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REVIEW ARTICLE

Predictive value of C-reactive protein for disease severity and survival in COVID-19 patients: a systematic review and meta-analysis

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease that can develop multiple complications and even be life-threatening. The aim of this study is to summarize current evidence of C-reactive protein's (CRP) predictive value for disease severity and survival of COVID-19 patients, focusing on curing patients and reducing the risk of death. We systematically searched related studies from four large databases: Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database, all published between December 2019 and June 2021. Then, we implemented meta-analysis using random-effects models through STATA 15.1 and Review Manager 5.3. We also implemented sensitivity analysis and used funnel plots to check publication bias. From the systematic search of the four databases, we were able to identify 18 studies containing a total of 3052 patients. Meta-analysis results showed that 1) CRP levels were lower in non-severe patients than in severe patients (Standardized Mean Difference (*SMD*) = −0.87 mg/L, 95% *Confidence Interval (CI)* = [−1.27, −0.47], $p < 0.001$); 2) CRP levels were lower in non-intensive care unit (ICU) patients than in ICU patients (*SMD* = −1.39 mg/L, 95% *CI* = [−1.68, −1.11], $p < 0.001$), and 3) CRP levels were lower in survivors than in non-survivors (*SMD* = −1.32 mg/L, 95% *CI* = [−1.95, −0.69], $p < 0.001$). Sensitivity analysis showed these results were stable. Funnel plots indicated no publication bias. The CRP level may timely reflect disease severity and predict survival of COVID-19 patients and may be worthy of further popularization and application in clinic practice.

Keywords COVID-19 · C-reactive protein · Meta-analysis · Systematic review · Survival

Introduction

Coronavirus disease 2019 (COVID-19) is characterized by high infectivity, high pathogenicity, and atypical clinical symptoms [1]. According to studies, it spreads faster and is more contagious than SARS [2]. Thus, COVID-19 poses a great threat to the health and safety of global public health [3]. With accumulating studies, scientists have realized that comprehensive monitoring of disease severity and effective early intervention are critical to reduce COVID-19 mortality [4]. Inflammatory markers can better monitor disease severity and detect mortality rate. Therefore, they play a significant role in the association of high-risk development to severe COVID-19 [5, 6]. These inflammatory markers include procalcitonin, serum ferritin, erythrocyte sedimentation rate, C-reactive protein (CRP), and interleukin-6. CRP is one of the sensitive markers of non-specific inflammatory response in human body. The literature CRP also increases in viral infection, although not as substantially as in bacterial infection [7]. Meanwhile, detection of

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CRP has the advantages of various methods, speed, point-of-care test, and low price. Therefore, besides the differential diagnosis of bacterial versus viral infection [8], CRP can be used for the diagnosis, differential diagnosis, and prognosis prediction of novel coronavirus infection [9].

To date, although multiple studies have reported the relationship between CRP levels and COVID-19 severity, the conclusions are inconsistent, and a systematic review is lacking. To fill this gap, we conducted this systematic review and meta-analysis to summarize the current evidence for the relationship of CRP levels with disease severity and survival of COVID-19 patients.

Methods

Search strategy

To identify studies eligible for inclusion, we conducted a comprehensive and systematic search of the literature published between December 2019 and June 2021. We searched the following electronic databases: Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database. Then, we used the following keywords, both separately and in combination, as part of the search strategy in each database: "COVID-19" "2019-nCoV" and "C-reactive protein". The detailed search strategy was saved for future inquiries and usages.

Selection criteria

We applied the following criteria to select eligible studies. Inclusion criteria: (1) patients diagnosed with COVID-19 and had a SARS-CoV-2 RNA-positive result; (2) patients divided into the intensive care unit (ICU) group and non-ICU group, or survivor group and non-survivor group; (3) relevant data of CRP level are available. Exclusion criteria: (1) studies with no control group; (2) no clear diagnostic criteria for COVID-19; (3) duplicate reports, incomplete data, or unusable literature; (4) reviews, case reports, and conference papers. In this meta-analysis, we classified patients with severe or critical COVID-19 as severe, and those with mild or moderate COVID-19 as non-severe.

Data extraction and quality assessment

The authors (LC & SW) screened the records of the initial search to rule out any duplicate and unrelated studies. The following data were extracted: first author, publication date, region, cases, age, sex, outcome, and CRP levels in diverse groups. We resolved all disagreements through group discussions with senior author (JL). To assess the quality of all potentially eligible studies, we used the Newcastle–Ottawa Scale (NOS). The NOS has a full score as nine, with four to six as "moderate," and seven to nine as "high" quality research.

