Journal of Babol University of Medical Sciences JBUMS
e-ISSN: 2251-7170 p-ISSN: 1561-4107

Assessment of Liver Enzymes in Hospitalized Patients with COVID-19 and Its Relationship with Length of Stay, Recovery and Death

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Article Type

Research Paper

Received: Jan 12th 2021
Revised: Apr 3th 2021
Accepted: Jul 11th 2021

ABSTRACT

Background and Objective: In the epidemic of COVID-19, intensive care units usually bear a heavy burden due to overcrowding of patients who need hospitalization, which can be due to liver involvement in these patients. This study was conducted to assess the relationship between liver enzymes in COVID-19 patients and the need for hospitalization in the intensive care unit, as well as to investigate its relationship with the length of stay in the intensive care unit.

Methods: In this analytical cross-sectional study, 622 hospitalized patients with COVID-19 who referred to Firoozgar Hospital were investigated in terms of length of stay, recovery or death and its relationship with abnormal liver enzymes.

Findings: The mean level of AST and ALT in people hospitalized in ICU was 49 (95% CI: 43.4-54.6) and 29.2 (95% CI: 24.1-34.2), respectively, and it was 42.5 (95% CI: 36.7-48.3) and 31.2 (95% CI: 25.8-36.6), respectively, in the general ward. The mean level of AST and ALT in patients hospitalized for less than 7 days was 49.4 (95% CI: 43.9-54.8) and 27 (95% CI: 21.6-32.3), respectively, and in patients hospitalized for more than 7 days was 41.6 (95% CI: 35.6-47.5) and 32.2 (95% CI: 37.3-27.1), respectively. None of the abnormal data was significant based on hospital department and length of stay.

Conclusion: The results of this study did not show any significant relationship between the need for admission to ICU and the abnormal levels of liver enzymes. Furthermore, no relationship was found between the length of stay and the severity of liver involvement based on the assessment of abnormal liver enzymes.

Keywords: *COVID-19, Liver, Infectious Disease.*

Cite this article: Safarnezhad Tameshkel F, Motamed N, Zamani F, Kimiyaee HS, Khoonsari MR, Faraji AH, et al. Assessment of Liver Enzymes in Hospitalized Patients with COVID-19 and Its Relationship with Length of Stay, Recovery and Death. *Journal of Babol University of Medical Sciences*. 2022; 24(1): 205-14.

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Introduction

COVID-19 is one of the viral infections of the corona virus family. Members of the family of coronaviruses, such as the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), cause severe disease in humans, and they also originate from Asian countries (1). Recently, a novel coronavirus with the scientific name SARS-CoV-2 originated from Wuhan, China and has rapidly become a global pandemic and a major public health threat worldwide (2). The disease caused by this viral agent was called COVID-19. The mortality rate of COVID-19 has been estimated at 5.2%, which was 9.6% in the SARS epidemic and 34.4% in the MERS epidemic (3). Estimates of death rate in COVID-19 vary between countries according to the efficiency of health care systems. In addition, the fact that many patients with mild signs and symptoms are not considered should also be noted (4). The high transmission rate of this disease, which was estimated in previous studies based on the relative proliferation index, has been determined (5).

Many patients with COVID-19 have other diseases such as high blood pressure, diabetes and cerebrovascular diseases (6). A large-scale study conducted in China showed the death of more than half of patients with COVID-19 who were clinically in acute conditions (7, 8). In case of COVID-19 disease, intensive care units (ICU) of hospitals often bear a heavy burden due to overcrowding of patients who need hospitalization (8-10). The high workload in the intensive care unit can not only lead to higher mortality in patients, but may also lead to mental health problems among the staff in these units (11, 12). According to previous studies, the increase in liver enzymes in severe cases of COVID-19 is higher than normal and mild cases (12-14). In this regard, considering the epidemic of COVID-19 disease and the lack of information about the type of pathogenesis and the possible difference in the pathogenesis of the disease in different regions, the present study was conducted to assess the relationship between liver enzymes in COVID-19 patients and the need for hospitalization in the intensive care unit and the length of stay at the hospital.

Methods

After being approved by the ethics committee of Iran University of Medical Sciences with ethics code IR.IUMS.FMD.REC.1399.408, this analytical cross-sectional study was conducted on 622 confirmed patients with COVID-19 referred to Firoozgar Hospital in Tehran in April 2020. Medical records and results of paraclinical tests of hospitalized people were collected based on checklists. Positive COVID-19 test was considered positive using real-time RT-PCR based on throat or nose samples of patients. Relevant data were collected and summarized by a team of doctors and researchers. The collected data were entered into a computer system and data re-checking processes were carried out.

