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Abnormal liver function tests in pregnant patients with COVID-19 — a retrospective cohort study in a tertiary center

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ABSTRACT

Objectives: The current study aimed to describe the incidence of abnormal liver function tests (LFTs) in pregnant COVID-19 patients, explore the association between LFTs with current medication, and provide a reference for medical therapy of pregnant patients with COVID-19.

Material and methods: This retrospective single tertiary center cohort study included 122 pregnant patients with confirmed COVID-19 admitted and treated from April 1, 2020, to May 31, 2020. We defined abnormal LFTs as the elevation of the following liver enzymes in serum per our hospital's laboratory reference range standards: AST > 35 U/L, ALT > 35 U/L, and TBIL > 1.2 mg/dL. We evaluated patients for demographic and clinical features, laboratory parameters, medications, and hospital length of stay (LOS).

Results: Patients in this cohort had clinical presentations of fever (84.4%), dry cough (78.6%), and shortness of breathing (6.5%). In total, 17 (13.9%) patients had abnormal LFTs during hospitalization. Critically ill patients were three-fold higher in the abnormal LFTs group (11.8%) than in the normal LFTs group (3.8%, p = 0.16). The proportion of patients

who used hydroxychloroquine and lopinavir/ritonavir were significantly higher in patients with abnormal LFTs (88.2% and 35.3%, respectively) than those with normal LFTs (62.9% and 15.2%, p = 0.04 and p = 0.04, respectively). The hospital length of stay (LOS) was significantly longer in the abnormal LFTs group (8.2 ± 5.8 days) than in the normal LFT group (6.0 ± 2.8 days, p = 0.02).

Conclusions: SARS-CoV-2 may induce liver injury and the LFT abnormality was generally mild in pregnant patients with COVID-19. Abnormal LFTs are associated with prolonged hospital LOS. Drug use was the most crucial risk factor for liver injury during hospitalization. The use of lopinavir/ritonavir and hydroxychloroquine were significantly higher, and the course of treatment of these drugs was significantly longer in pregnant women with abnormal LFTs than the patients with normal LFTs. Therefore, pregnant women with COVID-19 who received antiviral treatment should be closely monitored for evaluating LFTs.

Key words: COVID-19; liver function test; pregnancy; SARS-CoV-2

INTRODUCTION

The coronoviridae family of viruses has risen as a global threat to public health and can cause both respiratory and multisystemic diseases in numerous human species and humans [1, 2]. Of these, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) originated in Wuhan City in Hubei Province, central China, was responsible for the Coronavirus Disease 2019 (COVID-19) in December 2019, and rapidly spread across the globe [3]. As of August 2020, more than 20 million patients globally had been infected with Covid-19, and more than 700 000 deaths are associated with this virus [4]. Researchers reported that approximately 15% of patients infected with COVID-19 progress severe health complications, about 5–10% require intensive care unit due to the severe pneumonia type symptoms, and with 3–5% of high mortality risk [5]. As this disease continues to spread sustainably and indiscriminately across the world, it is expected to see pregnant patients with COVID-19 canvassed across all trimesters of gestation [6]. Therefore, further epidemiological and clinical features should be clarified to enhance our perception of the virus's correct extent, develop diagnostic and treatment abilities and diminish its overall morbidity and mortality.

COVID-19 patients typically present with fever, weakness, dry cough, and shortness of breathing [7]. SARS-CoV-2 has also been associated with different degrees of liver injury [8]. Previous studies reported that 14–76% of COVID-19 patients experience abnormal liver function tests (LFTs), primarily increased levels of serum alanine aminotransferase (ALT) and

