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Clinics and Research in Hepatology and Gastroenterology 46 (2022) 101894

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ORIGINAL ARTICLE

Abnormal liver tests and non-alcoholic fatty liver disease predict disease progression and outcome of patients with COVID-19

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Abbreviations: ALP, Alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COVID-19, coronavirus disease; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; HSI, hepatic steatosis index; LFTs, liver function tests; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; SaO_2, capillary oxygen saturation; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; TP, prothrombin time; ULN, upper limit of the normal.

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https://doi.org/10.1016/j.clinre.2022.101894
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Available online 25 February 2022

KEYWORDS
SARS-CoV-2 infection;
COVID-19 disease;
Liver function tests (LFTs);
Obesity;
Liver steatosis;
Liver fibrosis

Abstract
Background and aims: Coronavirus disease 2019 (COVID-19) is a serious public health issue that became rapidly pandemic. Liver injury and comorbidities, including metabolic syndrome, are associated with severe forms of the disease. This study sought to investigate liver injury, clinical features, and risk factors in patients with mild, moderate, and severe COVID-19.
Methods: We retrospectively included all consecutive patients hospitalized with laboratory-confirmed COVID-19 between February, 22 and May 15, 2020 at the emergency rooms of a French tertiary hospital. Medical history, symptoms, biological and imaging data were collected.
Results: Among the 1381 hospitalizations for COVID-19, 719 patients underwent liver tests on admission and 496 (68.9%) patients displayed abnormal liver tests. Aspartate aminotransferase was most commonly abnormal in 57% of cases, followed by gamma-glutamyl transferase, alanine aminotransferase, albumin, alkaline phosphatase, and total bilirubin in 56.5%, 35.9%, 18.4%, 11.4%, and 5.8%. The presence of hepatocellular type more than 2xULN was associated with a higher risk of hospitalization and a worse course of severe disease (odd ratio [OR] 5.599; 95%CI: 1.27−23.86; p = 0.021; OR 3.404; 95% CI: 2.12−5.47; $p < 0.001$, respectively). A higher NAFLD fibrosis score was associated with a higher risk of hospitalization (OR 1.754; 95%CI: 1.27−2.43, $p < 0.001$). In multivariate analyses, patients with high fibrosis-4 index had a 3-fold greater risk of severe disease ($p < 0.001$).
Conclusion: Abnormal liver tests are common in patients with COVID-19 and could predict the outcome. Patients with non-alcoholic fatty liver disease and liver fibrosis are at higher risk of progressing to severe COVID-19.
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Introduction

Coronaviruses are enveloped viruses that display the largest genome of all RNA viruses known to cause respiratory infections in humans [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the novel coronavirus disease that first occurred in 2019 (COVID-19) and became a serious global public health problem, declared by World Health Organization (WHO) as a global public health emergency. It can cause respiratory, intestinal, hepatic, and neuronal disease and may lead to acute respiratory distress syndrome, multiple organ failure, and death in severe cases [2].

As this infectious disease continues to spread, more information is needed to better identify the patients who require hospitalization or those who are likely develop severe COVID-19 disease. The identification of risk factors associated with outcomes should allow for patient stratification in view of personalized clinical care, in order to improve the outcome.

Liver impairment has been commonly reported in COVID-19 patients [3]. Abnormal liver function tests (LFTs) are present on admission, prior to initiating treatment with hepatotoxic drugs that may induce liver injury [4]. However, the association between LFTs and different degrees of COVID-19 severity of is still poorly described.

The features of metabolic syndrome, including obesity, diabetes, and hypertension, are associated with a severe COVID-19 course [5]. Non-alcoholic fatty liver disease (NAFLD) is associated with these metabolic comorbidities. The association and evolution of SARS-CoV-2 infection in patients with a preexisting liver disease like NAFLD are still incompletely understood.

The current study aimed to investigate liver injury, clinical features, and risk factors in patients with associated mild, moderate, and severe COVID-19.

Patients and methods

Study design and participants

We retrospectively included all consecutive patients hospitalized for SARS-CoV-2 infection between February, 22 and May, 16, 2020 at the emergency rooms (ERs) of two French tertiary hospitals (*Nouvel Hôpital Civil* and *Hôpital de Hautepierre* − University Hospital of Strasbourg). The study protocol was approved by the Ethics Committee of Strasbourg University Hospital (CE-2020−138−26/08/2020).

Data collection

The data collected for the hospitalized patients suffering from SARS-CoV-2 infection included their epidemiological and medical history, clinical signs, and biological and imaging data only at admission.

