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Role of serum metalloproteinases 2 and 9 to assess the severity of COVID-19 in pregnant women: a prospective cross-sectional study

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ABSTRACT

Objectives: To investigate the relationship between blood matrix metalloproteinases -2 and -9 levels and disease severity in pregnant women with COVID-19 infection.

Material and methods: A prospective cohort study was conducted at the Kanuni Sultan Suleyman Education and Research Hospital in Istanbul, Turkey. We measured serum MMPs-2 and-9 levels of the healthy pregnant controls and pregnant women with COVID-19 and sought to assess the status of these MMPs in pregnant women with COVID-19, especially in women with a severe form of COVID-19 as diagnosed by abnormal computed tomography (CT) findings in addition to severe clinical and laboratory findings.

Results: Of the healthy pregnant controls and pregnant women with COVID-19, the serum MMP-2 levels were comparable, but the MMP-9 level was lower in the pregnant women with COVID-19.

Although the serum MMP2 level was somewhat lower in the women with COVID-19 with abnormal CT findings. The serum MMP-9 level of pregnant women with COVID-19 with abnormal CT was meaningfully lower.

Conclusions: In the pregnant women, COVID-19 decreases the serum MMP-9 but does not change the serum MMP-2. COVID-19 with abnormal CT findings causes minimal decrease in the serum MMP-2 but decreases the serum MMP-9 with abnormal CT findings. Considering the study variables of current study, the probability of LMWH-related MMP alterations needs to be a study topic to clarify the possible contribution of LMWH to the status of serum MMPs in pregnant women with COVİD-19 especially in the women with COVID-19 with abnormal CT findings.

Key words: COVID-19; pregnancy; serum metalloproteinase-2; serum metalloproteinase-9; computed tomography; LMWH

INTRODUCTION

The health problems that COVID-19 can cause in pregnant women are extremely worrying, as cellular immunity under the influence of pregnancy may increase susceptibility to intracellular pathogens such as viruses. Anatomical and physiological changes that occur during pregnancy, such as increased transverse diameter of the thorax, elevation of the diaphragm, and decreases in the respiratory capacity of the lung, and accompanying mucosal edema and vasodilation, may reduce the mother's ability to withstand hypoxic states and subsequently progress to adverse clinical events. According to the current literature, it is noteworthy that the severity of the disease increases in pregnant women during the spread of COVID-19 [1, 2].

The results of a case-control study conducted in the United States, considering the clinical presentations of pregnant and non-pregnant women who developed severe COVID-19 requiring hospitalization, supported that the clinical course and severity of the disease were worse in pregnant compared to non-pregnant women. According to a report from the Centers for Disease Control and Prevention, hospitalizations and adverse outcomes were higher in pregnant women with COVID-19 than in women with COVID-19 who were not pregnant [3]. While COVID-19 generally progresses with a mild or asymptomatic clinical presentation in young patients, it can often lead to a more serious and symptomatic clinical presentation in pregnant women of the same age. Physicians, who have to treat an increasing number of pregnant women with gestational diabetes and obesity, have to develop and apply diagnostic and therapeutic methods that are critical for the treatment of pregnant women [4].

Matrix metalloproteinases (MMPs) are a family of zinc-dependent extracellular matrix (ECM) remodeling endopeptidases that are capable of degrading almost any component of the ECM [5]. MMP-2 and -9 can degrade collagen, elastin, fibronectin, gelatin, and laminin and cause both pro-inflammatory and anti-inflammatory effects on multiple tissues [6]. MMPs were first identified as secreted proteases capable of degrading extracellular matrix proteins under different physiological and pathological conditions. It is observed that the ECM becomes abnormal when the expression of MMPs is altered. It has important contributions in cell differentiation, proliferation, wound healing, tissue remodeling, apoptosis and angiogenesis. MMPs also function in the pathogenesis of different diseases such as cancer metastasis, tumor growth, inflammation, atherosclerosis and myocardial infarction [7]. Within the ECM, tissue inhibitors of MMPs (TIMPs) inhibit the proteolytic activity of MMPs. TIMPs are important regulators of ECM turnover, tissue remodeling and cellular behavior. Therefore, TIMPs (similar to MMPs) modulate angiogenesis, cell proliferation and apoptosis. Disruption of the balance between MMPs and TIMPs plays a role in the pathophysiology and progression of various diseases. MMP-2 and MMP-9, which are gelatinases,