aspartate aminotransferase (AST) [9, 10]. The extent and underlying mechanisms for liver injury in COVID-19 patients are not fully understood, but the pathogenesis seems multifactorial. The primary liver injury mechanism in COVID-19 patients is considered to be the binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptor, which is known as the host cell entry receptor and highly expressed cholangiocytes, and then damages these bile duct cells [11]. Cholangiocytes are dynamic players in many aspects of liver physiology, including regeneration and innate and adaptive immune response mechanisms, and the disruption of these cells' functions induces a systemic inflammatory response leading to hepatobiliary damage [12]. Moreover, an autopsy analysis of liver biopsy specimens from a COVID-19 patient showed moderate microvesicular steatosis and mild inflammation in the portal and lobular area, suggesting that the liver injury might be caused by SARS-CoV-2 infection or drug-induced liver injury (DILI) [13]. Studies also indicated that this virus could cause acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), driving to hepatic ischemia and hypoxia reperfusion injury in severe COVID-19 patients [14, 15].

Till present, a few data exist in the literature that has elaborately investigate the prevalence and severity of abnormal LFTs, their association with baseline LFTs before COVID-19 hospitalization, and clinical characteristics of liver failure among pregnant patients with COVID-19. Hence, the current study aimed to describe the incidence of abnormal LFTs in pregnant COVID-19 patients, explore the association between LFTs with current medication, and provide a reference for medical therapy of pregnant patients with COVID-19.

MATERIAL AND METHODS

This retrospective single tertiary center cohort study included 122 pregnant patients with confirmed COVID-19 admitted and treated from April 1, 2020, to May 31, 2020, at XX Hospital isolation ward. All patients had an exposure history and clinical presentation of COVID-19, including respiratory symptoms or fever. We diagnosed patients with COVID-19 based on the World Health Organization (WHO) interim guidance [16]. The ethics committee of the hospital approved the study (approval date: 10.06.2020, approval number: 2020.06.67). We detected SARS-CoV-2 nucleic acid in all patients by real-time nasopharyngeal swab polymerase chain reaction (PCR). Pregnant COVID-19 patients underwent clinical assessment of vital signs and symptoms, laboratory analysis, and radiologic chest evaluation at admission. We performed a chest X-ray and/or computed tomography (CT) for pneumonia diagnosis. As expected, concerns relating to the possible teratogenic impacts to the fetus from

radiation exposure are inevitable. The accepted cumulative dose of ionizing radiation in the course of pregnancy is 5 rad, and no single diagnostic examination exceeds this upper limit. The exposure amount to the fetus from a two-view chest X-ray of the pregnant woman is 0.00007 rad, and chest CT (10 slices with a slice thickness of 10 mm) exposes the fetus to < 0.1 rad [17]. Thus, Wang et al. suggested that, if indicated, in a pregnant patient with suspected COVID-19, chest X-ray and chest CT can be conducted safely [18]. Before undergoing chest X-ray and CT examinations, pregnant patients with COVID-19 signed an informed consent form and had their lower abdomen and pelvis covered with a lead blanket. We classified pregnant patients into mild or severe cases based on the results from symptoms, clinical findings, and chest radiography [10]. We identified patients with mild symptoms (i.e., fever, dry cough, expectoration) with or without mild changes on chest imaging as mild cases. We defined mild changes in chest radiography by multiple small patchy shadows and interstitial changes, primarily in the outer region of the lung and below the pleura. We described patients with severe pneumonia by any of the following findings' presence: increased respiration rate (RR, ≥ 30/minute), hypoxia (resting oxygen saturation ≤ 93%), the partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤ 300 mmHg in blood gas analysis, or respiratory or other organ failure occurrence that requires intensive care unit (ICU) admission, or shock.

Since there was no standard guidance on drug choice, therapeutic management was accommodated according to the clinical findings and guidelines [16]. All pregnant patients received supportive treatments, including intravenous fluid supplementation and maintenance of electrolyte and acid-base homeostasis, and a prophylactic dose of lower molecular weight heparin for preventing thromboembolic complications (LMWH) [19]. We closely monitored vital signs and finger oxygen saturation and gave oxygen treatment to hypoxemic patients. Since no antiviral therapy or antibiotic regimen was accepted for COVID-19 treatment, we treated patients with lopinavir/ritonavir, hydroxychloroquine, or azathioprine [20]. The decision of antiviral treatment regimen and/or antibiotic regimen was based on the infectious disease specialist's discretion.

