <b>S</b> <u>Mean</u> 208.3 98.67 106.7	36.85 59.03 <sup>2</sup> = 44.36 P < 0.00 <b>evere</b> 50 122.4 69.61 85.6	23 55 54 231 3, df = 1 1001) 1 Tota 1 1' 50	5.27 5.77 3.2 5 (P < 0 1 106 1 106 0 71.1 4 76	.00000 mik an .9 10 57 49 i.8 69	1 16( 1 16( 3 13) 53( 1); I <sup>2</sup> = 1); I <sup>2</sup> = 10 12.8 1.02 1.98	10.4%           18.0%           17.9%           100.0%           89%           5000000000000000000000000000000000000	5.76 [0.20, 1.21]           1.05 [0.73, 1.37]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           [ht         IV, Random, 95%           0.86 [-0.05, 1.7]           3%         0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]           0.39 [0.01, 0.7]	+ -4 21 2] 2] 7]	-2 Std. IV,	Mean Difference Random, 95% Cl	2
Xueral 2020           Zhang et al (1) 2020           Zhou et al 2020           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> =           Test for overall effect: 2           Study or Subgroup           Chen et al (1) 2020           Chen et al (2) 2020           Duan et al 2020           Huang et al 2020	25.7 36.97 0.38; Chi <sup>*</sup> Z = 4.51 ( <u>S</u> <u>Mean</u> 208.3 98.67 106.7 235.67	36.85 59.03 <sup>2</sup> = 44.36 P < 0.00 ievere SD 122.4 69.61 85.6 341.36	23 55 54 231 6, df = 1 001) Tota 1 1 50 1 4 1	5.27 5.77 3.2 5 (P < 0 1 106 0 71.1 4 76 3 127.1	.00000 mile an 1.9 10 57 49 1.8 69 57 99	1 16( 3 13) 53( 1); I <sup>2</sup> = d <u>SD T(</u> 12.8 1.02 1 1.98 1.99	10.4 x0         10.4 x0         10.4 x0         118.0 %         118.0 %         17.9 %         17.9 %         100.0 %         89 %         100.0 %         89 %         100.1 %         100.2	5.76 [0.20, 1.21]           1.05 [0.73, 1.37]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           Intervention           N, Random, 95% (           3%         0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]           3%         0.51 [0.20, 0.8]           3%         0.51 [0.20, 0.8]           3%         0.51 [0.20, 0.8]	+ -4 21 2] 2] 3]	-2 Std. IV,	Mean Difference Random, 95% Cl	2
Xueral 2020           Zhang et al (1) 2020           Zhou et al 2020           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 1           Test for overall effect: 2           Study or Subgroup           Chen et al (1) 2020           Chen et al (2) 2020           Duan et al 2020           Huang et al 2020           Jian-Ya et al 2020	25.7 36.97 0.38; Chi Z = 4.51 ( <b>S</b> Mean 208.3 98.67 106.7 235.67 41	36.85 59.03 <sup>2</sup> = 44.3€ P < 0.00 evere \$D 122.4 69.61 85.6 341.36 10.1	23 55 54 231 6, df = 1 001) <b>Tota</b> 1 1 50 1 4 1	5.27 5.77 3.2 5 (P < 0 1 106 0 71.3 4 76 3 127.7 7 62.3	.00000 mile an 5.9 10 57 49 5.8 69 57 99 33 35	d SD Te 10:12	10.4 x0         10.4 x0 <t< td=""><td>0.70 [0.20, 1.21]           1.05 [0.73, 1.37]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           Int           V, Random, 95% (           0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]           (2%)         0.39 [0.01, 0.7]           (%)         0.51 [-0.16, 1.1]           0.51 [-0.16, 1.4]         0.53 [-1.44, 0.1]</td><td>+4 4 </td><td>-2 -2 IV,</td><td>. Mean Difference Random, 95% Cl</td><td>2</td></t<>	0.70 [0.20, 1.21]           1.05 [0.73, 1.37]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           Int           V, Random, 95% (           0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]           (2%)         0.39 [0.01, 0.7]           (%)         0.51 [-0.16, 1.1]           0.51 [-0.16, 1.4]         0.53 [-1.44, 0.1]	+4 4 	-2 -2 IV,	. Mean Difference Random, 95% Cl	2
Xhang et al (1) 2020         Zhou et al 2020         Total (95% CI)         Heterogeneity: Tau <sup>2</sup> = 1         Test for overall effect: 2         Study or Subgroup         Chen et al (1) 2020         Duan et al (2020)         Juan-Ya et al 2020         Wang et al (1) 2020         Wang et al (1) 2020	25.7 36.97 0.38; Chi Z = 4.51 ( <b>S</b> Mean 208.3 98.67 106.7 235.67 41 138.667	36.85 59.03 <sup>2</sup> = 44.3€ P < 0.00 ievere SD 122.4 69.61 85.6 341.36 10.1 145.69	23 55 54 231 3, df = 1 1001) 1 Tota 1 1 50 1 4 1 1 1 30	5.27 5.77 3.2 5 (P < 0 1 106 0 71.4 4 76 3 127.1 7 62.3 5 87.3	.00000 mile an .9 10 57 49 .8 69 33 35 33 50	1 16( 3 13; 53( 1); I <sup>2</sup> = d <u>SD T(</u> ).02 : ).98 ).99 i.25 1.38	10.4 x0         10.4 x0         10.4 x0         100.0%         1100.0%         100.0% <th100.0%< th=""> <th100.0%< th=""> <th100.0%< td=""><td>Std. Mean Difference           http://www.science.com/science</td><td>+-4 -4 5] 22 7] 3] 3]</td><td>-2 Std. IV,</td><td>Mean Difference Random, 95% Cl</td><td>2</td></th100.0%<></th100.0%<></th100.0%<>	Std. Mean Difference           http://www.science.com/science	+-4 -4 5] 22 7] 3] 3]	-2 Std. IV,	Mean Difference Random, 95% Cl	2
Zhang et al (1) 2020         Zhou et al 2020         Total (95% CI)         Heterogeneity: Tau <sup>2</sup> = 1         Test for overall effect: 2         Study or Subgroup         Chen et al (1) 2020         Duan et al 2020         Huang et al 2020         Jian-Ya et al 2020         Wang et al (1) 2020         Wang et al (2) 2020         Wang et al (2) 2020	25.7 36.97 0.38; Chi Z = 4.51 ( 0.38; Chi Z = 4.51 ( 0.38; Chi Z = 4.51 ( 0.38; Chi Z = 4.51 ( 106.7 208.3 98.67 106.7 235.67	36.85 59.03 <sup>2</sup> = 44.36 P < 0.00 122.4 69.61 85.6 341.36 10.1 145.69 52.67	23 55 54 231 3, df = : 1001) 1001) 1001) 1001) 101 101 101 101	5.27 5.77 3.2 5 (P < 0 1 106 0 71.3 4 76 3 127.1 7 62.3 3 87.3 3 87.3 3 87.3	.00000 mile an 1.9 10 57 49 33 35 33 50 1.6 31	1 16( 3 13; 53( 53( 1);  ₹ = 1);  ₹ = 1);  ₹ = 10; 10;  ₹ = 10; 10;  ₹ = 10; 10;  ₹ = 10;  ₹	10.4 x0           118.0%           117.9%           1100.0%           89%           100           4.3           241           12.8           6.5           4.4           5.0           102           111           115           12.2	Std. Mean Difference           1.22 [0.69, 1.74]           1.22 [0.69, 1.74]           1.22 [0.69, 1.74]           Std. Mean Difference           Int           V, Random, 95% (           3%         0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]           2%         0.39 [0.01, 0.7]           3%         0.61 [-0.16, 1.1]           1%         0.63 [-1.44, 0.1]           3%         0.60 [0.21, 0.9]           0.61 [0.37, 1.0]         0.71 [0.37, 1.0]	+ -4 51 51 21 21 21 21 21 23 31 31 31 31 31 31 31	-2 Std. IV,	Mean Difference Random, 95% Cl	-
