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Mudatsir Mudatsir, Jonny Karunia Fajar, Laksmi Wulandari, Gatot Soegiarto, Muhammad Ilmawan, Yeni Purnamasari, Bagus Aulia Mahdi, Galih Dwi Jayanto, Suhendra Suhendra, Yennie Ayu Setianingsih, Romi Hamdani, Daniel Alexander Suseno, Kartika Agustina, Hamdan Yuwafi Naim, Muchamad Muchlas, Hamid Hunaif Dhofi Alluza, Nikma Alfi Rosida, Mayasari Mayasari, Mustofa Mustofa, Adam Hartono, Richi Aditya, Firman Prastiwi, Fransiskus Xaverius Meku, Monika Sitio, Abdullah Azmy, Anita Surya Santoso, Radhitio Adi Nugroho, Camoya Gersom, Ali A. Rabaan, Sri Masyeni, Firzan Nainu, Abram L. Wagner, Kuldeep Dhama, Harapan Harapan

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> in a high transmission setting increases the risk of **severe COVID-19** compared ... and hypertension were observed more frequent among patients with **severe COVID-19** than with the mild ones. Compared ... Reporting guidelines Figshare: PRISMA checklist for '**Predictors** of COVID-19 **severity**: a **systematic review** ...

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between cancerous and non-cancerous patients with coronavirus disease 2019 (**COVID-19**). However, no studies ... showing the study selection process. **Systematic review COVID-19 severity** and mortality in cancer patients ...

RESEARCH ARTICLE metrics

REVISED Association between convalescent plasma and the risk of mortality among patients with COVID-19: a meta-analysis [version 3; peer review: 2 approved]

Shinta Oktya Wardhani, Jonny Karunia Fajar, Laksmi Wulandari, Gatot Soegiarto, Yeni Purnamasari, Anisa Asmiragani, Helnida Anggun Maliga, Muhammad Ilmawan, Gloriana Seran, Dheka Sapti Iskandar, Conchita Emiliana Ndapa, Viviana Hamat, Rafika Ajeng Wahyuni, Linda Oktaviana Suci Cyntia, Feronika Maryanti Maarang, Yosef Andrian Beo, Olivera Agnes Adar, Iraky Mardya Rakhmadhan, Emilia Tiara Shantikaratri, Ayu Sekarani Damana Putri, Rizqa Wahdini, Endang Pati Broto, Agnes Wanda Suwanto, Fredo Tamara, Aditya Indra Mahendra, Eden Suryoiman Winoto, Pratista Adi Krisna, Harapan Harapan

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discuss the added value of your study regarding the existing **meta-analysis**. What is the novelty of your ... 0005). In **severe COVID-19** sub-group analysis, we found that patients without CCP had a 1.32 times higher risk ... selection in our **meta-analysis**. CCP efficacy against **COVID-19** A total of 1,937 patients treated with CCP ...

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intensive care unit (ICU) admission and death: a meta-analysis of 229 studies covering over 10M patients [version 1; peer review: awaiting peer review]

Bart G. Pijls, Shahab Jolani, Anique Atherley, Janna I.R. Dijkstra, Gregor H.L. Franssen, Stevie Hendriks, Evan Yi-Wen Yu, Saurabh Zalpuri, Anke Richters, Maurice P. Zeegers

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PUBLISHED 05 Jan 2022

human behaviours. References: Muurlink OT, Taylor-Robinson AW. **COVID-19** ... for hospitalization (RR = 1.33, 95%CI: 1.27 to 1.41), higher risk for **severe COVID-19** (RR = 1.22, 95%CI: 1.17 to 1 ... **COVID-19** outcomes, including death. A recent **systematic review** from our group summarized literature from ...

RESEARCH ARTICLE metrics *AWAITING PEER REVIEW*

Evaluation of the convalescent plasma therapy effectiveness and the factors that influence the therapeutic outcome in hospitalized COVID-19 patients: A retrospective cohort study. [version 1; peer review: awaiting peer review]

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a retrospective cohort study on 312 patients with either **severe** or critical **COVID-19**, who ... it is imperative to find an alternative treatment strategy, especially for **severe COVID-19** patients.2,3 For more ...

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control study on cigarette smoking on risk for hospitalization from **COVID-19**. The paper is lacking a clear ... and hospitalization from **COVID-19**. Interestingly, we found an association between current smoking status and COVID-19 ... of hospitalisation (**COVID-19** vs. another respiratory virus a year previous). The exposure variable was smoking status ... of contracting **COVID-19** and experiencing greater disease **severity** once infected. SARS-CoV-2 enters epithelial ...

STUDY PROTOCOL metrics

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Daniel G. Hamilton, Hannah Fraser, Fiona Fidler, Steve McDonald, Anisa Rowhani-Farid, Kyungwan Hong, Matthew J. Page

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and health research community at large. Therefore this **systematic review** aims to synthesise the findings ... data or code availability (i) as part of a single individual participant data (IPD) **meta-analysis**, (ii ...

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SYSTEMATIC REVIEW

Predictors of COVID-19 severity: a systematic review and meta-analysis [version 1; peer review: 2 approved]

Mudatsir Mudatsir[1], Jonny Karunia Fajar[1,2], Laksmi Wulandari[3], Gatot Soegiarto[4], Muhammad Ilmawan[5], Yeni Purnamasari[5], Bagus Aulia Mahdi[4], Galih Dwi Jayanto[2], Suhendra Suhendra[5], Yennie Ayu Setianingsih[6], Romi Hamdani[7], Daniel Alexander Suseno[8], Kartika Agustina[9], Hamdan Yuwafi Naim[10], Muchamad Muchlas[11], Hamid Hunaif Dhofi Alluza[5], Nikma Alfi Rosida[5], Mayasari Mayasari[5], Mustofa Mustofa[5], Adam Hartono[12], Richi Aditya[5], Firman Prastiwi[5], Fransiskus Xaverius Meku[5], Monika Sitio[5], Abdullah Azmy[7], Anita Surya Santoso[13], Radhitio Adi Nugroho[5], Camoya Gersom[2], Ali A. Rabaan[14], Sri Masyeni[15], Firzan Nainu[16], Abram L. Wagner[17], Kuldeep Dhama[18], Harapan Harapan[1,19]

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v1 **First published:** 09 Sep 2020, **9**:1107
https://doi.org/10.12688/f1000research.26186.1
Latest published: 09 Sep 2020, **9**:1107
https://doi.org/10.12688/f1000research.26186.1

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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 and extracted as of April 5, 2020. 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, high-sensitivity 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

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version 1 09 Sep 2020	✓ report	✓ report

1. **Morteza Arab-Zozani**, Birjand University of Medical Sciences, Birjand, Iran
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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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Competing interests: No competing interests were disclosed.

