Elevated matrix metalloproteinase-9 expression is associated with COVID-19 severity: A meta-analysis

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Abstract. The present meta-analysis investigated the clinical value of serum matrix metalloproteinase (MMP)-9 levels in Coronavirus Disease 2019 (COVID-19) patients. Studies assessing the outcomes of patients with COVID-19 in correlation with the MMP-9 levels were retrieved from PubMed, Web of Science, EMBASE, Cochrane, WANFANG, and CNKI. A meta-analysis was performed to compare the serum MMP-9 levels between different patient groups: Severe vs. non-severe; acute respiratory distress syndrome (ARDS) vs. non-ARDS; non-survivors vs. survivors; neurologic syndrome vs. non-neurologic syndrome; and obese diabetic vs. non-obese diabetic. A total of 2,062 COVID-19-confirmed patients from 12 studies were included in this meta-analysis. The serum MMP-9 levels were significantly higher in patients with severe COVID-19 than in those with non-severe COVID-19 [weighted mean difference (WMD) 246.61 (95% confidence interval (CI), 115.86-377.36), P<0.001]. Patients with ARDS exhibited significantly higher MMP-9 levels than those without ARDS [WMD 248.55 (95% CI, 63.84-433.25), P<0.001]. The MMP-9 levels in the non-survivors did not significantly differ from those in the survivors [WMD 37.79 (95% CI, -18.08-93.65), P=0.185]. Patients with comorbidities, including neurological syndromes, and obese diabetic patients had significantly higher MMP-9 levels than those without comorbidities [WMD 170.73 (95% CI, 95.61-245.85), P<0.001]. Serum MMP-9 levels were associated with COVID-19 severity and may serve as a therapeutic target for improving the prognosis of patients with COVID-19.

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Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; ROS, reactive oxygen species; ARDS, acute respiratory distress syndrome; MMP, matrix metalloproteinase; ECM, extracellular matrix; NET, neutrophil extracellular trap

Key words: COVID-19, MMP-9, comorbidity, severity, mortality

Introduction

In December 2019, COVID-19, caused by a then-novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused a global pandemic. According to the World Health Organization (WHO), COVID-19 cumulatively infected 700 million people and caused 60 million deaths by March 2023 (https://covid19.who.int, accessed on 31 March 2023). SARS-CoV-2 infects host cells by binding to angiotensin-converting enzyme 2 (ACE2) receptors (1) and stimulating the immune system resulting in a cytokine storm, reactive oxygen species (ROS) accumulation, and activation of coagulation components (2). The primary clinical manifestation of COVID-19 is lung infection, including acute respiratory distress syndrome and respiratory failure (3). Numerous studies have shown that COVID-19 affects various systems in the body, including the nervous system (4). In adult patients, the severity of COVID-19 is positively correlated with age and comorbidities (5). The European Academy of Neurology assessed the predictors of outcomes at the time of discharge and 6 months post-discharge in 971 patients from 19 countries between July 2020 and March 2021 using the modified Rankin Scale. They found a predisposition to neurological complications in patients with COVID-19, and neurological complications were important predictors of long-term prognosis. In particular, stroke and ataxia were associated with a poorer 6-month prognosis (6). Body Mass Index (BMI) was associated with an increased risk of ARDS and an increased length of hospital stay in a weight-dependent manner. ARDS is an independent risk factor for COVID-19. Therefore, obesity is associated with a poor prognosis for COVID-19 patients (7,8). The majority of available evidence suggests that patients with diabetes, especially those with poor glycemic control, experience a significant 2-4-fold increase in COVID-19 severity, hospitalization, and mortality compared with non-diabetic patients (9,10).

