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Possible Relationship among Inflammation, Liver Dysfunction, and COVID- 19 Severity: A Cross-sectional Study

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ABSTRACT

Introduction: The Coronavirus disease 2019 (COVID-19) pandemic has posed significant challenges to healthcare systems worldwide. This cross-sectional study aimed to investigate the relationship between inflammatory markers, liver enzymes, lung involvement severity, and mortality in 841 COVID-19 patients admitted to Imam Reza Hospital affiliated with the Mashhad University of Medical Sciences, Mashhad, Iran.

Methods: The study included demographic information, physical and clinical symptoms, laboratory findings, computed tomography (CT) scan scores, and final outcomes.

Results: Mean age of the patients was 58.23 ± 16.44 years, and 39.2% of them were female. The most common underlying disease was hypertension (51.3%), and the most frequent symptom at presentation was shortness of breath (87.1%). It should also be mentioned that the mortality rate was 33.8%. The results showed a significant direct correlation between CRP and LDH levels (r=0.129, P<0.001) as well as between CRP levels and CT scores (r=0.322, P<0.001). There was also a significant inverse correlation between CRP levels and patients' SPO2 (r=-0.309, P<0.001). Erythrocyte sedimentation rate (ESR) levels had no significant correlation with SPO2, LDH, AST, ALT, or CT scores. Expired patients had significantly lower SPO2 levels (P<0.001) and ALT (P=0.044), while CRP (P<0.001), LDH (P<0.001), and CT scores (P<0.001) were significantly higher in them, compared to the discharged patients.

Conclusion: The findings suggest that serum CRP levels at admission can be used as a predictive factor for the severity of lung involvement and mortality in COVID-19 patients. Liver damage was also associated with worse clinical outcomes. However, ESR levels had no significant relationship with lung involvement severity and mortality, possibly due to the delay in ESR elevation in response to inflammation.

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Introduction

In December 2019, patients with pneumonia-like symptoms in Wuhan, China, most of whom had been in contact with live animal vendors, presented to healthcare facilities. On December 31st, China announced the outbreak, and by January 7th, the virus was identified as a SARS-like coronavirus. With increased travel, cases were reported in other countries, and

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screening and quarantining of individuals from China began (1). Coronavirus disease 2019 (COVID-19) is the seventh human coronavirus, with the most important transmission route being coughing, sneezing, talking in close proximity as well as contact with an infected person (2). Some individuals may be more susceptible to COVID-19 infection due to risk factors (3). Few studies have addressed risk factors associated with COVID-19 infection, including advanced age, travel to high-risk areas, and contact with a severely symptomatic individual. Compared to the young age group (20-29 years old), children and the elderly are more susceptible to COVID-19, and children are more likely to contract the disease if they have contact with a patient aged 30-39 or 50-59 years old (3, 4). Moreover, women have a higher risk of infection than men, and those in close contact with a patient have the highest risk (5-8).

The interval between symptom onset in one family member and another (known as the serial interval) is 4-8 days (9). Social contacts, contact in public transportation, and contact in healthcare facilities increase the chance of infection; moreover, contact with a patient within the first five days especially at the peak of clinical symptoms leads to the highest chance of infection (8). The incubation period is usually 14 days, but symptoms often begin within the first 4-5 days, including fever, cough, dyspnea, bilateral pneumonia, myalgia, diarrhea, anosmia, and gastrointestinal symptoms (10-14).

Laboratory findings include lymphopenia, increased aminotransferases, lactate dehydrogenase (LDH), and inflammatory markers, such as ferritin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) (10, 15). Clinical symptoms, including fever, chills, shortness of breath, and laboratory signs, such as decreased lymphocytes and increased CRP can predict the chance of hospitalization (16). Older age, male gender, autoimmune disease, bilateral pulmonary infiltrates, decreased arterial blood oxygen saturation, increased lactate dehydrogenase, CRP, and D-dimer can predict Intensive Care Unit (ICU) admission (16).