We excluded patients with gestational hypertensive disorders, HELLP syndrome, intrahepatic cholestasis of pregnancy, pre-existing liver disease, other infections, and co-existing morbidities, including renal disease, collagen vascular disease, chronic hypertension, known malignancy, and ischemic heart disease.

Age, gestational week, gravida, parity, and BMI were obtained by examining patients' medical records. The gestational week was examined by sonographic measurement and confirmed according to the last menstrual period and a first-trimester ultrasound exam [21]. The CBC values of the patients were measured with Mindray BC 6800, an automatic blood counting device using laser and impedance measurement techniques. Hemoglobin (Hb), white blood cell count (WBC), neutrophil count, lymphocyte count, platelet (PLT) count, D-Dimer, ferritin, C-reactive protein (CRP), AST, ALT, total bilirubin (TBIL), direct bilirubin, indirect bilirubin, amylase, and lipase values were all derived from patient' medical files.

As COVID-19 is a recently identified infectious disease, there is no consensus or guidance on liver injury definition and classification. Therefore, abnormal LFTs were defined as the elevation of the following liver enzymes in serum per our hospital's laboratory reference range standards: AST > 35 U/L, ALT > 35 U/L, and TBIL > 1.2 mg/dL. We obtained admission values of LFTs and peak values of aminotransferases during hospitalization.

We discharged pregnant patients treated when the symptoms and clinical findings improved significantly, with no fever for at least three days, and obvious absorption of inflammation in pulmonary imaging. Patients who did not meet the discharge criteria continued hospitalization for treatment and close follow-up. We also recorded the hospital length of stay (LOS). We followed up on the patient outcomes until August 31, 2020. The delivery mode was determined by standard obstetric indications [22].

Statistical analysis

Continuous variables were presented as means ± standard deviations if normally distributed and medians [interquartile ranges (IQRs)] if not normally distributed, while categorical variables were given as percentages. The chi-squared (χ^2) test was used to compare categorical variables between the groups, while the Kolmogorov–Smirnov test was employed to assess whether the variables were normally distributed. A Student's t-test or Mann–Whitney U test was used to compare the continuous variables between the groups according to whether they were normally distributed or not. Spearman's rho correlation coefficient was calculated to describe the degree of correlation between the parameters. In order to determine the independent predictors of liver dysfunction, variables found to be associated at a $p<0.1$ level according to univariate analysis, were included in the multivariate logistic regression analysis by using the Backward LR method with the results reported as the odds ratios (OR) and 95% confidence intervals (CI). The threshold of statistical significance was established at $p<0.05$. All statistical analyses were performed using the Statistical

Package for the Social Sciences version 24.0 software program (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, a total of 134 pregnant women with COVID-19 were admitted to our hospital. After applying the exclusion criteria and withholding patients with missing medical records, 122 patients were included in our study.

Patients in this cohort had clinical presentations of fever (84.4%), dry cough (78.6%), and shortness of breathing (6.5%). There were two (1.6%) pregnant patients with abnormal LFTs on admission. One of them progressed to severe pneumonia during hospitalization and required ICU admission. Of patients with normal baseline LFTs, 15 patients developed elevated LFTs during hospitalization. One of them suffered from severe pneumonia and was admitted to ICU. In total, 17 (13.9%) patients had abnormal LFTs during hospitalization. Critically ill patient rates were three-fold higher in the abnormal LFTs group (11.8%) than in the normal LFTs group (3.8%). This difference was not statistically significant due to the low sample size ($p = 0.16$). All patients were discharged from the hospital by June 18th. No patient died in our study cohort.

The demographic variables, clinical characteristics, and the perinatal outcomes of the participants were summarized in Table 1. The mean age was significantly higher in the abnormal LFTs group (33.2 ± 6.1 years) than in patients with normal LFTs (28.1 ± 6.6 years). There were no significant differences between the two groups in terms of gravidity, parity, maternal weight, height, previous history of abortion, and the gestational week at admission.