Grant information: We thank to Lembaga Pengelola Dana Pendidikan (LPDP) Republik Indonesia for supporting this project.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Mudatsir M, Fajar JK, Wulandari L *et al*. **Predictors of COVID-19 severity: a systematic review and meta-analysis [version 1; peer review: 2 approved]** F1000Research 2020, **9**:1107 https://doi.org/10.12688/f1000research.26186.1

First published: 09 Sep 2020, **9**:1107 https://doi.org/10.12688/f1000research.26186.1

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[1,2]. 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[3]. 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-19[4,5]. Among patients with similar clinical characteristics and with similar treatment regiments, there may be a diversity in clinical outcomes[6]. 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[7–15]. 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[16]. 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[17–23], as well as to those recommended by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA)[24].

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. 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. 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) sample size of mild and severe cases, (4) clinical manifestations, (5) morbidities, and (6) laboratory findings. Data extraction was performed by two independent investigators (JKF and MI) using a pilot form.

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 ≤ 4), moderate quality (for scores between 5–6), or high quality (for scores ≥ 7)[23]. 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[26–42] 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 meta-analysis (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 systolic blood pressure (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 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°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,

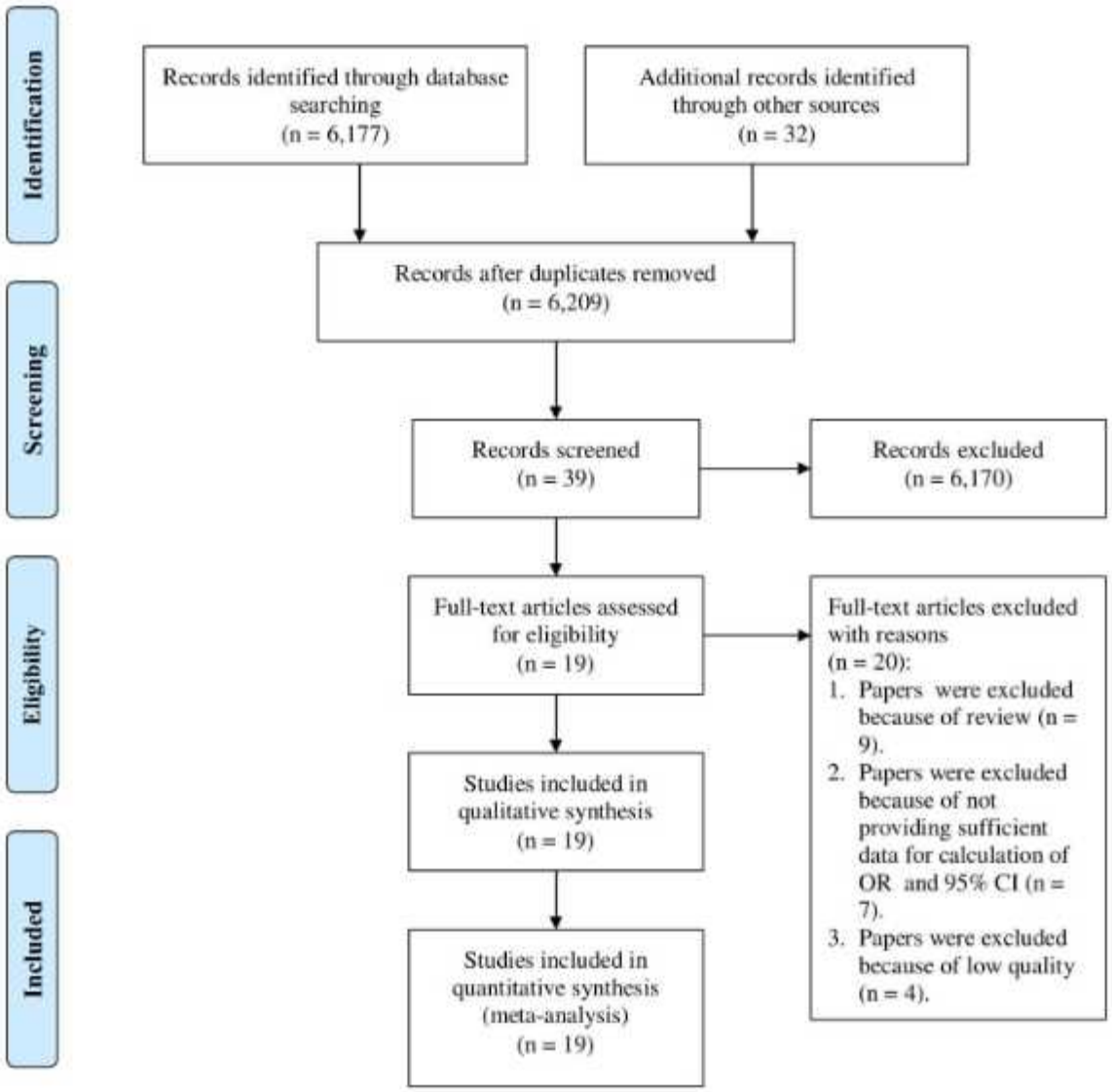

Figure 1. A flowchart of paper selection in our study.

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 results are consistent with those of previous meta-analyses[41,44] 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[45]. 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[46–48]. Since COVID-19 primarily affects the respiratory tract[49],