are involved in different cellular processes, including angiogenesis and neurogenesis; These enzymes can cause cell death by changing the molecules of the basal lamina [8]. Most of the cellular-damaging activities of MMP-2 are associated with increased expression/activity. In contrast, a recent review demonstrated that MMP-2 deficiency or insufficiency is associated with inflammation, metabolic dysregulation, and cardiovascular and skeletal pathologies [9]. Recent clinical trials indicate that MMP-2 levels will be useful biomarkers for diagnostic or prognostic evaluation [10]. MMP-9 is involved in the complex process of remodeling of the extracellular matrix in the lung and its activity is regulated by different TIMPs. Increased MMP-9 levels despite TIMP-2 levels within normal limits during the observation period indicate increased MMP-9 activity in COVID-19 patients. It is based on the role of MMP-9 in the inflammatory process of acute lung injury as well as in the development of pulmonary fibrosis [11].

Although it is recommended to avoid the use of ionizing radiation during pregnancy, chest computed tomography (CT) can be performed relatively safely with low-dose protocols by protecting the abdomen when necessary [2, 12]. Oshay et al. reviewed the studies reporting chest CT findings of 427 pregnant women with COVID-19 for either diagnosis or clinical management [2]. For those 65 patients, usage of low-dose protocol was reported. In our institution, we also preferred low-dose scanning protocol for chest CT in pregnant women with COVID-19 to determine the severity of disease. There was no study investigating the diagnostic value of MMPs in pregnant women with COVID-19. We thought that it would be helpful for the diagnosis and follow-up of COVID-19 in pregnant women, when we could add maternal blood MMPs-2 and -9. The objective of current study was to investigate the relationship between blood MMPs-2 and -9 levels and disease severity in pregnant women with COVID-19 infection and to assess the -contribution of extracellular matrix changes to the pathogenesis of COVID-19 in pregnant women.

MATERIAL AND METHODS

A prospective cohort study was conducted at our institution, a tertiary referral hospital. The study involved 46 pregnant women, with confirmed COVID-19 infection, who were admitted to the hospital because of COVID-19, and 21 pregnant women without COVID-19 as controls, who were diagnosed during routine screening and enrolled over the six months of the study. We collected and analyzed the demographic and clinical data of all patients, including age, comorbidities, clinical symptoms, medications and hospitalization days. We also evaluated the results of laboratory tests performed according to the clinical needs of patients, including white blood cells, lymphocyte, neutrophil, platelet, D-dimer, C-reactive protein and alanine aminotransferase, aspartate aminotransferase, total protein, total bilirubin, indirect bilirubin, direct bilirubin, amylase, lipase,

triglyceride, albumin, pro-calcitonin, and ferritin. All pregnant women with COVID-19 were divided into two groups according to the imaging of lungs: normal and abnormal CT findings.

Venous blood samples were collected in tubes containing heparin. Serum samples were removed by centrifugation for 10 at 3000 x rpm. The samples were maintained at –80°C before performing assays.

Before analyses, serum samples were thawed then Human Matrix Metalloproteinase 2 (MMP-2) (Catalogue No: E0904Hu, Bioassay Technology Laboratory, China) and Human Matrix Metalloproteinase 9 (MMP-9), (Catalogue No: E0936Hu, Bioassay Technology Laboratory, China) levels were measured in serum samples. Briefly; samples and standards were added to appropriate wells that is pre-coated with Anti-Human monoclonal antibody before incubation. Biotin was added to all wells and combined with Streptavidin-HRP to form immune complex; then carry out incubation again and washing to remove the uncombined enzyme. Then Chromogen Solution A, B were added for the color of the liquid changes into the blue. At the effect of acid, the color finally becomes yellow. Optical density was read on a standard automated plate reader at 450 nm (Thermo Scientific Microplate Reader, USA). The detection range of MMP-2 was between 10–3000 ng/mL and sensitivity was 5.64 ng/mL; detection range for MMP-9 was 30–9000 ng/L and sensitivity was 15.12 ng/L.

Our study was reviewed and approved by the Clinical Research Ethics Committee of our institution (Approval number: 2020.06.63), and additionally, official acceptance of research protocol was allowed from our Ministry of Health. Informed written consent was obtained from all participants.

