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Association of inflammatory markers with the severity of COVID-19: A meta-analysis

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ABSTRACT

Objectives: Studies reported associations of inflammatory markers with the severity of COVID-19, but conclusions were inconsistent. We aimed to provide an overview of the association of inflammatory markers with the severity of COVID-19.

Methods: We searched PubMed, Embase, Cochrane Library, Wanfang and China National Knowledge Infrastructure (CNKI) database until March 20, 2020. Weighted mean difference (WMD) and 95% confidence intervals (CIs) were pooled using random or fixed-effects models.

Results: A total of 16 studies comprising 3962 patients with COVID-19 were included in our analysis. Random-effect results demonstrated that patients with COVID-19 in the nonsevere group had lower levels for CRP (WMD = -41.78 mg/l, 95% CI = $[-52.43, -31.13]$, $P < 0.001$), PCT (WMD = -0.13 ng/ml, 95% CI = $[-0.20, -0.05]$, $P < 0.001$), IL-6 (WMD = -21.32 ng/l, 95% CI = $[-28.34, -14.31]$, $P < 0.001$), ESR (WMD = -8 mm/h, 95% CI = $[-14, -2]$, $P = 0.005$), SAA (WMD = -43.35 μ g/ml, 95% CI = $[-80.85, -5.85]$, $P = 0.020$) and serum ferritin (WMD = -398.80 mg/l, 95% CI = $[-625.89, -171.71]$, $P < 0.001$), compared with those in the severe group. Moreover, survivors had a lower level of IL-6 than non-survivors (WMD = -4.80 ng/ml, 95% CI = $[-5.87, -3.73]$, $P < 0.001$). These results were consistent through sensitivity analysis and publication bias assessment.

Conclusions: The meta-analysis highlights the association of inflammatory markers with the severity of COVID-19. Measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

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Introduction

The ongoing worldwide Coronavirus Disease 2019 (COVID-19) pandemic has posed a huge threat to global public health (WHO, 2020a). The pathogen has been identified as a novel single-stranded ribonucleic acid (RNA) betacoronavirus named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which shares an approximately 79% similarity at nucleotide level with

severe acute respiratory syndrome coronavirus (SARS-CoV) (Zhang and Holmes, 2020). As of March 21, 2020, a total of 266, 073 confirmed cases from 150 countries and territories were reported, including 11,183 deaths (WHO, 2020b). COVID-19 represents a spectrum of clinical severity ranged from asymptomatic to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death (Guan et al., 2020). Therefore, full monitoring the severity of COVID-19 and effective early intervention are the fundamental measures for reducing mortality.

Accumulating evidence has suggested that inflammatory responses play a critical role in the progression of COVID-19 (Mehta et al., 2020; Stebbing et al., 2020). Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines (Tay et al., 2020). These cytokines and chemokines then attract immune cells and activate immune

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responses, leading to cytokine storms and aggravations (Xu et al., 2020). Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality (Wu et al., 2020). Inflammatory markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of the development of severe COVID-19 (Cheng et al., 2020; Gao et al., 2020; Qin et al., 2020). Moreover, increased levels of serum amyloid A (SAA) are shown to be involved in COVID-19 pathogenesis and may serve as a potential biomarker for monitoring disease progression (Cheng et al., 2020; Xiang et al., 2020). However, these results remain controversial due to no observed difference in the levels of IL-6, SAA, ESR and CRP by other studies (Chen et al., 2020b; Wu et al., 2020; Zhang et al., 2020).

To the best of our knowledge, the overall inflammatory profile is missing to date due to the insufficient sample size. Here we performed a meta-analysis based on the current scientific literature to compare the levels of inflammatory markers between severe patients and nonsevere patients with COVID-19. Our study will highlight the association of inflammatory markers with the severity of COVID-19 and assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

Methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). Original studies

reporting COVID-19 were searched until March 20, 2020 through PubMed, Embase, Cochrane Library, Wanfang and China National Knowledge Infrastructure (CNKI) database. The following combined search terms were used in PubMed, Embase and Cochrane: (“Novel coronavirus” OR “Coronavirus disease 2019” OR “Coronavirus 2019” OR “nCoV-2019” OR “2019-nCoV” OR “COVID-19” OR “SARS-CoV-2”). The Chinese translation of the search terms was used in Wanfang and CNKI database. We did not apply any restriction on language or date or study design. All eligible articles were retrieved, and their references to identified publications were searched for further potentially relevant articles (Gao et al., 2020; Zhou et al., 2020a).