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

Author & year	Country	City	Hospital	Sample size		Outcome measure	NOS
				Severe	*Mild*		
Bai *et al.* 2020[24]	China	Wuhan	Jinyintan Hospital	91	36	Died vs. cured	7
Cai *et al.* 2020[47]	China	Shenzen	Third people's Hospital	58	240	Severe vs. non severe	9
Chen *et al.* 2020[28]	China	Wuhan	Tongji hospital	11	10	Severe vs. moderate	9
Chen *et al.* 2020[29]	China	Mixed	Multicenter	50	241	Severe vs. mild-moderate	9
Chen *et al.* 2020[30]	China	Wuhan	Zhongnan Hospital	14	11	Viral clearance vs. without viral clearance	9
Duan *et al.* 2020[31]	China	Wuhan	Wuhan Pulmonary Hospital	44	72	Uncured vs. cured	9
Gao *et al.* 2020[32]	China	Fuyang	Second People's Hospital	15	28	Severe vs. mild	7
Guan *et al.* 2020[33]	China	Guangdong	National Health Commision of China	926	173	Severe vs. non-severe	7
Huang *et al.* 2020[34]	China	Wuhan	Jinyintan hospital	13	28	ICU vs. non-ICU	9
Jian-Ya *et al.* 2020[35]	China	Chongqing	Three Gorges Hospital	7	44	Severe vs. non severe	9
Liu *et al.* 2020[36]	China	Wuhan	Union Hospital	69	69	Severe vs. non severe	7
Shi *et al.* 2020[37]	China	Wuhan	Renmin Hospital	48	53	Died <3 d vs. >3 d	9
Wang *et al.* 2020[38]	China	Mixed	Multicenter	50	115	CT imaging score >11 vs. <11	8
Wang *et al.* 2020[39]	China	Wuhan	Wuhan First People's Hospital	22	283	Survivor vs. non-survivor	8
Wang *et al.* 2020[48]	China	Wuhan	Zhongnan Hospital	36	102	ICU vs. non-ICU	9
Xu *et al.* 2020[40]	China	Mixed	Multicenter	25	44	Severe vs. mild	8
Zhang *et al.* 2020[41]	China	Wuhan	Zhongnan Hospital	55	166	Severe vs. non-severe	9
Zhang *et al.* 2020[44]	China	Wuhan	Wuhan Seventh Hospital	56	82	Severe vs. non-severe	7
Zhou *et al.* 2020[42]	China	Wuhan	Wuhan Pulmonary Hospital	54	137	Survivor vs. non-survivor	8

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.

Clinical characteristics	NS	Model	Value		pE	pHet	p	OR	95%CI
			Severe	*Mild*					
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

Clinical characteristics	NS	Model	Value		pE	pHet	p	OR	95%CI
			Severe	*Mild*					
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 characteristics	NS	Model	Value		pE	pHet	p	OR	95%CI
			Severe	*Mild*					
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 characteristics	NS	Model	Value		pE	pHet	p	OR	95%CI
			Severe	*Mild*					
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 biliruoin (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									
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.

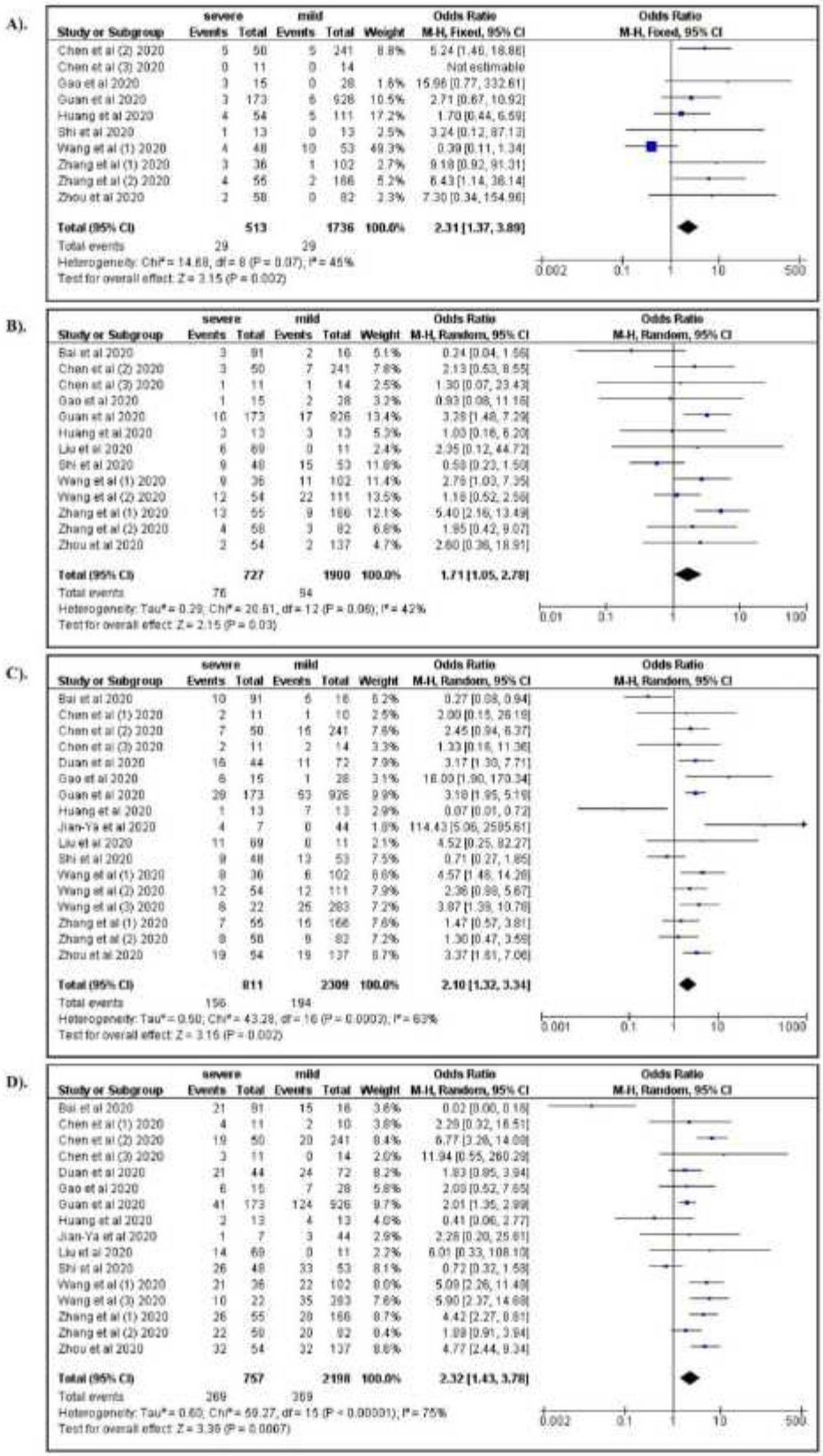

Figure 2. A forest plot of the association between comorbid factors and the risk of severe COVID-19. A) Chronic respiratory disease; **B**) Cardiovascular diease; **C**) Diabetes mellitus; **D**) Hypertension.