People who referred to Firoozgar Hospital in April 2020 and were diagnosed with COVID-19 based on PCR test or lung CT scan, and their underlying disease records and laboratory symptoms forms were completed and their laboratory information checklist was completely filled out were included in the study, and patients who did not have enough information in their medical profile were excluded from the study.

The need for ICU admission and length of hospital stay were considered as outcomes. ICU admission criteria were based on physician diagnosis (for any reason). The assessed variables were collected which included laboratory parameters such as liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], bilirubin, white blood cell count [WBC] and platelet count), demographic information (gender and age), clinical data (temperature, systolic blood pressure, type of treatment during hospitalization, respiratory rate, pulse rate), underlying disease history (diabetes, diseases related to coronary arteries, immune system diseases, medical history of chronic obstructive pulmonary disease, asthma, etc.). In this study, according to the method and laboratory kit used to measure the serum level of ALT and AST, the level above 40 (IU/dl) was considered abnormal for these two variables.

Statistical analysis: Descriptive statistics were presented using mean (±standard deviation), median (interquartile range), percentage and frequency along with 95% confidence interval (CI). Normal continuous data of two groups were compared using independent t test and non-normal data were compared using Mann-Whitney test. Chi-square test was used to determine the relationship between nominal qualitative variables. Analysis was done by STATA 12 (STATA Corp., Texas, USA) and SPSS version 16 (SPSS Inc., Chicago) software, and $p<0.05$ was considered significant.

Results

A total of 622 confirmed cases of COVID-19 were included in this study. The mean age of the patients in this study was 59.88±16.04 years and 59.3% (369 people) of the participants were male. 323 patients (51.9%) were admitted to ICU (Table 1). According to the analysis, it can be seen that there was a significant relationship between this grouping (patients hospitalized in the general ward and ICU) and variables such as breathing rate, pulse rate, history of asthma or chronic obstructive pulmonary disease, treatment with corticosteroids, intravenous immunoglobulin (IVIG), N-acetyl Cysteine (NAC), Kaletra and Sofosbuvir (Table 1).

Based on the findings of the present study, there was a significant difference in pulse rate, AST level, use of IVIG, NAC, steroid, ribavirin, hydroxychloroquine and sofosbuvir drugs between patients hospitalized for less than 7 days and 7 days or more. Table 2 separately shows the primary characteristics and potential predictors of prolonged hospitalization in patients with hospitalization of less than 7 days and 7 days or more.

Based on statistical tests, there was no significant difference between the groups regarding the high level of AST and ALT. Table 3 shows the relationship between the serum level of aspartate transaminase (AST) and serum alanine transaminase (ALT) and the rate of hospitalization in ICU and other hospital departments, as well as the length of stay.

The results of the present study did not show a significant relationship between the level of serum concentration of liver enzymes and the admission of patients to ICU and the length of stay. Table 4 shows the level of AST and ALT serum concentrations above the normal range (greater than or equal to 29 in men and 22 in women based on IU/dl) based on admission to the ICU or admission to the general ward and based on the length of stay.

Table 1. Clinical and laboratory characteristics of the studied patients on admission (n=622)