Selection criteria

English-language or Chinese-language publications reporting levels of inflammation markers in patients with COVID-19 were included if they met the following criteria: (1) patients were diagnosed with COVID-19 and had positive results of SARS-CoV-2 RNA; (2) patients could be grouped into severe group and nonsevere group, or intensive care unit (ICU) group and non-ICU group, or survivors group and non-survivors group; (3) literature sources and levels of inflammatory markers were available. The diagnosis and severity classification of COVID-19 was based on the New Coronavirus Pneumonia Prevention and Control Program in China (National Health Commission of China, 2020), which classified COVID-19 into four types including mild, moderate, severe, and critical pneumonia. In our meta-analysis, severe or critical COVID-19 patients were grouped into the severe group, and mild or moderate COVID-19 patients were grouped into the

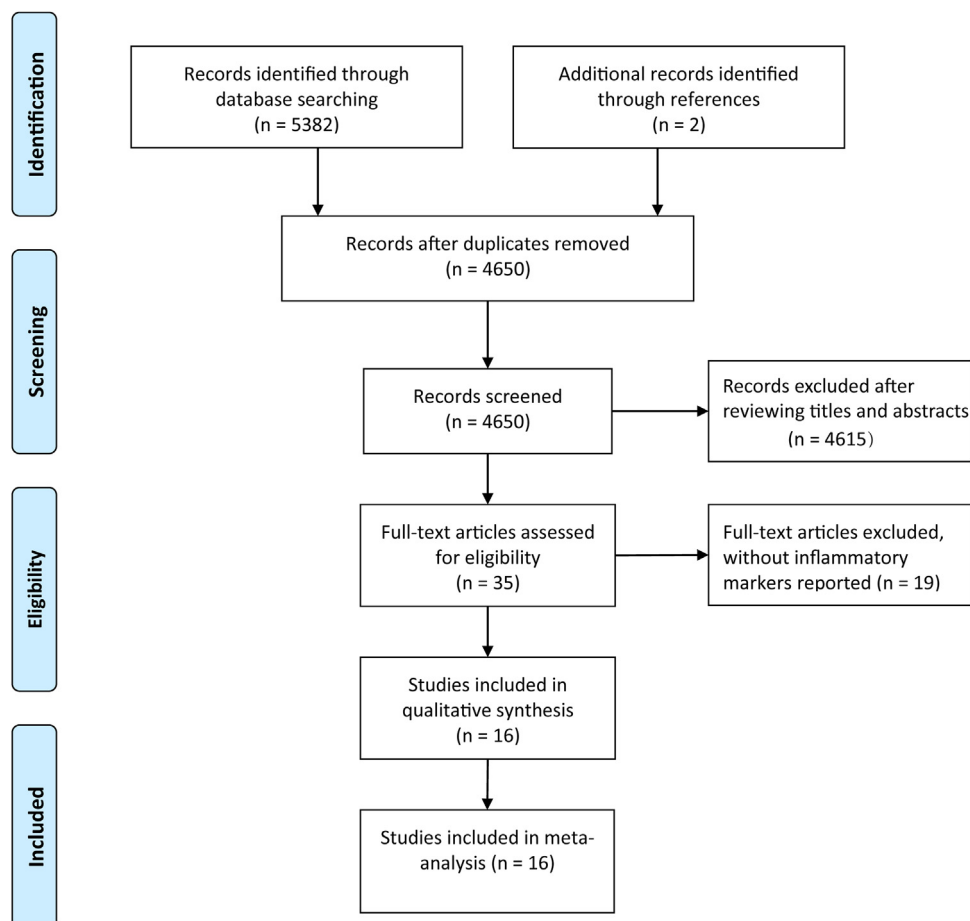


Figure 1. Literature search and filtering of studies.

nonsevere group. If there were two or more studies from the same authors or institutions, only the study with the largest sample size was chosen. Studies were excluded if patients were asymptomatic carriers and did not fulfil the inclusion criteria.

Data extraction and quality assessment

The records from the initial search were scanned by two authors to exclude any duplicate and irrelevant studies. The following data were extracted: first authors, publication date, country of origin, grouping situation, cases, age, sex and levels of inflammatory markers in different groups. Stratified data or interquartile range (IQR) were converted to mean (\pm SD) using mathematical formulas for meta-analysis (Luo et al., 2018; Wan et al., 2014). Any discrepancies were resolved by discussion. Quality assessments of all potentially eligible studies were conducted using the Newcastle-Ottawa Scale (NOS). There are eight items in three aspects: selection, comparability and exposure. The full score was 9 stars. Four to six stars was regarded as a moderate-quality study, and seven to nine stars as a high-quality study (Ga Wells et al., 2014). Studies with NOS scores lower than 7 were recognized to be of inferior quality and therefore excluded.