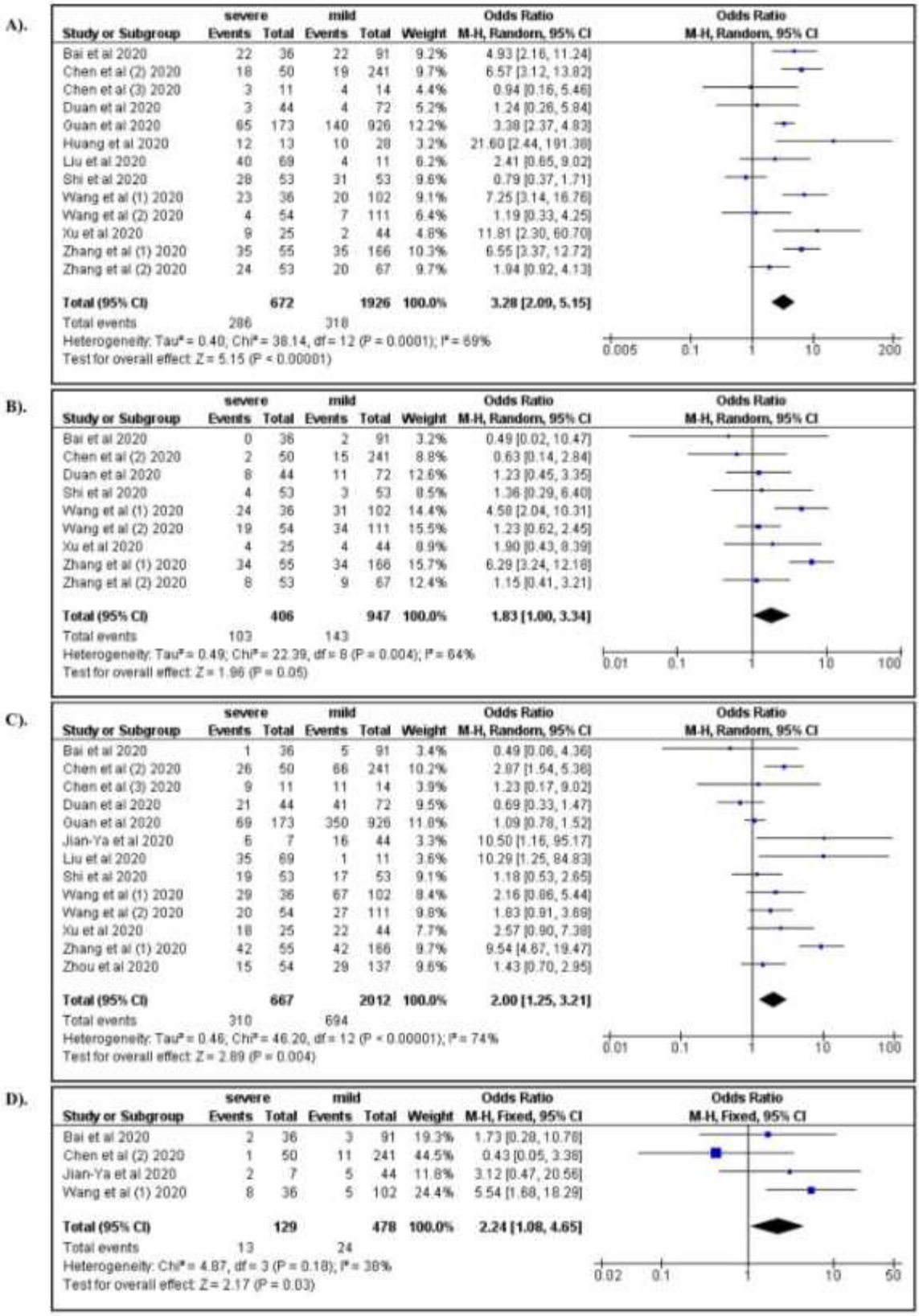

Figure 3. A forest plot of the association between clinical manifestations and the risk of severe COVID-19. A) Dyspnea; **B)** Anorexia; **C)** Fatique; **D)** Dizziness.

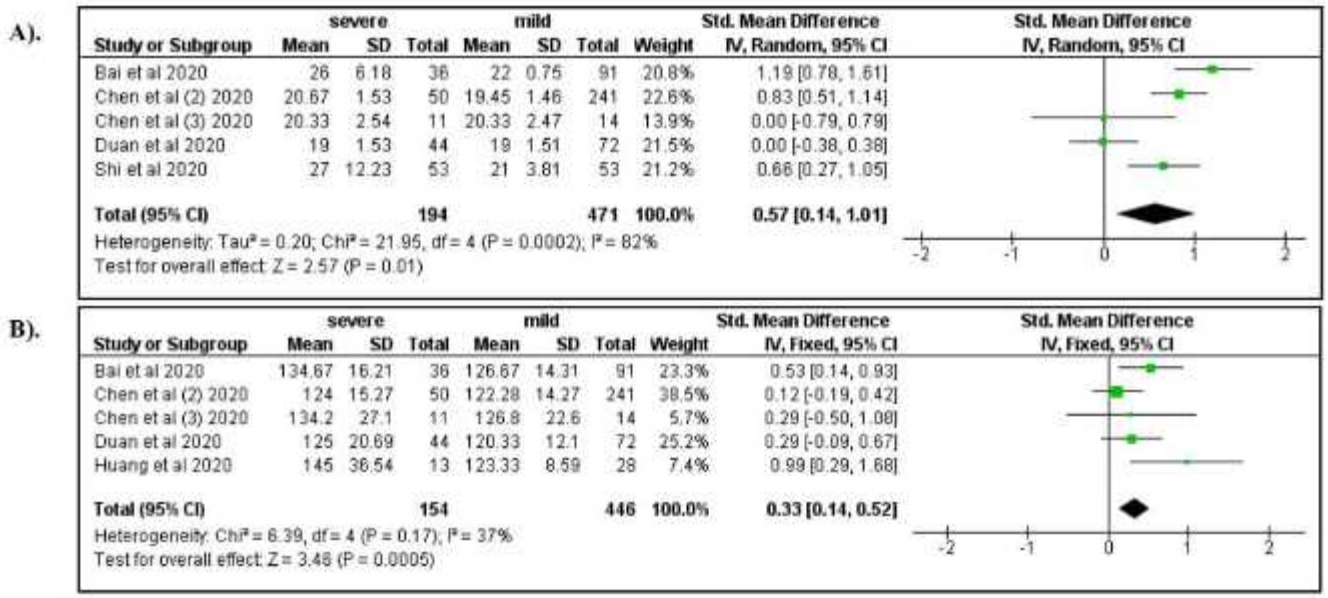

Figure 4. A forest plot of the association between clinical manifestation and the risk of severe COVID-19. A) Respiratory rate; **B)** Systolic blood pressure.

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[50].

