Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

A meta-analysis of the association between calprotectin and the severity of COVID-19

Dear Editor,

Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) is a new coronavirus that causes human Coronavirus Disease 2019 (COVID-19). Following an outbreak in Wuhan, China, the virus has rapidly spread globally. Disease severity is largely inconsistent as the virus spreads and mutates, as is patient status. Many studies were currently underway to identify prognostic predictors for patients; in particular, inflammatory factors such as C-reactive protein, ferritin, and D-dimer have been reported as poor prognosis predictors for patients with COVID-19.

We read with great interest the report in this Journal by Mentzer et al. who found that serum calprotectin levels were not an independent predictor of severe COVID-19 in ambulatory adult patients.[1] Other investigators have found that calprotectin levels in severe COVID-19 patient groups were significantly higher than in non-severe patient groups.[2] Moreover, the prognostic value of circulating calprotectin on the clinical course of COVID-19 as was shown to differ by sample type(such as serum, plasma, feces).[3] In view of several recently published studies on plasma calprotectin, we conducted an updated meta-analysis by systematically searching PubMed, Web Of Science, and The Cochrane Library between January 1st, 2019 and December 20th, 2021. In total, eight articles with 805 patients were identified (Table 1). Patients were divided into a severe group (intensive care unit treatment, invasive mechanical ventilation, multiple organ failure or death) and a non-severe group according to their disease condition. Our analysis of these eight cohort studies generated consistent results; calprotectin plasma levels in the severe group were significantly higher than the non-severe group. A meta-analysis forest plot showed the overall pooled estimate was 1.18 (95% confidence interval (CI): 0.74, 1.62) (Fig. 1). Also, the heterogeneity (I^2) was 82.3% and the Egger value was 0.469, indicating no publication bias.

Thus, plasma calprotectin levels were related to COVID-19 patient severity; the index was significantly higher in the severe group than the non-severe group. This observation was also consistent with a previous meta-analysis.[3] Typically, calprotectin is released upon initial inflammatory stimulus, and is triggered by the toll-like receptor-4 (TLR-4) on granulocytes, and is involved in neutrophil-related inflammation processes. Calprotectin exerts antibacterial effects toward some bacteria, including Escherichia coli and Staphylococcus aureus.[1,4] Therefore, calprotectin is an effective antibacterial protein.

Calprotectin concentrations greater than 24.1 mg/L are associated with a significant increase of approximately 25% in the risk of death,[5] thus the higher the calprotectin level, the more severe the inflammation, the more severe the patient's condition, and the worse the prognosis. Christensen et al. reported that patients with severe Novel Coronavirus Pneumonia had higher plasma B cell activity and calprotectin levels, while transcripts related to immune function were mostly reduced, affecting B cells in particular.[6] Therefore, these data suggest a new exploratory direction for COVID-19 patient treatments in the future.

Calprotectin is found not only in the blood (serum or plasma), but also in the feces. Several studies reported that SARS-CoV-2 bound to intestinal epithelial cells via specific receptors and promoted acute inflammation characterized by neutrophil and macrophage infiltration.[7] Therefore, fecal calprotectin levels may also be used to study patients with Novel Coronavirus Pneumonia. Similarly, fecal calprotectin levels in a COVID-19 plus diarrhea group were significantly higher than in controls.[8] Shokri-Afra et al. also identified higher plasma and fecal calprotectin levels in COVID-19 patients when compared with healthy subjects, but no differences in patients with or without gastrointestinal symptoms.[9]Ojetti et al. identified a significant association between high fecal calprotectin levels and COVID-19 pneumonia, and also disease severity.[10]

With the general acceptance of the COVID-19 epidemic,it is important to identify patients at higher risk of severe disease at early clinical stages. Our results support calprotectin as an important COVID-19 biomarker, and its clinical use in predicting disease severity. Although the number of studies in our meta-analysis was small, our data provide a key direction for future treatment possibilities.

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Table 1
The main results of studies that reported Calprotectin.

	Severe Group*		Non-severe Group		
ID	Sample Size (N)	Calprotectin**	Sample Size (N)	Calprotectin**	Primary Results/Conclusion
García, L. et al.2021	8	7.1 (4.5–10.3) mg/L	58	3.1 (1.9–4.4) mg/L	Calprotectin and GDF-15 might have a potential role in the assessment of prognosis in COVID-19 patients.
Kaya, T.et al.2021	38	44.8 (34.5–61.5) ng/mL	42	37.9 (30.3–46.2) ng/mL	Serum calprotectin level seems to be a useful biomarker that can predict the severity of COVID-19 disease. Serum calprotectin is a significant predictor of ICU requirement in patients with COVID-19.
Mentzer, A. J. et al. 2021	66	7.546 (3.992–11.685) μg/mL	53	2.715(1.493–4.628) μg/mL	Serum calprotectin does not support the prediction of COVID-19 deterioration in outpatients, but it supports the continued use of biomarkers such as CRP and standard clinical assessments as well as the prediction of the deterioration of other respiratory diseases in SDEC.
Nevejan, L. et al. 2021	25	3.7 (1.7–5.7) mg/L	179	2.1 (1.3–3.8) mg/L	Measuring cCLP in COVID-19 patients helps the clinician to predict the clinical course of COVID-19.
Shrivastava, S. et al. 2021	31	18,183 ± 2512 ng/mL	32	16,589 ± 2651 ng/mL	Induction of elevated levels of alpha-defensins and S100A8/A9 is associated with poor disease outcome in COVID19 patients.
Bauer, W. et.al. 2020	8	3.77(1.90–5.16) mg/L	11	2.08(1.36–2.59) mg/L	Calprotectin represents a novel and useful discriminator in COVID-19 patients admitted to the ED with respect to disease outcome, in particular MOF, with calprotectin measurement in blood samples being easily applicable in routine laboratories.
Shi, H. et al. 2020	32	8039±703 ng/ml	62	3365±3146 ng/ml	Serum calprotectin levels track closely with current and future COVID-19 severity, strongly implicating neutrophils as active perpetuators of inflammation and respiratory compromise in COVID-19.
Lee, A. et al.2021	30	12.60 (8.10– 18.50) μg/mL	75	2.60(1.40– 5.28) μg/mL	Serum calprotectin levels were significantly elevated in severe COVID- 19 cases. The prevalence of clinically significant aPL did not differ. The link between calprotectin and inflammatory pathway in COVID- 19 may help improve the management and outcomes of COVID- 19 patients.