In detail, CRP is a pattern recognition molecule that increases in inflammation and activates the immune system (17, 18). High CRP levels have been reported in COVID-19 and can assist in triage, diagnosis, and prognosis (19, 20). Although COVID-19 primarily affects the respiratory system, evidence of liver damage exists, resulting from systemic inflammation and endotheliopathy (21, 22). The most common pattern of liver damage is increased liver aminotransferases (23). Some individuals may be more susceptible to COVID-19 infection due to risk factors (3). Initially, radiography is normal in 18% of cases (24). The most common CT scan findings include ground-glass opacities, crazy paving, consolidation, bronchiectasis, vascular dilatation, and sub-pleural bands (25).

Some studies have also shown that male gender, middle age, underlying disease, oxygen deficiency, renal dysfunction, microvascular disorders, coagulation activation, association of coagulation activity markers, and microvascular dysfunction with renal dysfunction are factors that increase the risk of mortality and treatment failure in the ICU (26). Although respiratory failure is the most common cause of death in COVID-19 patients, cardiac damage following cytokine storm and secondary infection have also been suggested as fatal factors in this disease (27). Despite numerous studies on this disease, many unknowns still exist, and further research is essential. One issue that does not seem to have been thoroughly investigated is the relationship among inflammatory markers and liver enzymes, lung involvement severity, and mortality in these patients; therefore, the present study aimed to determine the relationship among inflammatory markers and liver enzymes, lung involvement severity, and mortality in COVID-19 patients.

Materials and Method

The present cross-sectional study included individuals who were admitted to Imam Reza Hospital affiliated with the Mashhad University of Medical Sciences, Mashhad, Iran and were identified as COVID-19 patients based on reverse transcription polymerase chain reaction (RT-PCR). However, in the early stages of the outbreak, due to the unavailability of PCR testing, the diagnosis of COVID-19 was made using clinical findings and CT scans, but later, when PCR testing became available, all patients underwent PCR testing. Sampling was performed by census strategy; for this purpose, the records of patients admitted to the hospital from February 2020 to November 2020 were studied and reviewed, and the necessary information was extracted. It should be noted that patients with a known history of liver disease, such as viral or autoimmune hepatitis or cirrhosis, were excluded from the present study.

Outcomes

The information recorded and evaluated in this project included the following:

1.Demographic information checklist, including gender, age, and underlying diseases (such as diabetes, hypertension, and cardiovascular

diseases).
2.Physical and clinical symptoms of patients, including fever, cough, fatigue, headache, hemoptysis, diarrhea, vomiting, nausea, shortness of breath, and oxygen saturation (SPO2).
3.Laboratory findings, including ESR, CRP, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH).
4.CT score
5.Final outcome (discharge or death).

The CT scans of patients were reported by two expert radiologists. The CT score of patients was calculated as follows: the extent of involvement of each of the 5 lung lobes was determined with a score of 0 to 5, and then the scores of the 5 lobes were summed. Accordingly, the lowest and highest scores were 0 and 25, respectively. The higher the score of the patient, the greater the lung involvement. In each lobe, a score of 0 to 5 was determined as follows (28):

- 0: No involvement.
- 1: Less than 5% involvement.
- 2: 5-25% involvement.
- 3: 25-50% involvement.
- 4: 50-75% involvement.
- 5: 75% involvement and above.

Statistical Analysis

Qualitative descriptive data were reported using frequency tables, and quantitative descriptive data were reported using central and dispersion indices. Independent t-tests were used to compare quantitative data between two groups, and chi-square or Fisher's exact tests were used to compare qualitative data. The samples of this study were selected using the census sampling method, and there was no need to calculate the sample size. Data analysis was performed in SPSS software (version 26). A P-value less than 0.05 was considered as the significance level.

Ethical Considerations

The present research project was proposed to and approved by the Organizational Ethics Committee of Mashhad University of Medical Sciences on February 1 (code: IR.MUMS.REC.1399.598). In all stages of the study, the ethical principles of the Helsinki Declaration were followed.

Results

During the study period, a total of 841 patients with COVID-19 were hospitalized, 329 (39.2%) of whom were female. Mean age of the patients included in the study was 58.23 ± 16.44 years. Demographic characteristics of the patients are examined in Table 1. It should be mentioned that 280 (33.8%) participants in this study died.

The underlying diseases of the patients included in the study are shown in Figure 1.