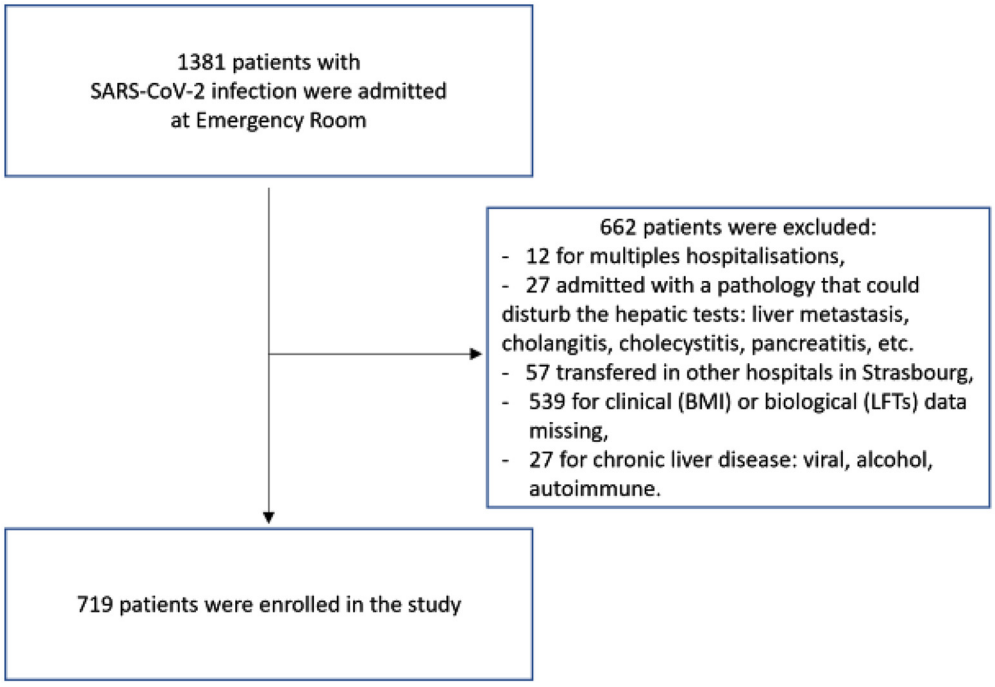

Fig. 1 Flowchart of patients included in the study.

Three groups of patients were defined according to the hospitalization: [1] *mild disease*: patients hospitalized at the emergency room (ER) and discharged from the hospital without any indication of admission to a conventional hospitalization unit (CHU) or intensive care unit (ICU); [2] *moderate disease*: patients admitted to the ER and hospitalized thereafter in a CHU without signs of severe disease that would need intensive care support; [3] *severe disease*: patients needing intensive care support on admission or during the hospitalization in a CHU, patients hospitalized in the ICU, and patients who died during hospitalization in a CHU.

Liver tests were considered abnormal if the liver enzyme values, i.e., aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), and total bilirubin (TBIL), were elevated according to our laboratory upper limit of normal (ULN). Different patterns were defined: hepatocellular, cholestatic, and mixed patterns. The hepatocellular pattern was considered if AST or ALT were elevated higher than ULN; the cholestatic pattern if GGT or PAL were elevated up to ULN; the mixed pattern was a combination of the first two ones.

The exclusion criteria were described in the Fig. 1, as follows: patients with multiple hospitalizations for COVID-19, hospitalization for a pathology that may disturb LFTs (liver metastasis, cholangitis, cholecystitis, pancreatitis), patients transferred to other hospitals in Strasbourg or elsewhere, lost to follow-up or with missing clinical and biological data, patients with underlying chronic liver disease (viral, alcohol, autoimmune). Patients with diagnosed NAFLD were included in the study.

Moreover, NAFLD was diagnosed using the hepatic steatosis index (HSI = 8 $\times$ [ALT/AST] + body mass index [BMI] [+ 2 if type 2 diabetes yes, + 2 if female]) $>$ 36 points [6] and the severity related to the stage fibrosis with NAFLD fibrosis score (NFS) [7]. This HSI has been validated in COVID-19 patients to evaluate NAFLD [8–10]. The fibrosis was also evaluated using fibrosis-4 index (FIB-4): low ($<$ 1.30), intermediate (1.30–2.67), and high ($>$ 2.67) [11]. To evaluate the severity of the metabolic liver disease, we analyzed the different FIB-4 scores in patients diagnosed with NAFLD according to the HSI score.

Quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests for SARS-CoV-2 nucleic acid were performed on admission with nasopharyngeal swabs. The primer and probe sequences targeted two regions on the RdRp gene and were specific to SARS-CoV-2. The assay sensitivity was around 10 copies/reaction (in-house method, *Institut Pasteur,* Paris, France) [12].

Chest computer tomography (CT) imaging was performed on admission for each patient. The images were classified based on the percentage of the whole lung parenchyma affected by COVID-19 in the following six groups: normal (no lesion), minimal (0%–10%), moderate (11%–25%), important (26%–50%), severe (51%–75%), and critical ($>$ 75%) [13]. To simplify clinical data analysis, the patients were divided into three subgroups: $\leq$ 25%, 26%–50%, and $>$ 50%, according to their lesion extension.

Statistics

The variables collected were expressed as the numbers and frequencies for qualitative variables (ordinal and categorical) and minimum, maximum, median, mean, and standard deviation for quantitative variables (discrete and continuous). These data were summarized in the descriptive phase.

Table 1 Characteristics of patients with mild and moderate COVID-19 on admission.

