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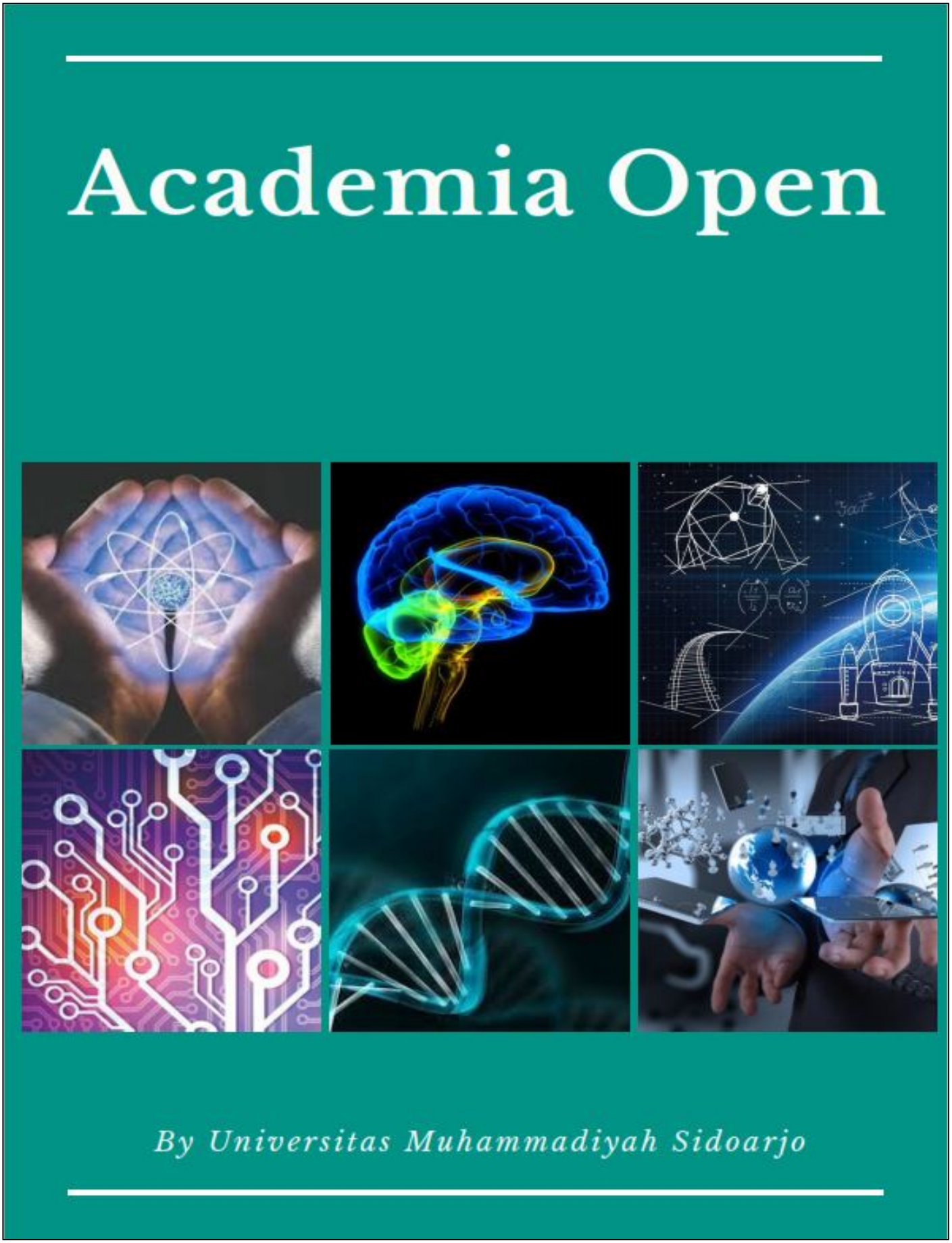


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# Higher Serum Level of MMP-3 and Homocysteine in Patients Admitted With COVID-19