The proportion of patients who used hydroxychloroquine and lopinavir/ritonavir were significantly higher in patients with abnormal LFTs (88.2% and 35.3%, respectively) than those with normal LFTs (62.9% and 15.2%, $p = 0.04$ and $p = 0.04$, respectively). Also, patients with elevated LFTs received significantly longer duration of treatment with hydroxychloroquine (4.7 ± 2.1 days) and lopinavir/ritonavir (2.7 ± 4.1 days) than those with normal LFTs (3.0 ± 2.5 days and 0.7 ± 2.1 days, $p = 0.01$ and $p < 0.01$, respectively). According to this, the hospital LOS was significantly longer in the abnormal LFTs group (8.2 ± 5.8 days) than in the normal LFTS group (6.0 ± 2.8 days, $p = 0.02$).

We presented the laboratory parameters of the study population in Table 2. The peak AST value on admission was 40 U/L, during hospitalization was 207 U/L. The peak ALT value on admission was 37 U/L, during hospitalization was 200 U/L. AST and ALT elevations

were generally (82.3%) mild, defined as < 5 times the upper reference limit. There were no significant differences between the groups in terms of neutrophil count, lymphocyte count, CRP, and D-Dimer value. Serum ferritin level was significantly higher in patients with elevated LFTs (243.6 ± 642 ng/mL) than in the normal LFTs group (48.9 ± 50 ng/mL, $p < 0.01$). Platelet count was demonstrated to be significantly higher in patients with abnormal LFTs (305 ± 169 (/mm^3 ×10^3) than those in patients with normal LFTs (231 ± 71/mm^3 × 10^3, $p < 0.01$).

We showed factors that were found to be independently associated with liver dysfunction in univariate analysis and multivariate logistic regression analysis in Table 3. On univariate analysis, maternal age, serum ferritin level, serum platelet level, parity, hydroxychloroquine use, and lopinavir/ritonavir use were associated with LFTs abnormality.

DISCUSSION

The current study demonstrates the results of LFTs and clinical outcomes in hospitalized pregnant patients with confirmed SARS-CoV-2 infection in a tertiary referral hospital. In our study cohort, 13.9% of pregnant patients with COVID-19 had elevated LFTs during hospitalization. Also, the pooled incidence of elevated aminotransferases determined during hospitalization appeared to be higher than that of at admission (1.6%), suggesting the disease progression and the toxicity of drugs used during hospitalization may both contribute to liver injury.

Rabaan et al. stated that SARS-CoV-2 shares similarities in terms of pathogenicity and structure with other coronaviruses, including SARS-CoV and MERS-CoV [23]. A study during the SARS outbreak in 2004 reported that abnormal LFTs were common (70%) in patients with SARS and might be associated with virus replication in the liver [24]. Also, liver specimens of SARS autopsies have demonstrated hepatocyte mitoses, fatty degeneration, central lobular necrosis, and lymphocytic infiltration, suggesting that SARS-CoV-2 can damage the liver tissue [25].

The liver plays an essential role in host defense against microorganisms and is frequently involved in most systemic infections as it receives a dual blood supply from the systemic and portal circulation. Various studies stated abnormal aminotransferase levels in COVID-19 patients and abnormal LFTs are common in hospitalized COVID-19 patients [10, 12, 26, 27]. The prevalence of AST elevations ranged between 4–53%, and that of ALT elevations ranged between 4–33% among COVID-19 patients in Chinese cohorts [26]. Sultan et al. reported that the pooled prevalence estimates of elevated LFTs were 15.0% [28]. Fan et

al. found significantly higher (37.2%) abnormal LFTs than previously reported rates, and elevated liver cell injury markers (AST, ALT) are more common. They suggested that liver damage in COVID-19 patients might be directly induced by the liver cells' viral infection [29]. Hundt et al. concluded that since the ACE2 receptor is dominantly expressed in cholangiocytes than in hepatocytes, the primary mechanism of liver injury is not due to the cytopathic effect of SARS-CoV-2 [27]. In our study, 13.9% of pregnant patients during hospitalization had abnormal LFTs. We also found that AST and ALT elevations were generally mild (1–2x the upper limit of normal). Likewise, Bertolini et al. reported that mild elevations of ALT and AST were often detected observed in COVID-19 patients on admission, and this elevation did not drive to notable liver dysfunction [26].