Variable	Total amount Mean±SD or number(%)	ICU Mean±SD or number(%)	General ward Mean±SD or number(%)	p-value
age (years)	59.8±16.04	60.59±15.84	59.8±16.04	0.258*
Systolic blood pressure (mmHg)	105.06±40.11	106.68±37.47	103.27±42.8	0.425*
body temperature (°C)	36.95±3.52	36.75±4.26	37.17±2.44	0.166*
median breathing rate (IQR)	18(4)	18(4)	18(4)	0.026**
median pulse rate (IQR)	80(13)	80(14)	80(10)	0.042**
Median aspartate transaminase value (IQR) (IU/dl)	39(29)	38(30)	37(28)	0.249**
Median alanine transaminase (IQR) (IU/dl)	30(28.5)	29(26)	32(24)	0.112**
Median alkaline phosphatase (IQR) (mg/dl)	166(90)	165(87)	176(94.5)	0.467**
Median total bilirubin (IQR) (mg/dl)	0.7(0.4)	0.7(0.4)	0.7(0.4)	0.333**
Mean white blood cell count (IQR) (per ml)	5900(3900)	6100(4000)	5800(3900)	0.080**
Mean platelet count (IQR) (per ml)	176000(93000)	182000(92000)	174000(91500)	0.418**
Percentage of history of diabetes (95% CI)	28.4 (24.4-32.4)	28.9 (23.5-34.3)	27.9 (22-33.9)	0.744***
Percentage of history of coronary artery disease (95% CI)	18.6 (15.2-22)	18.5 (13.8-23.2)	19.4 (14.1-24.6)	0.747***
Percentage of history of immune system deficiency (95% CI)	6.6 (4.4-8.8)	7.8 (4.6-11)	5.4 (2.4-8.4)	0.089***
Percentage of history of smoking (95% CI)	9.1 (6.6-11.7)	10.4 (6.7-14)	7.6 (4.1-11.2)	0.014***
Percentage of history of asthma or COPD (95% CI)	5.2 (3.2-7.2)	7 (4-10.1)	3.2 (0.8-5.5)	0.008***
Corticosteroid treatment percentage (95% CI)	21.5 (17.7-25.1)	30 (24.5-35.5)	11.3 (7.1-15.5)	<0.001***
Percentage of treatment with IVIG (95% CI)	7.2 (4.9-9.5)	10.4 (67.7-14)	3.6 (1.1-6.1)	0.003***
Percentage of treatment with NAC (95% CI)	16.2 (12.9-19.4)	21.1 (162.2-26)	9.9 (5.9-13.9)	0.002***
Percentage of treatment with Kaletra (95% CI)	49.9 (45.5-54.3)	46.7 (40.7-52.7)	53.6 (47-60.2)	0.024***
Percentage of treatment with hydroxychloroquine (95% CI)	86 (82.9-89.1)	87 (83-91.1)	84.7 (80-895.5)	0.832***
Percentage of treatment with ribavirin (95% CI)	21.9 (18.2-25.6)	20.4 (15.5-25.2)	23.9 (18.2-29.5)	0.118***
Percentage of treatment with sofosbuvir (95% CI)	52.1 (47.7-56.6)	58.5 (52.6-64.4)	44.6 (38-51.2)	<0.001***

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CI: confidence interval, COPD: Chronic obstructive pulmonary disease, NAC: N-Acetyl Cysteine, IQR interquartile range, IVIG: Intravenous immunoglobulin.

***Independent t-test was used. **Mann-Whitney test was used. ***Chi-square test was used.**

Table 2. Basic characteristics and potential predictors in patients hospitalized for less than 7 days and 7 days or more (n=622)

Variable	≥7 days Mean±SD or number(%)	<7 days Mean±SD or number(%)	p-value
age (years)	60.69±15.22	58.68±16.8	0.078*
Systolic blood pressure (mmHg)	104.07±41.17	106.06±38.97	0.645*
body temperature (°C)	37.11(3.74)	36.75±3.23	0.233**
median breathing rate (IQR)	18(4)	18(5)	0.212**
median pulse rate (IQR)	80(11)	80(14)	0.032**
Median aspartate transaminase value (IQR) (IU/dl)	39(29.25)	36(29)	0.045**
Median alanine transaminase (IQR) (IU/dl)	31.5(27.5)	29(24)	0.538**
Median alkaline phosphatase (IQR) (mg/dl)	165.50(90.50)	169(93)	0.415**
Median total bilirubin (IQR) (mg/dl)	0.7(0.4)	0.65(0.4)	0.616**
Mean white blood cell count (IQR) (per ml)	6100(4000)	5800(3800)	0.933**
Mean platelet count (IQR) (per ml)	174500(84750)	180000(96750)	0.348**
Percentage of history of diabetes (95% CI)	30 (24.4-35.5)	26.8 (20.9-32.6)	0.312***
Percentage of history of coronary artery disease (95% CI)	19.1 (14.4-2.8)	18.7 (13.6-23.9)	0.174***
Percentage of history of immune system deficiency (95% CI)	8.2 (4.9-11.5)	4.9 (2.1-7.7)	0.409***
Percentage of history of smoking (95% CI)	9.4 (5.8-12.9)	8.5 (4.8-12.2)	0.711***
Percentage of history of asthma or COPD (95% CI)	5.2 (2.5-7.9)	5.4 (2.2-8.3)	0.509***
Corticosteroid treatment percentage (95% CI)	28.8 (23.4-34.3)	12.9 (8.5-17.4)	< 0.001***
Percentage of treatment with IVIG (95% CI)	12.4 (8.4-16.3)	1.3 (0.0-2.6)	< 0.001***
Percentage of treatment with NAC (95% CI)	20.06 (15.7-25.5)	10.7 (6.6-14.8)	0.002***
Percentage of treatment with Kaletra (95% CI)	59.2 (53.2-65.1)	38.8 (32.4-45.3)	< 0.001***
Percentage of treatment with hydroxychloroquine (95% CI)	88 (84.1-91.9)	83.9 (79.1-88.8)	0.214***
Percentage of treatment with ribavirin (95% CI)	28.5 (23-33.9)	14.3 (9.7-18.9)	<0.001***
Percentage of treatment with sofosbuvir (95% CI)	59.2 (53.2-65.1)	44.2 (37.6-50.8)	0.001***
ALT: alanine aminotransferase, AST: aspartate aminotransferase, CI: confidence interval, COPD: Chronic obstructive pulmonary disease, NAC: N-Acetyl Cysteine, IQR interquartile range, IVIG: Intravenous immunoglobulin.			