## *Tingkat Serum MMP-3 dan Homosistein yang Lebih Tinggi pada Pasien yang Dirawat dengan COVID-19*

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**Abstract**

**Background:** SARS-CoV-2 predominantly affects the lungs, leading to severe acute respiratory syndrome (ARDS). The lack of specific biomarkers underscores the urgent need for novel indicators for early diagnosis and severity assessment of COVID-19. **Specific Background:** Matrix metalloproteinase-3 (MMP-3) is implicated in various inflammatory diseases, particularly viral infections, while homocysteine (Hcy) plays a crucial role in maintaining cell homeostasis and regulating inflammatory responses. **Knowledge Gap:** Despite their relevance in inflammation, the potential of MMP-3 and Hcy as biomarkers for COVID-19 remains underexplored. **Aims:** This study aimed to evaluate the serum levels of MMP-3 and Hcy in COVID-19 patients and assess their utility in diagnosis and severity prediction. **Results:** A study analyzing 90 serum samples from 60 ICU patients and 30 healthy controls found elevated CRP levels, higher Hcy and MMP-3 levels in the moderate group, but lower in the ICU group, with a significant correlation between MMP-3 activity and Hcy levels. **Novelty:** This research highlights the potential role of MMP-3 and Hcy as valuable

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biomarkers for COVID-19 diagnosis. **Implications:** While MMP-3 and homocysteine may aid in the diagnostic process, they could not be reliably used to predict severity outcomes in COVID-19 patients. Further studies are warranted to clarify the clinical implications of these biomarkers in the context of COVID-19.

**Highlights:**

1. MMP-3 and homocysteine identified as potential COVID-19 biomarkers.
2. No correlation found between biomarkers and disease severity.
3. Further research needed for clinical utility assessment.

**Keywords:** COVID-19, MMP-3, homocysteine, biomarkers, diagnosis

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# Introduction

Since December 2019, the covid-19 disease 2019 (COVID-19) in Wuhan, China outbreak has since become a pandemic. Most cases are mild or moderate and can be managed easily; however, severe cases may cause extensive alveolar damage and progressive respiratory failure that is called acute respiratory distress syndrome (ARDS), leading to mortality (1). According to the World Health Organization (WHO) report, about 15% of COVID-19 patients are severe, and nearly 5% are critical (2).

In terms of clinical symptoms, COVID-19 has shown a wide spectrum, ranging from asymptomatic or mild forms to severe ARDS, multiorgan and systemic failure (3). The virus agent SARS-CoV-2 enters cells through the angiotensin-converting enzyme-2 (ACE-2) receptor. Because the ACE-2 receptor is present in different types of cells, it can affect various organs such as the lung and liver, intestine heart, testis bladder kidney as well as brain and causing gastrointestinal symptoms respiratory liver heart or neurological manifestations in addition to fever (4).

Hypertension, diabetes, cardiovascular diseases (CVD), obesity, and chronic lung diseases are the major variables that worsen COVID-19 severity (5, 6). The usual initiation of COVID-19 clinical signs is five to seven days post-infection. Fever, coughing, weakness, fatigue, headache as well as diarrhea and vomiting are among the signs (2).

Currently, CT imaging and reverse transcription-polymerase chain reaction to the real-time quantitative detection (7) constitute major techniques in the diagnosis of SARS-CoV-2 infection. Also unspecific in confirming the disease at early stages but other laboratory findings are: ESR elevation, high-sensitivity serum C-reactive protein, IL-6 and IL-1β bioactivity, lymphopenia, lactate dehydrogenase; (8) additionally to these insufficiency in specificity for early detection of the disease other markers reflecting severity of COVID-19 are not common for a routine setting test and therefore their design would have to inspire sharpness as well on account of showing this disease's course duly and timely.

Matrix metalloproteinases constitute a large family of zinc (Zn)-dependent enzymes engaged in a wide variety of physiological activities and breaking down and remodeling components of the extracellular matrix (ECM). One of the major MMP constituents is MMP-3, often referred to as stromelysin-1. It contributes to several physiological processes: immunomodulation, control of an inflammatory response, and activation of other members belonging to the MMP family. According to previous studies, MMP-3 can be used as a tracking marker for immunological response, inflammation, and activators in inflammatory disease development with rheumatoid arthritis (RA). Besides that, important results were obtained showing the contribution of MMP-3 to maintain proper healing processes by lung tissue damage during respiration pathologies such as airway fibrosis, ARDS, or acute lung injury (ALI).

In COVID-19 patients' sera, MMP-3 was clearly associating with IL-6 and IL-1β based on a new study; this may imply the likely involvement of MMP-3 in SARS-CoV-2 infection via mechanisms such as cell entry (9). Another research found a high correlation between pneumonia and increased MMP-3 in COVID-19 patients (13). Therefore, MMP-3 might be a good biomarker for assessing the severity of the disease in COVID-19.