The liver is the major organ for drug metabolic processes and detoxification, and maintenance of function is crucial to participate in all feasible COVID-19 treatment modalities. Since an effective antiviral agent for COVID-19 has not been developed yet, supportive and symptomatic therapies are essential. Also, antiviral drugs previously utilized to treat other coronavirus infections have been considered as the first choice to treat COVID-19 patients [30]. All these drugs are used for the treatment or management of COVID-19 patients, including antiviral drugs (lopinavir/ritonavir, hydroxychloroquine), antibiotics, antipyretics (acetaminophen), corticosteroids, and herbal medicines are potentially hepatotoxic [26]. Fan et al. reported that the proportion of patients who were treated with lopinavir/ritonavir was significantly higher in patients with liver injury than in patients with sustained normal LFTs [29]. Wu et al. stated that compared with patients suffering mild clinical signs and symptoms, severe COVID-19 patients require longer antiviral treatment duration and multiple drug combinations. The number of drugs used ≥ 3 might be associated with liver injury [31]. In our study, the use of lopinavir/ritonavir and hydroxychloroquine were significantly higher, and treatment durations of these medications were significantly longer in the abnormal LFTs group than in the normal LFTs group. We also found that abnormal LFTs during hospitalization are associated with prolonged hospital LOS. This finding might be due to the toxicity of drugs used during hospitalization and the clinical course of the disease.

Regardless of the mechanisms implicated in the liver injury of COVID-19 patients, immune-mediated pathway activation considers to be crucial [12]. Virus particles spread through the respiratory mucosa, and then infect other cells, which induces a cytokine storm in the body and generates a series of immune responses [32]. COVID-19 patients present significant inflammatory marker activation, including neutrophils, CRP, and cytokines that

might contribute to pulmonary and extrapulmonary injuries [12]. Cytokine storm syndrome (CSS) is an uncontrolled or excessive proinflammatory cytokine release to external stimuli, which is correlated with disease severity [33]. Fan et al. found that patients with abnormal LFTs had higher inflammatory markers, including procalcitonin and CRP, and higher fever rates, which might be associated with the immune response following SARS-CoV-2 infection [29]. However, Zhao et al. indicated that abnormal LFTs in mild COVID-19 patients may not be associated with inflammatory status [34]. It was also considered that specific inflammation induced by SARS-CoV-2 is more prone to induce abnormal LFTs than general inflammation caused by other microorganisms. We did not find any significant differences between the groups regarding neutrophil count, lymphocyte count, and CRP. However, serum ferritin levels were significantly higher in pregnant women with abnormal LFTs than in the group with normal LFTs. Kernan et al. demonstrated that ferritin is a pivotal marker of and pathogenic player in the inflammatory process through its signaling as a component of the innate immune response and lymphocyte function modulation [35]. However, the accurate mechanism by which ferritin contributes to the course of this disease remains elusive.

The prevalence of pre-existing liver disease in patients with SARS-CoV-2 infection varies from 1–11% [26]. Previous studies stated that COVID-19 patients with pre-existing liver diseases might be more prone to suffer abnormal LFTs [10, 12, 29, 31]. Also, the highest proportion of deaths in COVID-19 patients were detected in elderly patients with underlying liver diseases [36]. Our study cohort consisted of reproductive-aged pregnant patients. We also excluded patients with pre-existing liver diseases from this study. We consider that these criteria could explain our lower rates of severe COVID-19 patients than the previous research.