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that are involved in extracellular matrix (ECM) degradation. MMPs are involved in various physiological processes such as angiogenesis, apoptosis, and tissue repair, as well as pathological processes such as hypertension, eclampsia, vascular inflammation, atherosclerosis, tumor

metastasis, cerebral ischemic stroke, peripheral arterial disease, kidney injury, and lung injury (11-15). It has also been reported that MMP-9 is elevated during ascending aortic aneurysms (16,17) Moreover, it has been shown that MMP-9 gene expression is upregulated in COVID-19 patients (18).

During the inflammatory process, neutrophils and macrophages are secreted which activate inflammatory mediators, and cytokines, such as IL-1 and TNF-α, increase the expression and activation of MMP-9. MMP-9 degrades the extracellular matrix and simultaneously results in the release of multiple components, such as heparin and fibronectin, which can act as chemotactic and immune-activating proteins (19). Taken together, MMP-9 contributes to the 'cytokine storm' in patients with COVID-19 by activating cytokines and chemokines (20).

Higher serum levels of MMP-9 were observed in patients with severe COVID-19, non-survivors, and ARDS COVID-19 patients (21-31). Of note, MMP-9 levels were proportional to the risk of respiratory failure (32). MMP-9 promotes platelet and neutrophil activation in patients with COVID-19, resulting in severe thrombotic events (25). Moreover, MMP-9 levels were increased in COVID-19 patients with comorbidities such as obesity, diabetes, and neurologic syndrome (22,24,25,30,33) However, all these studies were conducted with relatively small sample sizes and/or at single centers. Therefore, the predictive role of MMP-9 levels in the risk of poor outcomes in COVID-19 patients needs further validation.

MMP-9 may serve a potential role in the diagnosis and prognostic determination of COVID-19. Here, a comprehensive meta-analysis of COVID-19 studies was performed to determine the relationship between MMP-9 and the severity, mortality, and comorbidities of patients with COVID-19.

Materials and methods

Search strategy, selection criteria, and quality assessment. This study followed The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Diagnostic Test Accuracy (PRISMA-DTA) guidelines (34) and was registered at the International Prospective Register of Systematic Reviews (registration no. CRD42022369605). In the present analysis, two independent authors selected studies by searching 6 databases including PubMed, EMBASE, Web of Science, Cochrane, CNKI, and WANFANG. The last retrieval time was March 15, 2023. No restrictions on the language, region of the investigation, or ethnicity of the study populations were placed. The references of the retrieved articles were also examined. The search terms included 'Matrix Metalloproteinase 9' and 'COVID-19'.

The studies that assessed serum MMP-9 levels and had patients diagnosed with COVID-19 were initially included. The exclusion criteria were as follows: i) Review articles; ii) case reports; iii) studies without data on MMP-9; iv) studies with special subsets of COVID-19 (for example studies with patients all younger than 18 years old); and v) studies which did not stratify groups based on COVID-19 severity. The study quality was assessed using the Newcastle-Ottawa Scale (NOS) (35). Any disagreement between the two reviewers was resolved by a third investigator (HG).

Data extraction. The first author's name, number of study cases, age, sex, and region of the study in the different groups (non-ARDS vs. ARDS; non-survivors vs. survivors; non-severe vs. severe; and with comorbidities vs. without comorbidities) were extracted from the eligible studies. The levels and measurement scale (e.g., μg/l, ng/ml, or pg/ml) of MMP-9 were extracted from the article text, tables, figures, or the letter from the authors. In a meta-analysis, categorical variables (such as sex, region of the study, comorbidities, or outcomes) are treated as dichotomous variables, while for continuous variables (such as age and MMP-9 levels), median (interquartile range, IQR) or median (range) was converted to mean ± SD.

Statistical analysis. A random-effects model meta-analysis was performed using STATA MP version 17 (StataCorp LLC). The effect measure for comparison between different patient groups used weighted mean difference (WMD). Heterogeneity among eligible studies was evaluated using Cochrane's Q-statistic and the I^2-statistic. $P>0.10$ or $I^2>50\%$ indicated significant heterogeneity. Leave-one-out analysis was used to perform the sensitivity analysis to investigate the influence of an individual study on the entire risk estimate. Random effects meta-regression was performed to explore the source of heterogeneity. The publication bias of the analysis was performed using an Egger's test.