Table 1. Demographic characteristics of patients included in the study

Variable		Frequency (%)/Mean±SD
Gender	Male	511 (60.8%)
	Female	329 (39.2%)
Age (years)		58.23±16.44
Smoking		261 (31.1%)
Addiction		101 (12%)

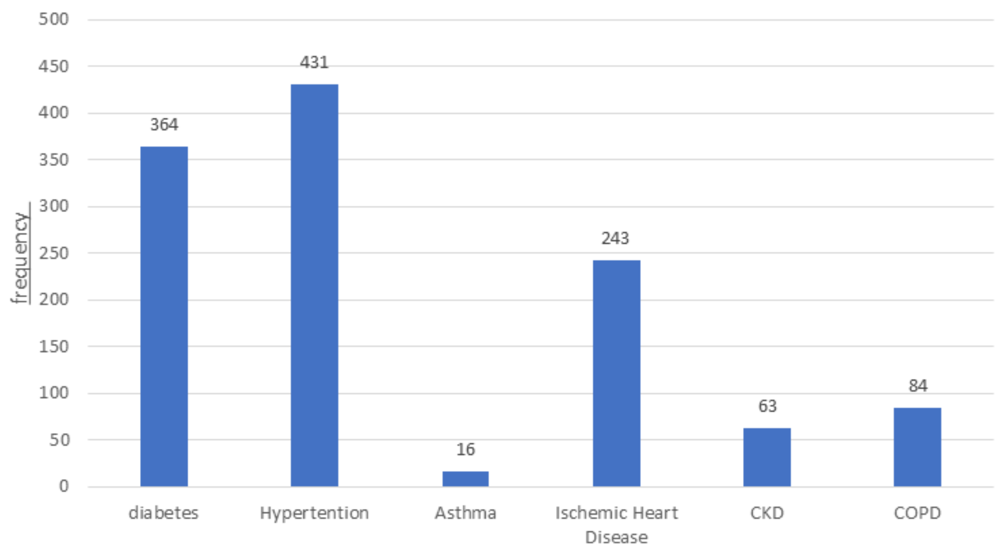

Figure 1. Underlying diseases of study participants

As can be seen, the most common underlying disease was hypertension, which was present in 431 patients (51.3%).

Figure 2 illustrates the signs and symptoms of patients at the time of referral. As can be seen, the most common symptom patients presented with was shortness of breath, which was reported in 732 patients (87.1%).

Table 2 tabulates the laboratory findings, SPO2 levels, and CT scores in patients included in the study. As can be seen, the mean SPO2 of patients was 79.59±8.94, and the mean CT score in patients was 14.11±5.32.

SPO2: oxygen saturation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate transaminase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CT: computed tomography

Table 3 summarizes the correlation between the levels of inflammatory markers (including ESR and CRP) with liver enzymes, CT scores, and SPO2 of patients. As can be seen, there was a significant and direct correlation between CRP levels and LDH levels (r=0.129, P<0.001) as well as between CRP levels and CT scores (r=0.322, P<0.001). There was also a significant and inverse correlation between CRP levels and SPO2 of patients (r=-0.309, P<0.001).

*Pearson correlation test, SPO2: oxygen saturation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate transaminase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CT: computed tomography

In Table 4, the relationship between laboratory findings, SPO2, and CT scores with patient outcomes was examined. As can be seen, in expired patients, SPO2 levels (P<0.001) and ALT (P=0.044) were significantly lower, compared to those in discharged patients. Moreover, CRP (P<0.001), LDH (P<0.001), and CT score (P<0.001) were significantly higher in expired patients in comparison with those in discharged patients.

*Independent t-test, SPO2: oxygen saturation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, AST: aspartate transaminase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CT: computed tomography

Table 2. Laboratory findings, SPO2 levels, and CT scores of patients included in the study

Characteristic	Mean±SD	Min	Max
SPO2 (%)	79.59±8.94	45	98
ESR (mm/h)	50.89±30.83	1	196
CRP (mg/dl)	118.26±84.81	0.1	554
AST (u/L)	64.30±160.04	4	2458
ALT (u/L)	65.88±207.11	5	3764
ALP (u/L)	221.03±131.52	21	1712
LDH (u/L)	843.06±754.09	4.20	10980
CT score	14.11±5.32	0	24