Patients with abnormal LFTs during hospitalization had a significantly higher risk of worsening to severe COVID-19 than patients with normal LFTs. Progressing to severe pneumonia describes the clinical situation with a high mortality rate that requires ICU admission or mechanical ventilation [10]. In this study, while 3.8% of patients with normal LFTs exacerbate severe COVID-19, 11.8% of pregnant women with elevated aminotransferases progressed to severe pneumonia. However, this difference was not statistically significant. We consider that the absence of significant difference was due to the low sample size.

There are some limitations to this study. This study has been designed retrospectively and has the potential to contain limitations of such studies [37]. Because of the dependence on information reported in the patient record, we could not identify risk factors for all pregnant patients with COVID-19. We also evaluated abnormal LFTs rather than liver injury, because

the description of liver damage was unclear in pregnant patients with COVID-19. The main strength of this study is that a few data exist in the literature that has comprehensively examine the prevalence and severity of abnormal LFTs.

CONCLUSIONS

We demonstrated that SARS-CoV-2 may induce liver injury and the LFT abnormality was generally mild in pregnant patients with COVID-19. Abnormal LFTs are associated with prolonged hospital LOS. Drug use was the most crucial risk factor for liver injury during hospitalization. The use of lopinavir/ritonavir and hydroxychloroquine were significantly higher, and the course of treatment of these drugs was significantly longer in pregnant women with abnormal LFTs than the patients with normal LFTs. Therefore, pregnant women with COVID-19 who received antiviral treatment should be closely monitored for evaluating LFTs.

Conflict of interest

The authors declared no conflict of interest.

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Table 1. Demographic and clinical parameters of the study cohort

Variables	**All population (n = 122)**	**Abnormal LFTs (–) (n = 105)**	**Abnormal LFTs (+) (n = 17)**	**P-value**
Age, years	28.8 ± 6.8	28.1 ± 6.6	33.2 ± 6.1	**< 0.01**
Height, cm	161.8 ± 5.9	161.7 ± 5.9	162.3 ± 6.1	0.71
Weight, kg	76.3 ± 12.8	75.6 ± 12.8	80.5 ± 12.6	0.18
Gravidity, n	2.7 ± 1.5	2.5 ± 1.4	3.3 ± 1.7	**0.05**
Parity, n	1.3 ± 1.2	1.2 ± 1.1	2.1 ± 1.6	**< 0.01**
Previous abortion, n (%)	30 (24.6)	27 (25.7)	3 (17.6)	0.47
Gestational week at admission	29.4 ± 9.3	29.2 ± 9.4	30.6 ± 8.6	0.57
Birth weight, g	3115 ± 634	3173 ± 607	2741 ± 713	**0.05**
Hydroxychloroquine usage, n (%)	81 (66.4)	66 (62.9)	15 (88.2)	**0.04**
Hydroxychloroquine usage time, days	3.3 ± 2.5	3.0 ± 2.5	4.7 ± 2.1	**0.01**
Lopinavir/Ritonavir usage, n (%)	22 (18)	16 (15.2)	6 (35.3)	**0.04**
Lopinavir/Ritonavir usage time, days	0.98 ± 2.5	0.7 ± 2.1	2.7 ± 4.1	**< 0.01**
Azithromycine usage, n (%)	24 (19.7)	19 (18.1)	5 (29.4)	0.28
Azithromycine time, days	0.84 ± 1.8	0.77 ± 1.8	1.2 ± 2.2	0.33
Severe disease, n (%)	6 (4.9)	4 (3.8)	2 (11.8)	0.16
Hospital length of stay, days	6.3 ± 3.4	6.0 ± 2.8	8.2 ± 5.8	**0.02**

Table 2. Laboratory parameters of the study population

Variables	**All population (n = 122)**	**Abnormal LFTs (–)**	**Abnormal LFTs (+)**	**P-value**

