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Relationship Between Cardiac and Liver Markers with In-hospital Mortality in COVID-19 Patients

Hedieh Moradi Tabriz[1], Maryam Dargahi[1], Mahnaz Montazeri[2] and Elham Nazar[1]*

1. Department of Pathology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Internal Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

*** Corresponding author**

Elham Nazar, MD
Department of Pathology, Tehran University of Medical Sciences, Tehran, Iran
Tel: +98 21 6634 8580
Email: elhamnazar@yahoo.com

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Abstract

Background: COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections has turn into a pandemic and has extended all over the world. Since the virus has the potential ability to severely impair heart and liver, analyzing the biochemical parameters is a suitable approach for clinicians to assess the outcome.

Methods: This study was conducted along with 614 recognized COVID-19 patients. All samples were from Emergency department of Sina Hospital in Tehran, Iran, from February to May, 2020.

Results: A total of 614 COVID-19 patients with mean age of 57.8 years (16-94 years) consisting of 385 (62.7%) male and 229 (37.2%) female were studied. Patients with COVID-19 had no significant difference between cardiac and liver parameters on the presentation and discharge time (p-value≥0.05). Patients with COVID-19 had significant correlation in Lactate dehydrogenase (LDH), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), and Total Bilirubin with recovery and mortality outcome (p-value≤0.05). Also, high sensitivity cardiac Troponin-I, LDH, AST, and ALT in patients with COVID-19 were significantly associated with high in-hospital mortality (p-value<0.05).

Conclusion: Several laboratory parameters may ease the evaluation of COVID-19 in-hospital mortality. Cardiac and liver parameters are critical in assisting COVID-19 cases.

Keywords: COVID-19, Cardiac, Liver, Mortality

Introduction

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is a new pathogen responsible for the new extensively known corona virus disease 2019 (COVID-19). The basis of managing is supportive care and no well-known treatment is available. Mortality statistics for the situation show a discrepancy, with a reported overall mortality rate among 1.4 and 2.3% (1). World Health Organization (WHO) reported more than 162 million established cases and over 3.3 million deaths across the world, up to 17 May 2021 (2). This number to be 3.5, about 56 million people in Iran will be infected (3). The contributing function of paraclinical including laboratory data is far beyond etiological recognition and it is now approximately obvious that these laboratory findings are efficiently concerned in epidemiologic surveillance, prediction of prognosis, patient follow-up, including COVID-19 (4). Since the virus has potential ability of severely damaging some vital organs such as heart, liver, and kidneys, analyzing the laboratory parameter is a proper way for clinicians to assess these organs' functions (5). Some laboratory data may aid the consideration of COVID-19 severity to select mild from severe COVID-19 disease (6). The role of COVID-19 in initiating pro-inflammatory condition has been well-known (7). Therefore, paraclinical evaluations include laboratory data play a main role in early diagnosis and treatment observation of COVID-19 (8). Infections, hospitalizations, and deaths are different among countries, prompting the question in relation to which patients are at higher risk and why (9). Also, most of these studies pay attention to the symptoms and radiologic findings, with only inadequate concentration on laboratory data, which could be useful in the diagnosis and determination of severity of COVID-19. Only data from observational studies is accessible. Therefore, it is required to summarize the laboratory findings in each study, the consequences of which can support the diagnosis and treatment of the disease in each country (10). There is restricted data obtainable describing the paraclinical findings of Iranian patients. Thus, we assessed cardiac and liver parameters on presentation and discharge time in our country to reveal the probable diversity with other countries and relationship with poor outcome and the need to intensive care. In this study, the laboratory markers were also summarized that might be useful in indicating in-hospital mortality in COVID-19 patients.

Materials and Methods

Study population and setting

This cross-sectional study was conducted on 614 recognized COVID-19 patients over 18 years of age, who referred to Emergency Department in Sina Hospital in Tehran in Iran affiliated to Tehran University of Medical Sciences and a government-designated hospital for COVID-19 treatment. From February to May 2020, patients with respiratory signs, fever, and weakness who suspected to COVID-19 infection (11) with positive COVID-19 result by Polymerase Chain Reaction (PCR) were included (12). Also, according to the Iranian national committee of COVID-19, we enrolled the highly suspicious patients with a compatible chest computed tomography (CT) scan findings with COVID-19 (13). Patients with incomplete laboratory data due to transfer to other hospitals were excluded.