Statistical analysis

We converted continuous data to mean ± SD (standard deviation) and calculated the 95% confidence intervals (CI) for weighted mean differences between patient groups. Standardized mean differences (SMD) were used to build forest plots of continuous data and to evaluate differences in CRP levels between COVID-19 patients with non-severe versus severe, non-ICU vs. ICU, or survivors vs. non-survivors. Heterogeneity of SMD across studies was tested by using the Q statistic (significance level at $p < 0.10$). The I^2 statistic, a quantitative measure of inconsistency across studies, was also calculated ($I^2 < 25\%$, no heterogeneity; I^2 between 25 and 50%, moderate heterogeneity; I^2 between 50 and 75%, large heterogeneity; and $I^2 > 75\%$, extreme heterogeneity) [10]. To assess potential impact of omitted studies, we implemented sensitivity analysis, and used the one-way sensitivity analysis. To detect potential publication bias, we used the funnel plots [11] together with the Egger asymmetry test [12]. For Meta-Analysis, we used the STATA software package, version 15.1 (Stata Corporation, College Station, Texas, USA) and the Review Manager 5.3 [13].

Results

Literature search and studies characteristics

From the initial literature search, we identified a total of 3052 records with 189 studies subsequently excluded due to duplication (Fig. 1). After reviewing the titles and abstracts,

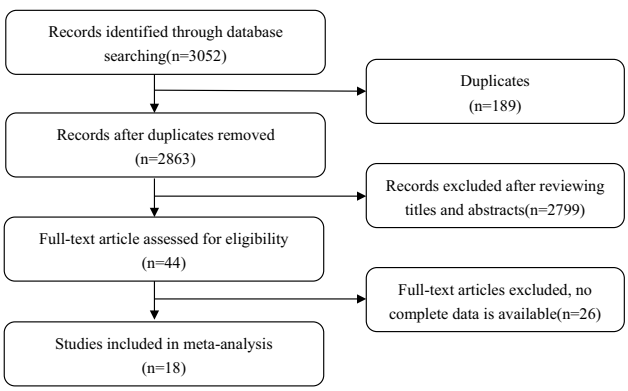

Fig. 1 Literature search and filtering of studies

we excluded 2,799 studies according to the inclusion and exclusion criteria and obtained 44 studies. We further excluded 26 studies by scrutinizing the full text and included 18 studies in our meta-analysis. All these studies were published in 2020 and involved 5,381 patients. We classified nine studies into non-severe and severe groups, two into non-ICU and ICU groups, and eight into COVID-19 survivors and non-survivors.

Individual study characteristics and patient demographics are shown in Table 1, and their qualities according to the Newcastle–Ottawa Scale (NOS) are listed in Table 2. Based on the NOS, all the 18 enrolled studies have high quality, with the NOS scores ranged from 7 to 9. Eighteen studies ($n = 5381$) described CRP levels in patients diagnosed with COVID-19. The mean age of patients included in the study was 59.25 ± 19.07 years, and 54.56% were male. Fifteen studies were conducted in China (the other three were performed in the USA, Morocco, and England), all of which involved hospitalized patients.

Association of CRP levels with the severity of COVID-19

Overall, elevated CRP levels were found in patients with COVID-19 in all included studies. The results of random-effects model showed that for patients grouped according to COVID-19 severity, CRP levels were higher in patients with