Results

Literature search and study characteristics. A total of 373 records were retrieved through searching the database and manual searches. From these, 349 studies (duplicates, review articles, case reports, and irrelevant articles) were removed after reading the abstracts and titles; 24 studies remained for a full-text review. After excluding studies without laboratory data on MMP-9, studies assessing a special subset of COVID-19 patients, and studies stratifying patients on criteria other than severity of COVID-19, a total of 12 records involving 2,062 COVID-19 patients were included in this meta-analysis (Fig. 1) (21-31,34); the details of the 12 studies are stated in Table I. Study quality was assessed using the NOS (Table II). All 12 studies were of a high quality with scores ranging from 7 to 9.

MMP-9 is associated with the severity of COVID-19. A forest plot of the random effects meta-analysis of 6 studies involving 1,471 patients with COVID-19 showed that the MMP-9 levels in patients with severe COVID-19 (n=776) were higher than those in patients with mild to moderate COVID-19 (n=695) [WMD 246.61 (95% CI, 115.86-377.36), $P<0.001$]; the meta-analysis had significant heterogeneity ($I^2=86.7\%$, $P<0.001$; Fig. 2) Sensitivity analysis showed that the studies had no significant impact on the results following a leave-one-out analysis (Fig. 3) Egger's test revealed no evidence of publication bias ($P=0.756$; Fig. 4) Furthermore, 3 studies involving 263 patients with COVID-19 showed that the MMP-9 levels in patients with ARDS (n=79) were higher than those in patients without ARDS (n=184) [WMD 248.5 (95% CI, 63.84-433.25), $P=0.008$]; the meta-analysis had significant heterogeneity ($I^2=87.1\%$, $P<0.001$), and 2 studies involving 87 patients with COVID-19 showed that the MMP-9 levels in the COVID-19 non-survivors did not significantly differ compared to those in

Table I. Characteristics of the studies included in the meta-analysis.

First author, year	Year	Cases, n	Age, years, mean ± SD	Male, n (%)	Group comparison	Country	(Refs.)
Mesa *et al*, 2021	2021	60	65.45±11.12	38 (63.33%)	Non-ARDS vs. ARDS and Non-survivors vs. survivors	Spain	(21)
Ramezani *et al*, 2022	2023	1000	55.45±10.15	620 (62%)	Non-severe vs. severe and non-neurologic syndrome vs. neurologic syndrome	Iran	(22)
Kassianidis *et al*, 2022	2022	181	60.60±13.89	128 (70.72%)	Non-severe vs. severe and non-ARDS vs. ARDS	Greece	(23)
Nasr El-Din *et al*, 2021	2021	70	58.87±7.05	29 (41.4%)	Non-ARDS vs. ARDS and non-obese diabetic vs. obese diabetic	Egypt	(24)
Bonetto *et al*, 2022	2022	228	63.73±10.23	155 (67.98%)	Non-neurologic syndrome vs. neurologic syndrome and non-survivors vs. survivors	Italy	(25)
Gelzo *et al*, 2022	2022	108	43.56±20.82	44 (40.74%)	Non-severe vs. severe	Italy	(26)
Mohammadhosayni *et al*, 2021	2021	20	60.36±11.13	10 (50%)	Non-neurologic syndrome vs. neurologic syndrome	Iran	(33)
Savic *et al*, 2022	2022	77	58.91±6.74	24 (31.17%)	Non-severe vs. severe	Serbia	(27)
Lerum *et al*, 2021	2021	108	58.0±11.3	67 (62%)	Non-severe vs. severe	Norway	(28)
Iwasaki-Hozumi *et al*, 2023	2023	55	40.04±47.74	40 (73%)	Non-severe vs. severe	Japan	(29)
Moin *et al*, 2020	2020	46	58.5±9.24	23 (50%)	Non-obese diabetic vs. obese diabetic	Qatar	(30)
Springall *et al*, 2022	2022	109	54±14.07	73 (66%)	Non-severe vs. severe	Mexico	(31)

ARDS, acute respiratory distress syndrome.