Statistical analysis

All the statistical analyses were carried out by STATA (Version 12.0; STATA Corporation, College Station, TX, USA) software. Statistical heterogeneity was assessed with I^2 and P-value. A fixed effects model was adopted without significant heterogeneity ($I^2 \leq 50\%$ and $P \geq 0.1$), while a random effects model was employed in all other instances ($I^2 > 50\%$ or $P < 0.1$) (Zeng et al., 2019; Zeng et al., 2020). Weighted mean difference (WMD) with 95% confidence interval (95% CI) was calculated for inflammatory

markers. Sensitivity analysis was performed by omitting one study each time through influence analysis to assess the stability of results. Additionally, standard mean difference (SMD) was used to explore the consistency of the conclusion. Publication bias was evaluated by Egger's test. If publication bias was conformed, the Duval's trim and fill method was implemented to adjust for this bias. $P < 0.05$ was considered statistically significant.

Results

Literature search and studies characteristics

The initial literature search generated altogether 5384 records with 734 studies subsequently excluded due to duplication (Figure 1). After a review of the titles and abstracts, we obtained 35 studies by excluding an additional 4615 studies. We further excluded 19 studies by scanning the full text which did not report inflammatory markers. Finally, 16 studies were included in our analysis (Chang et al., 2020; Chen et al., 2020a; Chen et al., 2020b; Cheng et al., 2020; Fang et al., 2020; Gao et al., 2020; Huang et al., 2020; Li et al., 2020; Peng et al., 2020; Qin et al., 2020; Ruan et al., 2020; Wu et al., 2020; Xiang et al., 2020; Xiao et al., 2020; Zhang et al., 2020; Zhou et al., 2020a). Characteristics of 16 eligible studies are presented in Table 1. All of these studies were published in 2020 and from China, involving 3962 patients. Eight studies were written in Chinese and the others in English. Twelve studies were grouped by nonsevere and severe groups, 2 studies grouped by non-ICU and ICU groups, and 2 studies grouped by survivors and non-survivors with COVID-19. Obviously, patients in the severe group, ICU group or non-survivors group were older than those in the corresponding control group. There was no obvious difference in the sex distribution of patients for each study. All studies were deemed of high quality with 7 or more NOS scores and details can be found in Table 2.

Table 1
Characteristics of enrolled studies in the meta-analysis.

First author	Year	Country	Groups	Cases	Age	Sex (male, %)	Inflammatory markers	Quality
Chang Z	2020	China	Nonsevere	93	–	–	CRP, PCT, IL-6	8
			Severe	57				
Chen C	2020	China	Nonsevere	126	57.0 \pm 15.6	66 (52.3)	CRP	7
			Severe	24	68.5 \pm 13.6	18 (75.0)		
Chen L	2020	China	Nonsevere	15	–	–	IL-6, CRP	7
			Severe	14				
Cheng K	2020	China	Nonsevere	282	49.7 \pm 11.9	145 (51.4)	IL-6, CRP, PCT, ESR, SAA, Serum ferritin	8
			Severe	181	54.7 \pm 13.5	99 (54.7)		
Fang X	2020	China	Nonsevere	55	39.9 \pm 14.9	27 (49.1)	CRP	7
			Severe	24	56.7 \pm 14.4	18 (75.0)		
Gao Y	2020	China	Nonsevere	28	43.0 \pm 14.0	17 (60.7)	IL-6, CRP, PCT, fibrinogen	9
			Severe	15	45.2 \pm 7.7	9 (60.0)		
Jin Z	2020	China	Nonsevere	82	51.6 \pm 10.7	38 (46.3)	CRP, PCT, SAA	7
			Severe	56	62.7 \pm 13.6	33 (56.9)		
Li K	2020	China	Nonsevere	58	41.9 \pm 10.6	29 (50.0)	CRP, PCT	7
			Severe	25	53.7 \pm 12.3	15 (60.0)		
Peng Y	2020	China	Nonsevere	96	61.5 \pm 9.4	44 (45.8)	CRP, PCT	8
			Severe	16	58.2 \pm 7.3	9 (56.3)		
Qin C	2020	China	Nonsevere	166	52.0 \pm 15.5	80 (48.2)	IL-6, CRP, PCT, ESR, Serum ferritin	7
			Severe	286	60.3 \pm 13.4	155 (54.2)		
Wu C	2020	China	Nonsevere	117	47.3 \pm 10.5	68 (58.1)	IL-6, CRP, ESR, Serum ferritin	7
			Severe	84	59.2 \pm 14.3	60 (71.4)		
Xiang T	2020	China	Nonsevere	40	40.6 \pm 14.3	25 (63.5)	CRP, PCT, ESR, SAA	8
			Severe	9	53.0 \pm 14.0	8 (88.9)		
Xiao K	2020	China	Nonsevere	107	43.1 \pm 1.1	52 (48.6)	IL-6, CRP, PCT	7
			Severe	36	51.3 \pm 5.6	20 (55.6)		
Huang C	2020	China	Non-ICU	28	49.2 \pm 12.9	19 (68.0)	PCT	9
			ICU	13	50.5 \pm 16.6	11 (85.0)		
Ruan Q	2020	China	Survivors	82	51.6 \pm 7.6	53 (65.0)	IL-6, CRP	7
			Non-survivors	68	64.3 \pm 14.0	49 (72.0)		
Zhou F	2020	China	Survivors	137	51.6 \pm 9.7	81 (59.0)	IL-6, PCT, Serum ferritin	7
			Non-survivors	54	69.4 \pm 9.9	38 (70.0)		

CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; ESR: erythrocyte sedimentation rate; SAA: serum amyloid A.

Table 2
Methodological quality of enrolled studies based on Newcastle-Ottawa Scale (NOS).

Included studies	Year	Is the definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of both groups	Ascertainment of diagnosis	Same ascertainment method for both groups	Nonresponse rate	Total scores
Chang Z	2020	☆	☆	☆	☆	☆	☆	☆	☆	8
Chen C	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Chen L	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Cheng K	2020	☆	☆	☆	☆	☆	☆	☆	☆	8
Fang X	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Gao Y	2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Jin Z	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Li K	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Peng Y	2020	☆	☆	☆	☆	☆	☆	☆	☆	8
Qin C	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Wu C	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Xiang T	2020	☆	☆	☆	☆	☆	☆	☆	☆	8
Xiao K	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Huang C	2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Ruan Q	2020	☆	☆	☆	☆	–	☆	☆	☆	7
Zhou F	2020	☆	☆	☆	☆	–	☆	☆	☆	7

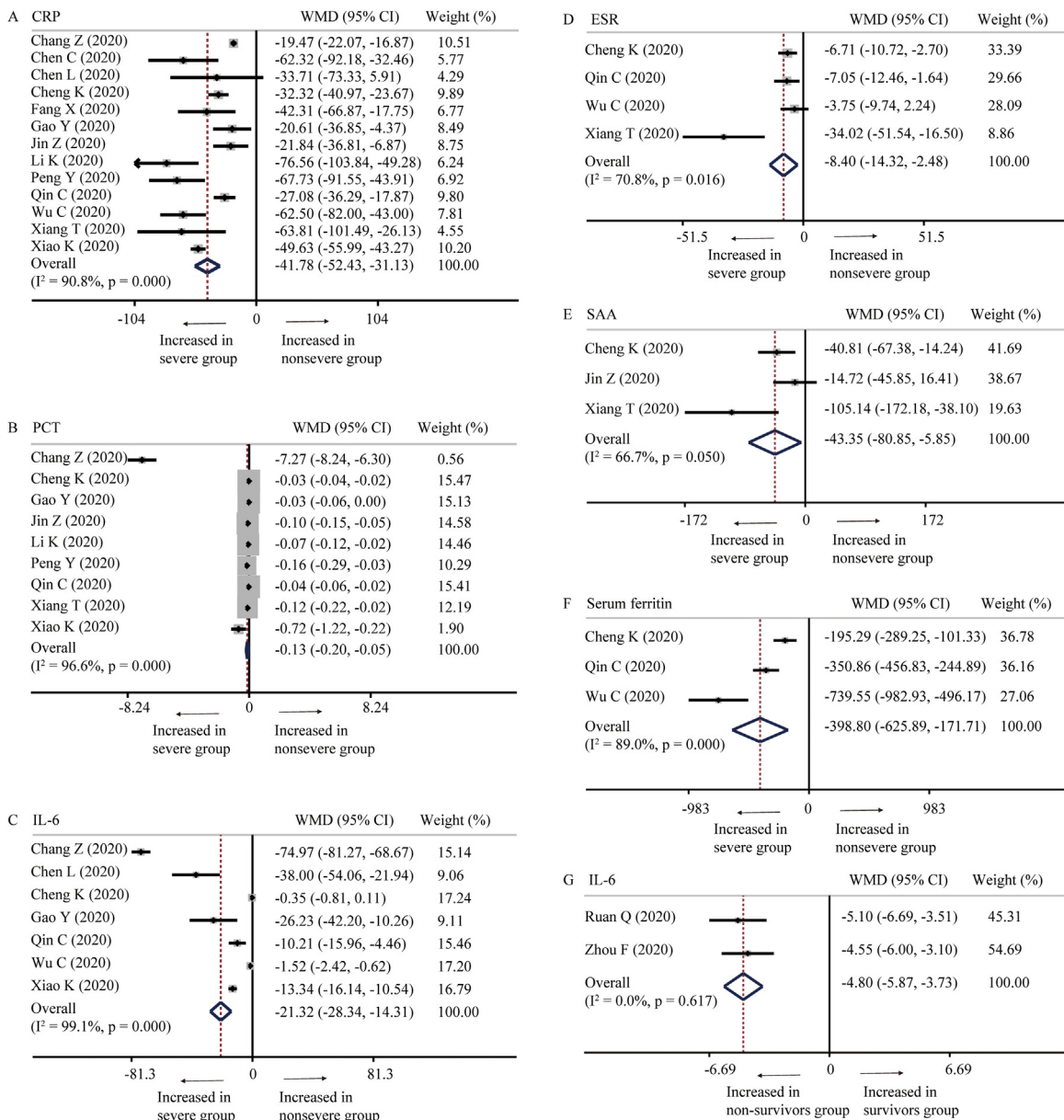


Figure 2. Forest plot of inflammatory markers. (A–F) Forest plot between nonsevere and severe groups for levels of CRP (A), PCT (B), IL-6 (C), ESR (D), SAA (E), and serum ferritin (F); G. Forest plot between survivors group and non-survivors group for levels of IL-6.