Table 1 Characteristics of the 18 enrolled studies in the meta-analysis

First author	Year	Country	Design	Cases	Age (years, Mean ± SD)	Sex (male, %)	Non-severe/severe (*n*)	non-ICU/ICU (*n*)	Survivors/non-survivors (*n*)
Hu, Xingsheng [14]	2020	China	Retrospective cohort	213	45.40 ± 17.91	102 (47.8)	175/38	193/20	–
Huang, Hui-huang [15]	2020	China	Retrospective cohort	64	47.80 ± 18.50	37 (57.8)	43/21	–	–
JV Thompson [16]	2020	England	Retrospective cohort	470	68.70 ± 17.40	255 (54.3)	301/169	–	–
Li, Jian [17]	2020	China	Retrospective cohort	326	60.95 ± 15.64	171 (52.5)	–	–	96/230
Luo, Xiaomin [18]	2020	China	Retrospective cohort	298	55.25 ± 21.60	150 (50.3)	–	–	214/84
Maryame, Ahnach [19]	2020	Morocco	Retrospective cohort	145	48.24 ± 23.21	75 (51.7)	101/44	–	–
Miao, Yang [20]	2020	China	Retrospective cohort	108	50.65 ± 23.29	42 (38.9)	84/24	–	—
Milad Sharifpour [21]	2020	USA	Retrospective cohort	268	63.00 ± 15.00	149 (55.6)	–	–	201/67
Pan, Feng [22]	2020	China	Retrospective cohort	124	63.59 ± 21.00	85 (68.6)	–	–	35/89
Wang, Jing-Bo [23]	2020	China	Retrospective cohort	56	48.89 ± 44.89	24 (42.9)	45/11	–	–
Wang, Jun-Hong [24]	2020	China	Retrospective cohort	1135	60.25 ± 14.10	545 (48.0)	–	–	1074/61
Wei, Zhang [25]	2020	China	Retrospective cohort	65	45.50 ± 14.40	37 (56.9)	49/16	–	–
Yang, Chongtu [26]	2020	China	Retrospective cohort	203	59.89 ± 14.93	115 (56.7)	–	–	145/58
Yu, Caizheng [27]	2020	China	Retrospective cohort	1663	62.25 ± 14.10	838 (50.4)	799/864	–	–
Zhang, Jin-jin [28]	2020	China	Retrospective cohort	140	56.30 ± 46.44	71 (50.7)	82/58	–	–
Zhang,Lin [29]	2020	China	Retrospective cohort	101	60.78 ± 12.98	87 (64.9)	–	–	101/33
Zheng, Yongli [30]	2020	China	Retrospective cohort	99	49.39 ± 18.45	51 (52.0)	67/32	–	–
Zhou, Jian [31]	2020	China	Retrospective cohort	201	45.98 ± 18.82	102 (50.7)	–	156/45	–

Table 2 Methodological quality of enrolled studies based on the 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
Hu, Xingsheng	2020	*	*	*	*	*	*	*	*	8
Huang, Huihuang	2020	*	*	*	*	*	*	*	*	8
J V Thompson	2020	*	*	*	*	–	*	*	*	7
Li, Jian	2020	*	*	*	*	*	*	*	*	8
Luo, Xiaomin	2020	*	*	*	*	**	*	*	*	9
Maryame Ahnach	2020	*	*	*	*	**	*	*	*	9
Miao, Yang	2020	*	*	*	*	*	*	*	*	8
Milad Sharifpour	2020	*	*	*	*	**	*	*	*	9
Pan, Feng	2020	*	*	*	*	*	*	*	*	8
Wang, Jing-Bo	2020	*	*	*	*	–	*	*	*	7
Wang, Jun-Hong	2020	*	*	*	*	–	*	*	*	7
Wei, Zhang	2020	*	*	*	*	**	*	*	*	9
Yang, Chongtu	2020	*	*	*	*	*	*	*	*	8
Yu, Caizheng	2020	*	*	*	*	**	*	*	*	9
Zhang, Jin-jin	2020	*	*	*	*	*	*	*	*	8
Zhang, Lin	2020	*	*	*	*	*	*	*	*	8
Zheng, Yongli	2020	*	*	*	*	*	*	*	*	8
Zhou, Jian	2020	*	*	*	*	–	*	*	*	7

more severe disease. (SMD = − 0.87 mg/L, 95% CI = [− 1.27, − 0.47], $p < 0.001$) (Fig. 2A). According to the outcomes of COVID-19 patients, CRP levels in non-survivors were 1.32 times higher than those in survivors (SMD = − 1.32 mg/L, 95% CI = [− 1.95, − 0.69], $p < 0.001$) (Fig. 2B). In addition, CRP levels were reported in two studies that categorized COVID-19 patients according to whether they required ICU treatment. Like fixed-effect results, CRP levels were significantly higher in ICU patients than in non-ICU patients (SMD = − 1.39 mg/L, 95% CI = [− 1.68, − 1.11], $p < 0.001$) (Fig. 2C).

Investigation of heterogeneity

Extreme heterogeneity between studies was observed ($I^2 = 91\%$ or 97%; $p < 0.001$). Sensitivity analysis showed that the heterogeneity decreased significantly from 91 to 71% after Yu's study was deleted between the non-severe group and the severe group (Fig. 3A). This prompts us to remove the study from the meta-analysis, while heterogeneity among studies remained high. Additionally, the exclusion of any study between the non-survivor and survivor groups did not affect the results (Fig. 3B).

