Matrix Metalloproteinase 3 as a Valuable Marker for Patients with COVID-19

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Abstract

Background: The situation of the corona virus disease 2019(COVID-19) continues to evolve, our study explored the significance of serum levels of Matrix Metalloproteinase 3 (MMP3) as a marker for patients with COVID-19. Methods: Sixty-two COVID-19 patients in the First Hospital of Hunan University of Chinese Medicine and Loudi Center for Diseases Prevention and Control, from January to March 2020, were sampled as the novel coronavirus pneumonia infected group. One hundred and thirty-one cases from the First Hospital of Hunan University of Chinese Medicine, including 67 healthy individuals and 64 non- COVID-19 inpatients, served as the non-infected group. Approximately every 5 d, sera from 20 cases were collected and analyzed thrice, using an automatic biochemical analyzer, to detect serum MMP3 concentrations. Following normality tests, differences in serum MMP3 levels between the infected and non-infected group were analyzed via SPSS (version 25.0) software, using the Wilcoxon rank sum test. Results: The MMP3 concentration was 44.44(23.46˜72.12)ng/ml in the infected group and 32.42 (28.16˜41.21)ng/ml in the non-infected group. The difference between the two groups was statistically significant (Z=-2.799, P=0.005<0.05). Serum MMP3 concentration, measured over three separate time points, were 55.98 (30.80˜75.97) ng/ml, 34.84 (0.00˜51.84) ng/ml, and 5.71 (0.00˜40.46) ng/ml, respectively. Conclusion: Detection of serum MMP3 levels may play an important role in the development of therapeutic approaches for COVID-19 and may indicate the severity of disease.

Introduction

A novel coronavirus, named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the WHO, was first reported in Wuhan, China in December 2019. SARS-CoV-2 causes Corona Virus Disease 2019 (COVID-19), and typical COVID-19 symptoms include dry cough, fever and fatigue. [1,2] Since its emergence, SARS-CoV-2 has spread rapidly all over the world, arousing widespread concern. To date, the viral nucleic acid test remains the main diagnostic tool used to detect COVID-19, whereas serum immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies can be used to detect the SARS-CoV-2 infection.[3] Laboratory examination plays a vital role in the diagnosis and treatment of COVID-19, wherein relevant test indicators may provide evidence-based support for clinicians. This article attempts to show a possible connection between matrix metalloproteinase 3 (MMP3) and COVID-19.

MMP3 is an important member of a large family of matrix metalloproteinases (MMPs) containing zinc-dependent endopeptidases. Matrix degradation and remodeling have been recognized as the main function of MMPs. However, subsequent studies reveal that MMPs may participate in diverse pathophysiological processes, such as the regulation of inflammatory and immune responses as well as cell-cell communication, among others. Reportedly, in addition to the above functions, MMP3 also activates other matrix metalloproteinases in the family. [4,5] In particular, it participates in many physiological and pathological processes that are associated with the inflammatory process. For example, studies have confirmed that MMP3 levels may be used to monitor the activity of rheumatoid arthritis and to predict its severity.[6,7] Recent studies have investigated the effects of MMP3 on respiratory disorders, including acute lung injury (ALI), acute

respiratory distress syndrome (ARDS), pulmonary fibrosis, and lung cancer.[4,8]Therefore, this study makes a major contribution to research on COVID-19 by demonstrating the significance of MMP3 and providing ideas for future scientific research.

Materials and Methods

Patients

Sixty-two Chinese patients with COVID-19, from the First Hospital of Hunan University of Chinese Medicine and Loudi Center for Diseases Prevention and Control, who met the diagnostic criteria for COVID-19 and the requirements of the treatment plan (trial version 6) issued by the Health Commission of the People's Republic of China[9], were included in the study as the infected group. A total of 131 cases from the First Hospital of Hunan University of Chinese Medicine, including 67 healthy individuals and 64 non- COVID-19 inpatients, served as the non-infected group. This study was approved by Ethics Committee of the First Hospital of Hunan University of Chinese Medicine, with an informed consent of patients and their families.