Zhang et al (1) 2020         Zhou et al 2020         Total (95% CI)         Heterogeneity: Tau <sup>2</sup> = 1         Test for overall effect: 2         Study or Subgroup         Chen et al (1) 2020         Chen et al (2) 2020         Duan et al 2020         Huang et al 2020         Wang et al (1) 2020         Wang et al (2) 2020         Zhan et al (2) 2020         Zhan et al (2) 2020         Zhan et al (2) 2020         Zhang et al (1) 2020         Zhang et al (1) 2020	25.7 36.97 0.38; Chi Z = 4.51 ( <u>Mean</u> 208.3 98.67 106.7 235.67 41 138.667 75.66 154	36.85 59.03 *= 44.36 P < 0.00 ievere SD 122.4 69.61 85.6 341.36 10.1 145.69 52.67 148.45	23 55 54 231 6, df = : 0001) 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	5.27 5.77 3.2 5 (P < 0 1 106 0 71.4 1 27.7 3 127.7 3 127.7 5 83.3	.00000 mile an i.9 10 57 49 33 35 33 50 '.6 31 33 55	1 16( 3 13; 53( 1);  ₹ = 1);  ₹ = 1);  ₹ = 10;  ₹ 1);  ₹ = 10;  ₹ 10;  ₹ = 10;  ₹ 10;  ₹ = 10;  ₹ 10;  ₹ = 10;	10.4 x0           118.0%           17.9%           100.0%           89%           10           4.3           241           228           6.5           44           5.0           102           115           12.6           12.6           12.6           12.6	Std. Mean Difference           1.07 [0.74, 1.40]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           Int           IV, Random, 95% (           3%         0.86 [-0.05, 1.7]           3%         0.51 [0.20, 0.8]           3%         0.51 [0.00, 1.7]           3%         0.51 [0.10, 0.7]           3%         0.51 [0.20, 0.8]           3%         0.51 [0.10, 1.7]           3%         0.51 [0.20, 0.8]           3%         0.51 [0.20, 0.8]           3%         0.63 [-1.44, 0.1]           3%         0.60 [0.21, 0.9]           3%         0.82 [0.50, 1.1]	+ -4 51 51 21 71 31 33 31 31 31 31 31 31 31	-2 Std. IV,	Mean Difference Random, 95% CI	- -
Zhang et al (1) 2020           Zhou et al 2020           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 1           Test for overall effect: 2           Study or Subgroup           Chen et al (1) 2020           Chen et al (2) 2020           Duan et al 2020           Huang et al 2020           Jian-Ya et al 2020           Wang et al (1) 2020           Zhang et al (1) 2020	25.7 36.97 0.38; Chi Z = 4.51 ( <u>Mean</u> 208.3 98.67 106.7 235.67 41 138.667 75.66 154 82.83	36.85 59.03 °= 44.36 P < 0.00 ievere 50 122.4 69.61 85.6 341.36 10.1 145.69 52.67 148.45 80.28	23 55 54 231 6, df = : 0001) 7 Tota 1 1 50 1 30 1 30 1 30 1 30 1 50 1 50	5.27 5.77 3.2 5 (P < 0 1 10€ 0 71.4 1 10€ 0 71.4 4 7€ 3 127.1 7 62.3 6 87.3 3 47.5 7 83.3 3 83.1	5.61 5.61 3.3 0.0000 <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>mile</b> <b>m</b>	1 16( 3 13; 53( 1); I <sup>2</sup> = d <u>SD T(</u> ).98 ).99 ).98 ).99 ).38 i.25 ).38 i.68 i.68	18.9 %           18.0 %           17.9 %           17.9 %           100.0 %           89 %           10           10           12           10           28           6.5           44           5.0           102           11.1           115           126           82           12.1	Std. Mean Difference           I.22 [0.69, 1.74]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           V, Random, 95%           (M. Random, 95%)           0.51 [0.20, 0.8           0.51 [0.21, 0.9           0.71 [0.37, 1.0           0.82 [0.50, 1.11]           0.01 [-0.35, 0.3	+ -4 21 21 77 33 33 33 33 33 33 33 33 33 33 33	-2 Std. IV,	Mean Difference Random, 95% Cl	- -
Zhang et al (1) 2020           Zhou et al 2020           Total (95% CI)           Heterogeneity: Tau <sup>2</sup> = 1           Test for overall effect: 2           Study or Subgroup           Chen et al (1) 2020           Duan et al 2020           Huang et al 2020           Jian-Ya et al 2020           Wang et al (1) 2020           Zhang et al (2) 2020           Zhou et al 2020	25.7 36.97 0.38; Chi Z = 4.51 ( 0.38; Chi Z = 4.51 ( 0.38; Chi 208.3 98.67 106.7 208.3 98.67 106.7 235.67 41 138.667 75.66 154 82.83 69.83	36.85 59.03 <sup>2</sup> = 44.36 P < 0.00 122.4 69.61 85.6 341.36 10.1 145.69 52.67 148.45 80.28 100.16	235 55 54 231 6, df = 1 1001) 7 Tota 1 1 50 1 1 1 1 50 1 1 1 1 50 1 50 1 50	5.27 5.77 3.2 5 (P < 0 1 106 0 71.4 1 106 0 71.4 3 127.7 6 87.3 0 47 5 83.3 3 83.1 4 27.4	.00000 .00000 .00000 .00000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .0000 .000000	1 16( 3 13; 53( 1); I <sup>2</sup> = d <u>SD T</u> ).98 ).99 ).25 ).28 .168 i1.6 i.26 i.67	10.4 x0           6         18.0%           17.9%         17.9%           100.0%         89%           10         4.3           241         12.8           72         11.2           28         6.5           44         5.0           1002         11.1           115         12.0           166         12.6           82         12.1	Std. Mean Difference           1.07 [0.74, 1.40]           1.07 [0.74, 1.40]           1.22 [0.69, 1.74]           Std. Mean Difference           Mit           N, Random, 95% (0.39)           3%           0.51 [0.20, 0.8           3%           0.51 [0.20, 0.8           3%           0.51 [0.10, 1.7]           3%           0.51 [0.10, 1.7]           3%           0.51 [0.10, 1.7]           3%           0.51 [0.10, 1.7]           3%           0.63 [-1.44, 0.1]           3%           0.61 [0.21, 0.9]           0.71 [0.37, 1.0]           3%           0.82 [0.50, 1.1]           3%           0.72 [0.39, 1.0]	+ -4 51 51 51 51 51 51 51 51 51 51 51 51 51	-2 Std. IV,	Mean Difference Random, 95% CI	- - -