Visual funnel plots were examined (Fig. 4), and Egger's linear regression test was performed to evaluate publication bias. The results showed that no significant publication bias was detected between the survival group and the non-survival group ($P = 0.241$). However, evidence of publication bias was observed between the non-severe group and the severe group ($P = 0.006$). The combined effect size did not significantly change after the trim-and-fill method (before trim-and-fill: − 0.87 [− 1.27, − 0.47] after trim-and-fill: − 0.88 [− 1.28, − 0.47]). Therefore, publication bias had no significant impact on the results of the meta-analysis. Due to the limited number of available studies included in the ICU and non-ICU groups, no publication bias assessment was performed.

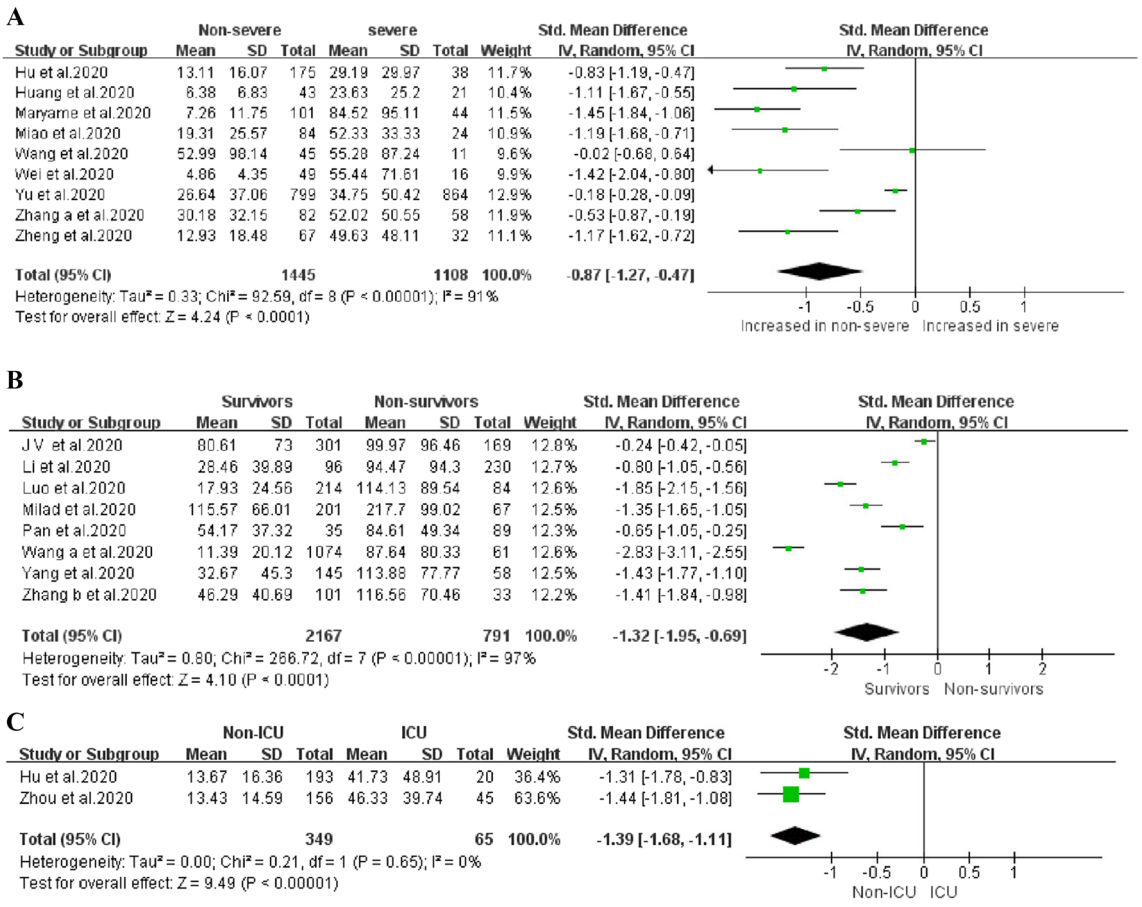

Fig. 2 Forest plots of CRP levels among subgroups of COVID-19 patients: **A**. Non-Severe vs. Severe; **B**. non-ICU vs. ICU; and C. Survivors vs. Non-survivors