Variable	Mild COVID-19 (*n* = 101)	Moderate COVID-19 (*n* = 393)	p-value
Age (years, SD*)	57.7 (18.4)	65.7 (7)	< 0.001
Gender (male,%)	52 (51.4)	198 (50.4)	0.468
BMI (kg/m^2, SD)	26.9 (4.9)	28.8 (5)	0.004
Comorbidity			
Diabetes (n,%)	21 (20.8)	105 (26.7)	0.251
Hypertension (n,%)	38 (37.6)	217 (55.2)	0.002
Dyslipidemia (n,%)	17 (16.8)	129 (32.8)	0.001
Chronic pulmonary disease (n,%)	19 (18.8)	94 (24)	0.291
Chronic cardiac disease (n,%)	19 (18.8)	106 (27)	0.097
Chronic kidney disease (n,%)	4 (4)	26 (6.6)	0.482
Cancer (n,%)	2 (2)	20 (5.1)	0.277
Symptoms onset			
"Flu-like" symptoms (n,%)	87 (86.1)	366 (93.1)	0.041
Respiratory symptoms (n,%)	87 (86.1)	351 (89.3)	0.014
Digestive symptoms (n,%)	40 (39.6)	208 (52.9)	0.019
Neurological symptoms (n,%)	45 (44.6)	184 (46.8)	0.738
Clinical features			
Oxygen saturation SaO_2 (%, SD)	96 (3.9)	92.1 (5.9)	< 0.001
Debit of oxygen at admission (L/mn, sd)	0.4 (1.8)	2.3 (7.4)	< 0.001
Systolic arterial pressure (mmHg, SD)	132.4 (17.9)	133.1 (25.8)	0.683
Laboratory tests			
AST U/L (reference range 11−34)	30.4 (20.4)	45.5 (36.2)	< 0.001
ALT U/L (reference range 8−41)	35.7 (27.5)	42.3 (34)	0.05
ALP U/L (reference range 41−117)	66.1 (13.2)	76.1 (40.6)	0.938
GGT U/L (reference range 6−40)	30.2 (23.7)	87.6 (119.2)	0.004
Bilirubin μmol/L, (reference range 1.7−21.0)	9.1 (4.9)	11.3 (18.3)	0.279
Albumin g/L, (reference range 35−50)	43.1 (3.9)	39.2 (5)	< 0.001
Abnormality type (n,%)			
Hepatocellular $>$ ULN	39 (38.6)	221 (56.2)	0.002
Cholestatic $>$ ULN	2 (16.7)	112 (61.2)	0.004
Mixed $>$ ULN	0 (0)	72 (39.3)	0.004
PT (normal range $>$ 70%) (%, SD)	92.6 (8)	87.9 (15.7)	0.042
CRP mg/L (reference range$<$ 4)	36.1 (54.1)	87.9 (70.5)	< 0.001
Leucocytes *10^9/L (reference range 4.5−6.5)	6.2 (2.6)	7(3.4)	0.02
Neutrophil count *10^9/L (reference range 1.3−7.7)	4.2 (2.2)	5.3 (3)	< 0.001
Lymphocytes *10^9/L (reference range 1.0−4.0)	1.5 (0.8)	1.2 (1.3)	< 0.001
Lymphocytes *10^9/L $\leq$ 1.0 (n,%)	31 (30.7)	200 (50.9)	0.001
Fibrinogen g/L (reference range: 2−4)	5(1.4)	5.9 (1.5)	0.016
Platelets *10^9/L (reference range: 150−400)	236.2 (104.6)	226.3 (99.8)	0.331
D-Dimers (reference range: 150−400)	765 (698)	2452.9 (4111.5)	0.05
Metabolic and fibrosis characteristics			
FIB-4 status (n,%)			< 0.001
$\leq$ 1.3	59 (58.4)	111 (28.3)	
1.3−2.67	29 (28.7)	142 (36.2)	
$>$ 2.67	13 (12.9)	139 (35.5)	
NAFLD (n,%)	62 (61.4)	249 (63.4)	0.73
NAFLD+ and FIB-4 (n,%)			< 0.001
NAFLD + FIB-4 $<$ 1.3	33(32.7)	62 (15.8)	
NAFLD + FIB-4 1.3−2.67	19 (18.8)	94(23.9)	
NAFLD + FIB-4 $>$ 2.67	49 (48.5)	237 (60.3)	
NFS (mean, SD)	−2 (1.5)	−0.7 (1.7)	< 0.001
Radiologic findings			
Severity of pneumonia (CT scan)			< 0.001

Table 1 (*Continued*)

Variable	Mild COVID-19 (n = 101)	Moderate COVID-19 (n = 393)	p-value
-absence	25 (26%)	24 (6.8%)	
-< 25%	58 (60.4%)	185 (52.6%)	
25−50%	10 (10.4%)	116 (33%)	
> 50%	3 (3.1%)	27 (7.7%)	
Delays from symptom onset to hospitalization (days, SD)	7.2 (6.8)	7.6 (6.8)	0.592
Time of hospitalization (days, SD)	1 (0.9)	10.6 (8.5)	< 0.001

BMI: body mass index; SD: standard deviation; COVID-19: coronavirus disease 2019; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ULN: upper limit of the normal; GGT: gamma-glutamyl transferase; LFTs: liver function tests; PT: prothrombin time; FIB-4: fibrosis-4; CRP: Creatine-reactive protein; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CT: computed tomography; HSI: hepatic steatosis index; NAFLD: non-alcoholic fatty liver disease; NFS: NAFLD fibrosis score; SaO_2: capillary oxygen saturation; TBIL: total bilirubin.

For the bivariate analysis between groups, Fisher's exact test or Chi-squared tests were applied to compare qualitative variables, and Wilcoxon or Student t-tests were employed to compare quantitative variables.

To analyze the primary outcome, logistic regression was carried out by selecting variables from the literature, performing bivariate analysis, and then further selecting using Akaike information criterion (AIC).

Missing data were imputed by multiple imputations if they did not concern more than 30% of the data available; otherwise, the variable was excluded from the model.

The alpha risk was set at 5%, and all analyses were performed using R software, Version 4.0.

A multivariate analysis was performed after adjusting for confounding factors that might disturb the LFTs on admission, such as hypoxemia (capillary oxygen saturation [SaO_2] < 93%, related to severe pneumopathy) [14] and hepatotoxic drugs (acetaminophen; antibiotics) administered prior to hospitalization. Hypotension, defined by systolic blood pressure < 90 mmHg, was not considered because of the low number of cases concerned (< 10).

Results

Between February, 22 and May, 15, 2020, a total of 1381 patients with SARS-CoV-2 infection were admitted to the ERs. After excluding 662 patients according to our exclusion criteria, 719 were included in the subsequent analyses, as presented in the study flowchart (Fig. 1).

According to COVID-19 severity, 101(14%) patients displayed mild disease, 393 (54.7%) presented with moderate disease, and 225 (31.3%) developed severe disease. The mean hospitalization length was 11.7 ± 12.8 days.

The mean age was 64.7 (19−97) years old, and 387 (58.8%) patients were men. Comorbidities were present in 513 (71.3%) patients, and the most common were BMI> 25 Kg/m^2 in 479 (70.6%) and BMI> 30 Kg/m^2 in 240 (33.3%), hypertension in 386 (53.7%), dyslipidemia in 226 (31.5%), diabetes in 201 (28%), chronic cardiac disease in 232 (32.3%), chronic respiratory disease in 176 (24.5%), chronic renal disease in 59 (8.2%), and cancer in 32 (4.5%).