Laboratory analysis

Serum level of MMP3 was measured via latex enhanced immunoturbidimetry with a human MMP3 determination kit (Shanghai Huachen Biological Reagent Company), using the Cobas8000 automatic biochemical analyzer (Roche Company in Germany). All tests were conducted by authorized, skilled laboratory personnel in accordance with manufacturer's specifications and instructions.

Statistical Analysis

Dates were analyzed using SPSS (version 25.0) software. Normality tests were conducted for measurement data, where normal data were expressed as the mean and standard deviation, while the t-test was used for comparison between two groups. Data that did not conform to normality were expressed as the median and interquartile, and the Wilcoxon rank sum test was used to compare the differences in serum MMP3 levels between the 2 groups. Statistical significance was set at $P < 0.05$.

Results

Comparison of serum MMP3 between infected group and non-infected group

Normality tests indicated that data from both the novel coronavirus pneumonia infected group and the non-infected group were not normal. Therefore, the Wilcoxon rank sum test was used to compare the 2 groups. The MMP3 serum levels in the infected and non-infected groups are shown (Table 1). MMP3 concentrations were 44.44(23.46˜72.12)ng/ml in the infected group and 32.42(28.16˜41.21)ng/ml in the non-infected group. A positive correlation was found between infected and non-infected groups (Z=-2.799, P=0.005<0.05). The distribution of MMP-3 and the statistical significance between the 2 groups were plotted using a quartile box (Fig. 1).

Changes of serum MMP3 concentration in novel coronavirus patients during hospitalization

In order to detect serum MMP3 concentrations, sera from 20 patients were collected thrice approximately every 5 days according to the duration of hospitalization. All were cured and discharged from hospital. Medians and interquartile ranges were used to describe these 3 serum MMP3 levels, the first time point being 55.98(30.80˜75.97) ng/ml, the second 34.84(0.00˜51.84) ng/ml and the third 5.71(0.00˜40.46) ng/ml. The 3 serum MMP3 concentration levels showed a decreasing trend. The distribution of MMP-3 serum concentrations over the 3 detection times is shown (Fig. 2).

Discussion

Several reports have indicated that MMP3 may play an important role in the process of lung pathology, including acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and pulmonary fibrosis. Studies conducted on animal models have found that the lungs of MMP3 gene deficient mice can be protected by inflammatory stimulation.[4,10,11] However, a study by Yamashita[12] (2016) indicated that MMP3

deficiency helps maintain the function of pulmonary surfactant to some extent and thereby protects the lungs from injury caused by physiological changes. This suggests that MMP3 plays a regulatory role in lung injury and repair. MMP3 is mainly secreted by fibroblasts and endothelial cells where inflammatory cells and cytokines can stimulate MMP3 secretion. It has been found that the non-matrix substrates of MMP3 are pro-inflammatory cytokines such as IL-1 β and TNF- α. Furthermore, MMP3 also activates other matrix metalloproteinases, including pro-MMP-1,3,7,8,9 and 13. While, the proteolysis function of MMP3 removes adhesion sites between cells and the matrix, contributing to in intracellular migration, MMP3 also plays a vital role in intercellular communication by regulating the activity of cytokines and chemokines, thus affecting and reflecting the progress of disease to a certain extent.[5,13,14]

The current study compared the serum MMP3 concentrations of the novel coronavirus pneumonia infected group with those of the non-infected group. Our results indicated that MMP3 may be utilized to monitor the state of COVID-19 patients. Some studies have identified the main pathological characteristics of COVID-19 patients as pulmonary inflammation and lung injury, in addition to which many severe cases may also develop into SARS.[15,16] Current literature on COVID-19 highlights the role of inflammation and immune responses in COVID-19, which, together with cytokine storm and proinflammatory factors like IL-1 β and TNF-α, undoubtedly contribute to the severity of disease.[17,18] It is important to consider the biological response of organisms to the SARS-CoV-2 infection from the point of view of protease and immune defense.