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[51]. The role of leukocytes in the pathogenesis of COVID-19 is conflicting. In most cases, viral infections have been observed to cause leukopenia[52]. Furthermore, a study also reported that leukopenia was observed at a significantly higher frequency among COVID-19 patients than among non-COVID-19 patients[53]. 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[54]. Consistent with our data, a study has confirmed that cytokine storm is significantly associated with severe COVID-19[55]. 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[56]. Furthermore, this might lead to neutrophil infiltration in pulmonary capillaries, organ damage, and the development of acute respiratory distress syndrome[57].

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[58]; 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[59]. Since ACE2 receptors are also expressed by lymphocytes[60], 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[61]. Moreover, our findings also confirmed the significant elevation in the levels of IL-6. Third, ACE2 receptors are expressed by cells from various organs, including the thymus and spleen[62]. 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[63]. Hyperlactic acidemia has been observed in patients with severe COVID-19[64].

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 data and meta-analyses prevents a holistic comparison. Certain

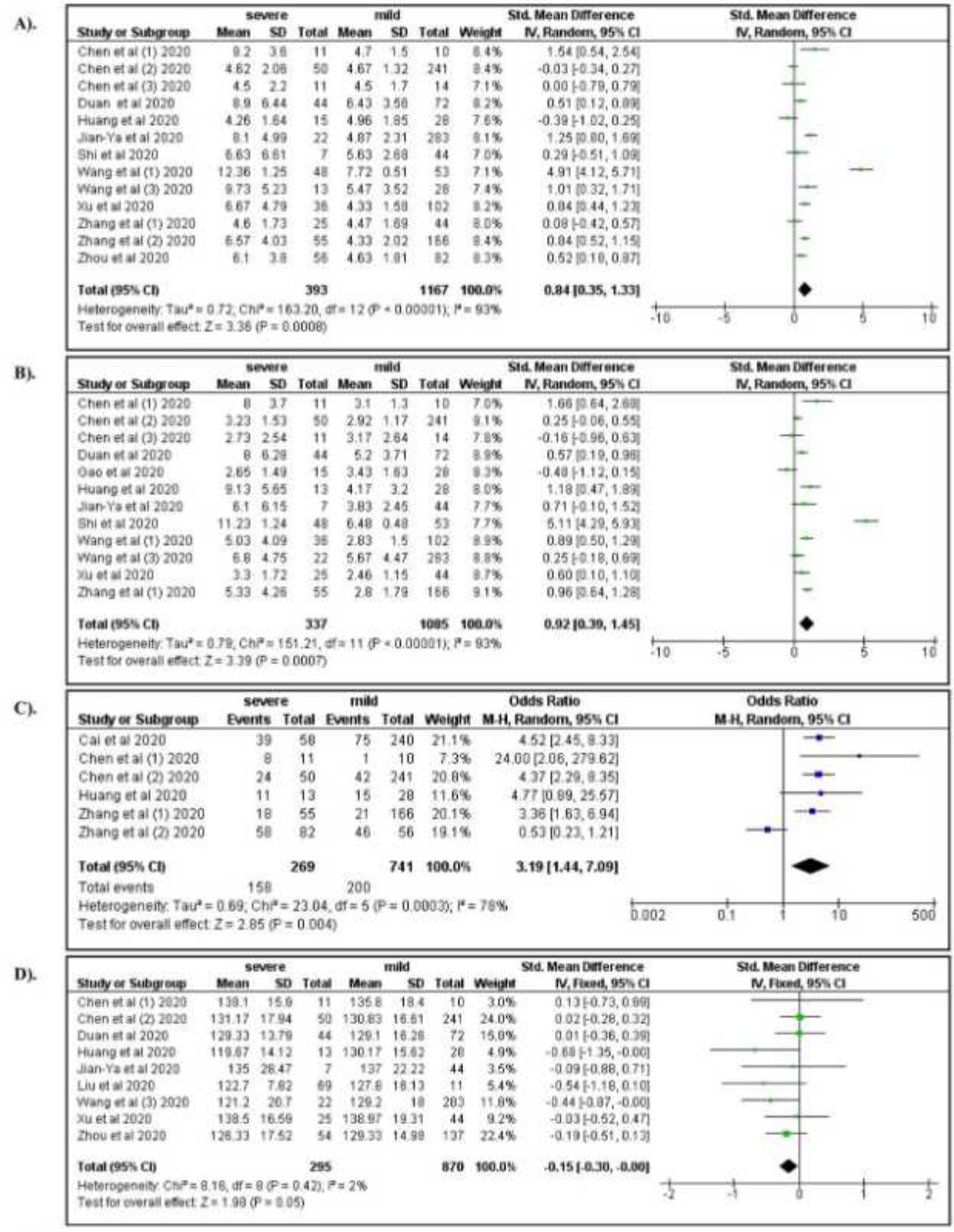

Figure 5. A forest of the association between complete blood count and the risk of severe COVID-19. A) White blood cells; **B)** Neutrophil count; **C)** Lymphocytopenia; **D)** Hemoglobin.