Liver tests were performed on admission. The frequency of different abnormal LFTs, such as AST, ALT, ALP, GGT, TBIL, albumin, and prothrombin time (PT), was 57%, 35.9%, 11.4%, 56.5%, 5.8%, 18.4%, and 9.1%, respectively, while the mean values for these parameters were 53.8 (±85.1) u/L, 46.2 (±67.6) u/L, 74.2 (±39.1) u/L, 84.4 (±104.4) u/L, 11.3 (±14.5) μmol/L, 38.2 (±5.5) g/dL, and 87.8% (±14.7), respectively.

The LFTs exhibited a hepatocellular pattern in 60.9%, cholestatic pattern in 63.1%, and mixed-type pattern in 46.8% of patients.

Comparison between mild and moderate COVID-19 on admission

Table 1 summarizes the clinical and biological characteristics on admission for patients with mild and moderate disease.

LFT laboratory data showed higher elevations of AST ($p < 0.001$), ALT ($p = 0.05$), and GGT ($p = 0.004$) in addition to lower albumin ($p < 0.001$) and PT ($p = 0.042$) in patients with moderate versus mild COVID-19 (Table 1). AST levels were higher in patients hospitalized in a CHU compared to those in ER: 1−2xULN ($p = 0.001$) and > 2xULN ($p = 0.001$).

Patients with moderate COVID-19 exhibited elevated GGT levels compared to mild disease, 53.6% vs 16.7% ($p = 0.016$), respectively and more disturbed hepatocellular ($p = 0.002$), cholestatic ($p = 0.004$) and mixed-type (0.004) patterns. These patients had also higher NFS ($p < 0.001$) and more severe liver fibrosis than patients with mild COVID-19: 71.7% had an intermediate/high FIB-4 fibrosis score compared to 41.6% with mild disease ($p < 0.001$). Patients with moderate disease had more NAFLD with an intermediate/high FIB-4 score compared to patients with mild disease ($p < 0.001$) (Table 1).

As can be seen in Table 2, after adjusting for confounding factors that could disturb LFTs, such as hypoxemia and hepatotoxic drugs, patients with AST 2xULN and hepatocellular pattern 2xULN had a 5.5-fold higher risk of being hospitalized (OR 5.599; 95% CI: 1.29−24.25, $p = 0.021$ and OR 5.499; 95%CI: 1.27−23.86; $p = 0.023$, respectively). Patients with metabolic syndrome (the association of 3 metabolic risk factors (MRF)) had more than 2.5-fold higher risk of hospitalization (OR 2.56; 95%CI: 1.292−5.09, $p = 0.007$).

Moderate disease was associated with an intermediate (OR 2.405; 95%CI: 1.39−4.15; $p = 0.002$) and high (OR 5.415; 95%CI: 2.69−10.89; $p < 0.001$) FIB-4 score. Similarly,

Table 2 Factors associated with moderate COVID-19, after adjusting for confounding factors.

	OR	95%CI	p-value
MS (MRF 1 + 2 + 3)	2.85	1.49−5.45	0.002
MS (MRF 1 + 2 + 4)	2.56	1.29−5.09	0.007
MS (MFR 1 + 3 + 4)	3.09	1.29−6.89	0.006
NFS score	1.754	1.27−2.43	< 0.001
FIB-4 (1.3−2.67)	2.405	1.39−4.15	0.002
FIB-4 > 2.67	5.415	2.69−10.89	< 0.001
NAFLD+ and FIB-4 < 1.30	0.404	0.20−0.81	0.011
ASTULN	0.395	0.23−0.66	< 0.001
AST>2 ULN	5.599	1.29−24.25	0.021
Hepatocellular type > 2 ULN	5.499	1.27−23.86	0.023
GGT ULN	0.108	0.01−0.89	0.039
Cholestatic type >ULN	11.915	1.45−98.27	0.021
Albumin	0.805	0.70−0.92	0.002
Neutrophil count	1.13	1.02−1.25	0.023
Lymphocytes < 1000/μL	2.196	1.33−3.64	0.002
Prothrombin time	0.963	0.94−0.99	0.01
CRP	1.017	1.01−1.02	<0.001
CRP < 100 mg/L	0.29	0.14−0.62	< 0.001

OR: odd ratio; CI: confidence interval; MS: metabolic syndrome, MRF: metabolic risk factors: 1-obesity; 2-diabetes, 3-dyslipidemia, 4-hypertension.
Adjustment for confounding factors that could disturb LFTs, as follows: hypoxemia (SaO_2 < 93% related to severe pneumopathy) [16]; hepatotoxic drugs (acetaminophen, antibiotics) administrated before hospitalization. Hypotension defined by systolic blood pressure < 90 mmHg was not considered because of low case number < 10.

patients with an elevated NFS had a higher risk of hospitalization (OR 1.754 95%CI: 1.27−2.43; $p < 0.001$).

In multivariate analyses, patients with metabolic syndrome had almost a 2.4-fold risk of being hospitalized (OR 2.37; 95% CI: 1.18−4.75, $p = 0.015$).

Comparison between mild/moderate and severe COVID-19

We compared the clinical and laboratory tests and radiological findings in patients with severe versus those with moderate and mild COVID-19 disease (Table 3).

The laboratory liver tests showed more elevated AST ($p < 0.001$), ALT ($p = 0.002$), and TBIL levels ($p = 0.01$), in addition to lower albumin ($p < 0.001$) and PT ($p < 0.001$) in severe disease patients (Table 3).

Concerning abnormal LFT patterns, severe COVID-19 was associated with all types of patterns: hepatocellular ($p < 0.001$), cholestatic ($p = 0.028$), and mixed ($p < 0.001$).

In severe disease patients, 89.3% had intermediate and high FIB-4 scores compared to 65.5% of patients with moderate and mild disease ($p < 0.001$). More patients with severe COVID-19 had NAFLD associated with a high FIB-4: 72.8% vs. 57.9%, respectively ($p < 0.001$) (Table 3).