* **Severe group (intensive care unit (ICU) treatment, invasive mechanical ventilation, multiple organ failure or death**.
** Plasma calprotectin level is displayed at the level of mean ± SD or median (IQR).

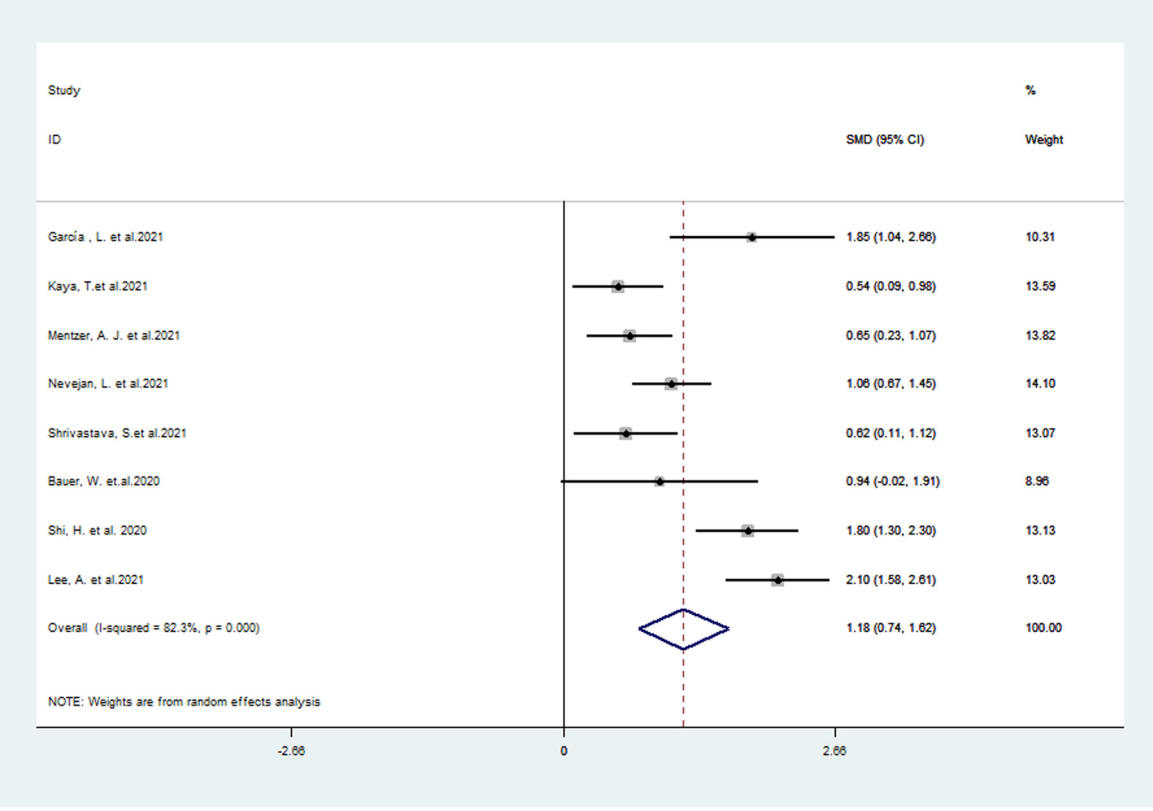

Fig. 1. Forest plot (FEM) comparing the mean differences in calprotectin level between severe and non-severe COVID-19.

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Declaration of competing interest

The authors declare no conflict of interest

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Qin Mao[$], Chunyi Wang[$], Wen Wen[$]
Hangzhou Institute of Cardiovascular Diseases, Affiliated Hospital of Hangzhou Normal University, Hangzhou Normal University, Hangzhou, 310015, China

Mengyun Zhou[$]
Department of Molecular & Cellular Physiology, Shinshu University School of Medicine,3900803, Japan

Jiake Tang, Chen Chen
Hangzhou Institute of Cardiovascular Diseases, Affiliated Hospital of Hangzhou Normal University, Hangzhou Normal University, Hangzhou, 310015, China

Yongran Cheng
School of Public Health, Hangzhou Medical College, Hangzhou, 311300, China

Qi Wu, Xingwei Zhang
Hangzhou Institute of Cardiovascular Diseases, Affiliated Hospital of Hangzhou Normal University, Hangzhou Normal University, Hangzhou, 310015, China

Zhanhui Feng[*]
Department of Neurology, Affiliated Hospital of Guizhou Medical University, Guiyang, 550004, China

Mingwei Wang[*]
Hangzhou Institute of Cardiovascular Diseases, Affiliated Hospital of Hangzhou Normal University, Hangzhou Normal University, Hangzhou, 310015, China

[*]Corresponding authors.
E-mail addresses: h9450203@126.com (Z. Feng), wmw990556@163.com (M. Wang)
[$] Qin Mao, Chunyi Wang, Mengyun Zhou and Wen Wen contributed equally to this work.