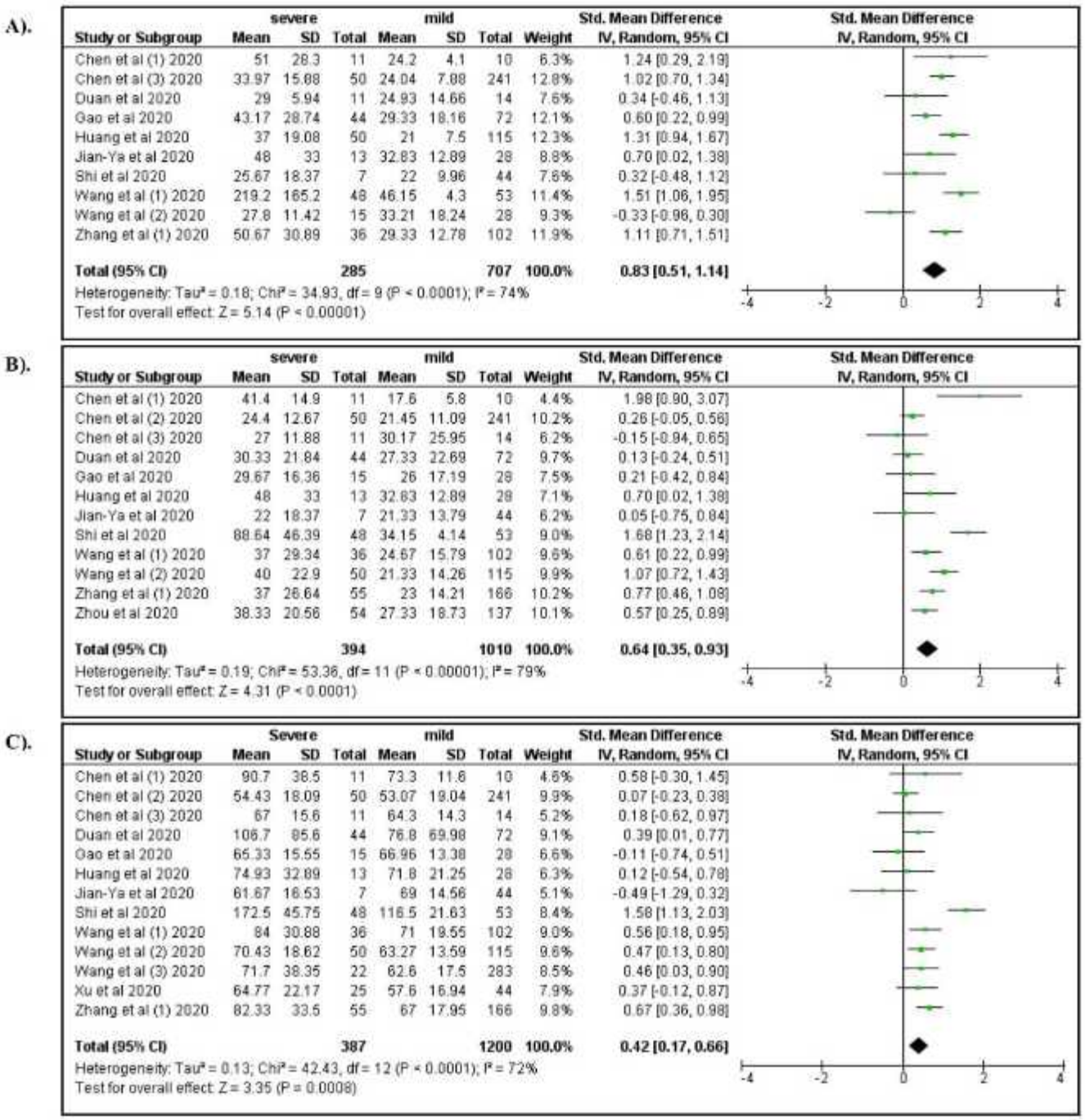

Figure 6. A forest plot of the association between the risk of severe COVID-19 and the levels of AST (**A**), ALT (**B**), and serum creatinine (**C**).

infectious diseases that cause abnormal coagulation have been associated with poor clinical outcomes[63]. 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[66]. Consequently, a massive inflammatory reaction may occur in endothelial cells owing to SARS-CoV-2 infection[67], which may lead to increased coagulation, disseminated intravascular coagulation[68], and increased fibrin degradation[69]. High fibrin degradation leads to elevated levels of fibrinogen and D-dimer[70], which might also explain the occurrence of venous thromboembolism

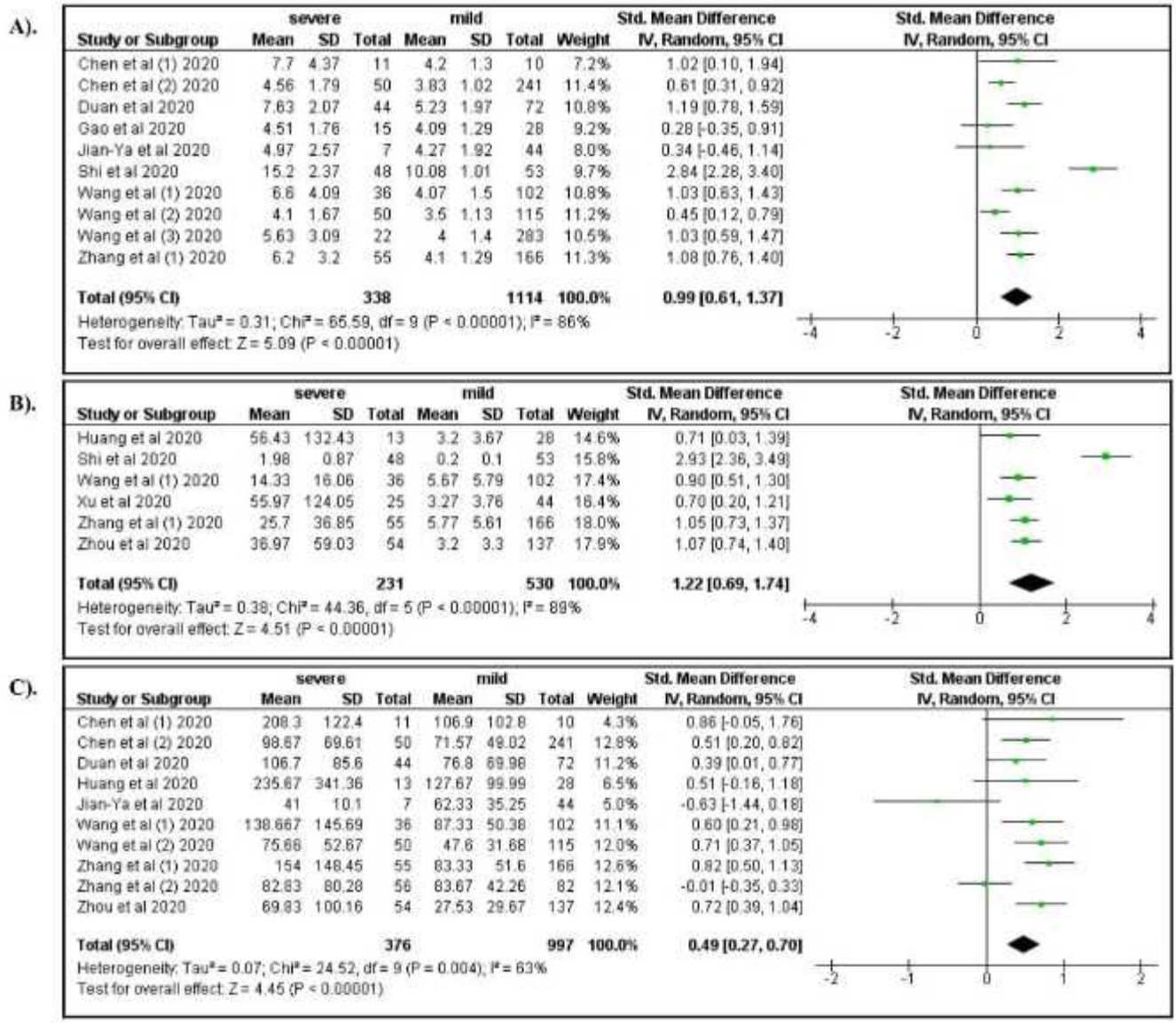

Figure 7. A forest plot of the association between the risk of severe COVID-19 and the levels of BUN (**A**), Hs-troponin (**B**), and creatine kinase (**C**).