All pregnant women who admitted to the hospital during the study period were preliminarily screened for COVID-19, with a focus on the disease's symptomatology and the patients' history of contact with affected individuals; a detailed clinical examination with all precautions issued by local authorities regarding personal protective equipment was performed. We took throat and nasal swabs of all admitted cases and tested them for SARS-CoV-2 antigen through the real-time polymerase chain reaction (RT-PCR). Both study groups were matched regarding age, body mass index (BMI). The exclusion criteria were co-morbidities such as preeclampsia and rheumatological diseases, as well as other infections.

During diagnosis of COVID-19 in pregnant women, we performed chest CT. When CT findings including bilateral involvement, unilateral involvement, multilobar involvement, peripheral distribution, central distribution, peripheral & central distribution, subpleural distribution, anterior involvement, posterior involvement, anterior and posterior involvement, ground-glass opacities, consolidation, or pleural effusion were present (2), we accepted disease positive. Since there is no

proven clinical treatment, symptomatic treatment such as supportive care and infection prevention was applied. Therapeutic drugs such as remdesivir, hydroxychloroquine, chloroquine and supportive drugs such as vitamin C, azithromycin, corticosteroids, low molecular weight heparin were used [13].

For the statistical analyses, we used the Statistical Package for the Social Sciences v23 (IBM SPSS Statistics, IBM Corp., Armonk, NY, US). The data were expressed as mean with standard deviation, median with minimum and maximum, or count (%) as appropriate. Kolmogorov-Smirnov test was used to determine the normality of numeric data. Numeric variables and proportions were compared with t or Mann-Whitney test or chi-square test as appropriate. We set a significant difference when $p < 0.05$.

RESULTS

The selected baseline characteristics of the study population are described in (Tab. 1). There was no significant difference between the healthy pregnant controls and pregnant women with COVID-19 regarding the age, gravidity, parity, miscarriage and gestational age at admission ($p > 0.05$).

Table 2 presents the selected clinical and laboratory characteristics of pregnant women with COVID-19 with or without abnormal CT findings. The mean hospital stay was significant longer in the women with COVID-19 with abnormal CT findings compare to the other group (26.0 ± 6.1 vs. 20.8 ± 6.7; $p = 0.026$).The median serum direct bilirubin concentration was significant higher in the women with COVID-19 with abnormal CT findings compare to the other group [0.17 (0.07–0.77) vs. 0.14 (0.05–0.44); $p = 0.021$].The median CRP concentration was significant higher in the women with COVID-19 with normal CT findings compare to the other group [19 (7–78) vs. 16 (14–124); $p = 0.003$]. There was no significant difference between the study groups regarding other clinical and laboratory findings ($p > 0.05$).

The median serum MMP-2 concentrations of healthy pregnant controls and pregnant women with COVID-19 were presented in the Figure 1. No significant difference was found between the study groups with regard to the median serum MMP-2 concentration ($p = 0.554$).

The median serum MMP-9 concentrations of healthy pregnant controls and pregnant women with COVID-19 were presented in the Figure 2. The median serum MMP-9 concentration of pregnant women was significantly lower than that of the healthy pregnant controls ($p = 0.037$).

The median serum MMP-2 concentrations of pregnant women with COVID-19 with or without abnormal CT findings were presented in the Figure 3. Although the median serum MMP2

concentration was lower in the women with COVID-19 with abnormal CT findings compared the other group, this difference did not reach statistical significance ($p = 0.131$).

The median serum MMP-9 concentrations of pregnant women with COVID-19 with or without abnormal CT findings were presented in the Figure 4. The median serum MMP-9 concentration of pregnant women with COVID-19 with abnormal CT was significantly lower than that of the other group ($p = 0.013$).