Discussion

In the present study, 841 patients with COVID-19 who were hospitalized at Imam Reza Hospital in Mashhad over a 9-month period were examined to assess the relationship between inflammatory markers and liver enzymes, severity of lung involvement, and mortality. This study investigated the relationship between two well-known inflammatory markers, ESR and CRP, with the desired factors. The findings indicated that ESR levels of patients at admission had no significant correlation with SPO2, LDH, AST, ALT, and CT scores. The only laboratory marker that

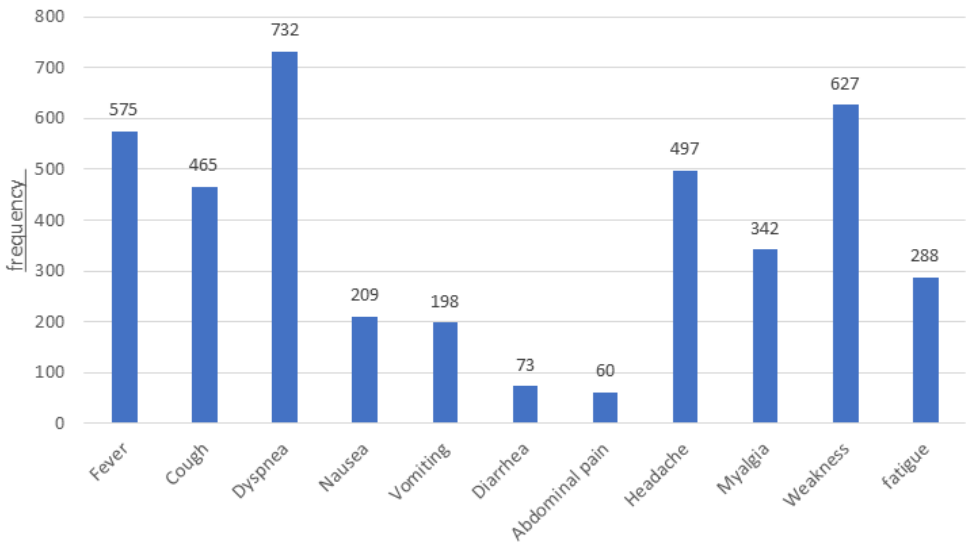

Figure 2. Signs and symptoms of patients at the time of referral

Table 3. Correlation of inflammatory marker levels (including ESR and CRP) with liver enzymes, CT score, and SPO2 of patients

Characteristic		ESR	CRP
(%) SPO2	r	0.027	-0.309
	P value	0.447	0.001>
AST (u/L)	r	-0.029	0.029
	P value	0.414	0.403
ALT (u/L)	r	-0.068	-0.026
	P value	0.057	0.469
ALP (u/L)	r	0.081	0.053
	P value	0.025	0.139
LDH (u/L)	r	-0.040	0.129
	P value	0.268	0.001>
CT score	r	0.041	0.322
	P value	0.254	0.001>

had a significant correlation with ESR was ALP, but the correlation was weak. Furthermore, the ESR level at admission did not differ significantly between patients who eventually died and those who recovered.

In the present study, serum CRP of patients at admission had a significant and inverse correlation with SPO2, meaning that patients with lower SPO2 at admission had higher CRP levels. The liver enzymes of patients in the present study had no significant correlation with CRP. However, a significant and direct correlation was observed between CT scores of patients and CRP, indicating that patients with higher CRP at the beginning of admission also had more severe lung involvement on CT scans. Finally, the relationship between CRP levels and the final outcomes of patients was also significant, and CRP at admission was significantly higher in expired patients, compared to discharged patients. The mortality rate of patients in this study was higher than the average reported mortality rate in patients hospitalized due to COVID-19. The reason for this is that Imam Reza Hospital, where the present study was conducted, serves as a referral hospital at the city and provincial levels; therefore, many critically ill patients are transferred to this hospital from other areas. This issue has led to an increase in mortality statistics in this study.

In a study conducted by Yazdi et al. in 2021, the results showed that CT scores of patients had no significant relationship with their ESR levels. However, the mean CT score in patients with CRP > 90 was significantly higher than that in other patients (29). This was similar to the findings of the present study, where there was no significant correlation between ESR levels of patients at admission and their CT scores. Therefore, it seems that the severity of lung involvement in patients is not significantly related to their ESR.