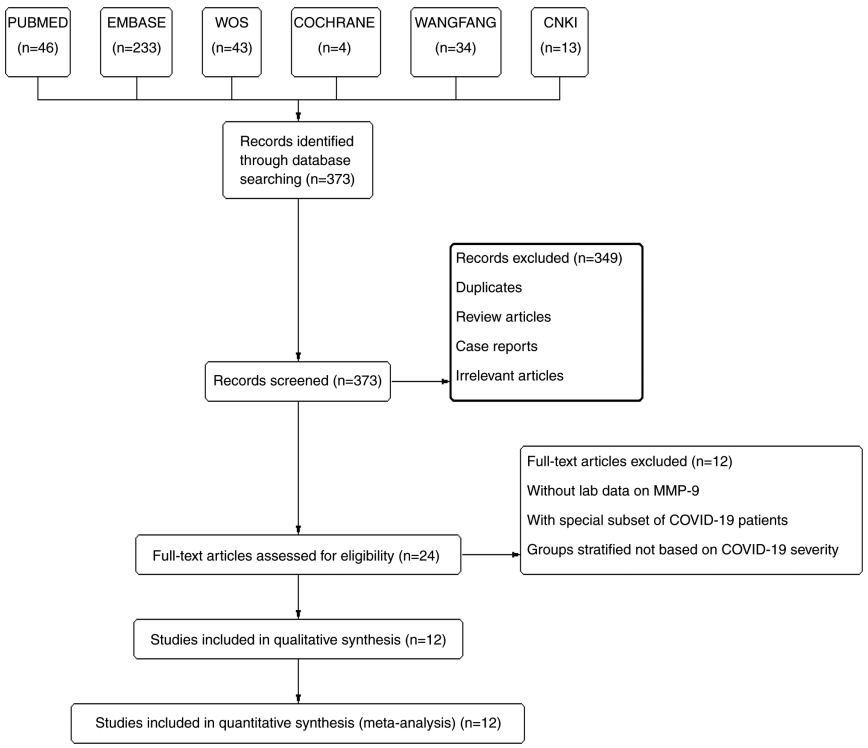

Figure 1. Flow chart of literature selection.

Table II. Quality assessment of the included studies according to the NOS.

First author, year	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of both groups for age	Comparability of both groups for sex	Ascertainment of diagnosis	Same method of ascertainment for cases and controls	Non-response rate	Total score	(Refs.)
Martinez Mesa *et al*, 2021	1	1	1	1	1		1	1	1	8	(21)
Ramezani *et al*, 2023	1	1	1	1			1	1	1	7	(22)
Kassianidis *et al*, 2022	1	1	1	1	1	1	1	1	1	9	(23)
Nasr El-Din *et al*, 2021	1	1	1	1			1	1	1	7	(24)
Bonetto *et al*, 2022	1	1	1	1	1		1	1	1	8	(25)
Gelzo *et al*, 2022	1	1	1	1	1		1	1	1	8	(26)
Mohammadhosayni *et al*, 2021	1		1	1	1	1	1	1	1	8	(33)
Savic *et al*, 2022	1	1	1	1	1		1	1	1	8	(27)
Lerum *et al*, 2021	1	1	1	1	1	1	1	1	1	9	(28)
Iwasaki-Hozumi *et al*, 2023	1	1	1	1		1	1	1	1	8	(29)
Moin *et al*, 2020	1		1	1		1	1	1	1	7	(30)
Springall *et al*, 2022	1	1	1	1	1	1	1	1	1	9	(31)

NOS, Newcastle-Ottawa Scale.