Methionine (Met) is demethylated in cells to homocysteine, an S-containing amino acid as a metabolic intermediate (14). Homocysteine (Hcy) plays a role in cellular homeostasis maintenance and control of the cell cycle (15). High plasma levels of homocysteine (> 15 µmol/L) indicate hyperhomocysteinemia (HHcy), a systemic pathological condition (16). Among many others, such as cancer, cardiovascular disease, thrombosis, and neurodegenerative disorders, HHcy is associated with the pathogenesis of these diseases (17). Homocysteine also increases during viral infections, for example by hepatitis C or human papillomavirus and HIV viruses (18, 19) which cause infection.

Homocysteine measurement is currently applied in clinical laboratories. According to one study, measurement of homocysteine levels together with monocyte lymphocyte ratio (MLR) might serve as a good indicator for COVID-19 disease severity (20). The study showed a relationship between increased COVID-19 disease severity and MLR as well as HHcy (20). Another research has it that Homocysteine could be a predictive marker for severity of COVID-19 among in-patients setting (21).

Yet another study that evaluated serum levels of liver enzymes found that a significant number of SARS-CoV-2-infected patients portray disordered liver function, this being related to a positive correlation with long hospitalization periods (22). Therefore, the assessment of these variables might reflect the relationship with COVID-19's severity (need for ICU and mechanical ventilation).

Early enough diagnosis and proper treatment, more research on these biomarkers and knowing their role in different stages of the COVID-19 disease appears to be necessary. Therefore, a research aim is to ascertain physiological, biochemical, and immunologic factors regarding the pathogenesis of COVID-19.

# Methods

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Subjects

From 1 Nov to 30 Dec 2021, 60 patients (30 male and 30 girl, elderly 18–85 years) engaged in this research. These people' COVID-19 became confirmed by CT scans and RT-qPCR. Exclusion from the trial changed into granted to contributors with negative RT-qPCR effects, underlying scientific conditions, or personal dissatisfaction. Additionally, 30 healthy individuals signed as much as serve as the observe's manipulate group. A peripheral blood sample of 20 milliliters turned into received by means of the individuals for you to check inflammatory markers in the serum. This have a look at protocol (IR.MUMS.MEDICAL.REC.1401.006) has been normal with the aid of the ethics committee of Mashhad University of Medical Sciences. COVID-19 patients are divided into two categories: slight and ICU, in line with WHO suggestions.

Homocysteine and MMP-3 assay

Blood samples were taken, centrifuged for 10 minutes at 1500 g, and saved at -20°C until the homocysteine and MMP-3 analysis. Homocysteine degrees in serum were measured using the direct enzyme-linked immunosorbent check (ELISA). Based on company procedure, a direct ELISA homocysteine assay (Human homocysteine ELISA package, ZellBio GmbH, Germany). 2.5 and 80 nmol/mL, respectively, have been the lowest and maximum detection limits. Before the immunoassay, the protein-sure hydroxycysteine (Hcy) is reduced to free Hcy and then enzymatically transformed to S-adenosyl-L-homocysteine (SAH). Additionally, MMP-three in serum turned into assessed via ELISA using the Human MMP-three ELISA Kit from ZellBio GmbH in Germany. Every operation turned into executed according with business exercise, and OD became measured at 450 nm. 0.4 to 12.8 ng/mL turned into the decrease and higher detection limits, respectively..

Biochemical and inflammatory factors

The BioSystems BA400 scientific chemistry analyzer changed into used to evaluate the ranges of alkaline phosphatase (ALP), lactate dehydrogenase (LDH), alanine transaminase (SGPT-ALT), aspartate transaminase (SGOT-ASP), and excessive-sensitive C-reactive protein (hsCRP) within the blood of COVID-19 participants..

Statistical analysis

All variable records, whether non-stop or express, are shown as percentages, imply, wellknown mistakes (SE), and preferred deviation (SD). The statistics's normality turned into assessed the usage of the Kolmogorov-Smirnov test and the unbiased-samples T-test/Mann-Whitney U take a look at and specific/Chi-rectangular Fisher's exams had been used to evaluate the categorical and quantitative variables. The correlation coefficient among the non-stop variables became shown the usage of Pearson and Spearman's rho. A statistically good sized end result was described as a p-value of much less than zero.05.

# Result and Discussion

Demographic findings:

Table 1 affords the demographic information for 30 controls and 60 COVID-19 patients, categorized in keeping with the World Health Organization (WHO) degree. Age differences between the controls and the instances have been not statistically sizeable..