After adjusting for confounding factors, as described, abnormal LFTs at admission such as AST> 2x ULN (OR 3.187; 1.99−5.08; $p < 0.001$), hepatocellular pattern > 2x ULN (2.265; 95% CI 1.48−3.45; $p < 0.001$), intermediate and high FIB-4 score (OR 2.006; 95%CI 1.09−3.67; $p = 0.024$ and OR 4.756; 95%CI: 2.68−8.43; $p < 0.001$, respectively) or metabolic syndrome (OR 2.45, 95%CI1.07−5.61, $p = 0.03$) were associated with a worse evolution of the disease (Table 4).

In multivariate analyses, patients with high FIB-4 index had 3-fold risk to develop a severe disease (OR 3.11; 95%CI 1.4−6.91, $p = 0.005$).

Discussion

Coronavirus disease 2019, the pandemic caused by SARS-CoV-2, has been associated with substantial morbidity and mortality [15]. More information concerning SARS-CoV-2 infection is needed to rapidly identify patients likely to develop severe disease, requiring adjusted care. This is the first monocentric study that describes the outcome of a large cohort of COVID-19 patients based on clinical, laboratory, and radiological data collected at admission, enabling us to rapidly identify factors associated with outcomes that predict mild, moderate, or severe disease at the time of hospital admission the hospital.

Recently published studies have shown that patients admitted for COVID-19 often present with abnormal liver test, the incidence of liver injury ranging from 14% to 78% [1,6,16]. Moreover, preexisting liver disease has been shown to be associated with worsening infection prognosis [17]. However, the mechanistic events remain to be determined, and the causes of LFTs may be multifactorial, including causes unrelated to COVID-19. In contrast to previous studies, we analyzed only the laboratory liver tests at baseline in

Table 3 Characteristics of patients with mild and moderate versus severe COVID-19 on admission.

Variable	Mild and Moderate COVID-19 (n = 494)	Severe COVID-19 (n = 225)	p-value
Age (years, SD*)	63.1 (17.5)	68.3 (16.9)	< 0.001
Gender (male,%)	251 (50.8)	138 (61.3)	0.94
BMI (Kg/m^2) (mean, SD)	28.4 (5.9)	28.9 (5.9)	0.255
Comorbidity			
Diabetes (n,%)	126 (25.5)	75 (33.3)	0.032
Hypertension (n,%)	255 (51.6)	131 (58.2)	0.107
Dyslipidemia (n,%)	146 (29.6)	80 (35.7)	0.118
Chronic pulmonary disease (n,%)	113 (23)	63 (28)	0.161
Chronic cardiac disease (n,%)	125 (25.3)	72 (32)	0.071
Chronic kidney disease (n,%)	30 (6.1)	29 (12.9)	0.003
Cancer (n,%)	22 (4.5)	10 (4.5)	1
Symptoms onset			
"Flu-like" symptoms (n,%)	453 (91.7)	210 (93.3)	0.549
Respiratory symptoms (n,%)	438 (88.7)	208 (92.4)	0.435
Digestive symptoms (n,%)	248 (50.2)	96 (42.7)	0.064
Neurological symptoms (n,%)	229 (46.4)	106 (47.1)	0.872
Clinical features			
Oxygen saturation SaO_2 (%, SD)	92.9 (5.7)	85.3 (9.1)	< 0.001
Debit of oxygen at admission (l/mn, sd)	1.9 (6.7)	6.5 (7.7)	< 0.001
Systolic arterial pressure, mmHg	132.5 (20.8)	131.5 (20.9)	0.375
Laboratory tests			
AST U/L (reference range, 11−34)	48 (87.8)	73.1 (64.6)	< 0.001
ALT U/L (reference range, 8−41)	40.9 (32.8)	57.9 (110)	0.002
ALP U/L (reference range, 41−117)	75.2 (39)	72.3 (39.4)	0.178
GGT U/L (reference range, 6−40)	84.2(116.5)	84.7 (79.6)	0.087
Total Bilirubin μmol/l (reference range, 1.7−21.0)	11.1 (17.5)	11.6 (6.9)	0.01
Conjugated Bilirubin μmol/l (reference range< 4.3)	3.7 (2.6)	4.2 (2.4)	0.055
Albumin g/, (reference range, 35−50)	39.7 (5)	36.4 (5.4)	< 0.001
PT (normal range $> 70\%$) (%, SD)	88.9 (14.6)	85.6 (14.7)	< 0.001
Abnormality type (n,%)			
Hepatocellular >ULN	260 (52.6)	178 (79.1)	< 0.001
Cholestatic>ULN	114 (58.5)	81 (71.1)	0.028
Mixed type >ULN	72 (36.9)	72 (63.7)	< 0.001
CRP mg/L (reference range< 4)	77.7 (70.6)	148.7 (92.6)	< 0.001
Leucocytes $*10^9/l$ (reference range 4.5−6.5)	6.9 (3.3)	8.6 (4.4)	< 0.001
Neutrophil count $*10^9/l$ (reference range 1.3−7.7)	5.1 (2.9)	6.9 (3.9)	< 0.001
Lymphocytes $*10^9/l$ (reference range: 1.0−4.0)	1.2 (1.2)	1 (1.5)	< 0.001
Lymphocytes $*10^9/L$ ≤ 1.0 (n,%)	231 (46.8)	137 (60.9)	0.001
Fibrinogen g/l (reference range 2−4)	5.8 (1.5)	6.8 (1.4)	< 0.001
Platelets $*10^9/L$ (reference range 150−400)	228.3 (99.8)	210.6 (5.4)	0.028
D-Dimers (reference range 150−400)	2302.9 (3956.9)	2849.6 (4072.5)	0.001
Metabolic and fibrosis characteristics			
FIB-4 score (n,%)			< 0.001
≤ 1.3	170 (34.5)	24 (10.7)	
1.3−2.67	171 (34.7)	67 (29.9)	
> 2.67	152 (30.8)	133 (59.4)	
NAFLD (n,%)	311 (63)	134 (59.8)	0.455
NAFLD+ and FIB-4 (n,%)			< 0.001
NAFLD + FIB-4 < 1.3	95 (19.2)	20 (8.9)	
NAFLD + FIB-4 1.3−2.67	113 (22.9)	41 (18.3)	