Data collection

Data including age, sex, and duration of hospitalization was gathered from the electronic medical records. Blood samples were collected from each participant and creatine kinase isoenzyme (CPK), creatine kinase isoenzyme-MB (CK-MB), and high sensitivity cardiac troponin-I (cTnI) in the serum were measured using standard assay kit and Siemens ADVIA Centaur XP automatic chemiluminescence immunoassay analyzer for all the patients according to the manufacturer's instructions. Furthermore, liver enzymes such as Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP) as well as Bilirubin (Total and Direct), Albumin and lactate dehydrogenase (LDH) in the serum were assessed using standard assay kit by Mindray BS-200 automated biochemistry analyzer. Laboratory data were recorded within 24 hours of admission and time of discharge or death.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (ethical code: IR.TUMS.SINAHOSPITAL.1399.009).

Statistical analysis

All analyses were done by using the Statistical

Package of Social Science Software (SPSS version 20; IBM Company) and p-value level of 0.05 or below was described as statistically significant. Categorical variables were presented in percentage (%) while continuous data were reported as mean ± SD. Dependent upon the nature of variable, Chi-square, Fisher's exact tests, Mann–Whitney *U* Test, or independent *t* test were used as proper, to evaluate the patients' laboratory data on presentation and discharge time. The accuracy of diverse laboratory parameters in predicting cases with COVID-19 positive patients was assessed by Area under the ROC curve (AUC).

Results

From 647 hospitalized patients, 33 (5.1%) patients with incomplete date were excluded. Among 614 patients, the mean age was 57.8 years (18-64years) which consists of 385 (62.7%) male and 229 (37.3%) female. Average period of hospitalization was 5.06 (0-55) days (Table 1).

Table 2 compares the cardiac and liver parameters of patients with COVID-19 on presentation and discharge time. Patients with COVID-19 had no significant difference between cardiac and liver parameters on presentation and discharge time (p-value≥0.05). Table 3 compares the cardiac and liver parameters of COVID-19 patients with recovery and mortality outcome. Patients with COVID-19 had significant correlation in LDH, AST, ALT and Total Bilirubin recovery and mortality outcome (p-value≤0.05).

The ROCs were calculated to assess the associations between cardiac and liver parameters and mortality. cTnI, LDH, AST, and ALT in patients with COVID-19 had significant correlation with mortality (p-value<0.05). Cardiac and liver parameters of patients with COVID-19 had significant correlation with mortality (Table 4).

Table 1. Demographic data with recovery and in-hospital mortality outcome

		Recovery	In-hospital mortality
Age (year)		55.68 ± 15.68	69.74 ± 13.31
44 years ≥		+	4 (4.2%)
45-64 years		216 (35.1%)	30 (48.8%)
65-74 years		102 (16.6%)	20 (32.5%)
years ≥ 75		60 (9.7%)	41 (66.7%)
Sex	Male	323 (83.8%)	62 (16.2%)
	Female	162 (70.7%)	67 (29.3%)
Duration of hospitalization (day)		4.43 ± 3.96	5.46 ± 8.06

Laboratory parameters.

Table 2. Comparison of the cardiac and liver parameters of COVID-19 patients at presentation and discharge time

Cardiac and liver parameters	Presentation time	Discharge time	p-value
cTnI (*ng/mL*)	850.71±3290.50	203.29±461.56	0.409
LDH (*U/L*)	717.00±342.17	452.50±117.24	0.273
AST (*U/L*)	56.40±23.18	57.76±50.27	0.863
ALT (*U/L*)	50.14±41.25	47.83±43.70	0.703
ALP (*IU/L*)	231.48±168.66	220.26±142.19	0.398
Serum Albumin (*g/dL*)	3.10±0.49	2.64±0.70	0.093
Total Bilirubin (*mg/dL*)	1.53±1.53	1.32±1.39	0.510
Direct Bilirubin (*mg/dL*)	0.90±1.85	0.62±0.70	0.461

Table 3. Comparison of the cardiac and liver parameters of COVID-19 patients with recovery and mortality outcome