Table 4. Relationship between laboratory findings, SPO2, and CT score with patient outcomes

Characteristic	Expired	Discharged	P value
	Mean±SD		
SPO2 (%)	71.59±7.60	83.61±6.56	<0.001
ESR (mm/h)	52.06±31.11	50.57±30.61	0.520
CRP (mg/dl)	131.94±88.40	100.44±77.26	<0.001
AST (u/L)	62.10±111.63	65.91±181.24	0.748
ALT (u/L)	50.85±60.25	73.89±252.19	0.044
ALP (u/L)	218.83±109.42	222.42±142.42	0.715
LDH (u/L)	1011.73±756.85	758.98±744.82	<0.001
CT score	17.46±4.28	12.49±5	<0.001

The probable reason for this is that it takes a few days for ESR to increase from the onset of inflammation in the body, while CRP usually increases rapidly. Therefore, it can be expected that if ESR levels of patients are re-checked during the course of the disease, their relationship with the extent of lung involvement can be observed.

In another study conducted by Beydoğan et al. in Turkey on 974 patients with COVID-19, the results showed a significant correlation between CRP levels of patients and the severity of lung involvement on CT scans. Additionally, CRP at admission was significantly higher in patients requiring ICU, compared to those who did not require ICU, and there was a significant correlation between CRP and CT scores of patients (30), which confirmed the results of the present study. Based on these findings, it can be concluded that in patients with COVID-19, CRP can be used as an inexpensive test to predict the severity of lung involvement and the likelihood of a patient requiring intensive care.

In a study conducted by Krishnan et al. in 2022 on 3,380 patients with COVID-19 in a hospital in the United States, the results showed that the most common abnormality among liver function tests was observed in ALT, with 70% of patients having elevated ALT. Furthermore, the analyses showed that higher levels of AST, ALT, and ALP were associated with greater disease severity. In addition, higher levels of AST and total bilirubin were associated with the need of patients for mechanical ventilation (31). This is inconsistent with the results obtained in the present study, as in this study, the mean ALT level was higher in discharged patients, compared to expired patients. The exact reason for this cannot be determined. It should be noted that the sample size of the present study was lower than that of the study performed by Krishnan, and this may have led to a reduction in the accuracy of the results obtained.

In another study conducted by Zhang et al. in 2021 on 440 patients with COVID-19, the results indicated that the severity of COVID-19 was an independent predictor of increased liver damage, and higher levels of AST and total bilirubin at admission were associated with a higher risk of patient mortality (32). In a study carried out by Shao et al. in 2021 on 1,520 patients with COVID-19 who were hospitalized in Wuhan, China, the results showed that 17.9% of patients had developed liver damage. Furthermore, the analyses showed that patients who developed liver damage during hospitalization had higher mortality rates and ICU admissions, compared to patients without liver damage or liver damage at admission, which is consistent with the results obtained in the present study (33).

In a study conducted by Fu et al. in 2021 on 482 patients with COVID-19 who were hospitalized in Wuhan, China, the results showed that about one-third of patients (29.5%) had abnormal liver enzyme levels at admission, with most cases showing mild elevations in ALT, AST, and total bilirubin. Additionally, patients with abnormal liver enzymes had a higher percentage of severe cases and underlying diseases, compared to other patients. Shortness of breath, chest pain, increased CRP, increased white blood cells, and hemoglobin were identified as independent factors associated with elevated liver enzymes. Moreover, patients with elevated AST or total bilirubin had higher rates of severe cases, mortality, acute respiratory distress syndrome, and cardiac injury (34).

In a study performed by Zhang et al. in 2020 on 218 patients with COVID-19 at a central hospital in Wuhan, China, the results showed that 36.2% of patients had liver damage at admission, with most cases showing mild elevations in AST and ALT. Furthermore, patients with liver damage were older (with a mean age of 12 years), had a higher frequency of males (68.4% vs. 28.8%), and had more underlying diseases, compared to the group with normal liver function. In addition, fever and shortness of breath were significantly more common in the group with liver damage, indicating that male gender, high D-dimer levels, and high neutrophil percentages are important predictors of liver damage in patients with COVID-19, which is consistent with the results obtained in the present study, as in this study, male gender was also associated with an increased risk of liver damage (35).