***Independent t-test was used. **Mann-Whitney test was used. ***Chi-square test was used.**

Table 3. Serum level of AST and ALT higher than normal (≥40 IU/dl) based on hospitalization in ICU or general ward and based on length of stay

Based on the place of hospitalization				Based on the length of stay		
Liver enzymes (IU/dl)	**Admission to the ward (IU/dl) (95% CI)**	**Admission to the ICU (IU/dl) (95% CI)**	**p-value***	**≥7 days (IU/dl) (95% CI)**	**<7 days (IU/dl) (95% CI)**	**p-value***
Aspartate transaminase						
<40	57.5 (51.8-63.3)	51 (45.5-56.5)	0.107	50.6 (45.2-56.1)	58.4 (52.5-64.4)	0.058
≥40	42.5 (36-48.3)	49 (43.4-54.6)		49.4 (43.9-54.8)	41.6 (35.6-47.5)	
Alanine transaminase						
<40	68.8 (63.4-74.2)	70.8 (65.8-75.9)	0.583	67.8 (62.7-72.9)	73 (67.7-78.4)	0.165
≥40	31.2 (25.8-36.6)	29.2 (24.1-34.2)		322.2 (27.1-37.3)	27 (21.6-32.3)	

***Chi-square test was used.**

Table 4. Level of AST and ALT serum concentrations above the normal range (greater than or equal to 29 in men and 22 in women based on IU/dl) based on admission to the ICU or admission to the general ward and based on the length of stay

Based on the place of hospitalization				Based on the length of stay		
Liver enzymes (IU/dl)	**Admission to the ward (IU/dl) (95% CI)**	**Admission to the ICU (IU/dl) (95% CI)**	**p-value**	**≥7 days (IU/dl) (95% CI)**	**<7 days (IU/dl) (95% CI)**	**p-value**
Aspartate transaminase						
<22 in women and <29 in men	22.8 (17.9-27.7)	21.8 (17.2-26.4)	0.767	22.8 (17.8-27.9)	22.1 (17.6-26.6)	0.825
≥22 in women and ≥29 in men	77.2 (72.3-82.1)	78.2 (73.6-82.8)		77.2 (72.1-82.2)	77.9 (73.4-82.4)	
Alanine transaminase						
<22 in women and <29 in men	39.3 (33.6-45.0)	43.3 (37.7-48.8)	0.325	43.4 (37.5-49.4)	40.2 (34.8-45.5)	0.423
≥22 in women and ≥29 in men	60.7 (55.0-66.4)	56.7 (51.2-62.2)		56.6 (50.6-62.5)	59.8 (54.5-65.2)	

In order to eliminate potentially confounding variables such as age, gender, heart rate and breathing rate, and type of treatment, logistic regression was conducted, in which admission to ICU (hospitalization/non-hospitalization in ICU) as the outcome variable and the level of liver enzymes as the predictor variable entered into the model. The results showed that liver enzymes had no significant relationship with the outcome of the study (hospitalization in ICU). (OR= 1.003, 95% CI= 0.999-1.013 for ALT with p= 0.471 and OR= 0.996, 95% CI=0.988-1.003 for AST with p= 0.262).