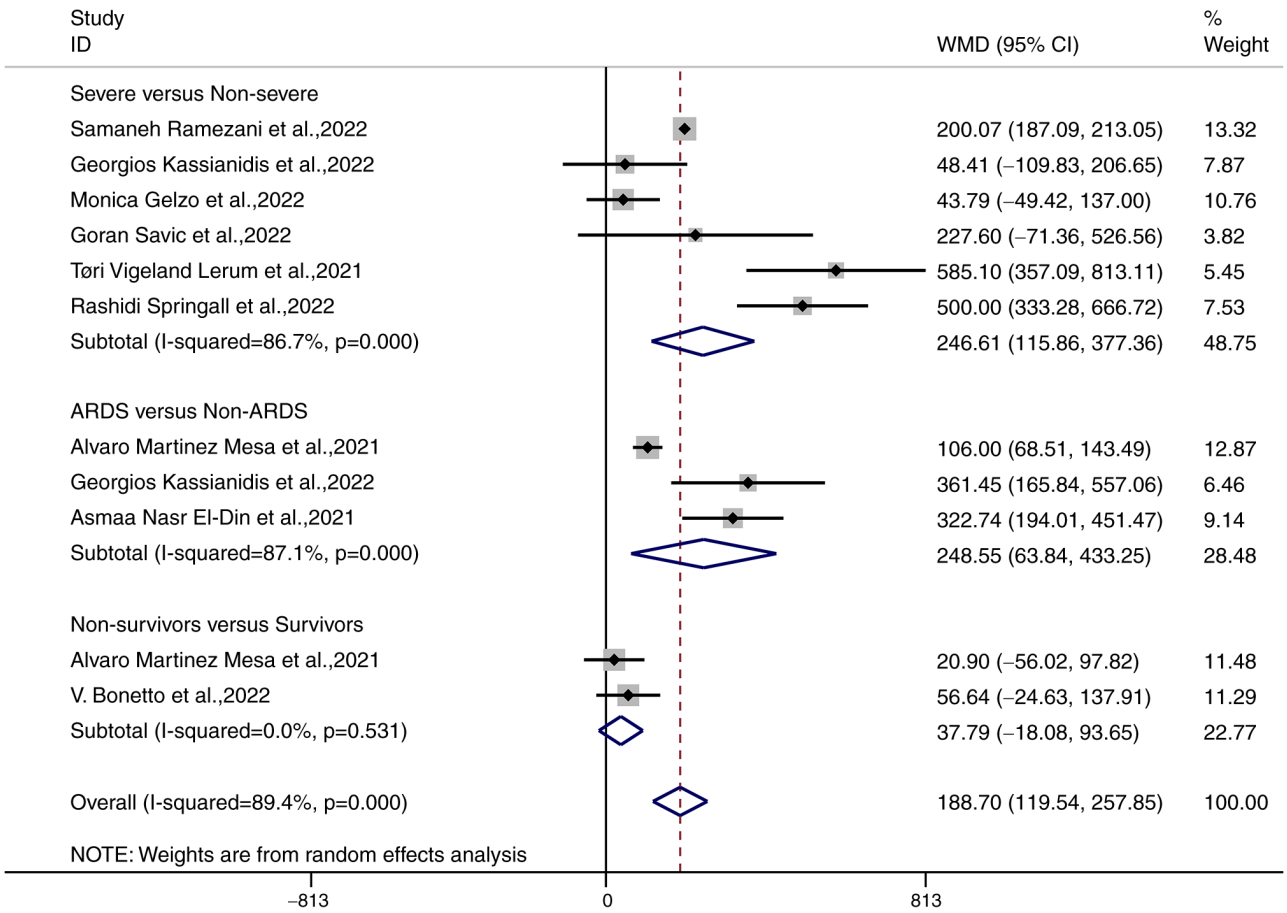

Figure 2. Forest plot of the serum MMP-9 levels based on the severity of COVID-19 patients. MMP, matrix metalloproteinase; WMD, weighted mean difference; CI, confidence interval.