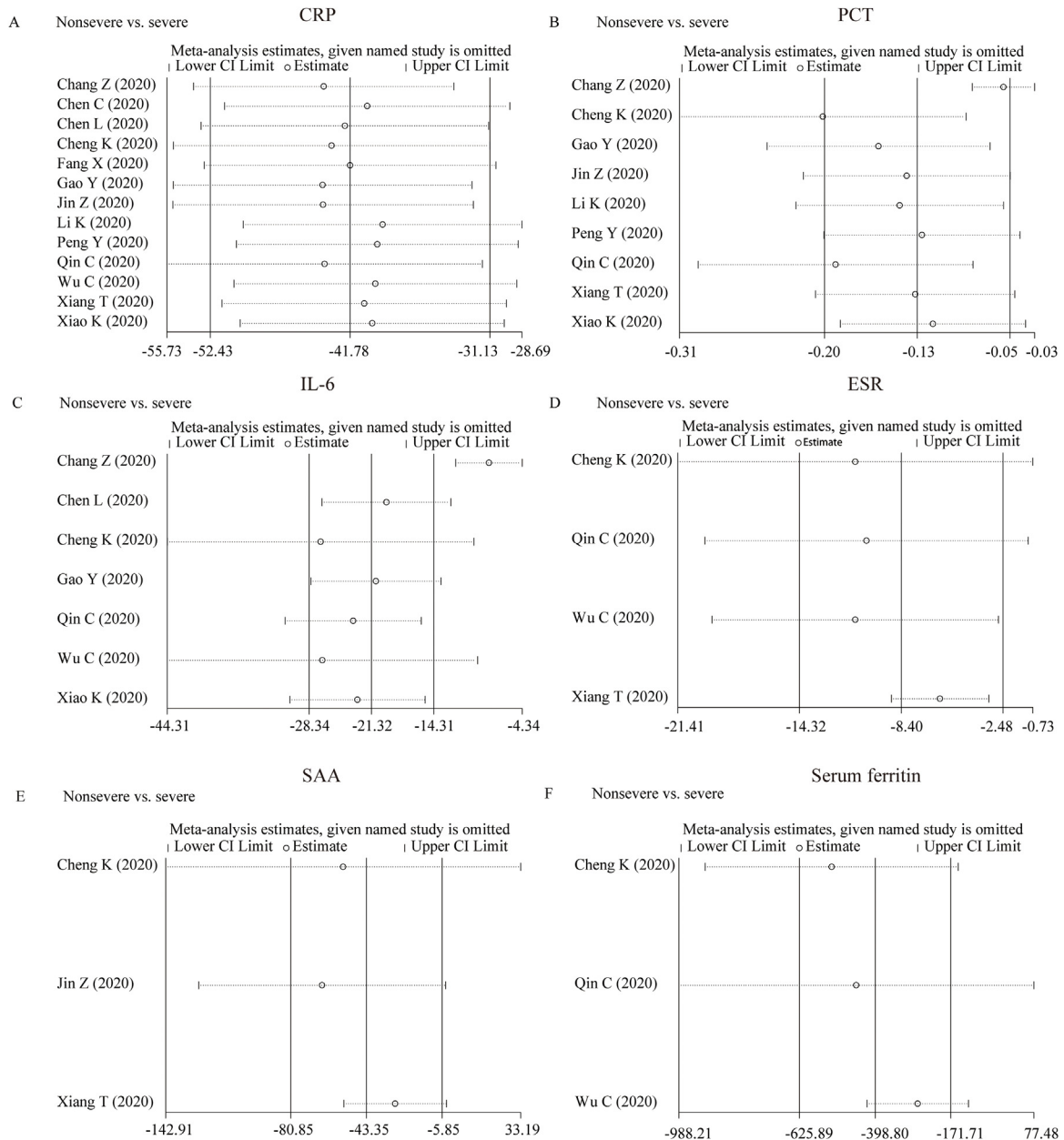


Figure 3. Sensitivity analyses. (A–F) Sensitivity analyses between nonsevere and severe groups for levels of CRP (A), PCT (B), IL-6 (C), ESR (D), SAA (E), and serum ferritin (F).

Association of inflammatory markers with the severity of COVID-19

For the patients stratified by severity of COVID-19, random-effect results demonstrated that compared with patients in the severe group, patients in the nonsevere group had lower levels for CRP (WMD = -41.78 mg/l, 95% CI = [-52.43, -31.13], $P < 0.001$), PCT (WMD = -0.13 ng/ml, 95% CI = [-0.20, -0.05], $P < 0.001$), IL-6 (WMD = -21.32 ng/l, 95% CI = [-28.34, -14.31], $P < 0.001$), ESR (WMD = -8 mm/h, 95% CI = [-14, -2], $P = 0.005$), SAA (WMD = -43.35 μ g/ml, 95% CI = [-80.85, -5.85], $P = 0.020$) and serum ferritin (WMD = -398.80 mg/l, 95% CI = [-625.89, -171.71], $P < 0.001$) (Figure 2A–F). Additionally, there are two studies grouped by survivors and non-survivors with COVID-19 reporting the level of IL-6, and fixed-effect results arrived at a similar conclusion that survivors had lower levels for IL-6 than non-survivors with COVID-19 (WMD = -4.80 ng/ml, 95% CI = [-5.87, -3.73], $P < 0.001$) (Figure 2G).

Additionally, one study on the level of fibrinogen between the nonsevere group and severe group, one study on the level of PCT between the non-ICU group and ICU group, and one study on the level of CRP and PCT between non-survivors and survivors, were not included in the meta-analysis due to their inadequate data; however, the results reported by these studies were consistent with the pooled results of our meta-analysis.

Investigation of heterogeneity

Strong evidence of heterogeneity was found in all the comparisons (Figure 2). Sensitivity analyses indicated that the results were not influenced by excluding any one specific study in CRP, PCT, IL-6 and ESR between the nonsevere and severe groups (Figure 3A–D). As for SAA and serum ferritin, the conclusions changed when deleting Cheng K’s study and Qin C’s study, separately, while the heterogeneity became larger,