Figure 7. A forest plot of the association between the risk of severe COVID-19 and the levels of BUN (**A**), Hs-troponin (**B**), and creatine kinase (**C**).

data and meta-analyses prevents a holistic comparison. Certain infectious diseases that cause abnormal coagulation have been associated with poor clinical outcomes<sup>65</sup>. The theory behind this mechanism is not understood clearly. It is widely known that ACE2 receptors are important for the infection of host cells by SARS-CoV-2, and ACE2 receptors are expressed in various cells in the human body, including endothelial cells<sup>66</sup>. Consequently, a massive inflammatory reaction may occur in endothelial cells owing to SARS-CoV-2 infection<sup>67</sup>, which may lead to increased coagulation, disseminated intravascular coagulation<sup>68</sup>, and increased fibrin degradation<sup>69</sup>. High fibrin degradation leads to elevated levels of fibrinogen and D-dimer<sup>70</sup>, which might also explain the occurrence of venous thromboembolism

in critical patients of COVID-19<sup>71</sup>. In addition, a study with a short follow-up period also reported the existence of a dynamic correlation between the D-dimer levels and the severity of COVID-19<sup>72</sup>. Furthermore, pulmonary embolism and deep vein thrombosis were also observed in patients with severe COVID-19<sup>73,74</sup>, which suggests that D-dimer might play a prominent role in governing the severity of COVID-19 patients.