in critical patients of COVID-19[71]. 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[72]. Furthermore, pulmonary embolism and deep vein thrombosis were also observed in patients with severe COVID-19[73,74], 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 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[75], 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[76]. 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

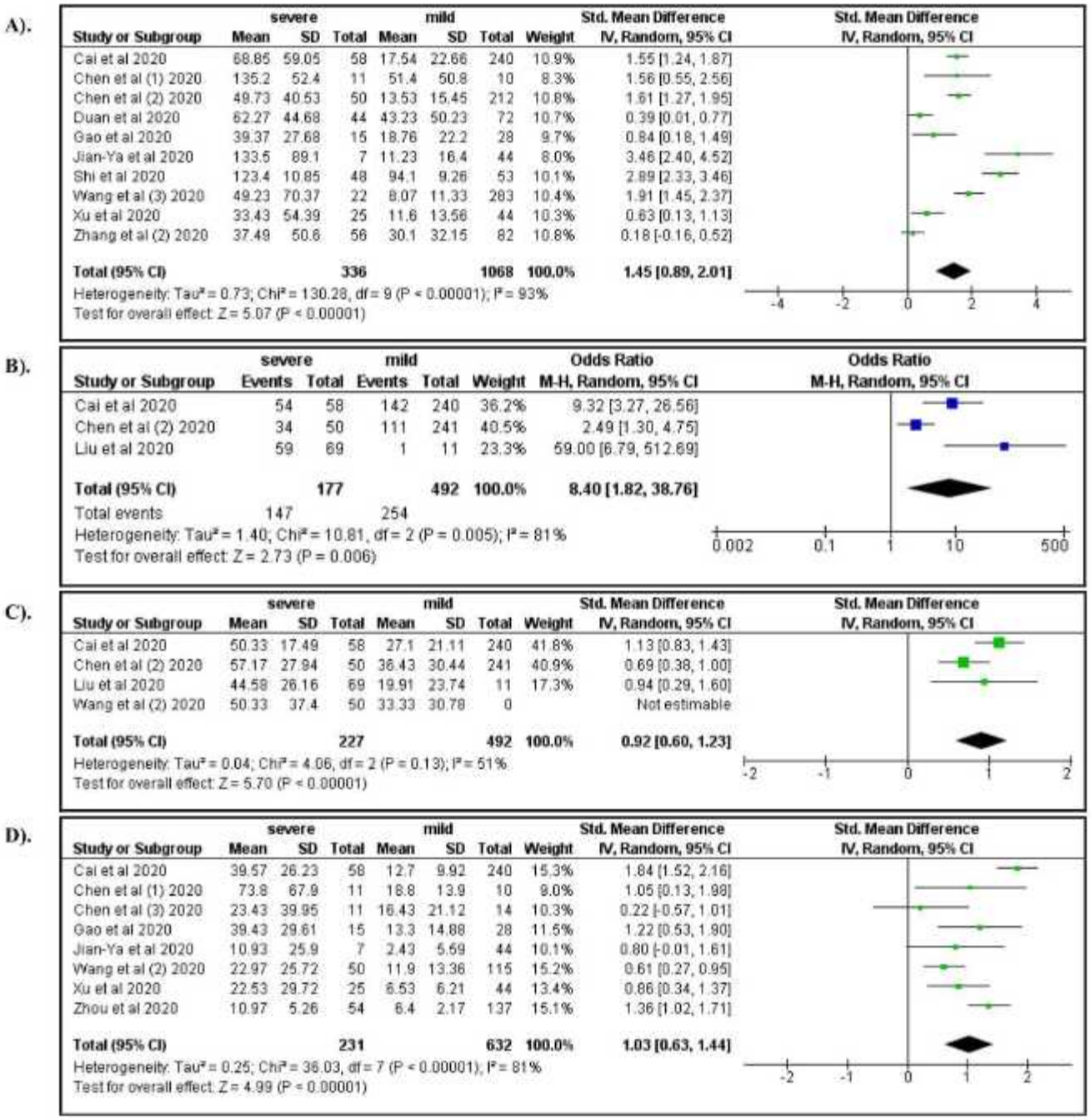

Figure 8. A forest plot of the association between the risk of severe COVID-19 and the levels of CRP (**A**), Hs-CRP (**B**), ESR (**C**), and IL-6 (**D**).

multiple organs, including the lung, heart, kidney, and liver[77]. 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 results[78,79]. Moreover, anatomical studies have reported significant renal inflammation in patients with severe COVID-19[75,80,81]. 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.