Cardiac and liver parameters	Recovery	In-hospital mortality	p-value
LDH (*U/L*)	578.13±226.83	820.35±561.03	<0.001
AST (*U/L*)	54.90±40.17	104.52±227.08	<0.001
ALT (*U/L*)	40.68±24.14	70.17±119.93	0.002
ALP (*IU/L*)	206.31±168.79	233.00±145.24	0.120
Serum albumin (*g/dL*)	3.45±0.66	3.09±0.82	0.110
Total bilirubin (*mg/dL*)	1.41±1.20	0.69±0.38	0.009
Direct bilirubin (*mg/dL*)	0.66±1.26	0.43±0.31	0.463

Table 4. Cardiac and liver parameters of patients with COVID-19 had significant correlation with mortality

Cardiac and liver parameters	AUC	Cut of point	Sensitivity	Specificity	p-value
cTnI (*ng/mL*)	0.754	>8.05	77.4%	63.6%	<0.001
LDH (*U/L*)	0.678	>631.5	67.3%	68.5%	<0.001
AST (*U/L*)	0.701	>54.5	70.5%	65.4%	<0.001
ALT (*U/L*)	0.623	>33.5	72.6%	47.7%	0.02

Discussion

Four months after the first cluster of cases were reported in Wuhan, China, coronavirus disease 2019 (COVID-19) persisted as a major cause of morbidity and mortality worldwide (14). Several laboratory parameters may facilitate the assessment of disease severity (6). Due to the rapid spread of the COVID-19 pandemic, affected countries have taken a heterogeneous and evolving approach to diagnosis of infection in patients and continue to have different strategies, and every country needs to evaluate the COVID-19 patients' findings (15).

A series of recently published studies have reported the epidemiological and clinical characteristics of patients with COVID-19 disease, but data regarding the laboratory characteristics of infected individuals are limited (16). In the Zhang *et al* study, of the 4,663 patients included, the most prevalent laboratory finding was increased C-reactive protein, followed by decreased albumin, increased erythrocyte sedimentation rate, and increased LDH. Also, meta-analysis of seven studies with 1905 patients showed that increased CRP and LDH were significantly associated with severity. These results demonstrated that more attention is warranted when interpreting laboratory findings in patients with COVID-19 (10). Also, there were significant increases in creatinine, CPK, LDH, and potassium levels between ICU-admitted and non-ICU patients (17). Therefore, one of predominant laboratory findings was LDH elevation (18).

COVID-19 is causing considerable morbidity and mortality worldwide. Serious respiratory complications aside, the heart is also frequently involved. The mechanisms and the extent of the myocardial injury in COVID-19 survivors remain unclear (19). Since the first data analyses in China, elevated cardiac troponin has been noted in a substantial proportion of patients, implicating myocardial injury as a possible pathogenic mechanism contributing to severe illness and mortality. Accordingly, high troponin levels are associated with increased mortality in patients with COVID-19 (20). In a recent study summarizing clinical course of patients with COVID-19, detectable cTnI was observed in most patients, and cTnI was significantly elevated in more than half of the patients

died (21). Risk with elevated cTnI is independent of baseline cardiovascular disease (22). These findings were correlated with our data and observed in our population.

Furthermore, serum LDH was validated for its potential usefulness as markers for evaluating clinical severity and monitoring treatment response in COVID-19 pneumonia. It was demonstrated that increase or decrease of LDH was indicative of disease progress or improvement (23). Our data was similar and we demonstrated increased cTnI and LDH and significant relationship with mortality. Thus, careful monitoring of the cardiac enzyme profiles is of great importance in reducing the complications and mortality in patients with COVID-19 (24). Evidence from the Chinese cohort suggests that patients demonstrate high C-Reactive Protein (CRP) and less common elevations in liver enzymes ALT and AST (25) which was similar to our findings. Pazoki *et al* reported a considerable percentage of admitted patients who presented with cardiac, liver, and kidney impairment (26). Furthermore, in a systematic analysis of 11 articles, Lippi and Plebani have documented laboratory abnormalities reported in cases of COVID-19. Patients may also present with decreased albumin, or increases in LDH, total bilirubin, and also cTnI (27). Patients with abnormal liver tests were at higher risk of progressing to severe disease. Also, we showed liver enzymes related to mortality. The detrimental effects on liver injury were mainly associated with certain medications used during hospitalization, which should be monitored and evaluated frequently (28). Bilirubin levels have been found altered in patients with Covid-19, but the dynamics of such alteration are not clear, especially in relation to the severity of the disease (29).