We also observed that inflammatory markers, including elevated levels of CRP, ESR, and IL-6, were found both in patients with severe and mild COVID-19, with a significant increase detected in patients with severe COVID-19. Other variables associated with adverse outcomes, such as ferritin, lactate

	s	evere	-		mila	-		Std. Mean Difference		Stu		Diner	ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C		IV	Rando	om, 95	% CI	
Cai et al 2020	68.85	59.05	58	17.54	22.66	240	10.9%	1.55 [1.24, 1.87]	1				•	
Chen et al (1) 2020	135.2	52.4	11	51.4	50.8	10	8.3%	1.56 [0.55, 2.56]	1				•	
Chen et al (2) 2020	49.73	40.53	50	13.53	15.45	212	10.8%	1.61 [1.27, 1.95]	]			8		
Duan et al 2020	62.27	44.68	44	43.23	50.23	72	10.7%	0.39 [0.01, 0.77]	]			-		
∋ao et al 2020	39.37	27.68	15	18.76	22.2	28	9.7%	0.84 [0.18, 1.49]	1				-	
ian-Ya et al 2020	133.5	89.1	7	11.23	16.4	44	8.0%	3.46 [2.40, 4.52]	1				-	-
Shi et al 2020	123.4	10.85	48	94.1	9.26	53	10.1%	2.89 [2.33, 3.46]	1				-	-
Vang et al (3) 2020	49.23	70.37	22	8.07	11.33	283	10.4%	1.91 [1.45, 2.37]	1				-	
u et al 2020	33.43	54.39	25	11.6	13.56	44	10.3%	0.63 [0.13, 1.13]	1					
(hang et al (2) 2020	37.49	50.6	56	30.1	32.15	82	10.8%	0.18 (-0.16, 0.52)	1			-		
otal (95% CI)	0.70.04	7-400	336	- 0 /D		1068	100.0%	1.45 [0.89, 2.01]	l					
Fest for overall effect:	Z = 5.07	(P < 0.0	10001)	= 9 (F 4	0.0000	)), r = s	1370		-4	-2		ò	ź	
	se	vere		mild			C	)dds Ratio		c	dds R	atio		=
Study or Subgroup	Even	ts To	tal Ev	/ents	Total	Weight	t M-H, I	Random, 95% Cl		M-H, F	andor	n, 95%	CI	
Cai et al 2020		54	58	142	240	36.2%	5 9	32 [3.27, 26.56]				-		
Chen et al (2) 2020		34	50	111	241	40.5%		2.49 [1.30, 4.75]			-	-		
Liu et al 2020	1	59	69	1	11	23.3%	59.0	00 [6.79, 512.69]						-
fotal (95% CI)		1	77		492	100.0%	8	.40 [1.82, 38,76]						
			<u>.</u>	254			· ·							
Fotal evente	1	17								120				
Fotal events	1 - 1 40	47 Chiz-	10.91	df = 2	(P - 0.0	061	- 91%	+		_			+	_
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effec	1 = 1.40; ct: Z = 2.3	47 Chi²= 73 (P =	10.81,	df = 2 )	(P = 0.0	005); I²:	= 81%	<del>6</del> .0	002	0.1	1		10	
Total events Heterogeneity: Tau <sup>a</sup> Test for overall effec	1 s= 1.40; ct: Z = 2.5	47 Chi <sup>z</sup> = 73 (P =	10.81, 0.006	df = 2	(P = 0.0	005); I²:	= 81%	+ 0.0	002	0.1	1 . Mean	Differ	10 ence	_
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effec Study or Subgroup	1; s= 1.40; ct: Z = 2.3 s Mean	47 Chi <sup>2</sup> = 73 (P = evere SD	10.81, 0.006 Total	df = 2 df = 2 df	(P = 0.( mild SD	005); I <sup>2</sup> : Total	= 81% Weight	+ 0.( Std. Mean Difference IV, Random, 95% Ci	002	0.1 Std	1 . Mean , Rando	Differ om, 95	10 ence % CI	_
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effec Study or Subgroup Cai et al 2020	1 = 1.40; ct: Z = 2.3 <b>s</b> <u>Mean</u> 50.33	47 Chi <sup>2</sup> = 73 (P = evere SD 17,49	10.81, 0.006 Total 58	df = 2 ) <u>Mean</u> 27.1	(P = 0.0 mild SD 21.11	005); I <sup>2</sup> : Total 240	= 81% Weight 41.8%	+ 0.( Std. Mean Difference IV, Random, 95% Cl 1.13 [0.83, 1.43]	1	0.1 Std	1 . Mean , Rando	Differ om, 95	IO ence % CI	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020	1 = 1.40; ct: Z = 2.5 <u>Mean</u> 50.33 57.17	47 Chi <sup>z</sup> = 73 (P = evere <u>SD</u> 17.49 27.94	10.81, 0.006 Total 58 50	df = 2 ) Mean 27.1 36.43	(P = 0.0 mild SD 21.11 30.44	005); I <sup>2</sup> : <u>Total</u> 240 241	= 81% Weight 41.8% 40.9%	+ 0.( Std. Mean Difference IV, Random, 95% Cl 1.13 [0.83, 1.43] 0.69 [0.38, 1.00]	)02 I	0.1 Std	1 . Mean . Rando	Differ om, 95	ence % Cl	F
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effec Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020	1: = 1.40; = 1.40; = 2.3 <b>S</b> <b>Mean</b> 50.33 57.17 44.58	47 Chi <sup>≥</sup> = 73 (P = evere SD 17.49 27.94 26.16	10.81, 0.006 Total 58 50 69	df = 2 ) Mean 27.1 36.43 19.91	(P = 0.0 mild 21.11 30.44 23.74	005); I <sup>z</sup> : <u>Total</u> 240 241 11	= 81% Weight 41.8% 40.9% 17.3%	+ 0.6 Std. Mean Difference IV, Random, 95% Cl 1.13 [0.83, 1.43] 0.69 [0.38, 1.00] 0.94 [0.29, 1.60]	002 I	0.1 Std	1 . Mean . Rando	Differ om, 95 	ence % CI	F
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020	1: = 1.40; = 1.40; = 2.3 <b>Second Second </b>	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4	10.81, 0.006 Total 58 50 69 50	df = 2 ) <u>Mean</u> 27.1 36.43 19.91 33.33	(P = 0.0 mild SD 21.11 30.44 23.74 30.78	005); I <sup>≠</sup> : Total 240 241 11 0	<b>Weight</b> 41.8% 40.9% 17.3%	1         0.1           Std. Mean Difference         IV, Random, 95% Cl           1.13 [0.83, 1.43]         0.69 [0.38, 1.00]           0.94 [0.29, 1.60]         Not estimable		0.1 Std	1 . Mean . Rando	Differ om, 95 	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effec Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Fotal (95% CI)	1. = 1.40; t: Z = 2.3 <u>Mean</u> 50.33 57.17 44.58 50.33	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4	10.81, 0.006 Total 58 50 69 50 227	df = 2 ) <u>Mean</u> 27.1 36.43 19.91 33.33	(P = 0.0 mild 21.11 30.44 23.74 30.78	005);  ₹: Total 240 241 11 0 492	= 81% Weight 41.8% 40.9% 17.3%	Image: 10.0           Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]	002 I	0.1 Std	. Mean Rando	Differo om, 95' 	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> =	1 = 1.40; = 2.3 <b>Mean</b> 50.33 57.17 44.58 50.33 0.04; Ch	47 Chi <sup>2</sup> = 73 (P = <b>so</b> 17.49 27.94 26.16 37.4 i <sup>2</sup> = 4.00	10.81, 0.006 <b>Total</b> 58 50 69 50 <b>227</b> 6, df = 2	df = 2 ( ) 27.1 36.43 19.91 33.33 2 (P = 0	(P = 0.0 mild 21.11 30.44 23.74 30.78 13); P=	005);  ₹: <u>Total</u> 240 241 11 0 492 = 51%	= 81% Weight 41.8% 40.9% 17.3% 100.0%	1.0.1           Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]		0.1	1 . Mean Rando	Differo om, 95 	HID HID HID HID HID HID HID HID	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Fotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect:	1 = 1.40; t: Z = 2.3 <b>S</b> Mean 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4 i <sup>2</sup> = 4.00 (P < 0.0	10.81, 0.006 58 50 69 50 227 6, df = 2 00001)	df = 2 ) 27.1 36.43 19.91 33.33 2 (P = 0	(P = 0.0 mild 21.11 30.44 23.74 30.78	005);  ² : Total 240 241 11 0 492 : 51%	= 81% <u>Weight</u> 41.8% 40.9% 17.3% <b>100.0</b> %	Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]		0.1 Std V	1 . Mean . Rando	<b>Differ</b> om, 95 	ence % Cl	-