Table 3 (*Continued*)

Variable	Mild and Moderate COVID-19 (n = 494)	Severe COVID-19 (n = 225)	p-value
NAFLD + FIB-4 > 2.67	286 (57.9)	163 (72.8)	
NAFLD fibrosis score (mean, SD)	−0.8 (1.8)	−0.6 (1.6)	0.435
Radiologic findings			
Severity of pneumonia (CT scan)			< 0.001
-absence (n,%)	49 (10.9%)	10 (5%)	
-<25%	243 (54.2%)	53 (26.6%)	
25−50%	126 (28.1%)	75 (37.7%)	
> 50%	30 (6.7%)	61 (30.7%)	
Delays from symptoms onset to hospitalization (days, SD)	6.6 (6.2)	7.2 (5.3)	0.062
Time of hospitalization	8.7 (8.5)	19.1 (12.8)	< 0.001

SD, standard deviation mean values; BMI: body mass index; SD: standard deviation; COVID-19: coronavirus disease 2019; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; ULN: upper limit of the normal; GGT: gamma-glutamyl transferase; LFTs: liver function tests; PT: prothrombin time; FIB-4: fibrosis-4; CRP: Creatine-reactive protein; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CT: computed tomography; HSI: hepatic steatosis index; NAFLD: non-alcoholic fatty liver disease; NFS: NAFLD fibrosis score; SaO_2: capillary oxygen saturation; TBIL: total bilirubin.

order to avoid the anomalies induced by different drugs administrated during the hospitalization.

In this present cohort, on admission, abnormal LFTs were present in 68.9% of patients, being more elevated than those previously reported in China at 14.9%, yet similar to those estimated in the United States at between 40%−67.5%. This controversy could be explained by the higher proportion of obese and diabetic patients in occidental countries [18].

Hepatocellular parameters, such as the AST and ALT, were elevated in 57% and 35.9% of patients, respectively, being beyond 2xULN in 17.4% and 4%, respectively. Patients with severe disease had a higher AST compared with moderate and mild disease patients ($p < 0.001$). The ALT was also more elevated in severe COVID-19 patients when compared with the other patient groups ($p = 0.02$). After adjusting for confounding factors, elevated transaminases, such as AST > 2xULN, and hepatocellular pattern type > 2xULN were associated with a 3-fold ($p < 0.001$) and almost 3.5-fold ($p < 0.001$) higher risk, respectively, of a poorer clinical outcome.

Recent studies have shown that SARS-CoV-2 binds angiotensin converting enzyme 2 *(*ACE2) receptors localized both in the liver and bile duct cells. The expression is higher in the cholangiocytes that may be associated with cholestatic abnormalities (elevated ALP and GGT) rather than hepatocellular abnormalities (AST and ALT) [1,20].

In our study, the ALP, GGT, and TBIL were elevated in 11.4%, 56.5%, and 5.8% of patients, respectively. Only an abnormal GGT was associated with moderate disease (GGT ULN, OR 0.108; 95%CI: 0.013−0.89, $p = 0.039$). Interestingly, ALP > 1−2xULN was more common in moderate and mild disease (91.5%) than in severe disease (83.9%) ($p = 0.045$). Our data confirm the hypothesis of Hundt et al. reporting that the mechanism of liver damage may be not caused by direct cytopathic effects of the novel coronavirus [19].

Obesity was associated with COVID-19 disease severity [21,22]. Indeed, in our study, 72.5% of patients that required hospitalization were overweight, with 34.6% being obese. The proportion of overweight patients increased with disease severity, as follows: 58.4% in mild, 71.8% in moderate, and 73.3% in severe COVID-19. Moreover, the hospitalized patients had a higher BMI compared to those discharged from an ER: 28.9 vs. 26.9 Kg/m^2 ($p = 0.001$).

A strong association between obesity and the severity of COVID-19 was previously reported, even in the absence of other comorbidities, yet the underlying mechanism is unclear [23].

Obesity is characterized by a chronic inflammatory state and disrupted immune response. The main cytokines responsible for chronic inflammation are tumor necrosis factor-alpha (TNF-α), interleukin (Il)−6, and IL-1 beta(β) [5]. Moreover, SARS-CoV-2 may cause a hyper-inflammatory reaction through the excessive release of cytokines, a condition known as “cytokine storm,” that may be enhanced by obesity, particularly in patients with a preexisting liver disease like NAFLD [24]. Adipose tissue may also be a viral reservoir and an immunological hub for the inflammatory response [25]. Individuals with severe obesity, diabetes, and hypertension are more likely to be infected and are at a higher risk of complications and death due to COVID-19 [2].

Indeed, in our study, metabolic factors were associated with the severity of COVID-19. Hypertension ($p = 0.002$) and dyslipidemia ($p = 0.001$) were associated with moderate disease, and diabetes was associated with a severe course of the disease ($p = 0.032$). Patients with metabolic syndrome had a 2.5-fold higher risk to develop a moderate ($p = 0.007$) or a severe disease ($p = 0.033$).

Abnormal GGT is commonly observed in NAFLD and is a sensitive marker of steatosis [11]. In our study, the ALP was elevated only in 11.4% of patients, and the mean values were not significantly higher in mild disease compared to moderate ($p = 0.938$) and severe forms ($p = 0.178$). Moreover, 56.5% of patients had abnormal GGT levels, and this was correlated with the severity of COVID-19 when comparing severe versus moderate ($p = 0.02$) and mild disease forms ($p = 0.016$).

Table 4 Factors associated with moderate severe COVID-19 after adjusting for confounding factors.