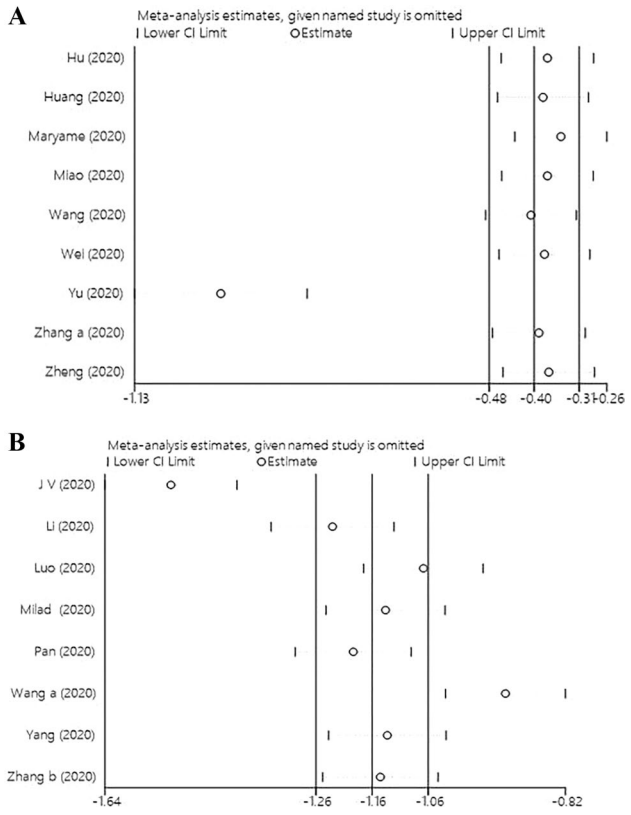

Fig. 3 Sensitivity analyses. **A**. Severe and non-severe patients. **B**. Survivors and non-survivors

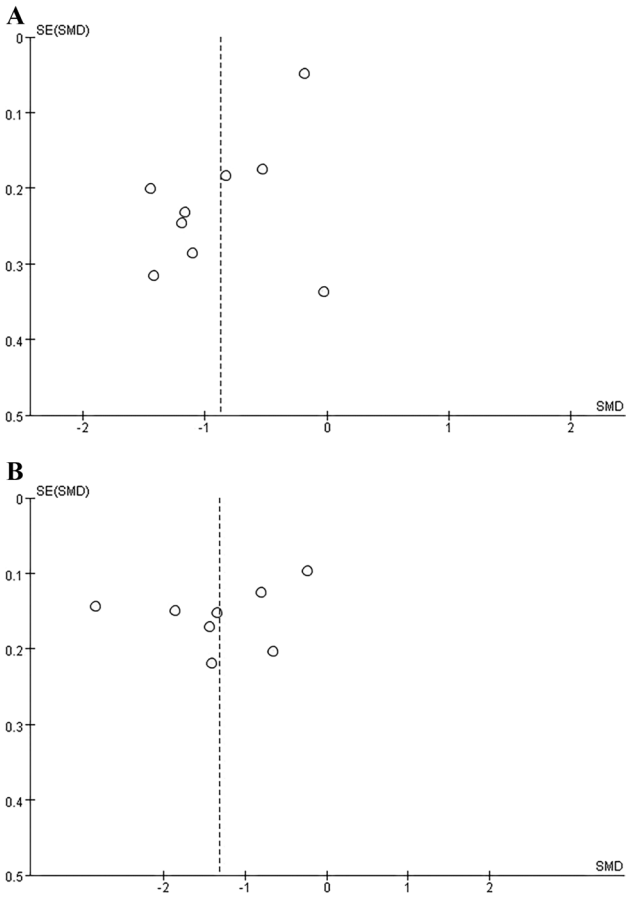

Fig. 4 **A**. Funnel plot of CRP levels in severe and non-severe COVD-19 patients and **B**. survivors and non survivors

Discussion

CRP is an extremely sensitive systemic marker of the acute phase of inflammation, infection, and tissue injury and can be used as an indicator of inflammation [32]. In this study, we found a significant increase in serum CRP levels in severe COVID-19 disease, consistent with the findings of an earlier study [4]. Meta-analysis showed that this increase was significantly associated with adverse clinical outcomes, including ICU admission and death. CRP levels were 0.87 times higher in patients with severe COVID-19 than in patients without severe COVID-19 and 1.32 times higher in non-survivors than in survivors. More precisely, the higher the CRP level, the worse the prognosis.