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect:	st Z = 2.1 <b>S</b> Mean 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4 i <sup>2</sup> = 4.0i (P < 0.0 <b>evere</b>	10.81, 0.006 58 50 69 50 <b>227</b> 6, df = : 00001)	df = 2 ) 27.1 36.43 19.91 33.33 2 (P = 0	(P = 0.0 mild 21.11 30.44 23.74 30.78 13); P = mild	005);   <sup>₽</sup> = 240 241 11 0 <b>492</b> = 51%	= 81% Weight 41.8% 40.9% 17.3% 100.0%	1.0.1           Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]	002	0.1 Std V	. Mean Rando	Differo om, 95 – – 0 Differo	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: Study or Subgroup	st Z = 2.1 <b>S</b> Mean 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> Mean	47 Chi <sup>2</sup> = 73 (P = <b>so</b> 17,49 27,94 26,16 37,4 ii <sup>2</sup> = 4,00 (P < 0,0 <b>evere</b> <b>so</b>	10.81, 0.006 58 50 69 50 227 6, df = : 00001) Total	Mean 27.1 36.43 19.91 33.33 2 (P = 0 Mean	(P = 0.0 mild SD 21.11 30.44 23.74 30.78 13); P= mild SD	005);   <sup>2</sup> : 240 241 11 0 492 = 51% Total	= 81% Weight 41.8% 40.9% 17.3% 100.0% Weight	1.0.1           Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]           Std. Mean Difference           IV, Random, 95% Cl		0.1 Std V -1 Std	. Mean Rando	Differo om, 95 – – – 0 Differo om, 95	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Cai et al 2020	1 = 1.40; t: Z = 2.1 <b>S</b> 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> Mean 39.57	47 Chi <sup>2</sup> = 73 (P = <b>sb</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.00 (P < 0.0 <b>evere</b> <b>sb</b> 26.23	10.81, 0.006 58 50 69 50 227 6, df = 2 00001) Total 58	Mean 27.1 36.43 19.91 33.33 2 (P = 0 <u>Mean</u> 12.7	(P = 0.0 mild SD 21.11 30.44 23.74 30.78 13); P = mild SD 9.92	005);   <sup>₽</sup> : 240 241 11 0 <b>492</b> = 51% <u>Total</u> 240	= 81% Weight 41.8% 40.9% 17.3% 100.0% Weight 15.3%	1.0.0           Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]           Std. Mean Difference           IV, Random, 95% Cl           1.84 [1.52, 2.16]		0.1 Std V	. Mean Rando	Differo om, 95°	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Wang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Cai et al 2020 Chen et al (1) 2020	1 = 1.40; t: Z = 2.1 <b>S</b> <u>Mean</u> 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> <u>Mean</u> 39.57 73.8	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.00 (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9	10.81, 0.006 58 50 69 50 227 6, df = 2 00001) Total 58 11	df = 2 )	(P = 0.( mild 21.11 30.44 23.74 30.78 .13); P = mild SD 9.92 13.9	005);  ₹ <u>Total</u> 240 241 11 0 <b>492</b> 51% <u>Total</u> 240 10	= 81% 41.8% 40.9% 17.3% 100.0% Weight 15.3% 9.0%	Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]           Std. Mean Difference           IV, Random, 95% Cl           1.43           1.13 [0.22, 1.60]           1.14 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]		0.1 Std V	. Mean Rando	Differo om, 95 	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Cai et al 2020 Chen et al (2) 2020 Jue et al 2020 Vang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Cai et al 2020 Chen et al (1) 2020 Chen et al (3) 2020	s <b>Mean</b> 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> <u>Mean</u> 39.57 73.8 23.43	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.00 (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95	10.81, 0.006 58 50 50 227 6, df = : 00001) Total 58 11 11	df = 2 ) <u>Mean</u> 27.1 36.43 19.91 33.33 2 (P = 0 <u>Mean</u> 12.7 18.8 16.43	(P = 0.0 mild 21.11 30.44 23.74 30.78 13); P = mild SD 9.92 13.9 21.12	005);   <sup>2</sup> : <u>Total</u> 240 241 11 0 <b>492</b> 51% <u>Total</u> 240 10 14	= 81% <u>Weight</u> 41.8% 40.9% 17.3% <b>100.0%</b> <u>Weight</u> 15.3% 9.0% 10.3%	H         0.1           Std. Mean Difference         IV, Random, 95% Cl           1.13 [0.83, 1.43]         0.69 [0.38, 1.00]           0.94 [0.29, 1.60]         Not estimable           0.92 [0.60, 1.23]         Std. Mean Difference           IV, Random, 95% Cl         1.84 [1.52, 2.16]           1.84 [1.52, 2.16]         0.22 [-0.57, 1.01]		0.1 Std V	. Mean Rando	Differo om, 95 – – – – – –	ence % Cl 1 ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Wang et al (2) 2020 Fotal (95% Cl) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: Study or Subgroup Cai et al 2020 Chen et al (3) 2020 Chen et al (3) 2020 Sao et al 2020	1 = 1.40; = 1.40; = 2.1 <b>S</b> <b>Mean</b> 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> <b>Mean</b> 39.67 73.8 23.43 39.43	47 Chi <sup>2</sup> = 73 (P = <b>sou</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.00 (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95 29.61	10.81, 0.006 58 50 69 50 <b>227</b> <b>227</b> <b>227</b> <b>6</b> , df = : 00001) <b>Total</b> 58 11 11	Mean           27.1           36.43           19.91           33.33           2 (P = 0           Mean           12.7           18.8           16.43           13.3	(P = 0.( mild SD 21.11 30.44 23.74 30.78 13); P = mild SD 9.92 13.9 21.12 14.88	005);   <sup>≠</sup> : 240 241 11 0 492 = 51% Total 240 10 14 28	<ul> <li>81%</li> <li>Weight 41.8% 40.9% 17.3%</li> <li>100.0%</li> <li>Weight 15.3% 9.0% 10.3% 10.3%</li> </ul>	H         0.1           Std. Mean Difference         IV, Random, 95% Cl           1.13 [0.83, 1.43]         0.69 [0.38, 1.00]           0.94 [0.29, 1.60]         Not estimable           0.92 [0.60, 1.23]         Std. Mean Difference           IV, Random, 95% Cl         1.84 [1.52, 2.16]           1.05 [0.13, 1.98]         0.22 [-0.57, 1.01]           1.22 [0.53, 1.90]         1.92		0.1 Std V	1 . Mean Rando	Differo om, 95' – – Differo om, 95'	ence % CI	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Cai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Fotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: Study or Subgroup Cai et al 2020 Chen et al (1) 2020 Chen et al (2) 2020 Jao et al 2020 Jian-Ya et al 2020	*= 1.40; *= 1.40; t: Z = 2.1 <b>S</b> 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> Mean 39.57 73.8 23.43 39.43 10.93	47 Chi <sup>z</sup> = 73 (P = <b>svere</b> <b>SD</b> 17.49 27.94 26.16 37.4 i <sup>2</sup> = 4.00 (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95 29.61 25.9	10.81, 0.006 58 50 69 50 227 6, df= 2 50 00001) Total 58 11 11 15 7	Mean           27.1         36.43           36.43         19.91           33.33         2 (P = 0           Mean         12.7           18.8         16.43           13.33         2,43	(P = 0.( mild SD 21.11 30.44 23.74 30.78 13); P = mild SD 9.92 13.9 21.12 14.88 5.59	005);   <sup>2</sup> : Total 240 241 11 0 492 = 51% Total 240 10 14 240 10 14 244	<ul> <li>81%</li> <li>Weight 41.8% 40.9% 17.3%</li> <li>100.0%</li> <li>Weight 15.3% 9.0% 10.3% 11.5%</li> <li>10.1%</li> </ul>	+ 0.1 Std. Mean Difference IV, Random, 95% Cl 1.13 [0.83, 1.43] 0.69 [0.38, 1.00] 0.94 [0.29, 1.60] Not estimable 0.92 [0.60, 1.23] Std. Mean Difference IV, Random, 95% Cl 1.84 [1.52, 2.16] 1.05 [0.13, 1.98] 0.22 [-0.57, 1.01] 1.22 [0.53, 1.90] 0.80 [-0.01, 1.61]		0.1 Std V	1 . Mean Rando	Difference m, 95' – – Difference m, 95'	ence % CI	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Jue et al 2020 Wang et al (2) 2020 Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: Study or Subgroup Cai et al 2020 Chen et al (3) 2020 Chen et al (2) 2020 Wang et al (2) 2020 Wang et al (2) 2020	1         F = 1.40;         St: Z = 2.1         St: Z = 2.1         50.33         57.17         44.58         50.33         0.04; Ch         Z = 5.70         St: Z = 5.70         St: Z = 5.70         39.57         73.8         23.43         39.43         10.93         22.97	47 Chi <sup>2</sup> = 73 (P = <b>svere</b> <b>SD</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.0i (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95 29.95 29.572	10.81, 0.006 58 50 69 50 <b>227</b> 50 <b>227</b> 50 <b>227</b> 50 <b>201</b> 50 <b>217</b> 50	df = 2 ) 27.1 36.43 19.91 33.33 2 (P = 0 <u>Mean</u> 12.7 18.8 16.43 13.3 2.43 11.9	(P = 0.