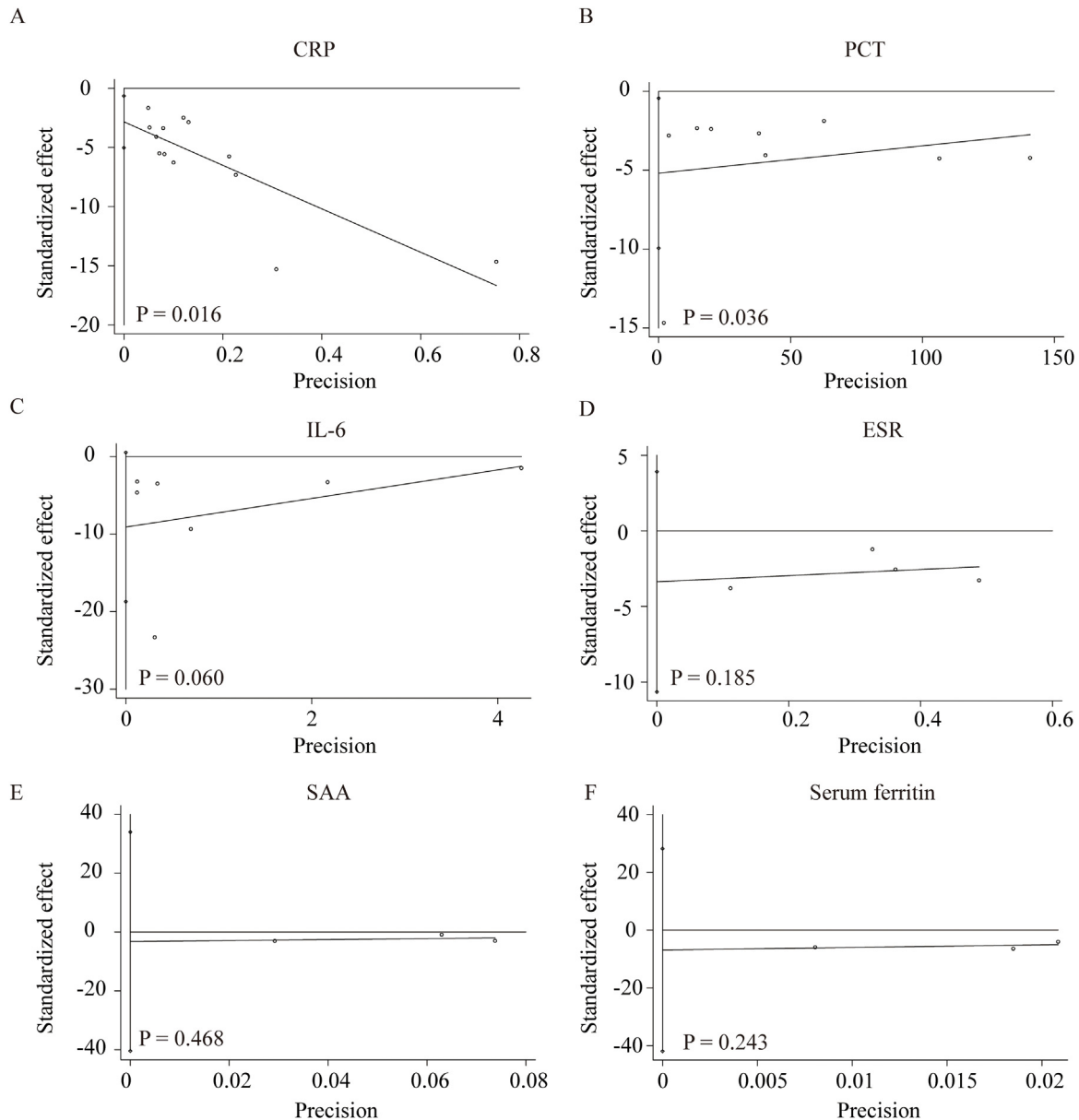


Figure 4. Publication bias by Egger's test. (A–F) Publication bias by Egger's test between nonsevere and severe groups in CRP (A), PCT (B), IL-6 (C), ESR (D), SAA (E), and serum ferritin (F).

suggesting that it is better to keep these studies in the meta-analysis (Figure 3E and F). Egger's test was conducted to evaluate the publication bias (Figure 4). No significant publication bias was detected in most of the studies except for CRP ($P = 0.012$) and PCT ($P = 0.036$). When applying the trim-and-fill method, there were no trials trimmed and filled in CRP. Regarding PCT, after filling one trial, the revised result was still consistent using a random model (WMD = -0.17 ng/ml, 95% CI = $[-0.26, -0.08]$, $P < 0.001$) or fixed model (WMD = -0.06 ng/ml, 95% CI = $[-0.07, -0.05]$, $P < 0.001$). Additionally, using standard mean difference (SMD) for the meta-analysis still did not change the conclusions (Table 3).

Discussion

COVID-19, caused by SARS-CoV-2, is rapidly expanding worldwide. Despite the fact that most cases have mild symptoms and a good prognosis, COVID-19 can develop into ARDS and even

death. To date, there is no effective therapy for COVID-19 (Li and De Clercq, 2020; Russell et al., 2020). Therefore, it is imperative to identify the markers monitoring the progression of disease and treat patients early.

Several studies have shown increased proinflammatory cytokines in serum of COVID-19 patients. Also, anti-inflammatory agents for COVID-19 therapy highlight the critical role of inflammation in the progression of COVID-19 (Mehta et al., 2020; Stebbing et al., 2020). However, the role of inflammatory markers in monitoring the severity of COVID-19 is still controversial. In this study, through analyzing the 16 retrospective studies, we concluded that inflammatory markers, especially CRP, PCT, IL-6 and ESR, were positively correlated with the severity of COVID-19.

IL-6 has been implicated in the 2003 SARS outbreak and the H5N1 avian influenza infections (Law et al., 2005; Saito et al., 2018). Recent studies showed that IL-6 and granulocyte-macrophage colony stimulating factor (GM-CSF) could be secreted by the

Table 3

The results of the meta-analysis based on standard mean difference (SMD).