Moreover, logistic regression was conducted on the outcome of hospital stay (less than 7 days/more than or equal to 7 days), in which the predictive variables of ALT and AST entered into the model and the confounding variables of age, gender, heart rate and breathing rate, and type of treatment were included in the model. The results showed that the level of ALT and AST had no significant relationship with the length of stay. (OR= 0.999, 95% CI= 0.995-1.003 for ALT with p= 0.580 and OR= 1.001, 95% CI= 0.999-1.003 for AST with p= 0.614).

Discussion

In this study, variables such as breathing rate, pulse rate, history of asthma or COPD, treatment with corticosteroids, IVIG, NAC, Kaletra and sofosbuvir showed a significant relationship between patients hospitalized in the ward and ICU. Furthermore, pulse rate, AST level, use of IVIG, NAC, steroid, ribavirin, hydroxychloroquine, and sofosbuvir drugs were significantly different between patients treated for less than 7 days and 7 days or more. However, no significant relationship was observed between the need for hospitalization in ICU and the abnormal level of liver enzymes according to the findings of this study. Moreover, no relationship was found between the length of stay in the hospital and liver complications based on the increase in liver enzymes above the normal range (≥40 IU/dl). Contrary to the results of this study, in a study conducted by Lee et al., the increase in liver enzymes in patients hospitalized in the intensive care unit was reported to be much higher than in other units (15). Liver damage is a common finding in COVID-19. The increase in AST and ALT was 21.6% and 18.2%, respectively. According to another study, 45.9% and 30.2% of patients respectively had AST and ALT levels higher than 40 units (abnormal) (12).

However, this increase in most cases of COVID-19 is mild and transient, and it can return to normal levels without any therapeutic intervention (16). In a study among 1950 patients with COVID-19, abnormally elevated levels of AST and LDH were found, which showed a significant relationship with hospitalization in the ICU, and they concluded that the measurement of these markers can be a guide for a better understanding of the stage of the disease (17). Another study considered abnormally elevated levels of liver enzymes to be a predictor of the severity of COVID-19 disease (18). According to the results of the present study, the abnormal levels of liver enzymes did not show a significant difference in relation to hospitalization in ICU, which could be due to the small sample size of our study.

Immune-related responses, especially cytokine storm, can cause liver damage in some patients with various forms of COVID-19 (19, 20). Of course, the fact that the use of corticosteroids can prevent some inflammatory reactions such as cytokine storms should also be considered. According to the assessments in the present study, the use of corticosteroids in people who were admitted to the intensive care unit was nearly three times more than the patients who were admitted to the normal wards.

On the other hand, sometimes, iatrogenic liver involvement by positive end-expiratory pressure (PEEP) applied by a ventilator in mechanically ventilated patients can cause elevated liver enzymes in people with COVID-19 (21). Due to the fact that mechanical ventilation is mainly performed in the intensive care unit, and the purpose of this study was to investigate the relationship between the increase in liver enzymes and the need for hospitalization in the intensive care unit, so this issue had little effect on the results of this study. Follow-up studies with a longer period of time and examining more risk factors can be helpful in this area. In addition, the effect of drug toxicity is not particularly associated with the results of this study because drug administration and dietary modification occurred mainly after the initial measurement of liver enzymes. The present study shows that treatment with steroids, IVIG and N-acetylcysteine is significantly more common in people requiring ICU admission than in other people. This result is obvious because the conditions of those admitted to the intensive care unit are usually critical and they do not respond to the usual treatments. As a result, other treatment methods are physiologically effective in acute respiratory diseases, are used in other similar diseases, and are also used experimentally in patients with COVID-19.

According to our study data, a higher percentage of people requiring hospitalization had asthma or chronic obstructive pulmonary disease (COPD). This result can be expected, because people with chronic lung disease are more vulnerable to respiratory infections and are likely to have more critical conditions than other patients and need to be admitted to the intensive care unit. In the present study, we found no significant association between the need for ICU admission and liver enzyme levels. There was no significant relationship between the length of stay and liver complications based on liver enzymes. In the present study, based on the desired time period, all referring patients who had the necessary criteria to enter the study were selected. Of course, this is a cross-sectional study and due to the complications of the disease, there is no claim about its validity in the whole society. However, it has been tried to use a large sample size for the analyses to provide better information to the society and specialists. Also, due to the lack of sufficient space, some patients unwittingly received their treatments at home or hired personal nurses before complete recovery, and it cannot be accurately stated that the discharge from the hospital was the complete recovery of the patients. Considering the lack of information on the pathogenesis of this emerging disease at the beginning of its pandemic and epidemic in Iran, this study has been carried out with the efforts of researchers to identify some weak points in this field. Although our current information is more about understanding the behavior of this virus, there are still many unclear points and research in any area can provide us with new information.