Biochemical findings:

Data evaluation revealed that ICU sufferers had a extensively higher CRP degree (128.61±17.80) than the manage group (6.82±0.5) and moderate organization (73.49±10.98) ($p<0.001$). Moreover, ALT tiers inside the slight group (45.37±6.45) and ICU (128.89±11.06) have been greater than the ones inside the control organization (20.67±3.04) ($p<0.05$); likewise, AST stages inside the mild organization (40.56±4.15) and ICU (47.3±6.81) one had been better than the ones within the manipulate organization (17.25±2.38) ($p<0.01$). Regarding the extent of ALP, there were no sizeable differences discovered most of the manipulate group (198.25±19.92), mild organization (208.12±19.71), and ICU institution (203.58±17.21).

The homocysteine tiers inside the control and COVID-19 patient subgroups, which consist of the mild and ICU corporations, are proven in Figure 1. The interquartile variety is shown through containers; the median fee is proven via strains inside the containers; the 5th and ninety fifth percentiles are shown by way of whiskers. The homocysteine stages inside the moderate group have been substantially higher ($p<0.0001$) than those within the manipulate organization, according to the statistics. Additionally, there was a large difference ($p<0.01$) inside the homocysteine levels among the ICU and mild businesses.

The MMP-3 level inside the control participants and the mild and ICU affected person subgroups of COVID-19 is shown in Figure 2. The interquartile range is shown via boxes; the median cost is proven with the aid of traces within the containers; the fifth and 95th percentiles are shown with the aid of whiskers. Figure 2 shows that the homocysteine degrees had been drastically higher ($p<0.001$) inside the slight organization compared to the control

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institution. Moreover, the levels of MMP-3 within the ICU organization have been lower than inside the moderate organization ($p<0.05$).

Based on desk 2, the affiliation between the CT severity factors and CRP, LDH, ALT, AST, ALP, homocysteine, and MMP3 changed into tested the use of Pearson's correlation evaluation. The findings of the 2-tailed Pearson correlation check and Friedman analysis in repeated corporations confirmed a considerable association between CRP stages and AST ($r=0.308$, $p=0.031$) and MMP3 pastime ($r=-0.29$, $p=0.1/2$). There exists a noteworthy affiliation among the stages of LDH enzyme interest and ALT ($r=0.365$, $p=0.04$), AST ($r=0.465$, $p=0.009$), and the severity rating on the CT test report ($r=0.733$, $p<0.001$).

Furthermore, a significant association ($r=0.480$, $p<0.001$) was found among the MMP3 enzyme hobby and homocysteine; however, no giant correlation become seen among MMP3 interest and the score acquired from the CT scan file.

Discussion:

Patients with moderate and severe COVID-19 phases were covered in our studies. MMP-three serum stages had been plenty extra in COVID-19 patients than in a healthful assessment organization. In addition, ICU sufferers' MMP-3 levels have been decrease than the ones of the moderate group. MMP-3's position in the pathogenesis of lung contamination at some stage in irritation and the ensuing tissue regeneration is but unknown (23). However, it's also broadly recognized that endothelial harm is a end result of intense COVID-19 contamination and other issues, and that this harm might have an effect on pulmonary cells.

Furthermore, the principle resources of MMP-3 production are endothelial cells, and cytokines will enhance their secretion (24, 25). Furthermore, it's far widely known that cytokine typhoon and hyper inflammatory reactions, which result in the improvement of COVID-19-related severities, are some of the most not unusual effects in the course of COVID-19 (26). Therefore, it stands to motive that expanded cytokines may be the purpose of more MMP-3 stages in COVID-19 patients. It has formerly been suggested that in COVID-19, serum stages of MMP3 rose.

According to latest reports, sixty two COVID-19 patients in a studies exhibited better blood MMP3 ranges than the manipulate group (nine). Furthermore, it has been shown that MMP-3 tiers upward push during COVID-19, which may be linked to the deterioration of the basement membranes of lung cells (12, 27).

Not long ago, homocysteine was brought forth as a likely predictive biomarker in the continuum of COVID- 19 infection (28). In our study, we observed that homocysteine levels in COVID-19 patients were higher when compared to non-infected persons.

It is now well established that COVID-19 leads to coagulopathy, thrombosis, and CVD with it that increases the rates of severity and death (29–31). Moreover, it indicated that cardiovascular disease can be caused by homocystinuria where there is characterized high plasma homocysteine levels in an 32. On the other hand there is much controversy surrounding weak association between slightly elevated homocysteine levels and cardiovascular diseases (CVD). Refsum et al.'s (33) research involved more than 18,000 subjects and confirmed a relationship with hyperhomocysteinemia increased chances for hospital treatment. Van der Meer et al.'s study also established links between high levels of homocysteine development venous thrombosis (34). These results bring hope that parameters such as homocysteine levels— especially among those who have several diseases—could serve as a useful predictor in the course of COVID-19.