Some studies demonstrated that serum albumin analysis may be useful to identify patients at higher risk of death in COVID-19 patients (30). A low albumin level can potentially lead to early recognition of severe disease and assist clinicians in making informed decision for their patients (31). Chen *et al* found that LDH had significantly increased in most patients, while albumin had decreased, but ALT and AST showed no significant changes (32). In agreement, Huang *et al* introduced decreased albumin along with increased LDH, ALT, and total bilirubin levels as appropriate biomarkers with the ability to discriminate between severe and non-severe groups (33). Between these markers, we revealed the correlation among AST, ALT, total bilirubin, LDH, and cTnI with mortality. But, relationship between Albumin level and mortality was not observed in our population which may be due to the disparity in race.

Our study had some limitations. The study population was small and included only patients from Sina Hospital, one of the main hospitals in Iran. There may be a selection bias when identifying factors that differ between patients even though the results were adjusted for known confounders, including age, sex, race, and comorbidities. Also, some patients presented elevated biomarker data in some laboratory measures, and they were not excluded from the analysis due to the small sample size and because those numbers were physiological and not due to the technical errors. Further studies including more cases and ancillary tests are necessary to elucidate the mechanism of disease progression and fatal outcome.

Conclusion

The present study suggests that liver and cardiac measurement could predict outcome and in-hospital mortality associated with COVID-19. Thus, it is necessary to continue these measures. There is an increased urgent need to detect new biomarkers in order to identify cases of COVID-19 that will evolve unfavorably. These biomarkers must be easy to measure and accessible to most hospitals such as liver and cardiac markers that manage COVID-19 cases and determine in-hospital mortality.

Ethics approval

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (ethicalcode:IR.TUMS.SINAHOSPITAL.1399.009). Participants were informed about the components of the study and its objectives upon entering the study. The current research was conducted in accordance with the Declaration of Helsinki.

Data availability

The data of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. All

authors were equally involved in preparing the manuscript (Conceptualization and design of the study, searching for articles, writing the final draft, *etc.*).

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Conflict of Interest

None declared.

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References

1. Chapman AR, Bularga A, Mills NL. High-sensitivity cardiac troponin can be an ally in the fight against COVID-19. Circulation 2020 Jun 2;141(22):1733-5.

2. Noori M, Nejadghaderi SA, Sullman MJ, Carson-Chahhoud K, Kolahi AA, Safiri S. Epidemiology, prognosis and management of potassium disorders in Covid-19. Rev Med Virol 2022 Jan;32(1):e2262.

3. Alimohamadi Y, Holakouie-Naieni K, Sepandi M, Taghdir M. Effect of social distancing on COVID-19 incidence and mortality in Iran since February 20 to May 13, 2020: an interrupted time series analysis. Risk Manag Healthc Policy 2020 Sep 23;13:1695-1700.

4. Pourbagheri-Sigaroodi A, Bashash D, Fateh F, Abolghasemi H. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta 2020 Nov;510:475-482.

5. Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet 2020 Mar 21;395(10228):e52.

6. Thirumalaisamy P, Meyer C. Mild versus severe COVID-19: Laborytorma markers. Int J Infect Dis 2020;95:304-7.

7. Ashrafi F, Zali A, Ommi D, Salari M, Fatemi A, Arab-Ahmadi M, et al. COVID-19-related strokes in adults below 55 years of age: a case series. Neurol Sci 2020 Aug;41(8):1985-9.

8. Vakili S, Savardashtaki A, Jamalnia S, Tabrizi R, Nematollahi MH, Jafarinia M, et al. Laboratory findings of COVID-19 infection are conflicting in different age groups and pregnant women: a literature review. Arch Med Res 2020 Oct;51(7):603-7.

9. Mackey K, Ayers CK, Kondo KK, Saha S, Advani SM, Young S, et al. Racial and ethnic disparities in COVID-19–related infections, hospitalizations, and deaths: a systematic review. Ann Intern Med 2021 Mar;174(3):362-73.