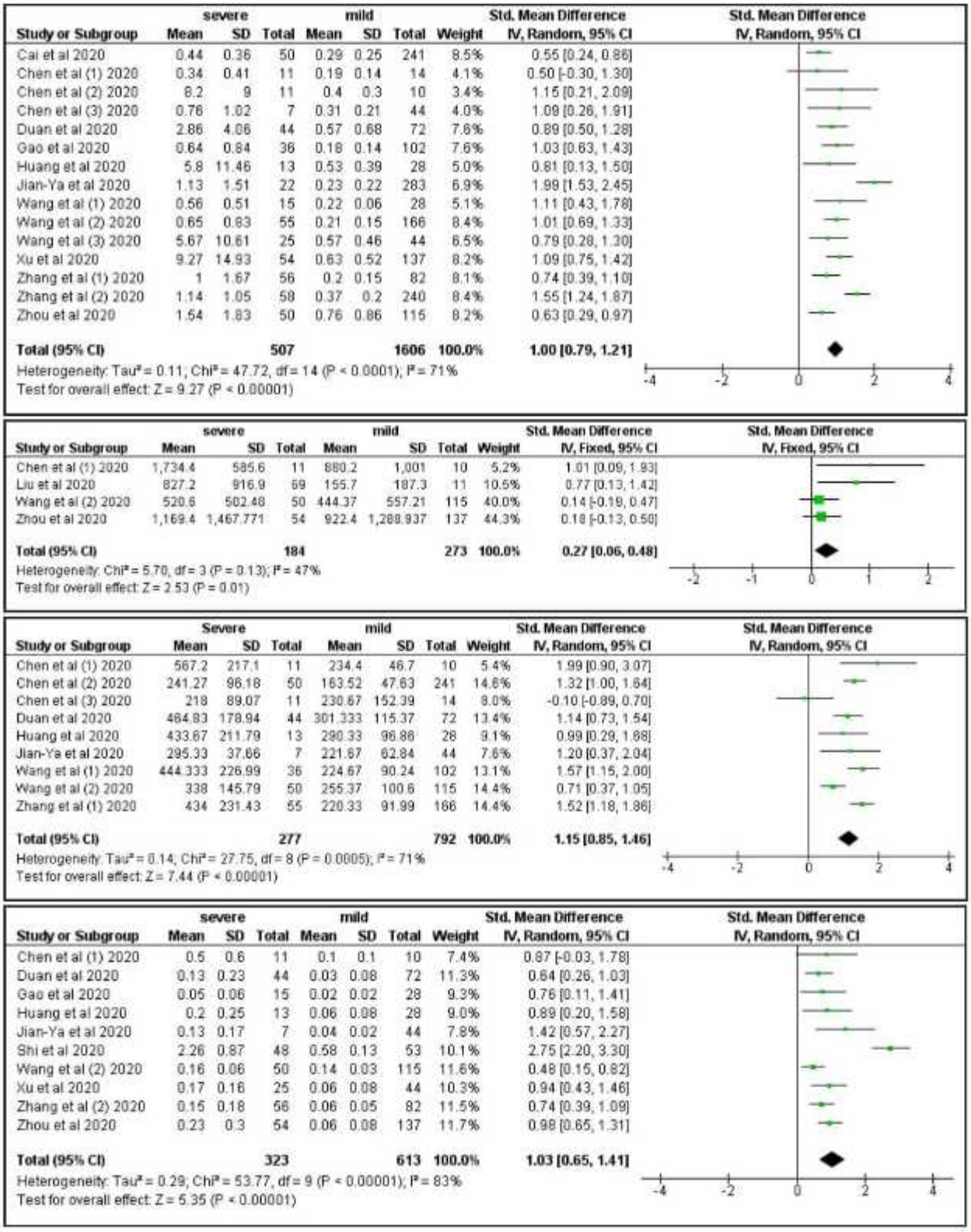

Figure 9. A forest plot of the association between the risk of severe COVID-19 and the levels of D-dimer (**A**), serum ferritin (**B**), lactate dehydrogenase (**C**), and procalcitonin (**D**).

Consequently, acute tubular necrosis, podocytopathy, microangiopathy, and collapsing glomerulopathy might occur owing to the massive inflammation in renal tubular epithelial cells and podocytes[82,83]. 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[84,85].

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[86]. 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[87]. 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[45,44,75,76,88–91]. However, compared to previous studies, our study has the following strengths. The previous studies only reported limited factors, such as clinical manifestations[43,88,90,91], laboratory findings[76,89], or a combination of only clinical manifestations and laboratory findings[75]. 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. Longitudinal studies may reveal more long-term impacts of SARS-CoV-2 infection[92].

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.

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[93]

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Reviewer Report 02 November 2020

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

✔ **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.[1]

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?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?
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.

Reviewer Report 21 September 2020

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

Morteza Arab-Zozani
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?
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?
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.

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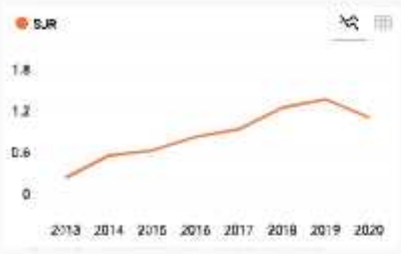

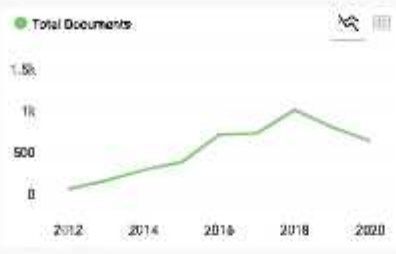

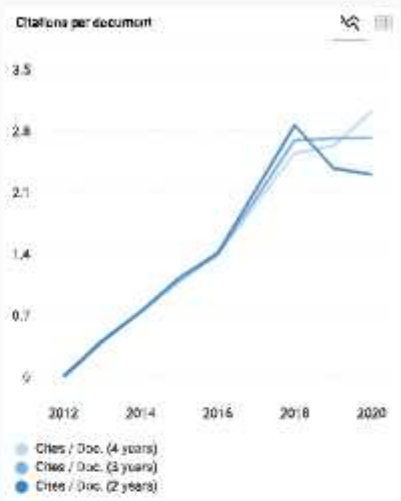

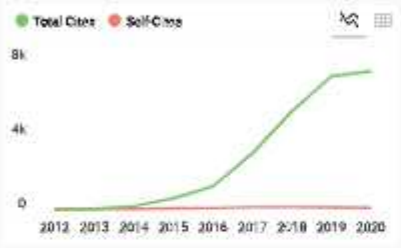

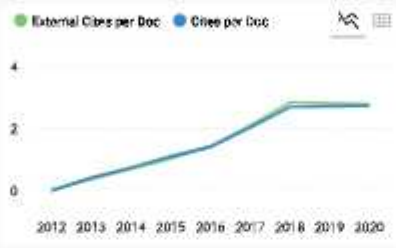

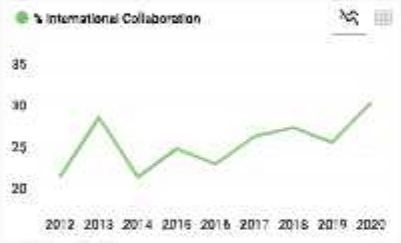

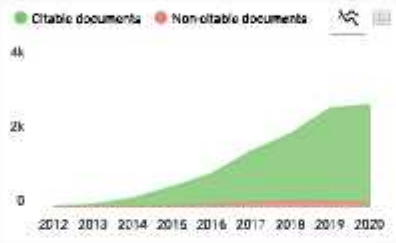

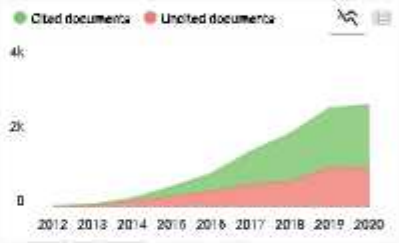

Metrics based on Scopus® data as of April 2021

hany alsool naji 8 months ago

I have been waiting about one year for my article to publish or review but till now nothing happened

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SCImago Team

Melanie Ortiz 8 months ago

Dear Hany,
Thank you for contacting us.
Unfortunately, we cannot help you with your request, we suggest you contact the journal's editorial staff , so they could inform you more deeply.
Best Regards, SCImago Team

alemu 12 months ago

Background: Nowadays, people die due to metabolic aging than chronological age worldwide.