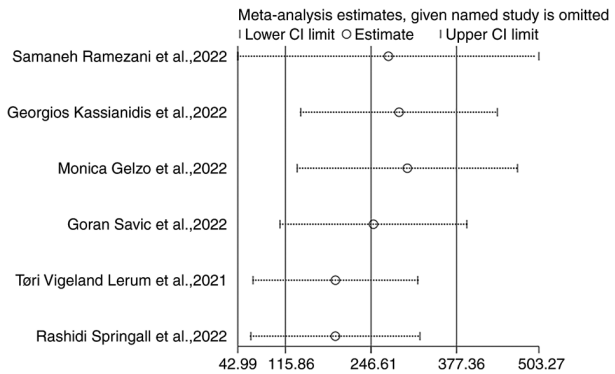

Figure 3. Analysis of the serum MMP-9 levels between severe and mild to moderate COVID-19 patients. MMP, matrix metalloproteinase; CI, confidence interval.

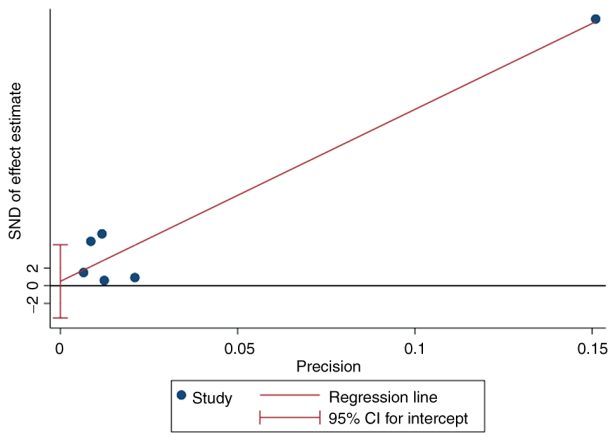

Figure 4. Egger's tests of the serum MMP-9 levels between severe and mild to moderate COVID-19 patients. MMP, matrix metalloproteinase. SND, standard normal deviation; CI confidence interval.

the COVID-19 survivors [WMD 37.79 (95% CI, -18.08-93.65), P=0.185], no heterogeneity was observed in this meta-analysis (I^2=0%, P=0.593; Fig. 2). Finally, the MMP-9 levels were positively correlated with the severity of COVID-19 [WMD 188.70 (95% CI, 119.54-257.85), P<0.001]; the meta-analysis had significant heterogeneity (I^2=89.7%, P<0.001).

MMP-9 levels are associated with comorbidities in patients with COVID-19. Patients with comorbidities, including obese diabetic patients and those with neurological syndromes had significantly higher MMP-9 levels than those without comorbidities [WMD 170.73 (95% CI, 95.61-245.85), P<0.001]; the meta-analysis had significant heterogeneity (I^2=96.3%, P<0.001). Patients with neurological syndromes had higher MMP-9 levels than those without [WMD 176.62 (95% CI, 40.67-312.57), P=0.011]; the meta-analysis had significant heterogeneity (I^2=98.7%, P<0.001). Obese diabetic patients did have different levels compared with non-obese diabetic