10. Zhang ZL, Hou YL, Li DT, Li FZ. Laboratory findings of COVID-19: a systematic review and meta-analysis. Scand J Clin Lab Invest 2020 Oct;80(6):441-7.

11. Xie Y, Wang Z, Liao H, Marley G, Wu D, Tang W. Epidemiologic, cinical, and laboratory findings of the COVID-19 in the current pandemic. Res Sq 2020 May 28;rs.3.rs-28367.

12. Saleh SK, Oraii A, Soleimani A, Hadadi A, Shajari Z, Montazeri M, et al. The association between cardiac injury and outcomes in hospitalized patients with COVID-19. Intern Emerg Med 2020 Nov;15(8):1415-24.

13. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus disease 2019 (COVID-19): a systematic

review of imaging findings in 919 patients. AJR Am J Roentgenol 2020 Jul;215(1):87-93.

14. Somani SS, Richter F, Fuster V, De Freitas JK, Naik N, Sigel K, et al. Characterization of patients who return to hospital following discharge from hospitalization for COVID-19. J Gen Intern Med 2020 Oct;35(10):2838-44.

15. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. Int J Lab Hematol 2020 Jun;42 Suppl 1(Suppl 1):11-18.

16. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. Travel Med Infect Dis 2020 Mar-Apr;34:101623.

17. Fahimzad A, Sedighi I, Pak N, Khalili M, Farahmand M, Shokrollahi MR, et al. A comparative analysis of clinical characteristics and laboratory findings of COVID-19 between intensive care unit and non-intensive care unit pediatric patients: a multicenter, retrospective, observational study from Iranian network for research in viral diseases (INRVD). Front Emerg Med. 2021;5(4):e41.

18. Andreas Kronbichler M, Daniela Kresse M, Sojung Yoon B, Keum Hwa Lee M. Asymptomatic patients as a source of COVID-19 infections: a systematic review and meta-analysis. Int J Infect Dis 2020 Sep;98:180-6.

19. Shchendrygina A, Nagel E, Puntmann VO, Valbuena-Lopez S. COVID-19 myocarditis and prospective heart failure burden. Expert Rev Cardiovasc Ther 2021 Jan;19(1):5-14.

20. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with coronavirus disease 2019 (COVID-19): possible mechanisms. J Card Fail 2020 Jun;26(6):470-5.

21. Januzzi JL. Troponin and BNP use in COVID-19. Cardiol Mag 2020 Mar 18;18.

22. Majure DT, Gruberg L, Saba SG, Kvasnovsky C, Hirsch JS, Jauhar R, et al. Usefulness of elevated troponin to predict death in patients with COVID-19 and myocardial injury. Am J Cardiol 2021 Jan 1;138:100-6.

23. Wu MY, Yao L, Wang Y, Zhu XY, Wang XF, Tang PJ, et al. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia. Respir Res2020 Jul 6;21(1):171.

24. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol 2020 Jul;92(7):819-23.

25. Wang T, Tang C, Chen R, Ruan H, Liang W, Guan W, et al. Clinical features of coronavirus disease 2019 patients with mechanical ventilation: a nationwide study in China. Crit Care Med 2020 Sep;48(9):e809-e812.

26. Pazoki M, Payandemehr P, Montazeri M, Kafan S, Sheikhvatan M, Sotoodehnia M, et al. Risk Stratification for In-Hospital Mortality in Adult Patients with COVID-19. J Iran Med Counc 2021 Dec 1;4(4):322-34.

27. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020 Jun 25;58(7):1131-4.

28. Pawlotsky JM. COVID-19 and the liver-related deaths to come. Nat Rev Gastroenterol Hepatol 2020 Sep;17(9):523-5.

29. Fernandez LS, Anis K, Fox JV. Severe hyperbilirubinemia associated with novel coronavirus infection. Chest 2020 Oct 1;158(4):A2574.

30. Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, et al. Is albumin predictor of mortality in COVID-19? Antioxid Redox Signal 2021 Jul 10;35(2):139-42.

31. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care 2020 May 26;24(1):255.

32. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020 Feb 15;395(10223):507-13.

33. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020 Feb 15;395(10223):497-506.