Despite the strong evidence that suggests liver enzymes increase in COVID-19 patients, some others are contrary. A systematic review and meta-analysis study by Ebrahimi et al. reported no significant abnormality in liver function laboratory findings (e.g. AST, ALT, LDH, and bilirubin) (36). Kumar et al stated that AST and ALP are better indicators of COVID-19 induced liver injury than ALT and total bilirubin. In their study, mean ALT and total bilirubin levels were statistically non-significant (P>0.05) to present the COVID-19 severity. Abdul-Husseein et al. revealed that the risk of liver function abnormalities was not significantly different among all age groups and infected males had a higher incidence of liver dysfunction with significant differences in serum AST and ALT levels, compared to females; however, there was no significant differences between males and females in terms of their ALP and total bilirubin levels (37). Despite the fact that these contrary findings can be against our hypothesis, strong similar results can make us still stay on the hypothesis.

Furthermore, it should be stated that COVID-19 is not the only cause of liver enzyme elevation. If fact, several conditions can potnentially increase the serum levels of liver enzayms which can be categorized as follows: liver disease (hepatitis A, B, and C, cirrhosis, liver cancer [hepatocellular carcinoma], autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis), pancreatitis (acute or chronic pancreatitis and pancreatic cancer), muscle damage (rhabdomyolysis [muscle breakdown], musculoskeletal disorders [e.g., polymyositis, dermatomyositis], trauma, or injury), kidney disease (chronic kidney disease, acute kidney injury, and nephrotic syndrome), heart disease (myocardial infarction [heart attack], cardiomyopathy, and congestive heart failure), medications (certain antibiotics [e.g., tetracycline, erythromycin], anti-inflammatory drugs [e.g., ibuprofen, naproxen], statins, aspirin, certain antidepressants [e.g., tricyclic antidepressants]), nutritional deficiencies (vitamin D deficiency, B12 deficiency, and iron deficiency), infections (sepsis, bacterial infections [e.g., endocarditis, osteomyelitis], fungal infections [e.g., histoplasmosis, coccidioidomycosis], parasitic infections [e.g., toxoplasmosis, cryptosporidiosis]), genetic disorders (inherited liver disorders [e.g., Wilson's disease, alpha-1 antitrypsin deficiency], and mitochondrial disorders), other causes (shock, hypothyroidism, hyperthyroidism, pregnancy, and cancer [metastatic disease]). Therefore, it could be stated that liver enzyme elevation can occur in COVID-19, but it is not the only reason (38-41).

Despite the fact that the present study investigated a large number of COVID-19 patients, it was limited to the assessed factors. Additionally, we focused on the COVID-19 in-patients and their laboratory findings. It is suggested that further factors be evaluated and the studied population be compared with the normal population in future studies.

Conclusion

Overall, the results of the present study showed that in hospitalized patients with COVID-19, serum CRP levels at admission were significantly associated with the severity of lung involvement and patient mortality. In fact, the higher the CRP levels in patients at the time of hospitalization, the higher the likelihood of severe lung involvement and mortality, which is consistent with the results of similar studies. Therefore, CRP can be used as an inexpensive and readily available factor in predicting the outcomes of COVID-19. Moreover, ESR levels of patients had no significant relationship with the severity of lung involvement and mortality, which is probably due to the delay in ESR elevation in response to inflammation. Regarding the relationship between inflammatory markers and liver enzyme levels, the results of the present study showed that ESR and CRP had no significant correlation with ALT, AST, and ALP, which is consistent with some studies and inconsistent with others. These inconsistencies may be due to differences in sample size, population characteristics, and inclusion criteria in the studies. However, similar to many other studies, the present study also found that liver damage was associated with greater disease severity and mortality in patients with COVID-19. Overall, the present study showed that serum CRP levels in COVID-19 patients at the time of hospitalization can be used as a predictive factor for the severity of lung involvement and mortality. Liver damage is also associated with worse clinical outcomes in patients.

Conflict of interest

The authors declare no conflicts of interest.