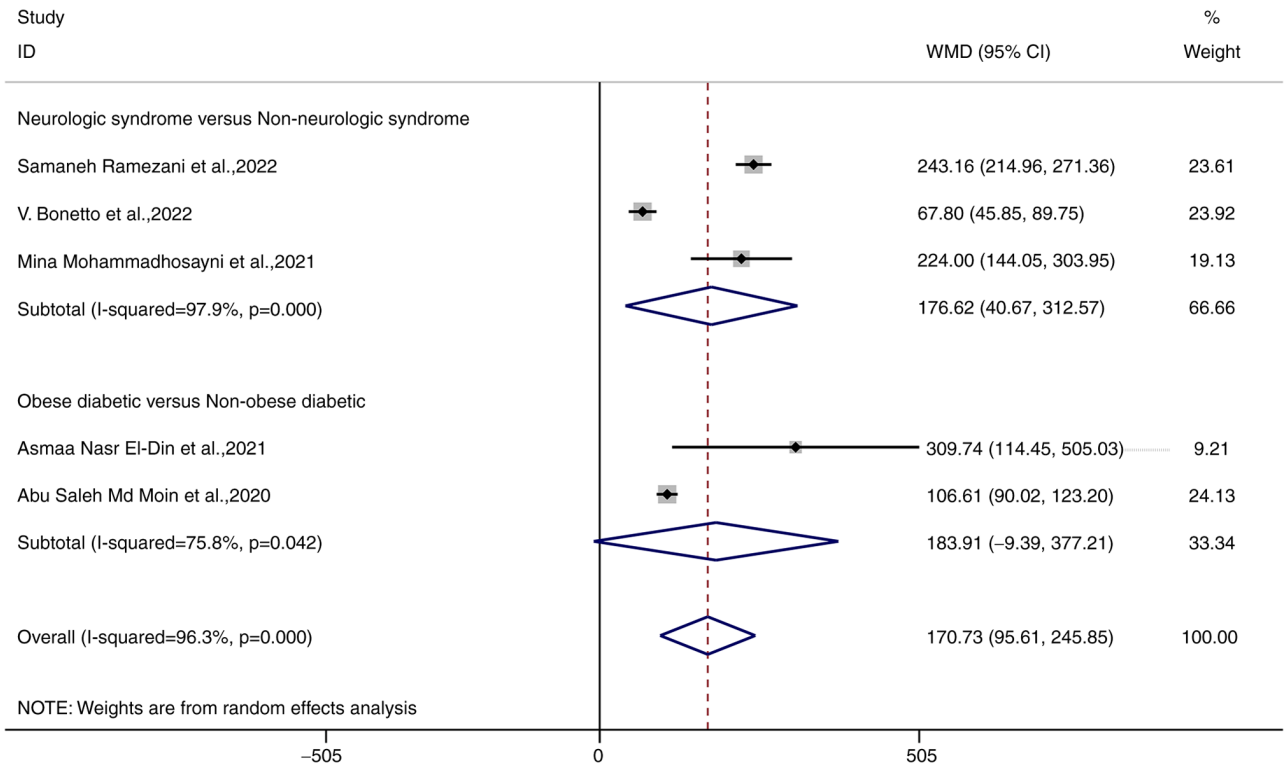

Figure 5. Forest plot of the serum MMP-9 levels based on the comorbidities of COVID-19 patients. MMP, matrix metalloproteinase; WMD, weighted mean difference; CI, confidence interval.

patients [WMD 183.91 (95% CI -9.39-377.21), P=0.042]; the results of the meta-analysis had significant heterogeneity (I^2=75.8%, P=0.0042; Fig. 5).

Discussion

The global impact of SARS-CoV-2 was reduced from 2020 to the present due to the emergence of COVID-19 nucleic acid testing technology and improved epidemic prevention policies (36). However, the emergence of novel mutant strains and the daily increase in the number of confirmed cases and deaths attracted significant attention. It is important to predict patients who are likely to develop severe COVID and ARDS through laboratory tests to improve patient prognosis and reduce mortality. The present meta-analysis included 12 studies that investigated the association between MMP-9 levels with severe COVID and patients with comorbidities in COVID-19 patients. The results showed that elevated MMP-9 levels were observed in 1,471 severe COVID-19 patients in 6 studies and 263 patients with ARDS in 3 studies. However, it was not clear whether elevated MMP-9 levels were significantly associated with patient mortality in the 87 COVID-19 patients in 2 studies. In addition, 5 studies assessed COVID-19 patients with a poorer prognosis due to comorbidities, such as diabetic obese patients or neurologic syndrome, showed significantly higher MMP-9 levels than in patients without comorbidities.