	OR	95%CI	p-value
MS (MRF 1 + 2 + 3 + 4)	2.45	1.07−5.61	0.033
NFS	1.181	1.01−1.37	0.033
FIB-4 (1.3−2.67)	2.006	1.09−3.67	0.024
FIB-4 > 2.67	4.756	2.68−8.43	< 0.001
AST ULN	0.406	0.27−0.61	< 0.001
AST > 2 ULN	3.187	1.99−5.08	< 0.001
ALT ULN	0.716	0.48−1.05	0.09
Hepatocellular type>ULN	2.265	1.48−3.45	< 0.001
Hepatocellular type >2 ULN	3.404	2.12−5.47	< 0.001
GGT> 1−3 ULN	1.676	0.97−2.88	0.062
Albumin ULN	0.422	0.21−0.82	0.01
Albumin	0.871	0.82−0.92	< 0.001
Leucocytes count	1.104	1.05−1.16	< 0.001
Neutrophil count	1.136	1.07−1.21	< 0.001
CRP > 200 mg/L	2.785	1.66−4.66	< 0.001
CRP < 100 mg/L	0.441	0.29−0.65	< 0.001
Fibrinogen	1.317	1.05−1.64	0.015
Lupus-anticoagulant	4.453	1.49−13.23	0.007

OR: odd ratio; CI: confidence interval; MS: metabolic syndrome, MRF: metabolic risk factors: 1-obesity; 2-diabetes, 3-dyslipidemia, 4-hypertension.
Adjustment for confounding factors that could disturb LFTs, as follows: hypoxemia (SaO2 < 93% related to severe pneumopathy) [16], and hepatotoxic drugs (acetaminophen, antibiotics) administrated before the hospitalization. Hypotension defined by systolic blood pressure < 90 mmHg was not considered because of the low number of cases < 10.

The prognosis of liver mortality was related to liver fibrosis [26]. Liver fibrosis evaluated with the FIB-4 score was associated with the severity of COVID-19 illness: 71.7% of patients with intermediate/high FIB-4 scores needed hospitalization compared to 41.6% of those with only mild disease ($p < 0.001$), and it was higher in patients with severe SARS-CoV-2 infection than in those with moderate and mild disease (89.3% compared to 65.5%, respectively) ($p < 0.001$). Patients who needed hospitalization had a more elevated NFS compared to those who were discharged from an ER ($p = 0.001$).

We associated the FIB-4 scores in patients diagnosed with NAFLD (Tables 2 and 4). In the hospitalized patients, 84.2% had an intermediate/high FIB-4 compared to 67.3% of those discharged from an ER ($p < 0.001$). In patients with a high FIB-4, 72.8% had severe disease compared to the 57.9% of those with moderate and mild disease ($p < 0.001$). Moreover, the patients with NAFLD without fibrosis (FIB-4 < 1.3) were at a lower risk of hospitalization (OR 0.404; 95%CI: 0.20−0.81; $p < 0.011$).

In the multivariate-adjusted analysis, patients with high FIB-4 scores had an almost 3-fold greater risk of hospitalization ($p = 0.011$), and a worse course of disease ($p < 0.001$).

In the context of the COVID-19 pandemic, along with the high prevalence of NAFLD in the general population, it is mandatory to early identify patients at risk of developing a severe disease. Applying non-invasive tests such as the FIB-4 and NFS in patients with metabolic liver disease could enable us to better and more quickly identify these patients that may have a poorer prognosis [27].

Our study had some limitations. First, the data were collected retrospectively, and there was missing information regarding the tobacco and alcohol consumption, several clinical parameters (waist and hip circumferences), and laboratory tests pertaining to metabolic syndrome, including glucose, glycated hemoglobin, cholesterol, and triglycerides levels. Second, while all patients underwent transaminase measurements at admission, only half of them underwent cholestasis enzyme assessment at admission, which could be deemed as a limitation in the statistical analysis. Third, HIS index was used in several publications to define NAFLD in COVID 19 patients [8−10]. It is a simple, disponible score that may help us to easy identify high-risk patients. His-limitation is related to the elevated transaminases levels that could underestimate the index.

In conclusion, obese patients with metabolic syndrome and a preexisting liver disease, including NAFLD and liver fibrosis, display a dysregulated hepatic innate immunity and pro-inflammatory state that is likely to enhance the “cytokine storm” due to SARS CoV-2 infection, leading to severe COVID-19 disease. Thus, abnormal LFTs at admission predict the outcome of COVID-19 patients.

Authors’ contributions

ST conceived and designed the study, collected patient data, performed data analysis and interpretation, and drafted the manuscript. MD conceived and designed the study, analysis, and interpretation of the manuscript and contributed to the critical revision of the manuscript. FC, JM contributed to data collection. TFB, DM, FM contributed to the critical revision of the manuscript. TF performed statistical analysis. All the others contributed to COVID-19 recruitment. All authors contributed to the manuscript revision and approved the submitted final version.

Acknowledgments

We acknowledge all the members of SELHVA (Service Expert de Lutte contre les Hépatites Virales d'Alsace) for their contribution to this research. In addition, we acknowledge the different medical teams: Francois DANION, Yves HANSMANN, Charlotte KAEUFFER, Yvon RUCH (Department of Infectious Disease), Murielle RONDEAU-LUTZ, Juliette JEANNEL, Cornelia KUHNERT, Esther NOEL, Philippe MERTZ, Jean-Christophe WEBER (Department of Internal Medicine, Nouvel Hôpital Civil), Abrar-Ahmad ZULFIQAR, Hanane SALEM (Department of Internal Medicine, Medical clinic B, Nouvel Hôpital Civil), Samira FAFI-KREMER (Virology Laboratory), Bernard GOICHOT (Department of Internal Medicine, Diabetes and Metabolic Disorders, Hôpital de Hautepierre), Frédéric de BLAY (Department of Pneumology), Gérald ROUL (Departement of Cardiology),Thierry MARTIN (Department of Rheumatology), Thierry HANNEDOUCHE (Department of Nephrology), the physicians in charge of patients at the Emergency Room, and all the departments at the Hôpitaux Universitaires de Strasbourg that were in charge of patients with SARS-CoV-2 infection. Moreover, we acknowledge all health-care workers involved in the diagnosis and treatment of COVID-19 patients, as well as the general management of the hospital for the organization of care in Hôpitaux Universitaires de Strasbourg. We thank all patients involved in the study.