( mild SD 21.11 30.44 23.74 30.78 .13);   <sup>2</sup> = mild SD 9.92 13.9 21.12 14.88 5.59 13.36	005);  ₹ Total 240 241 11 0 492 51% Total 240 10 14 240 10 14 240 10 14 240 11 11 11 11 11 11 11 11 11 1	<ul> <li>81%</li> <li>Weight 41.8% 40.9% 17.3%</li> <li>100.0%</li> <li>Weight 15.3% 9.0% 10.3% 10.3% 10.1%</li> <li>10.1% 10.1%</li> </ul>	H         0.1           Std. Mean Difference         IV, Random, 95% Cl           1.13 [0.83, 1.43]         0.69 [0.38, 1.00]           0.94 [0.29, 1.60]         Not estimable           0.92 [0.60, 1.23]         IV           Std. Mean Difference         IV, Random, 95% Cl           1.84 [1.52, 2.16]         1.05 [0.13, 1.98]           0.22 [-0.57, 1.01]         1.22 [0.53, 1.90]           0.80 [-0.01, 1.61]         0.81 [0.27, 0.95]		0.1 Std V	1 . Mean Rando	Differo m, 95' – – Differo m, 95'	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Cai et al 2020 Chen et al (2) 2020 Wang et al (2) 2020 Fotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Study or Subgroup Cai et al 2020 Chen et al (1) 2020 Chen et al (2) 2020 Chen et al 2020 Dian-Ya et al 2020 Wang et al 2020 Kue get al 2020 Chen et al 2020 Chen et al 2020 Chen et al 2020	1 = 1.40; t: Z = 2.1 <b>S</b> <u>Mean</u> 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> <u>Mean</u> 39.57 73.8 23.43 39.43 10.93 22.93	47 Chi <sup>≠</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.0i (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95 29.61 25.72 29.72	10.81, 0.006 58 50 69 50 <b>227</b> <b>227</b> <b>207</b> <b>50</b> <b>227</b> <b>50</b> <b>50</b> <b>50</b> <b>50</b> <b>50</b> <b>50</b> <b>50</b> <b>50</b>	df = 2 df = 2	(P = 0.( mild SD 21.11 30.44 23.74 30.78 .13); P = mild SD 9.92 13.9 21.12 14.88 5.59 13.36 6.21	005);  ₹ Total 240 241 11 0 492 = 51% Total 240 10 14 28 415 44	<ul> <li>81%</li> <li>Weight 41.8% 40.9% 17.3%</li> <li>100.0%</li> <li>105.3% 9.0% 10.3% 10.1% 15.5% 10.1% 15.2% 13.4%</li> </ul>	H         0.1           Std. Mean Difference         IV, Random, 95% Cl           1.13 [0.83, 1.43]         0.69 [0.38, 1.00]           0.94 [0.29, 1.60]         Not estimable           0.92 [0.60, 1.23]         0.92 [0.60, 1.23]           Std. Mean Difference         IV, Random, 95% Cl           1.84 [1.52, 2.16]         1.05 [0.13, 1.98]           0.22 [-0.57, 1.01]         1.22 [0.53, 1.90]           0.80 [-0.01, 1.61]         0.61 [0.27, 0.95]           0.61 [0.27, 0.95]         0.86 [0.34, 1.37]		0.1 Std V	. Mean Rando	Differo m, 95' 	ence % Cl	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Dai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Fotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: Study or Subgroup Dai et al 2020 Chen et al (1) 2020 Chen et al (2) 2020 Chen et al 2020 Dian-Ya et al 2020 Kang et al 2020 Chou et al 2020 Chou et al 2020	10 F = 1.40; Ct: Z = 2.1 <b>S</b> 60.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> Mean 39.57 73.8 23.43 39.43 39.43 10.93 22.97 22.53 10.97	47 Chi <sup>≠</sup> = 73 (P = <b>svere</b> <b>SD</b> 17.49 27.94 26.16 37.4 ii <sup>2</sup> = 4.00 (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95 29.61 25.9 25.72 29.72 5.26	10.81, 0.006 58 50 69 50 <b>227</b> 6, df = 2 50 10001) <b>Total</b> 11 15 7 50 25 54	Mean           27.1         36.43           36.43         19.91           33.33         2 (P = 0           Mean         12.7           18.8         16.43           13.33         2.43           14.9         6.53           6.4         6.4	(P = 0.( mild SD 21.11 30.44 23.74 30.78 13); P = mild SD 9.92 13.9 21.12 14.88 5.59 13.36 6.21 2.17	005);  ₹ Total 240 241 11 0 492 51% Total 240 10 14 240 10 14 240 10 14 240 10 14 240 10 14 240 10 13 240 11 240 241 11 0 492 240 11 11 10 492 240 11 11 10 492 240 11 10 10 10 10 10 10 10 10 1	<ul> <li>81%</li> <li>Weight 41.8% 40.9% 17.3%</li> <li>100.0%</li> <li>100.0%</li> <li>10.3% 10.3% 11.5% 10.1% 15.2% 13.4% 15.1%</li> </ul>	H         0.1           Std. Mean Difference         IV, Random, 95% Cl           1.13 [0.83, 1.43]         0.69 [0.38, 1.00]           0.94 [0.29, 1.60]         Not estimable           0.92 [0.60, 1.23]         IV           Std. Mean Difference         IV, Random, 95% Cl           1.84 [1.52, 2.16]         1.05 [0.13, 1.98]           0.22 [0.57, 1.01]         1.22 [0.53, 1.90]           0.80 [-0.01, 1.61]         0.61 [0.27, 0.95]           0.86 [0.34, 1.37]         1.36 [1.02, 1.71]		0.1 Std V	1 . Mean Rando	Difference m, 95°	ence % CI	
Total events Heterogeneity: Tau <sup>2</sup> Test for overall effect Study or Subgroup Dai et al 2020 Chen et al (2) 2020 Liu et al 2020 Wang et al (2) 2020 Fotal (95% CI) Heterogeneity: Tau <sup>2</sup> = Fest for overall effect: Study or Subgroup Dai et al 2020 Chen et al (3) 2020 Dhen et al (3) 2020 Dhen et al (2) 2020 Chan et al 2020 Jian-Ya et al 2020 Wang et al 2020 Chu et al 2020 Chu et al 2020 Chou et al 2020	1.5 = 1.40; t: Z = 2.1 <b>S</b> Mean 50.33 57.17 44.58 50.33 0.04; Ch Z = 5.70 <b>S</b> Mean 39.57 73.8 23.43 39.43 10.93 22.97 22.53 10.97	47 Chi <sup>2</sup> = 73 (P = <b>evere</b> <b>SD</b> 17.49 27.94 26.16 37.4 $ii^2 = 4.0i$ (P < 0.0 <b>evere</b> <b>SD</b> 26.23 67.9 39.95 29.61 25.9 25.72 29.72 5.26	10.81, 0.006 58 50 69 50 <b>227</b> 6, df = : 00001) <b>Total</b> 11 15 7 50 25 54 <b>231</b>	df = 2 ) Mean 27.1 36.43 19.91 33.33 2 (P = 0 (P = 0 12.7 18.8 16.43 13.3 2.43 11.9 6.53 6.4	(P = 0.( mild SD 21.11 30.44 23.74 30.78 13); P = mild SD 9.92 13.9 21.12 14.88 5.59 13.36 6.21 2.17	005);  ₹ Total 240 241 11 0 492 51% Total 240 10 14 28 44 115 44 137 632	<ul> <li>81%</li> <li>Weight 41.8% 40.9% 17.3%</li> <li>100.0%</li> <li>100.0%</li> <li>15.3% 9.0% 10.3% 10.1% 15.2% 15.2% 15.1%</li> <li>100.0%</li> </ul>	H           0.1           Std. Mean Difference           IV, Random, 95% Cl           1.13 [0.83, 1.43]           0.69 [0.38, 1.00]           0.94 [0.29, 1.60]           Not estimable           0.92 [0.60, 1.23]           Std. Mean Difference           IV, Random, 95% Cl           1.84 [1.52, 2.16]           1.05 [0.13, 1.98]           0.22 [-0.57, 1.01]           1.22 [0.53, 1.90]           0.80 [-0.01, 1.61]           0.61 [0.27, 0.95]           0.86 [0.34, 1.37]           1.36 [1.02, 1.71]           1.03 [0.63, 1.44]		0.1 Std V	1 . Mean Rando	Difference m, 95' 	ence % CI	