DISCUSSION

In the current study, we measured serum MMPs-2 and-9 levels of the healthy pregnant controls and pregnant women with COVID-19 and sought to assess the status of these MMPs in pregnant women with COVID-19, especially in women with severe form of COVID-19 as diagnosed by abnormal CT findings in addition to severe clinical and laboratory findings. Of the healthy pregnant controls and pregnant women with COVID-19, the serum MMP-2 levels were comparable but the MMP-9 level was lower in the pregnant women with COVID-19. Although the serum MMP2 level was somewhat lower in the women with COVID-19 with abnormal CT findings. The serum MMP-9 level of pregnant women with COVID-19 with abnormal CT findings was meaningfully lower [2]. During pregnancy, COVID-19 is associated with preeclampsia, stillbirth, preterm delivery, and NICU admission. Severe COVID-19 infection is strongly associated with adverse maternal and neonatal outcomes [14, 15]. Lassi et al. reviewed the course of COVID-19 in pregnant women worldwide from 62 studies who have been assessed for the clinical presentation, risk factors, and pregnancy and perinatal outcomes in terms of disease severity. They suggested that the risk of severe COVID-19 rises among pregnant women with maternal pre-existing co-morbidities, and that the risk of poor pregnancy and perinatal outcomes in women with severe COVID-19 are also higher, considering the spreading of the COVID-19 pandemic around the world, that most likely many pregnant women may be affected by COVID-19 [15]. These findings in accordance with those findings supporting the importance of maternal and fetal care during pregnancy with severe COVID-19.

MMPs and their TIMPs play a decisive role in the remodeling of the extracellular matrix and cell signal transduction activity [16]. Following their secretion into the intercellular and extracellular space, MMPs migrate into the blood, from this perspective, plasma and serum concentrations of different MMPs continue to be investigated as potential markers of various disease processes. However, what is the most important source of MMPs in plasma and serum is still a matter of hot debate, most importantly because it is understood that differences between serum and plasma can affect measurement results. The MMP-2 level does not differ significantly

between plasma and serum, while the concentrations of MMP-9 forms are strongly affected by anticoagulants and sample handling/processing. Higher concentrations of MMP-9 can be detected in serum than in plasma; this is caused by the release of MMP from leukocytes and platelets during coagulation and fibrinolysis. Plasma should be preferred for determining circulating MMP levels as a reflection of extracellular matrix remodeling in tissue. It has been shown that high molecular weight heparin affects gelatinase measurements differently and MMP-2 does not change blood concentrations in measurements performed by ELISA. In addition, heparin has been shown to significantly suppress MMP-9 release from leukocytes and platelets (16). It is known that LMWH treatment reduces coagulation disorders as well as decreases MMP-9 activity. The observed LMWH-induced reduction in MMP-9 activity is probably indirect [17]. Mannello et al. noted that heparin has a potential to affect the concentrations of MMP2 and MMP9 in blood samples. They suggested that while the measurement activities of these MMPs, researchers need to pay attention to the choice of appropriate blood sampling technique [16].

The biochemist assessing the patient's blood MMP-9 concentration is often unaware of the patient's medical treatment, and the effect of concomitant medications on measured MMP-9 levels has not been adequately studied [5].

In a recent study, the associations of MMPs-2 and -9 with COVID-19 and its outcome were investigated [18]. In that study, patients with PCR-confirmed COVID-19 were 53 subjects who were admitted to the Intensive Care Unit (ICU) and controls consisted of 28 healthy subjects without COVID-19. Blood samples were drawn from all patients with COVID-19 within 48 H of the ICU admission. Average ages of the controls and patients were 57.8 ± 2.4 and 59.5 ± 1.7, respectively. They demonstrated that as compared to that of the controls, in the patients with COVID-19, the plasma MMP-2 was lower and that plasma MMP-9 was higher. Their survival analysis revealed that COVID-19-related mortality was associated with increased MMPs-2 and -9 levels. Our findings related to the changes of MMPs-2 and 9 levels of maternal blood had some contradictory properties. In that study, their study had no participants with pregnancy; their drugs used to reduce complaints of patients were considerably different; the subject required ICU management; and the study population had chronic disorders like hypertension and diabetes mellitus. The fact that the patients with COVID-19 in this study had diabetes and vascular diseases may have caused the MMP levels to change independently of the disease. The difference in MMP levels in our study regarding the findings of D Avila-Mesquita et al. may be due to the following: the participants were younger pregnant women; the participants did not have chronic diseases such as diabetes and hypertension that could affect MMP levels; and that blood samples with MMP measurements were obtained from the participants undergone LMWH administration for the

treatment of COVID-19.

There are limitations of this study regarding the nature of its design as prospective cohort study including the measurements of MMPS at the beginning of COVID-19 management. It may have more informative findings when it has serial measurements of MMPs. With or without LMWH administration, MMPs could be measured to clarify their regulation.