According to the results of the present study, despite the fact that there was a significant relationship between the breathing rate, pulse rate, history of asthma or chronic obstructive pulmonary disease, treatment with corticosteroids, IVIG, NAC, Kaletra, and sofosbuvir between patients hospitalized in the ward and ICU on admission and there was also a significant difference between patients hospitalized for less than 7 days and 7 days or more in pulse rate, AST level, use of IVIG, NAC, steroid, ribavirin, hydroxychloroquine and sofosbuvir drugs, but no significant relationship was found in abnormal levels of liver enzymes (AST and ALT) in patients admitted to the general ward or ICU and length of stay (less than 7 days and 7 days or more). Based on these interpretations, it seems that the abnormal level of liver enzymes is not involved in the hospitalization process of patients, the length of stay and admission to ICU. Prospective studies are suggested to investigate the outcomes of treatment in these people.

Acknowledgment

We hereby thank the efforts of all the staff of Firoozgar Teaching Hospital in Tehran.

References

1.Morens DM, Daszak P, Taubenberger JK. Escaping Pandora's box - another novel coronavirus. N Engl J Med. 2020;382(14):1293-5.

2.Azimi M, Hasheminasab FS, Mokaberinejad R, Qaraaty M, Mojahedi M. A Review of Prevention and Adjuvant Therapy in Acute Respiratory Syndrome Caused by COVID-19 from the Perspective of Persian Medicine. J Babol Univ Med Sci. 2021;23(1):177-88. [In Persian]

3.Taherizadeh M, Tabibzadeh A, Panahi M, Safarnezhad Tameshkel F, Golahdooz M, Karbalaie Niya MH. An Introduction to SARS Coronavirus 2; Comparative Analysis with MERS and SARS Coronaviruses: A Brief Review. Iran J Public Health. 2020;49(Suppl 1):30-7.

4.Golahdooz M, Tabibzadeh A, Taherizadeh M, Laali A, Khoonsari M, Ajdarkosh H, et al. A review on Coronavirus 2019 Disease (COVID-19, SARS-CoV-2): Control and Prevention. Razi J Med Sci. 2020;27(5):98-107. [In Persian]

5.Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med. 2020;46(5):837-40.

6.Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. Lancet Infect Dis. 2020;20(7):773.

7.Qiu H, Tong Z, Ma P, Hu M, Peng Z, Wu W, et al. Intensive care during the coronavirus epidemic. Intensive Care Med. 2020;46(4):576-8.

8.Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med. 2020;8(5):506-17.

9.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;395(10223):507-13.

10.Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.

11.Remuzzi A, Remuzzi G. COVID-19 and Italy: what next?. Lancet. 2020;395(10231):1225-8.

12.Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020;18(7):1561-6.

13.Laali A, Tabibzadeh A, Esghaei M, Yousefi P, Soltani S, Ajdarkosh H, et al. Liver function tests profile in COVID-19 patients at the admission time: A systematic review of literature and conducted researches. Adv Biomed Res. 2020;9:74.

14.Khoonsari M, Zamani F, Karbalaie Niya MH, Hemmasi G, Ajdarkosh H, Faraji A, et al. Liver Enzymes and Inpatient Deaths in COVID-19 Hospitalized Patients. Hepat Mon. 2020;20(11):e109076.

15.Lee A, Cheung YSL, Joynt GM, Leung CCH, Wong W-T, Gomersall CD. Are high nurse workload/staffing ratios associated with decreased survival in critically ill patients? A cohort study. Ann Intensive Care. 2017;7(1):46.

16.Zhang C, Shi L, Wang F-S. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5(5):428-30.

17.Solmaz I, Özçaylak S, Alakuş ÖF, Kılıç J, Kalın BS, Güven M, et al. Risk factors affecting ICU admission in COVID-19 patients; Could air temperature be an effective factor?. Int J Clin Pract. 2021;75(3):e13803.

18.Weber S, Hellmuth JC, Scherer C, Muenchhoff M, Mayerle J, Gerbes AL. Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: a prospective cohort study. Gut. 2021;70(10):1925-32.

19.Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004.
20.Su T-H, Kao J-H. The clinical manifestations and management of COVID-19-related liver injury. J Formos Med Assoc. 2020;119(6):1016-8.
21.Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.