Outcome	Studies	Participants	Heterogeneity		Model	SMD	95% CI	P
			I ²	P				
Nonsevere vs. Severe								
1. CRP	13	2092	95%	<0.001	Random	-1.48	[-1.95, -1.00]	<0.001
2. PCT	9	1633	94%	<0.001	Random	-1.11	[-1.58, -0.63]	<0.001
3. IL-6	7	1481	98%	<0.001	Random	-1.54	[-2.38, -0.71]	<0.001
4. ESR	4	1165	67%	0.03	Random	-0.34	[-0.57, -0.10]	0.005
5. SAA	3	650	73%	0.03	Random	-0.41	[-0.82, -0.00]	0.050
6. Serum ferritin	3	1116	80%	0.007	Random	-0.62	[-0.90, -0.34]	<0.001
Non-survivors vs. Survivors								
IL-6	2	341	9%	0.30	Fixed	-1.23	[-1.47, -0.98]	<0.001

CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; ESR: erythrocyte sedimentation rate; SAA: serum amyloid.

active pathogenic T cell upon SARS-CoV-2 infection. Also, CD14+CD16+ inflammatory monocytes activated by GM-CSF could secrete more IL-6 and other inflammatory factors (Zhou et al., 2020b). According to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission of China, decreasing level of IL-6 indicates the deterioration of COVID-19. Our study firstly provided evidence-based medicine evidence through meta-analysis. Moreover, the level of IL-6 could not be routinely detected in many hospitals in China, but some inflammatory markers such as CRP, PCT and ESR usually could be detected. Our study firstly put forward that in addition to IL-6, other inflammatory markers such as CRP, PCT and ESR were also positively correlated with the severity of COVID-19. These conclusions were consistent through sensitivity analysis and publication bias assessment.

CRP is an exquisitely sensitive systemic marker of acute-phase response in inflammation, infection, and tissue damage, which could be used as indicator of inflammation (Pepys and Hirschfield, 2003). In the study by Chen et al., although no statistically significant difference was found in the level of CRP between the nonsevere and the severe group, the mean level of CRP was higher in the severe group than in the nonsevere group (Chen et al., 2020b). Other studies all reported CRP level was positively related to the severity of COVID-19. PCT is also a main inflammatory marker routinely measured in clinical practice. Among 9 studies, the levels of PCT were all higher in the severe group than the nonsevere group. ESR is a non-specific inflammatory marker, which mainly reflects the changes of plasma protein types (Wu et al., 2018). In our meta-analysis, we found a higher ESR level in the severe group than in the nonsevere group. One reason is that patients in the severe group had higher inflammation. Another possible explanation is that patients with older age in the severe group contributed to the higher level of ESR considering that the level of ESR increased with age (Piva et al., 2001).

We also found patients with COVID-19 in the severe group had higher levels of SAA and serum ferritin than those in the nonsevere group. Considering that only three studies reported their levels and sensitivity analysis changed the conclusion, we temporarily could not conclude their association with the severity of COVID-19. SAA is a sensitive acute response protein and is used as a sensitive index to reflect the control of infection and inflammation. Serum ferritin is a surrogate marker of stored iron and increases in inflammation, liver disease, and malignancy (Cohen et al., 2010; Facciorusso et al., 2014; Kowdley et al., 2012). All of these highlight that an over-exuberant inflammatory response is associated with the severity of COVID-19.

To our knowledge, this is the first meta-analysis on the associations of a series of inflammatory markers with the severity of COVID-19. Admittedly, our meta-analysis had some limitations. Firstly, noticeable heterogeneity exists in most of the analyses. Sensitivity analysis and SMD were used for the meta-analysis, yet

the heterogeneity could not be eliminated completely. Secondly, reporting and publication bias may result from the lack of information or unpublished negative studies although the conclusion did not change through the trim-and-fill method. Thirdly, the studies included in our meta-analysis were mainly from China and whether the conclusion is consistent in other countries needs to be further investigated. Finally, this study is underpowered to investigate the underlying mechanism of these inflammatory markers with the severity of COVID-19.

In conclusion, inflammatory markers, especially CRP, PCT, IL-6 and ESR, were positively correlated with the severity of COVID-19. The association of SAA and serum ferritin with the severity of COVID-19 needs to be further clarified. Measurement of inflammatory markers might assist clinicians to monitor and evaluate the severity and prognosis of COVID-19.

Authors contribution

GD, LX and FZ were responsible for study design; YH and YG were involved in data collection; GD and YH analyzed the data; FZ and YH wrote the manuscript. GD, LX, MY and XC revised the manuscript.

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Ethics in publishing

Approval was not required.

Declaration of interest

The authors declare no conflicts of interest.

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