As one of the most widely studied MMPs, MMP-9 plays important roles in several biological processes (37). Neutrophils secrete large quantities of MMP-9 when inappropriately triggered or overactivated, resulting in cytokine storms and effector cell transfer (38). This results in acute lung injury and ARDS, exacerbating the condition of COVID-19 patients (39). The present meta-analysis confirmed that MMP-9 levels were higher in patients with ARDS than in those without ARDS. Cytokine storms are the primary cause of death in COVID-19 patients (40): Elevated MMP-9 levels were correlated (although not significantly) with mortality in COVID-19 patients in the present meta-analysis, likely due to the small number of cases and patients included in the original studies. In addition, MMP-9 was a potential biomarker for cardiac remodeling in sepsis and hypertension (41,42). Heart failure due to heart remodeling, a common complication in elderly patients with COVID-19, poses an additional threat (43). MMP-9 can bind to Neutrophil Extracellular Traps (NETs) to induce endothelial cell dysfunction, leading to a significantly higher risk of thrombosis in COVID-19 patients with abnormal coagulation (44,45). MMP-9 is a potential drug target, and effective inhibitors of MMPs are available for clinical treatment (46). Therefore, detecting the serum MMP-9 levels in COVID-19 patients and providing timely treatment can effectively improve the prognosis of certain COVID-19 patients.

Desforges *et al* (47) found that MMP-9 increases the permeability of the blood-brain barrier, promotes the migration of monocytes to the central nervous system, and promotes the secretion of inflammatory mediators, leading to neuronal damage. The meta-analysis demonstrated a significant increase in the serum MMP-9 levels of patients with neurologic syndromes. Unal *et al* (48) discovered that elevated MMP-9 levels were associated with obesity and insulin resistance. The present meta-analysis found that elevated MMP-9 levels were associated with obesity in diabetic patients. The

relationship between MMP-9 levels and COVID-19 patients with type I diabetes caused by insulin resistance requires further investigation.

This meta-analysis has several limitations. First, there was significant heterogeneity in this meta-analysis. A sensitivity analysis showed that the results of the meta-analysis were stable and not influenced by factors such as the number of cases in the combined results. Other factors, including variations in the species of the virus, changes in the method of measuring MMP-9, criteria for confirming the diagnosis, and classifying the severity of the disease; may cause this residual heterogeneity. Second, most of the included studies were published in high-impact journals; however, several journals have provided green lanes for the publication of COVID-19-related articles to combat this epidemic. Thus, some studies may be at risk of bias. The limited number of included studies prevented the investigation of study publication bias in the meta-analysis of comorbidities. Third, the studies in this meta-analysis were retrospective, and the primary information was obtained by querying electronic medical records; therefore, there was a lack of data and information. In summary, more prospective studies are required to confirm the relationship between serum MMP-9 levels and severity and mortality in COVID-19 patients. The corresponding therapeutic targets can be identified by studying the related molecular mechanisms to reduce the severity of COVID-19 and improve patient prognosis.

In conclusion, the present meta-analysis revealed an association between serum MMP-9 levels and clinical characteristics (including severity, mortality, and comorbidities) in patients with COVID-19. Thus, testing serum MMP-9 levels in COVID-19 patients may be useful for predicting the deterioration of patients for early interventions and targeted treatment. Future clinical studies are required to clarify the mechanism of action of MMP-9 in the long-term prognosis of patients with COVID-19.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

LD made substantial contributions to the conception and design of the meta-analysis. HJ and XG performed the literature search and initial screening for the acquisition of data. CZ and TL performed the full-text reading of the initial screening literature and decided on the inclusion of articles and analyzed the data. LD and HG interpreted the data and confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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