Homocysteine, according to some research, is a proper indicator regarding COVID-19 and its severity (20, 35). Moreover, several other research papers have found this factor to be a biomarker for predicting COVID-19-related cardiovascular problems (28, 36, 37). Therefore, the lower homocysteine values in ICU patients than in moderate patients in our study may indicate a higher risk of cardiovascular disease developing in these patients. Also, evidence has been produced that increased activity of MMP3 and higher levels of homocysteine are factors causing the development of heart diseases (38); our study results thus showed a correlative prevalence concerning high levels of MMP3 and elevated homocysteine.

Several research has shown that CRP could be used in determining the severity of COVID-19 and as well as prognostic indicators (39, 40). In our research, hsCRP levels showed a significant difference between the COVID-19 patient group and the control group. Additionally, a progression of COVID-19 will lead to an increase in hsCRP levels. Our results agree with other studies that have shown a very high relationship with blood hsCRP levels and severity of COVID-19 (41, 42).

Elevated hs-CRP efficiently discriminates COVID-19 suspects from other fever clinic patients with an onset similar to the first symptoms of COVID-19. This may be useful in setting up triage protocols in an epidemic area when COVID-19 and other respiratory diseases are very common and when there is a lack of medical resources available for RT-qPCR and CT scan examination. Examples may include:

In line with our findings, another research has shown a strong correlation with COVID-19 and an increase in MMP3 levels (44). Also, it proved that MMP3 levels decrease with increased periods of hospitalization (44), similarly to our

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results showing negative relationships between CRP and MMP3 and indicating higher MMP3 for ICU compared to moderate patients.

Liver function tests were another parameter checked in this study. The problem of impaired liver functioning as a possible consequence of COVID-19 disease is known (45–47). According to our results, activity levels of ALT and AST in COVID-19 patients show much higher values than in the control group. Several research papers have shown elevated LFTS at various levels during COVID-19, which have been related to how severe the infection is (48–50).

It is speculated that in patients with COVID-19, SARS-CoV-2 probably directly caused the liver damage (51). In addition, liver damage may be related to diarrhea and blood in the stool in subjects with COVID-19 (47, 52, 53). The dysregulation of the innate immune response might be a major contributory component to this COVID-19 hepatitis. In other words, hypoxia as a result of lung damage and immune-mediated inflammation (such as cytokine storm) are two potential processes implicated in the damage to the liver of patients with COVID-19 (47).

Some other studies have shown abnormal liver enzymes in COVID-19 patients, which might indicate severe disease and the likelihood of death (54-56). our findings of an adverse relationship between ALT, AST, ALP, LDH with COVID-19 agrees with these studies. More research is needed to determine the relationship between abnormal liver chemistries and COVID-19 mortality.

The enzyme lactate dehydrogenase (LDH) catalyzes the conversion of lactate to pyruvate intracellularly (52). There are five isozymes of this enzyme. LDH-3 is for pneumocytes, and LDH-5 is for the liver (53). Some other researchers have discovered that LDH can be a good indicator for bad outcomes in COVID-19 patients (54, 55). Therefore, our findings confirm some earlier investigations (56, 57) about an unfavorable relationship between levels of LDH and severity in chest CT. These findings indicate that LDH could be a useful marker for COVID-19 severity; however, more studies are needed in this regard.

In general, this research showed that the levels of many biochemical variables were much higher among COVID-19 patients, such as homocysteine MMP-3, ALT, AST, and hsCRP than it is among those in the control group. This research also indicated that the levels of these biochemistry factors among COVID-19 patients vary based on how ill they are. Therefore, it seems that more research in this area is needed.

# Conclusion

In conclusion, our study has shown that MMP-3 and homocysteine levels may be useful indicators for COVID-19 diagnosis. A better prognosis for COVID-19 patients may depend on using biochemical parameters for monitoring. However, homocysteine levels and MMP-3 could not be used in this investigation to predict the severity of the result. To establish the MMP-3 and homocysteine alterations' particular benefits or drawbacks for COVID-19 results, further research is needed.