Hoffmann et al., [19] found that novel coronavirus (SARS-CoV-2), enters host cells in a manner similar to that of SARS-CoV, relying on ACE2 and serine protease, TMPRSS2. This complex process via which the virus infects cells, involves a variety of proteases, and thus it is important to investigate antiviral intervention through correlative proteases. A recent study by Phillips(2017) explored the role of various proteases in coronavirus infection and reported that zinc metalloproteases, such as matrix metalloproteinase, may be potential contributors to coronavirus fusion.[20]Therefore, it may be inferred that MMP3 is potentially associated with SARS-CoV-2 infection of host cells, via processes such as cell fusion. However, a literature review did not reveal any data on the association between MMP3 and coronavirus infection. In conclusion, future studies may lead to further progress in determining the relationship between MMP-3 and SARS-CoV-2 infection.

This study has some limitations. First of all, due to a small number of patients, this paper cannot provide a comprehensive review of the correlation between MMP3 levels and disease severity. As COVID-19, which is caused by a novel coronavirus virus, is a previously unknown disease, timely and effective measures have prevented the disease from causing a local pandemic. Another potential problem is that, conditionally, the study did not take other diseases associated with COVID-19 patients into account. A further study with more focus on excluding the influence of other factors is therefore suggested. Additionally, the future study may also contain the experiments on animal or cell model to explore more details.

In conclusion, the objective of the current study was to determine whether MMP3 levels have a role to play in the treatment of COVID-19 patients. Detection of serum MMP3 levels may be useful in assessing disease severity, as indicated by the positive correlation found between novel coronavirus pneumonia infected patients and non-infected patients. Insights gained from this study may assist in the monitoring, diagnosis, and treatment of COVID-19. Thus, further studies regarding the role of MMP3 in the pathology of COVID-19 are deemed to be useful.

NOTES

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Conflict of Interest

The authors declare no conflicts of interest.

Ethics approval

This study was approved by the Ethics Committee of the First Hospital of Hunan University of Chinese Medicine.

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Table 1. Comparison of serum MMP3 concentration between the two groups

Group	N	M(P_{25}˜P_{75}) ng/ml
Infected	62	44.44(23.46˜72.12)
Non-infected	131	32.42(28.16˜41.21)

Figure Legends

Fig 1. Comparison of serum concentration of MMP3 between the COVID-19 infected group and non-infected group. Box above with the median as a line shows the distance between the quartiles, and the maximum and minimum values of MMP3 were presented by the whiskers. Outliers are displayed as separate points. The P-values show that there was significant difference between groups.

Fig 2. Changes of serum MMP3 concentration in novel coronavirus patients during hospitalization. The interval of each test was 6 days, and a total of 5 times were tested. Box above with the median as a line shows the distance between the quartiles, and the maximum and minimum values of MMP3 were presented by the whiskers. Outliers are displayed as separate points.

Fig.1

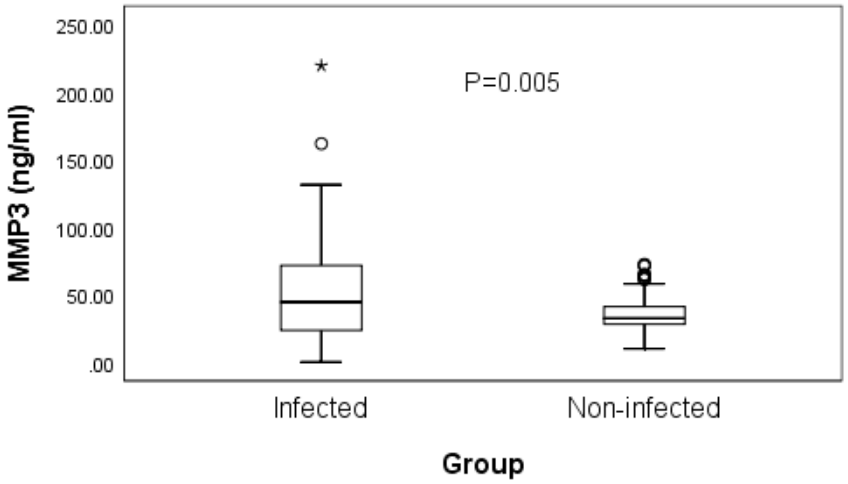

Fig.2