CONCLUSIONS

In the pregnant women, COVID-19 decreases the serum MMP-9 but does not change the serum MMP-2. COVID-19 with abnormal CT findings causes minimal decrease in the serum MMP-2 but decreases the serum MMP-9 with abnormal CT findings. Considering the study variables of current study, the probability of LMWH-related MMP alterations need to be a study topic to clarify the possible contribution of LMWH to the status of serum MMPs in pregnant women with COVİD-19 especially in the women with COVID-19 with abnormal CT findings.

Conflict of interests

The authors have no conflict of interests to declare.

Contributions

All authors participated in the concept and design of the present study, in the analysis and interpretation of the data, in the draft or revision of the manuscript, and they have approved the manuscript as submitted. All authors are responsible for the reported research.

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Table 1. Selected baseline characteristics of the study groups

	Controls (n = 21)	**COVID-19 (n = 46)**	**Significance**
Age (y)	28.4 ± 9.5	28.2 ± 6.4	0.913
Gravidity	3 (1–9)	3 (1–6)	0.883
Parity	1 (0–5)	1 (0–4)	0.814
Miscarriage	0 (0–3)	0 (0–2)	0.721
Gestational age at admission (w)	22 (11–28)	23 (9–32)	0.297

Table 2. Selected clinical and laboratory characteristics of pregnant women with COVID-19 with or without abnormal CT findings

	COVID-19 with normal CT (n = 31)	**COVID-19 with abnormal CT (n = 14)**	**Significance**
Hospitalization [d]	20.8 ± 6.7	26.0 ± 6.1	**0.026**
Need for NICU	1 (3.4%)	1 (6.3%)	0.661
Cesarean delivery	13 (44.8%)	10 (62.5)	0.256
Gestation age at birth [w]	39 (32–41)	39 (32–40)	0.740
Length of stay in NICU [d]	5 (0–12)	5.5 (2–14)	0.814
Aspartate transaminase [U/L]	25 (12–44)	17 (14–35)	0.685
Alanine transaminase [U/L]	15.5 (7–26)	12 (8–64)	0.531
Albumin [g/L]	32.9 (29–42)	36 (28–38)	0.345
Total protein [g/L]	61 (54–80)	69 (54–73)	0.199
Total bilirubin [mg/dl]	0.29 (0.15–0.63)	0.27 (0.14–1.82)	0.155
Direct bilirubin [mg/dL]	0.14 (0.05–0.44)	0.17 (0.07–0.77)	**0.021**
Indirect bilirubin [mg/dL]	0.14 (0.06–0.34)	0.1 (0.05–0.17)	0.825
Amylase [U/L]	61 (30–114)	55 (38–279)	0.484
Lipase [U/L]	26.8 (16–57)	35 (20–120)	0.512
Triglyceride [mg/dL]	165 (99–500)	264 (52–414)	0.503
C-reactive protein [mg/L]	19 (7–78)	16 (14–124)	**0.003**
Procalcitonin [ng/mL]	0.06 (0.02–0.12)	0.05 (0.03–0.09)	0.505
White blood cell [10^3/μL]	5725 (4520–9750)	4570 (3610–8670)	0.128
Platelet [10^3/μL]	202500 (131000–272000)	261000 (167000–288000)	0.797
Neutrophil [10^3/μL]	4.4 (1.99–3690)	2.4 (1.68–7.15)	0.122
Lymphocyte [10^3/μL]	1.4 (0.70–3)	1.6 (1–2.20)	0.731

D-dimer [mg/L]	1.05 (0.19–4.03)	1.08 (0.47–1.60)	0.207
Ferritin [ng/mL]	78 (8.80–345)	62 (28–237)	0.556
Birth weight [g]	3220 (2030–4200)	3350 (2000–4460)	0.941
Apgar score at 1 min	7 (0–9)	7.5 (7–8)	0.557
Apgar score at 5 min	9 (010)	9 (8–9)	0.456
NICU — neonatal intensive care unit			