Figure 8. A forest plot of the association between the risk of severe COVID-19 and the levels of CRP (A), Hs-CRP (B), ESR (C), and IL-6 (D).

dehydrogenase, and procalcitonin levels, were found to be elevated predominantly in patients with severe COVID-19. Our findings were consistent with those of a previous meta-analysis<sup>75</sup>, and indicated that high levels of CRP, lactate dehydrogenase, and ESR were associated with adverse outcomes in COVID-19. Another meta-analysis had also confirmed that elevated levels of IL-6 were observed in patients with COVID-19 who exhibited poor clinical outcomes<sup>76</sup>. Therefore, the levels of CRP, ESR, IL-6, ferritin, procalcitonin, and lactate dehydrogenase can serve as potential markers for the evaluation of COVID-19 prognosis.

The high mortality rate and treatment failure in patients with COVID-19 can be attributed to the fact that COVID-19 affects multiple organs, including the lung, heart, kidney, and liver<sup>77</sup>.

Std. Mean Difference

IV, Random, 95% CI

Std. Mean Difference

IV, Fixed, 95% CI

IV. Random, 95% CI

-4

-2

A).

Study or Subgroup

Cai et al 2020

Chen et al (1) 2020 0.34 0.41 0.19 0.14 14 4.1% 0.50 [-0.30, 1.30] 11 Chen et al (2) 2020 8.2 9 10 3.4% 1.15 [0.21, 2.09] 11 0.4 0.3 Chen et al (3) 2020 0.76 1.02 7 0.31 0.21 44 4.0% 1.09 [0.26, 1.91] Duan et al 2020 0.89 [0.50, 1.28] 2.86 4.06 44 0.57 0.68 72 7.6% Gao et al 2020 0.64 0.84 36 0.18 014 102 7 6% 1.03 [0.63, 1.43] Huang et al 2020 5.8 11.46 13 0.53 0.39 28 5.0% 0.81 [0.13, 1.50] Jian-Ya et al 2020 1.51 0.23 0.22 283 6.9% 1.99 [1.53, 2.45] 1.13 22 Wang et al (1) 2020 0.56 0.51 15 0.22 0.06 28 51% 1.11 [0.43, 1.78] 0.65 1.01 [0.69, 1.33] Wang et al (2) 2020 0.83 55 0.21 0.15 166 8.4% 0.79 [0.28, 1.30] Wang et al (3) 2020 5.67 10.61 25 0.57 0.46 44 6 5% Xu et al 2020 9.27 14.93 54 0.63 0.52 137 8.2% 1.09 [0.75, 1.42] Zhang et al (1) 2020 1.67 56 0.2 0.15 8.1% 0.74 [0.39, 1.10] 82 1 Zhang et al (2) 2020 1.14 1.05 58 0.37 0.2 240 8.4% 1.55 [1.24, 1.87] Zhou et al 2020 1.54 1.83 50 0.76 0.86 115 8 2% 0.63 [0.29, 0.97] Total (95% CI) 507 1606 100.0% 1.00 [0.79, 1.21] Heterogeneity: Tau<sup>2</sup> = 0.11; Chi<sup>2</sup> = 47.72, df = 14 (P < 0.0001); l<sup>2</sup> = 71% -4 -2 Test for overall effect: Z = 9.27 (P < 0.00001) mild Std. Mean Difference severe Study or Subgroup Mean SD Weight IV. Fixed. 95% CI Mean SD Total Total Chen et al (1) 2020 1,734.4 585.6 11 880.2 1,001 10 5.2% 1.01 [0.09, 1.93] Liu et al 2020 916.9 155.7 10.5% 0.77 [0.13, 1.42] 827.2 69 187.3 11 Wang et al (2) 2020 520.6 502.48 50 444.37 557.21 115 40.0% 0.14 [-0.19, 0.47] 0.18 [-0.13, 0.50] Zhou et al 2020 1.169.4 1.467.771 54 922.4 1.288.937 137 44.3% Total (95% CI) 273 100.0% 0.27 [0.06, 0.48] 184 Heterogeneity: Chi<sup>2</sup> = 5.70, df = 3 (P = 0.13); l<sup>2</sup> = 47% Test for overall effect: Z = 2.53 (P = 0.01) mild Std. Mean Difference Std. Mean Difference Severe Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% CI Chen et al (1) 2020 567.2 217.1 11 234.4 46.7 10 5.4% 1.99 [0.90, 3.07] 14.6% 1.32 [1.00, 1.64] Chen et al (2) 2020 241.27 96.18 50 163.52 47.63 241 Chen et al (3) 2020 218 89.07 11 230.67 152.39 14 8.0% -0.10 [-0.89, 0.70] Duan et al 2020 464.83 178.94 44 301.333 115.37 72 13.4% 1.14 [0.73, 1.54] Huang et al 2020 433.67 211.79 13 290.33 96.86 28 9.1% 0.99 [0.29, 1.68] Jian-Ya et al 2020 295.33 37.66 221.67 62.84 44 7.6% 1.20 [0.37, 2.04] 7 Wang et al (1) 2020 444.333 226.99 36 224 67 90.24 102 13.1% 1.57 [1.15, 2.00] 0.71 [0.37.1.05] Wang et al (2) 2020 338 145.79 50 255 37 100.6 115 14 4% Zhang et al (1) 2020 434 231.43 55 220.33 91.99 166 14.4% 1.52 [1.18, 1.86] Total (95% CI) 792 100.0% 1.15 [0.85, 1.46] 277 Heterogeneity: Tau<sup>2</sup> = 0.14; Chi<sup>2</sup> = 27.75, df = 8 (P = 0.0005); l<sup>2</sup> = 71%

mild

SD Total

0.25

241

Weight

8.5%

Mean

50

0.29

severe

SD Total

0.36

Mean

Test for overall effect: Z = 7.44 (P < 0.00001)

n 44

Std. Mean Difference

IV, Random, 95% CI

0.55 [0.24, 0.86]

C).

B).

	severe			mild				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Chen et al (1) 2020	0.5	0.6	11	0.1	0.1	10	7.4%	0.87 [-0.03, 1.78]	
Duan et al 2020	0.13	0.23	44	0.03	0.08	72	11.3%	0.64 [0.26, 1.03]	-
Gao et al 2020	0.05	0.06	15	0.02	0.02	28	9.3%	0.76 [0.11, 1.41]	
Huang et al 2020	0.2	0.25	13	0.06	0.08	28	9.0%	0.89 [0.20, 1.58]	
Jian-Ya et al 2020	0.13	0.17	7	0.04	0.02	44	7.8%	1.42 [0.57, 2.27]	
Shi et al 2020	2.26	0.87	48	0.58	0.13	53	10.1%	2.75 [2.20, 3.30]	_
Wang et al (2) 2020	0.16	0.06	50	0.14	0.03	115	11.6%	0.48 [0.15, 0.82]	
Xu et al 2020	0.17	0.16	25	0.06	0.08	44	10.3%	0.94 [0.43, 1.46]	
Zhang et al (2) 2020	0.15	0.18	56	0.06	0.05	82	11.5%	0.74 [0.39, 1.09]	-
Zhou et al 2020	0.23	0.3	54	0.06	0.08	137	11.7%	0.98 [0.65, 1.31]	-
Total (95% CI)			323			613	100.0%	1.03 [0.65, 1.41]	•
Heterogeneity: Tau <sup>2</sup> =	0.29; Ch	i <sup>z</sup> = 53	.77. df	= 9 (P <	0.000	01); I <sup>2</sup> =	83%		<del>t t 1 1</del>

Figure 9. A forest plot of the association between the risk of severe COVID-19 and the levels of D-dimer (A), serum ferritin (B), lactate dehydrogenase (C), and procalcitonin (D).

4

Our data suggest that elevated levels of urea and creatinine, and not chronic kidney disease, were associated with severe COVID-19, which indicates that acute inflammation might be caused by SARS-CoV-2 infection. Previous meta-analyses have also reported findings consistent with our results78,79. Moreover, anatomical studies have reported significant renal inflammation in patients with severe COVID-1975,80,81. There might be two mechanisms by which SARS-CoV-2 induces renal inflammation. First, SARS-CoV-2 might directly infect renal tubular epithelial cells and podocytes through ACE2 receptors, which facilitates the targeted infection of certain cells by the virus. Consequently, acute tubular necrosis, podocytopathy, microangiopathy, and collapsing glomerulopathy might occur owing to the massive inflammation in renal tubular epithelial cells and podocytes<sup>82,83</sup>. Second, the binding between SARS-CoV-2 and ACE2 receptors might activate angiotensin II and induce cytokine production, which may lead to hypercoagulopathy and microangiopathy, and eventually cause renal hypoxia<sup>84,85</sup>.

Conversely, with respect to liver function, we observed that the levels of liver enzymes were higher in patients with severe COVID-19. Previous studies in this context have elucidated that ACE2 receptors are highly expressed in bile duct cells; therefore, infection of these cells by coronaviruses might lead to abnormalities in the levels of liver enzymes<sup>86</sup>. However, a recent anatomical study on liver biopsy specimens from patients with severe COVID-19 revealed that moderate microvascular steatosis and mild lobular and portal activities were observed<sup>87</sup>. These data suggest that it cannot be determined clearly whether the elevated levels of liver enzymes in patients with severe COVID-19 are caused by direct infection or by drug-induced liver injury. Therefore, further studies are required to elucidate the precise mechanism underlying the elevation of liver enzymes levels in patients with severe COVID-19.

Meta-analyses on this topic have been performed previously<sup>43,44,75,76,88–91</sup>. However, compared to previous studies, our study has the following strengths. The previous studies only reported limited factors, such as clinical manifestations<sup>43,88,90,91</sup>, laboratory findings<sup>76,89</sup>, or a combination of only clinical manifestations and laboratory findings<sup>75</sup>. In our study, we

included all comorbidities, clinical manifestations, and laboratory characteristics. Additionally, compared to previous studies, this study has a larger sample size; the data on 1,934 patients with mild and 1,644 patients with severe COVID-19 treated across 19 hospitals were retrieved. However, this study also has certain limitations. Certain crucial factors that might play an important role in the pathogenesis of COVID-19, including secondary infection, treatment, and immunological status were not controlled for. Our current findings should be interpreted with caution because the majority of studies included were cross-sectional, and the samples corresponding to the data analyzed originated only in China. Moreover, in our study, we did not perform the sub-group analysis according to the transmission area. As already reported, the transmission of COVID-19 in China was also affected by the transmission area<sup>92</sup>. Therefore, this limitation might also affect the final findings of our study. Longitudinal studies may reveal more long-term impacts of SARS-CoV-2 infection93.

#### Conclusion

COVID-19 is an emergent infectious disease, and the major problem associated with it is the unknown pattern of disease development. We identified 34 factors that are associated with severe COVID-19. This might improve our understanding of COVID-19 progression and provide baseline data to compile or improve the prediction models for the estimation of COVID-19 prognosis. Moreover, our current findings may also contribute to guide the prioritization of high-risk target populations for vaccination.