# References

1. . S. S. Batah and A. T. Fabro, “Pulmonary Pathology of ARDS in COVID-19: A Pathological Review for Clinicians,” Respiratory Medicine, vol. 176, p. 106239, 2021.
2. . World Health Organization, “Responding to Community Spread of COVID-19: Interim Guidance, 7 March 2020,” 2020.
3. . C. Huang et al., “Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China,” The Lancet, vol. 395, no. 10223, pp. 497–506, 2020.
4. . M. Sharif-zak et al., “CCR2 and DPP9 Expression in the Peripheral Blood of COVID-19 Patients: Influences of the Disease Severity and Gender,” Immunobiology, vol. 227, no. 2, p. 152184, 2022.
5. . E. A. Wang, J. Zenilman, and L. Brinkley-Rubinstein, “Ethical Considerations for COVID-19 Vaccine Trials in Correctional Facilities,” JAMA, vol. 324, no. 11, pp. 1031–1032, 2020.
6. . N. Chams et al., “COVID-19: A Multidisciplinary Review,” Frontiers in Public Health, vol. 8, p. 383, 2020.
7. . F. Khatami et al., “A Meta-Analysis of Accuracy and Sensitivity of Chest CT and RT-PCR in COVID-19 Diagnosis,” Scientific Reports, vol. 10, no. 1, pp. 1–12, 2020.
8. . Z. L. Zhang, Y. L. Hou, D. T. Li, and F. Z. Li, “Laboratory Findings of COVID-19: A Systematic Review and Meta-Analysis,” Scandinavian Journal of Clinical and Laboratory Investigation, vol. 80, no. 6, pp. 441–447, 2020.
9. . S. Shi et al., “Matrix Metalloproteinase 3 as a Valuable Marker for Patients with COVID-19,” Journal of Medical Virology, vol. 93, no. 1, pp. 528–532, 2021.
10. . A. Lerner et al., “MMP3 Is a Reliable Marker for Disease Activity, Radiological Monitoring, Disease Outcome Predictability, and Therapeutic Response in Rheumatoid Arthritis,” Best Practice & Research Clinical Rheumatology, vol. 32, no. 4, pp. 550–562, 2018.
11. . L. Nissinen and V.-M. Kähäri, “Matrix Metalloproteinases in Inflammation,” Biochimica et Biophysica Acta (BBA) - General Subjects, vol. 1840, no. 8, pp. 2571–2580, 2014.
12. . A. Davey, D. McAuley, and C. O'Kane, “Matrix Metalloproteinases in Acute Lung Injury: Mediators of