References

1. Morillo F, Bordons M, Gómez I. Interdisciplinarity in science: A tentative typology of disciplines and research areas. Journal of the American Society for Information Science and technology. 2003;54(13):1237-49.
2. Cirrincione L, Plescia F, Ledda C, Rapisarda V, Martorana D, Moldovan RE, et al. COVID-19 pandemic: Prevention and protection measures to be adopted at the workplace. Sustainability. 2020;12(9):3603.
3. Srivastava S, Zhao X, Manay A, Chen Q. Effective ventilation and air disinfection system for reducing coronavirus disease 2019 (COVID-19) infection risk in office buildings. Sustainable Cities and Society. 2021;75:103408.
4. AkbariRad M, Allahyari A, Ravanshad S, Mahali SN, Ebrahimzadeh F, Mozdourian M, et al. Clinical characteristics of 200 COVID-19 patients in Mashhad, Iran, February and March 2020. Journal of Family Medicine and Primary Care. 2022;11(5):1949-56.
5. Liu T, Liang W, Zhong H, He J, Chen Z, He G, et al. Risk factors associated with COVID-19 infection: a retrospective cohort study based on contacts tracing. Emerging microbes & infections. 2020;9(1):1546-53.
6. Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. The Lancet infectious diseases. 2020;20(8):911-9.
7. Sabir DK, Khwarahm NR, Ali SM, Abdoul HJ, Mahmood KI, Kodzius R. Children protection against COVID-19 at the pandemic outbreak. Journal of Immunological Sciences. 2020;4(2).
8. Cheng H-Y, Jian S-W, Liu D-P, Ng T-C, Huang W-T, Lin H-H. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. JAMA internal medicine. 2020;180(9):1156-63.
9. Park M, Cook AR, Lim JT, Sun Y, Dickens BL. A systematic review of COVID-19 epidemiology based on current evidence. Journal of clinical medicine. 2020;9(4):967.
10. McIntosh K, Hirsch MS, Bloom A. Coronavirus disease 2019 (COVID-19). UpToDate Hirsch MS Bloom. 2020;5(1):873.
11. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New England journal of medicine. 2020;382(13):1199-207.
12. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20.
13. McMichael TM, Currie DW, Clark S, Pogosjans S, Kay M, Schwartz NG, et al. Epidemiology of COVID-19 in a long-term care facility in King County, Washington. New England Journal of Medicine. 2020;382(21):2005-11.
14. Cheung KS, Hung IF, Chan PP, Lung K, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from a Hong Kong cohort: systematic review and meta-analysis. Gastroenterology. 2020;159(1):81-95.
15. Esmaealzadeh D, Ghalibaf AM, Rad MS, Rezaee R, Razavi BM, Hosseinzadeh H. Pharmacological effects of Safranal: An updated review. Iranian Journal of Basic Medical Sciences. 2023;26(10):1131.
16. Sisó-Almirall A, Kostov B, Mas-Heredia M, Vilanova-Rotllan S, Sequeira-Aymar E, Sans-Corrales M, et al. Prognostic factors in Spanish COVID-19 patients: A case series from Barcelona. PloS one. 2020;15(8):e0237960.
17. Osmand AP, Friedenson B, Gewurz H, Painter RH, Hofmann T, Shelton E. Characterization of C-reactive protein and the complement subcomponent C1t as homologous proteins displaying cyclic pentameric symmetry (pentraxins). Proceedings of the National Academy of Sciences. 1977;74(2):739-43.
18. Pathak A, Agrawal A. Evolution of C-reactive protein. Frontiers in immunology. 2019;10:452737.
19. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal transduction and targeted therapy. 2020;5(1):33.
20. Beidollahkhani S, Fayedeh F, Shoja A, Hassan Nejad E, Hoseinpour M, Fazlpour F, et al. d-dimer as a biomarker for COVID-19-associated pulmonary thromboembolism: a narrative review from molecular pathways to the imaging findings. The Egyptian Journal of Bronchology. 2023;17(1):44.
21. McConnell MJ, Kawaguchi N, Kondo R, Sonzogni A, Licini L, Valle C, et al. Liver injury in COVID-19 and IL-6 trans-signaling-induced endotheliopathy. Journal of hepatology. 2021;75(3):647-58.