#### Data availability

#### Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

#### **Reporting guidelines**

Figshare: PRISMA checklist for 'Predictors of COVID-19 severity: a systematic review and meta-analysis', https://doi.org/ 10.6084/m9.figshare.12813683.v1<sup>94</sup>

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).

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Version 2

Reviewer Report 19 January 2021

https://doi.org/10.5256/f1000research.30622.r76646

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# Morteza Arab-Zozani 匝

Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

The authors responded to my comments clearly and the manuscript is accepted for publication in your journal.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 02 November 2020

https://doi.org/10.5256/f1000research.28897.r72568

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# **Annelies Wilder-Smith**

Heidelberg Institute of Global Health, University of Heidelberg, Heidelberg, Germany

The strength of this paper is the meta-analysis in terms of effect estimates. The weakness is the focus of data from China, while we should learn more from global data including the comparison between HIC and LMIC.

In China, severity was also found to correlate with the force of infection, eg those in high transmission areas had more severe disease outcomes than those from lower transmission areas in China, see: Exposure to SARS-CoV-2 in a **high transmission** setting increases the risk of severe **COVID**-19 compared with exposure to a low **transmission** setting?

Chen D, Hu C, Su F, Song Q, Wang Z. **J Travel Med**. 2020 Aug 20;27(5):taaa094. doi: 10.1093/jtm/taaa094.<sup>1</sup>

The authors highlight the need for a scoring system for the prediction of severity. There is another reason why it is important to identify risk factors for severe disease: to guide prioritization of high risk target populations for vaccination

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Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?  $\ensuremath{\mathsf{Yes}}$ 

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?  $\ensuremath{\mathsf{Yes}}$ 

*Competing Interests:* No competing interests were disclosed.

Reviewer Expertise: COVID-19, Zika and dengue

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 03 Nov 2020

Mudatsir Mudatsir, Syiah Kuala University, Banda Aceh, Indonesia

Response to comments from reviewers: Reviewer 2#

1. The strength of this paper is the meta-analysis in terms of effect estimates. The weakness is the focus of data from China, while we should learn more from global data including the comparison between HIC and LMIC. In China, severity was also found to correlate with the force of infection, eg those in high transmission areas had more severe disease outcomes than those from lower transmission areas in China, see: Exposure to SARS-CoV-2 in a high transmission setting increases the risk of severe COVID-19 compared with exposure to a low transmission setting? Chen D, Hu C, Su F, Song Q, Wang Z. J Travel Med. 2020 Aug

20;27(5):taaa094. doi: 10.1093/jtm/taaa094.1 Response: The additional limitation has been added, as suggested

2. The authors highlight the need for a scoring system for the prediction of severity. There is another reason why it is important to identify risk factors for severe disease: to guide prioritization of high risk target populations for vaccination. Response: The additional clinical implication has been added, as suggested.

*Competing Interests:* We have no competing interest.

Reviewer Report 21 September 2020

# https://doi.org/10.5256/f1000research.28897.r71054

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# Morteza Arab-Zozani 匝

Social Determinants of Health Research Center, Birjand University of Medical Sciences, Birjand, Iran

In this meta-analysis, you investigated the predictors of COVID-19 severity through the literature. You considered a topic of interest and provided a well-written manuscript. However, there are some things that will improve your reporting.

- Abstract, method section, please insert detail about critical/quality appraisal of the included studies.
- Abstract, method section, line 1, please remove " and extracted" from the text. It maybe causes a misunderstanding between this step and the data extraction step.
- Method section, please remove line five. "the protocols for the ...". Mentioning the PRISMA is enough.
- Method section, eligibility criteria, (2) please mention the type of data for adequate data. what is adequate data?
- Method section, search strategy, why is Scopus not searched? You may have missed some articles that are only indexed in Scopus.
- Method section, search strategy, this sentence not related to this section. If you limit the search to EN publication then you need to change the verb. If not this sentence related to inclusion criteria.
- Method section, search strategy, based on PRISMA, add at least one search strategy for one

database as a supplement.

- Method section, data extraction, please added the country of origin for each study. The predictors may be different from one setting to another setting.
- Method section, data extraction, please add details about how resolved disagreement between reviewers.
- Method section, how did you handle the publication bias?
- Result section, there is some problem in figure 1. Please fill it considering other related studies. The number for "record screened" is incorrect.
- Result section, table 1, all studies are from China. If all studies are from China it is better to change the title. these are a predictor of severity in China. In my opinion, this is a limitation of your study.

## Cheers

Are the rationale for, and objectives of, the Systematic Review clearly stated?  $\ensuremath{\mathsf{Yes}}$ 

Are sufficient details of the methods and analysis provided to allow replication by others? Partly

# Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?  $\ensuremath{\mathsf{Yes}}$ 

Competing Interests: No competing interests were disclosed.

**Reviewer Expertise:** Systematic review and meta-analysis in health and medical intervention

# I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 03 Nov 2020

Mudatsir Mudatsir, Syiah Kuala University, Banda Aceh, Indonesia

Response to comments from reviewers:

Reviewer 1#

1. In this meta-analysis, you investigated the predictors of COVID-19 severity through the literature. You considered a topic of interest and provided a well-written manuscript. However, there are some things that will improve your reporting. Abstract, method section, please insert detail about critical/quality appraisal of the included studies.

Response: The description of the quality assessment of included papers has been added in the method of abstract.

2. Abstract, method section, line 1, please remove " and extracted" from the text. It maybe causes a misunderstanding between this step and the data extraction step. Response: We have removed "and extracted".

3. Method section, please remove line five. "the protocols for the ...". Mentioning the PRISMA is enough.

Response: PRISMA checklist may be interpreted as the general guideline in meta-analysis. The specific protocols may differ among meta-analysis studies; for example, the protocols of meta-analysis in gene polymorphism may differ from the protocols of meta-analysis in risk factors identification. In our manuscript, we referred to previous meta-analysis studies in the context of risk factors identification.

4. Method section, eligibility criteria, (2) please mention the type of data for adequate data. what is adequate data?

Response: The additional information related to adequate data has been provided.

5. Method section, search strategy, why is Scopus not searched? You may have missed some articles that are only indexed in Scopus.

Response: We also performed the searching strategy in Scopus as of 5 April 2020, however, we did not find additional articles.

6. Method section, search strategy, this sentence not related to this section. If you limit the search to EN publication then you need to change the verb. If not this sentence related to inclusion criteria. Response: English publication language has been added to eligibility criteria.

7. Method section, search strategy, based on PRISMA, add at least one search strategy for one database as a supplement.

Response: The additional database has been added as the additional database.

8. Method section, data extraction, please added the country of origin for each study. The predictors may be different from one setting to another setting. Response: Country of origin has been added in data extraction.

9. Method section, data extraction, please add details about how resolved disagreement between reviewers.

Response: The additional sentence has been added to describe how to resolve the disagreement.

10. Method section, how did you handle the publication bias? Response: The assessment of publication bias has been described in statistical analysis using Egger test. In the results, we presented in Tables 2 & 3.

11. Result section, there is some problem in figure 1. Please fill it considering other related

studies. The number for "record screened" is incorrect. Response: In Figure 1, we used the template from PRISMA for the article selection pathway.

12. Result section, table 1, all studies are from China. If all studies are from China it is better to change the title. these are a predictor of severity in China. In my opinion, this is a limitation of your study.

Response: We tried to search articles in all regions, however, at the time frame of our searching, we only found articles in China.

*Competing Interests:* We have no competing interest.

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