Injury and Drivers of Repair," European Respiratory Journal, vol. 38, no. 4, pp. 959–970, 2011.
13. . R. Kadry, A. S. Newsome, and P. R. Somanath, "Pharmacological Inhibition of MMP3 as a Potential Therapeutic Option for COVID-19 Associated Acute Respiratory Distress Syndrome," Infectious Disorders Drug Targets, vol. 21, no. 6, p. e170721187996, 2021.
14. . A. Keskin et al., "Homocysteine as a Marker for Predicting Disease Severity in Patients with COVID-19," Biomarkers in Medicine, vol. 16, no. 7, pp. 559–568, 2022.
15. . J. D. Finkelstein and J. J. Martin, "Homocysteine," The International Journal of Biochemistry & Cell Biology, vol. 32, no. 4, pp. 385–389, 2000.
16. . R. Yoshitomi et al., "Plasma Homocysteine Concentration Is Associated with the Expression Level of Folate Receptor 3," Scientific Reports, vol. 10, no. 1, pp. 1–8, 2020.
17. . L. Koklesova et al., "Homocysteine Metabolism as the Target for Predictive Medical Approach, Disease Prevention, Prognosis, and Treatments Tailored to the Person," EPMA Journal, vol. 12, no. 4, pp. 477–505, 2021.
18. . F. Abike et al., "Human Papilloma Virus Persistence and Neopterin, Folate and Homocysteine Levels in Cervical Dysplasias," Archives of Gynecology and Obstetrics, vol. 284, no. 1, pp. 209–214, 2011.
19. . X. Roblin, J. Pofelski, and J.-P. Zarski, "Steatosis, Chronic Hepatitis Virus C Infection and Homocysteine," Gastroenterologie Clinique et Biologique, vol. 31, no. 4, pp. 415–420, 2007.
20. . Z. Yang et al., "Predictors for Imaging Progression on Chest CT from Coronavirus Disease 2019 (COVID-19) Patients," Aging (Albany NY), vol. 12, no. 7, pp. 6037–6050, 2020.
21. . A. Keskin, G. U. Ustun, R. Aci, and U. Duran, "Homocysteine as a Marker for Predicting Disease Severity in Patients with COVID-19," Biomarkers in Medicine, vol. 16, no. 7, pp. 559–568, 2022.
22. . Z. Fan et al., "Clinical Features of COVID-19-Related Liver Functional Abnormality," Clinical Gastroenterology and Hepatology, vol. 18, no. 7, pp. 1561–1566, 2020.
23. . K. C. Nerusu et al., "Matrix Metalloproteinase-3 (Stromelysin-1) in Acute Inflammatory Tissue Injury," Experimental and Molecular Pathology, vol. 83, no. 2, pp. 169–176, 2007.
24. . A. G. Vassiliou et al., "Endothelial Damage in Acute Respiratory Distress Syndrome," International Journal of Molecular Sciences, vol. 21, no. 22, p. 8793, 2020.
25. . R. L. Warner et al., "Matrix Metalloproteinases in Acute Inflammation: Induction of MMP-3 and MMP-9 in Fibroblasts and Epithelial Cells Following Exposure to Pro-Inflammatory Mediators In Vitro," Experimental and Molecular Pathology, vol. 76, no. 3, pp. 189–195, 2004.
26. . B. Hu, S. Huang, and L. Yin, "The Cytokine Storm and COVID-19," Journal of Medical Virology, vol. 93, no. 1, pp. 250–256, 2021.
27. . M. Gelzo et al., "Matrix Metalloproteinases (MMP) 3 and 9 as Biomarkers of Severity in COVID-19 Patients," Scientific Reports, vol. 12, no. 1, p. 1212, 2022.
28. . G. Ponti, C. Ruini, and A. Tomasi, "Homocysteine as a Potential Predictor of Cardiovascular Risk in Patients with COVID-19," Medical Hypotheses, vol. 143, p. 109859, 2020.
29. . I. Cheruiyot et al., "Arterial Thrombosis in Coronavirus Disease 2019 Patients: A Rapid Systematic Review," Annals of Vascular Surgery, vol. 70, pp. 273–281, 2021.
30. . J. E. Gomez-Mesa et al., "Thrombosis and Coagulopathy in COVID-19," Current Problems in Cardiology, vol. 46, no. 3, p. 100742, 2021.
31. . M. Bansal, "Cardiovascular Disease and COVID-19," Diabetes & Metabolic Syndrome: Clinical Research & Reviews, vol. 14, no. 3, pp. 247–250, 2020.
32. . F. Skovby, M. Gaustadnes, and S. H. Mudd, "A Revisit to the Natural History of Homocystinuria Due to Cystathionine β-Synthase Deficiency," Molecular Genetics and Metabolism, vol. 99, no. 1, pp. 1–3, 2010.
33. . H. Refsum et al., "The Hordaland Homocysteine Study: A Community-Based Study of Homocysteine, Its Determinants, and Associations with Disease," The Journal of Nutrition, vol. 134, no. 5, pp. 1121S–1128S, 2004.
34. . F. J. van der Meer, T. Koster, J. Vandenbroucke, E. Briet, and F. R. Rosendaal, "The Leiden Thrombophilia Study (LETS)," Thrombosis and Haemostasis, vol. 78, no. 07, pp. 631–635, 1997.
35. . G. Ponti, L. Roli, G. Oliva, M. Manfredini, T. Trenti, S. Kaleci, et al., "Homocysteine (Hcy) Assessment to Predict Outcomes of Hospitalized Covid-19 Patients: A Multicenter Study on 313 Covid-19 Patients," Clinical Chemistry and Laboratory Medicine (CCLM), vol. 59, no. 9, pp. e354–e357, 2021.
36. . A. Berbert, "Further Comment on Articles Pertaining to 'Homocysteine as a Potential Predictor of Cardiovascular Risk in Patients with COVID-19'," Medical Hypotheses, vol. 155, p. 110676, 2021.
37. . O. Ć. Ibrahimagić, D. Smajlović, Z. Dostović, M. Vidović, E. Tupković, and S. Kunić, "Comment on an Article: 'Homocysteine as a Potential Predictor of Cardiovascular Risk in Patients with COVID-19'," Medical Hypotheses, vol. 143, p. 110107, 2020.
38. . K. Tsarouhas, C. Tsitsimpikou, S. Apostolakis, A. Haliassos, M. Tzardi, M. Panagiotou, et al., "Homocysteine and Metalloprotease-3 and -9 in Patients with Ascending Aorta Aneurysms," Thrombosis Research, vol. 128, no. 5, pp. e95–e99, 2011.
39. . Y. Y. Luan, C. H. Yin, and Y. M. Yao, "Update Advances on C-Reactive Protein in COVID-19 and Other Viral Infections," Frontiers in Immunology, vol. 12, p. 3153, 2021.
40. . M. Kermali, R. K. Khalsa, K. Pillai, Z. Ismail, and A. Harky, "The Role of Biomarkers in Diagnosis of COVID-19—A Systematic Review," Life Sciences, vol. 254, p. 117788, 2020.
41. . W. Chen, K. I. Zheng, S. Liu, Z. Yan, C. Xu, and Z. Qiao, "Plasma CRP Level Is Positively Associated with the Severity of COVID-19," Annals of Clinical Microbiology and Antimicrobials, vol. 19, no. 1, pp. 1–7, 2020.
42. . B. R. Sahu, R. K. Kampa, A. Padhi, and A. K. Panda, "C-Reactive Protein: A Promising Biomarker for Poor Prognosis in COVID-19 Infection," Clinica Chimica Acta, vol. 509, pp. 91–94, 2020.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