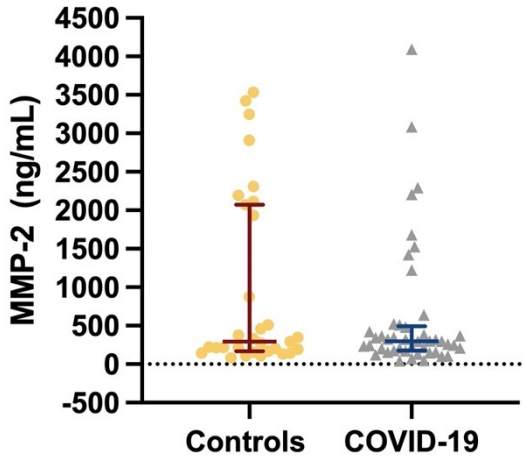

Figure 1. Median serum metalloproteinase-2 (MMP-2) concentrations of healthy pregnant controls and pregnant women with COVID-19. Data were presented as median with 25–75% interquartile range. Mann-Whitney test revealed no significant difference between the study groups ($p = 0.554$)

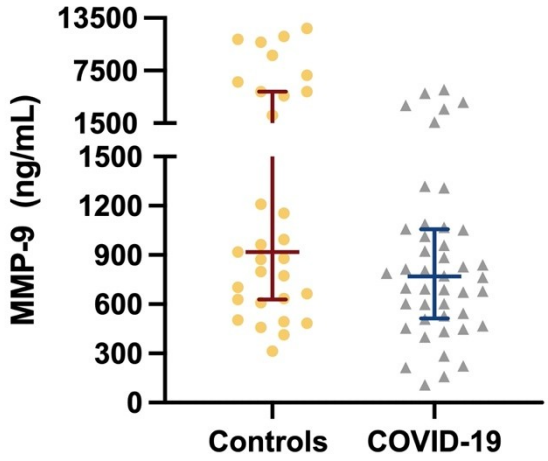

Figure 2. Median serum metalloproteinase-9 (MMP-9) concentrations of healthy pregnant controls and pregnant women with COVID-19. Data were presented as median with 25–75% interquartile range. Mann-Whitney test revealed that the median serum MMP-9 concentration of pregnant women with COVID-19 was significantly lower than that of the healthy pregnant controls ($p = 0.037$)

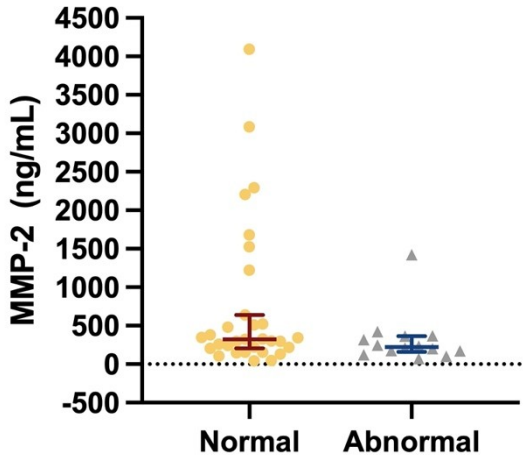

Figure 3. Median serum metalloproteinase-2 (MMP-2) concentrations of pregnant women with COVID-19 with or without abnormal CT findings. Data were presented as median with 25–75% interquartile range. Mann-Whitney test revealed that although the median serum MMP2 concentration was lower in the women with COVID-19 with abnormal CT findings compared to the other group, this difference did not reach statistical significance ($p = 0.131$)

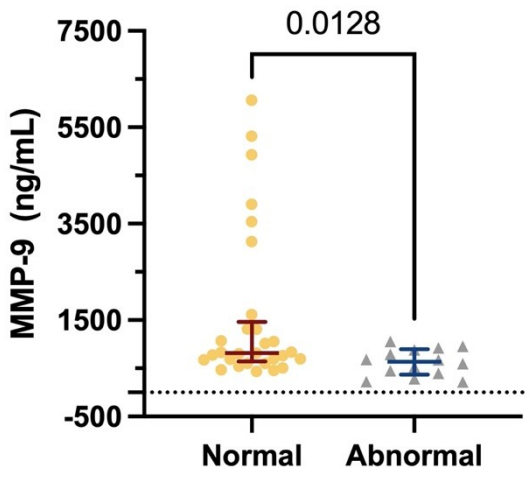

Figure 4. Median serum metalloproteinase-9 (MMP-9) concentrations of pregnant women with COVID-19 with or without abnormal CT findings. Data were presented as median with 25–75% interquartile range. Mann-Whitney test revealed that the median serum MMP-9 concentration of pregnant women with COVID-10 with abnormal CT findings was significantly lower than that of the other group ($p = 0.013$)