22. Saeedi N, Gohari NSF, Ghalibaf AAM, Dehghan A, Owlia MB. COVID-19 infection: a possible induction factor for development of autoimmune diseases? Immunologic Research. 2023;71(4):547-53.
23. Moon AM, Barritt AS. Elevated liver enzymes in patients with COVID-19: look, but not too hard. Springer; 2021. p. 1767-9.
24. Rodrigues J, Hare S, Edey A, Devaraj A, Jacob J, Johnstone A, et al. An update on COVID-19 for the radiologist-A British society of Thoracic Imaging statement. Clinical radiology. 2020;75(5):323-5.
25. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for radiologists on COVID-19: an update—radiology scientific expert panel. Radiological Society of North America; 2020. p. E113-E4.
26. Eid MM, Al-Kaisy M, Regeia WAL, Khan HJ. The prognostic accuracy of neutrophil-lymphocyte ratio in COVID-19 patients. Frontiers in Emergency Medicine. 2021;5(1):e8-e.
27. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care medicine. 2020;46(5):846-8.
28. Sharma S, Aggarwal A, Sharma RK, Patras E, Singhal A. Correlation of chest CT severity score with clinical parameters in COVID-19 pulmonary disease in a tertiary care hospital in Delhi during the pandemic period. Egyptian Journal of Radiology and Nuclear Medicine. 2022;53(1):166.
29. Yazdi NA, Ghadery AH, SeyedAlinaghi S, Jafari F, Jafari S, Hasannezad M, et al. Predictors of the chest CT score in COVID-19 patients: a cross-sectional study. Virology journal. 2021;18:1-8.
30. Beydoğan E, Yürük Atasoy P. The relationship between CRP at admission and thorax CT findings in patients diagnosed with COVID-19. International Journal of Clinical Practice. 2021;75(12):e14962.
31. Krishnan A, Prichett L, Tao X, Alqahtani SA, Hamilton JP, Mezey E, et al. Abnormal liver chemistries as a predictor of COVID-19 severity and clinical outcomes in hospitalized patients. World journal of gastroenterology. 2022;28(5):570.
32. Zhang S-S, Dong L, Wang G-M, Tian Y, Ye X-F, Zhao Y, et al. Progressive liver injury and increased mortality risk in COVID-19 patients: a retrospective cohort study in China. World journal of gastroenterology. 2021;27(9):835.
33. Shao J, Liang Y, Li Y, Ding R, Zhu M, You W, et al. Implications of liver injury in risk-stratification and management of patients with COVID-19. Hepatology international. 2021;15:202-12.
34. Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, et al. Clinical features of patients infected with coronavirus disease 2019 with elevated liver biochemistries: a multicenter, retrospective study. Hepatology. 2021;73(4):1509-20.
35. Zhang H, Liao Y-S, Gong J, Liu J, Zhang H. Clinical characteristics and risk factors for liver injury in COVID-19 patients in Wuhan. World journal of gastroenterology. 2020;26(31):4694.
36. Ebrahimi M, Malehi AS, Rahim F. COVID-19 Patients: A Systematic Review and Meta-Analysis of Laboratory Findings, Comorbidities, and Clinical Outcomes Comparing Medical Staff versus the General Population. Osong Public Health Res Perspect. 2020;11(5):269-79.
37. Karim Abdul-Husseein H, Akram Al- Akkam K, Karim Abdul-Husseein M, Abdul-Amir Makki Al-Hindy H. Liver Function Abnormalities in COVID-19 Patients and their Association with Age and Sex: a Cross-Sectional Study. Archives of Razi Institute. 2023;78(1):453-8.
38. Lee TH, Kim WR, Poterucha JJ. Evaluation of elevated liver enzymes. Clinics in liver disease. 2012;16(2):183-98.
39. Oh RC, Hustead TR, Ali SM, Pantsari MW. Mildly elevated liver transaminase levels: causes and evaluation. American family physician. 2017;96(11):709-15.
40. Malakouti M, Kataria A, Ali SK, Schenker S. Elevated liver enzymes in asymptomatic patients–what should I do? Journal of clinical and translational hepatology. 2017;5(4):394.
41. Shakeri M, Ghalibaf AAM, Ghodsi-Moghadam M, Ghorbannezhad G, Ahmadi SP, Mashahiri S, et al. Clinical manifestations and associated mortality factors of COVID-19: a large population-based study in the northeast of Iran during 2020-2021. Epidemiology and Health System Journal. 2023;10(1):31-8.