43. . Q. Li, X. Ding, G. Xia, H.-G. Chen, F. Chen, Z. Geng, et al., “Eosinopenia and Elevated C-Reactive Protein Facilitate Triage of COVID-19 Patients in Fever Clinic: A Retrospective Case-Control Study,” EClinicalMedicine, vol. 23, p. 100375, 2020.
44. . M. Gelzo, S. Cacciapuoti, B. Pinchera, A. De Rosa, G. Cernera, F. Scialò, et al., “Matrix Metalloproteinases (MMP) 3 and 9 as Biomarkers of Severity in COVID-19 Patients,” Scientific Reports, vol. 12, no. 1, pp. 1–7, 2022.
45. . E. Vespa, N. Pugliese, D. Piovani, A. Capogreco, S. Danese, and A. Aghemo, “Liver Tests Abnormalities in COVID-19: Trick or Treat?” Journal of Hepatology, vol. 73, no. 5, pp. 1275–1276, 2020.
46. . Z. Y. Ding, G. X. Li, L. Chen, C. Shu, J. Song, W. Wang, et al., “Association of Liver Abnormalities with In-Hospital Mortality in Patients with COVID-19,” Journal of Hepatology, vol. 74, no. 6, pp. 1295–1302, 2021.
47. . N. Ali, “Relationship Between COVID-19 Infection and Liver Injury: A Review of Recent Data,” Frontiers in Medicine, vol. 7, p. 458, 2020.
48. . X. Y. Zhao, X. X. Xu, H. S. Yin, Q. M. Hu, T. Xiong, Y. Y. Tang, et al., “Clinical Characteristics of Patients with 2019 Coronavirus Disease in a Non-Wuhan Area of Hubei Province, China: A Retrospective Study,” BMC Infectious Diseases, vol. 20, no. 1, pp. 1–8, 2020.
49. . Q. Cai, D. Huang, P. Ou, H. Yu, Z. Zhu, Z. Xia, et al., “COVID-19 in a Designated Infectious Diseases Hospital Outside Hubei Province, China,” MedRxiv, 2020.
50. . T. Chen, D. Wu, H. Chen, W. Yan, D. Yang, G. Chen, et al., “Clinical Characteristics of 113 Deceased Patients with Coronavirus Disease 2019: Retrospective Study,” BMJ, vol. 368, 2020.
51. . I. Garrido, R. Liberal, and G. Macedo, “COVID-19 and Liver Disease—What We Know on 1st May 2020,” Alimentary Pharmacology & Therapeutics, vol. 52, no. 2, pp. 267–275, 2020.
52. . C. Yeo, S. Kaushal, and D. Yeo, “Enteric Involvement of Coronaviruses: Is Faecal–Oral Transmission of SARS-CoV-2 Possible?” The Lancet Gastroenterology & Hepatology, vol. 5, no. 4, pp. 335–337, 2020.
53. . C. Zhang, L. Shi, and F.-S. Wang, “Liver Injury in COVID-19: Management and Challenges,” The Lancet Gastroenterology & Hepatology, vol. 5, no. 5, pp. 428–430, 2020.
54. . U. Boregowda, M. M. Aloysius, A. Perisetti, M. Gajendran, P. Bansal, and H. Goyal, “Serum Activity of Liver Enzymes Is Associated with Higher Mortality in COVID-19: A Systematic Review and Meta-Analysis,” Frontiers in Medicine, vol. 7, p. 431, 2020.
55. . H. Wu, S. Liu, H. Luo, and M. Chen, “Progress in the Clinical Features and Pathogenesis of Abnormal Liver Enzymes in Coronavirus Disease 2019,” Journal of Clinical and Translational Hepatology, vol. 9, no. 2, pp. 239–245, 2021.
56. . Q. Cai, D. Huang, H. Yu, Z. Zhu, Z. Xia, Y. Su, et al., “COVID-19: Abnormal Liver Function Tests,” Journal of Hepatology, vol. 73, no. 3, pp. 566–574, 2020.

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