		(n = 105)	**(n = 17)**	
AST, (mean) (median, [IQR])	22.1 ± 12.5 20 [16–25]	20.9 ± 8.3 19 [15–24]	34.9 ± 22.5 29 [22–40]	< **0.01**
AST (peak), (mean) (median, [IQR])	34.4 ± 76 20 [15–25]	19.5 ± 5.6 18 [15–24]	145.6 ± 195 46 [42–207]	< **0.01**
ALT, (mean) (median, [IQR])	17 ± 15 14 [9–19]	15.6 ± 8.4 13 [9–16]	35.8 ± 30.5 26 [19–37]	< **0.01**
ALT (peak), (mean) (median, [IQR])	29.5 ± 73.5 15 [10–20]	15.7 ± 5.4 14 [10–17]	147.4 ± 180.9 43 [41–200]	< **0.01**
Total Bilurubin, (mean) (median, [IQR])	0.4 ± 0.3 0.28 [0.2–0.39]	0.3 ± 0.2 0.27 [0.2–0.36]	0.7 ± 0.5 0.69 [0.28–0.84]	< **0.01**
Indirect Bilurubin, (mean) (median, [IQR])	0.15 ± 0.09 0.13 [0.09–0.19]	0.1 ± 0.08 0.13 [0.09–0.18]	0.8 ± 2.4 0.18 [0.12–0.31]	< **0.01**
Direct Bilurubin, (mean) (median, [IQR])	0.4 ± 2.1 0.14 [0.09–0.20]	0.4 ± 2.2 0.13 [0.09–0.17]	0.5 ± 0.5 0.20 [0.15–0.64]	0.96
Amylase, (mean) (median, [IQR])	65 ± 26 59 [49–79]	65 ± 24 58 [50–77]	79 ± 39 79 [38–95]	0.33
Lipase, (mean) (median, [IQR])	27 ± 19 23 [18–29]	24 ± 10 22 [18–28]	50 ± 44 30 [26–64]	< **0.01**
Neutrophil, median, (mean) (median, [IQR])	5.7 ± 2.4 5.3 [4.1–7.1]	5.6 ± 2.3 5.1 [4.1–7.0]	6.6 ± 2.9 6.3 [4.1–8.7]	0.98
Lymphocyte, (mean) (median, [IQR])	1.4 ± 0.5 1.3 [1.0–1.8]	1.3 ± 0.6 1.3 [1.0–1.7]	1.7 ± 0.6 1.7 [1.0–2.1]	0.17
Platelet, median, (mean) (median, [IQR])	237 ± 100 221 [181–278]	231 ± 71 219 [181–277]	305 ± 169 253 [172–401]	< **0.01**
CRP, median, (mean) (median, [IQR])	26 ± 28 16 [4.3–28]	31.8 ± 40 16 [4.3–39]	25.7 ± 30 16 [4.5–40]	0.55

D-Dimer, median, (mean) (median, [IQR])	2.3 ± 2.2 1.7 [1.1–2.5]	2.2 ± 2.1 1.6 [1.1–2.5]	2.1 ± 1.7 2.0 [1.3–3.8]	0.80
Ferritin, median, (mean) (median, [IQR])	83.8 ± 302 31.2 [16.8–62.2]	48.9 ± 50 30 [16.5–52.8]	243.6 ± 642 75.8 [55.8–160]	**< 0.01**

Table 3. Univariable and multivariable logistic regression analysis for determining the predictors of the liver dysfunction

	Univariate		**Multivariate***	
Variables	**OR (95%CI)**	**p**	**OR (95%CI)**	**p**
Maternal age	1.116 (1.031–1.207)	< 0.01	1.156 (1.044–1.281)	< 0.01
Ferritin	1.010 (1.002–1.018)	< 0.01	1.011 (1.002–1.020)	0.01
Platelet	1.007 (1.001–1.013)	0.02	1.008 (1.001–1.015)	0.02
†Parity	1.703 (1.145–2.532)	0.01		
†Hydroxychloroquine	0.226 (0.049–1.040)	0.06		
†Lopinavir/Ritonavir	3.034 (0.982–9.375)	0.05		

* Multivariate logistic regression analysis by using Backward LR method

† Not included in multivariate analysis according to Backward LR method