In recent years, large numbers of CRP deposits have been found in inflammatory lesions of vascular endothelium infected with pathogens [33]. However, CRP usually has the largest deposits and is accompanied by the most obvious inflammatory reactions [34]. It is extremely sensitive in the acute stage of the disease while patients have tumor infection or inflammation. The concentration of CRP in plasma will rise rapidly, which is 2000 times the normal level [35]. At present, due to the different sensitivity of measurement methods, the normal value of CRP remains controversial, most people believe that it is less than 10 mg/L [36]. But an increasing number of studies have shown that even a slight increase in CRP indicates the presence of inflammation [37]. In this study, we found that the serum CRP content of severe COVID-19 patients was significantly higher than that of non-severe patients, and CRP was consistently expressed at an elevated level during persistent infection. This finding suggests that CRP increased rapidly in inflammation, and the extent of increase was correlated with the severity of inflammation. On the contrary, the extent of increase was not obvious in viral infection. CRP increased significantly in critically ill patients. We speculated the reason was these patients were accompanied by bacterial infection along with the development of the disease. In addition, endotoxin or cytokines were inhibited and decomposed. This resulted in an increase in the content of CRP, which indirectly indicated that some patients with COVID-19 rapidly develop severe disease. Additionally, Vitamin D (VD) and its active metabolites have immunomodulatory effects and may play an important role in COVID-19 infection [38]. However, vitamin D deficiency (VDD) is common in the general population [39]. VDD (< 20 ng/dL) increases the risk of respiratory

infections, promotes the progression of pulmonary disease, and is associated with poor outcomes for patients in intensive care units [40]. Meanwhile, studies have shown that hypocalcemia (serum total calcium < 8 mg/dL) patients had poorer clinical and laboratory parameters, higher rates of organ failure and septic shock, and higher 28-day mortality [41]. Therefore, we propose that combined the detection of vitamin D and CRP levels in the body to better predict the severity of disease in patients.

One comprehensive review on COVID-19 and the endocrine system [42] is instrumental to our study. In that review [42], Lisco and colleagues thoroughly summarized topics related to COVID-19 and the endocrine system. They found that patients with COVID-19 were not necessarily at higher risk for endocrine disorders or dysfunction. But the risk is higher if the patient's disease is related to the hypothalamic-pituitary region, thyroid and parathyroid glands, calcium phosphate homeostasis and osteoporosis, or adrenal glands and gonads. In the current COVID-19 pandemic, it is recommended to strengthen the education of high-risk groups and the management of endocrine diseases. Medical consultation, laboratory testing and digital telemedicine should be used to further improve the capacity of epidemic prevention and control. Therefore, this study paves the road to explore and apply our findings.

To our knowledge, the novel coronavirus pneumonia has been studied by [43–45], among others. It is confirmed that CRP is an important indicator to predict deterioration of the COVID-19 condition and poor prognosis. But it does not reflect the level and change of the level of the patients under different conditions (such as severe and non-severe, ICU and non-ICU, AND survivors and non-survivors). It also failed to deeply explore the application value of CRP in the evaluation of the condition and prognosis of patients with covid-19. This study is filling this gap.

Admittedly, our meta-analysis has limitations. First, most studies had heterogeneity, which could not be eliminated despite sensitivity analysis. Second, the studies included in this meta-analysis were from China, and further investigation is needed to determine whether the conclusions of other countries are consistent. Finally, this study is not enough to explore the potential molecular mechanism between CRP and COVID-19 severity, and in-depth studies are warranted.

In conclusion, our systematic review of studies in China found that the level of inflammation marker CRP may be positively correlated with the severity of COVID-19, and that measuring CRP levels may be helpful for clinicians to monitor and evaluate the severity and prognosis of COVID-19.

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Author's contributions Conceptualization was contributed by LC, SW, CY, and JL. Data curation was contributed by LC, SW, and XW. Formal analysis was contributed by LC, SW, XW, CY, and JL. Funding acquisition was contributed by JL. Investigation was contributed by LC, SW, XW, CY, and JL. Methodology was contributed by LC, SW, CY, and JL. Project administration was contributed by LC, SW, and XW. Resources were contributed by JL. Supervision was contributed by CY and JL. Validation was contributed by LC, SW, XW, CY, and JL. Visualization was contributed by LC, SW, XW, CY, and JL. Writing—original draft was contributed by LC, SW, XW, and JL. Writing—review and editing was contributed by LC, SW, XW, CY, and JL.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All analyses were based on previous published studies; thus, no ethical approval is required.

Informed consent All analyses were based on previous published studies; thus, no informed consent is required.

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