References

[1] Xu L, Liu J, Lu M, et al. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40(5):998–1004 MayEpub 2020 Mar 30. PMID: 32170806; PMCID: PMC7228361. doi: 10.1111/liv.14435.

[2] Zhu N, Zhang D, Wang W, et al. China novel coronavirus investigating and research team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33 Feb 20 Epub 2020 Jan 24. PMID: 31978945; PMCID: PMC7092803. doi: 10.1056/NEJMoa2001017.

[3] Zhang Y, Zheng L, Liu L, et al. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. Liver Int 2020;40(9):2095–103 SepEpub 2020 Apr 28PMID: 32239796. doi: 10.1111/liv.14455.

[4] Bertolini A, van de Peppel IP, Bodewes FAJA, et al. Abnormal liver function tests in patients with COVID-19: relevance and potential pathogenesis. Hepatology 2020 Jul 2310.1002/hep.31480.Epub ahead of print. PMID: 32702162; PMCID: PMC7404414. doi: 10.1002/hep.31480.

[5] Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol 2020;16(7):341–2 JulPMID: 32327737; PMCID: PMC7187148. doi: 10.1038/s41574-020-0364-6.

[6] Lee JH, Kim D, Kim HJ, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42(7):503–8 JulEpub 2009 Sep 18. PMID: 19766548. doi: 10.1016/j.dld.2009.08.002.

[7] Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45(4):846–54 AprPMID: 17393509. doi: 10.1002/hep.21496.

[8] Ji D, Qin E, Xu J, Zhang D, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73(2):451–3 AugEpub 2020 Apr 8. PMID: 32278005. doi: 10.1016/j.jhep.2020.03.044.

[9] Huang R, Zhu L, Wang J, et al. Clinical features of COVID-19 patients with non-alcoholic fatty liver disease. Hepatol Commun 2020;4(12):1758–68 Aug 6Epub ahead of print. PMID: 32838108; PMCID: PMC7436597. doi: 10.1002/hep4.1592.

[10] Lopez-Mendez I, Aquino-Matus J, Gall SM, et al. Association of liver steatosis and fibrosis with clinical outcomes in patients with SARS-CoV-2 infection (COVID-19). Ann Hepatol 2021;20:100271 Jan-FebEpub2020 Oct 21. PMID: 33099028; PMCID: PMC7577265. doi: 10.1016/j.aohep.2020.09.015.

[11] Sterling RK, Lissen E, Clumeck N, et al. APRICOT clinical investigators. development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43(6):1317–25 JunPMID: 16729309. doi: 10.1002/hep.21178.

[12] World health organization protocol: real-time RT-PCRassays for the detection of SARS-CoV-2 institut pasteur, paris. https://www.who.int/docs/default-source/coronaviruse/real-time-rt-pcr-assays-for-the-detection-of-sars-cov-2-institut-pasteur-paris.pdf?sfvrsn=3662fcb6_2 Google Scholar

[13] Revel MP, Parkar AP, Prosch H, et al. COVID19 patients and the radiology departmentdadvice from the European society of radiology (ESR) and the European society of thoracic imaging (ESTI). Eur Radiol 2020. doi: 10.1007/s00330-020-06865-y.

[14] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a Report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020 Feb 24. doi: 10.1001/jama.2020.2648.

[15] Drosten C, Günther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003;348(20):1967–76 May 15Epub 2003 Apr 10. PMID: 12690091. doi: 10.1056/NEJMoa030747.

[16] Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol 2020;73(3):566–74 SepEpub 2020 Apr 13. PMID: 32298767; PMCID: PMC7194951. doi: 10.1016/j.jhep.2020.04.006.

[17] Saviano A, Wrensch F, Ghany MG, Baumert TF. Liver disease and COVID-19: from pathogenesis to clinical care. Hepatology 2020 Dec 17Epub ahead of print. PMID: 33332624. doi: 10.1002/hep.31684.

[18] Hajifathalian K, Krisko T, Mehta A, et al. Gastrointestinal and hepatic manifestations of 2019 novel coronavirus disease in a large cohort of infected patients from New York: clinical implications. Gastroenterology 2020 May 1. doi: 10.1053/j.gastro.2020.05.010.

[19] Hundt MA, Deng Y, Ciarleglio MM, et al. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1827 patients in a major U.S. hospital network. Hepatology 2020 Jul 29. Epubahead of print. PMID: 32725890. doi: 10.1002/hep.31487.

[20] Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV infection. bioRxiv 2020. doi: 10.1101/2020.02.03.931766.

[21] Simonnet A, Chetboun M, Poissy J, LICORN and the Lille COVID-19 and Obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020;28(7):1195–9 (Silver Spring)JulEpub 2020 Jun 10. Erratum in: Obesity (Silver Spring).2020 Oct;28(10):1994. PMID: 32271993; PMCID: PMC7262326. doi: 10.1002/oby.22831.

[22] Kaeuffer C, Le Hyaric C, Fabacher T, et al. Clinical characteristics and risk factors associated with severe COVID-19: prospective analysis of 1,045 hospitalised cases in North-Eastern France, March 2020. Euro Surveill 2020;25(48):2000895 DecPMID: 33272355; PMCID: PMC7716399. doi: 10.2807/1560-7917.ES.2020.25.48.2000895.

[23] Korakas E, Ikonomidis I, Kousathana F, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab 2020;319(1):E105–9 Jul 1Epub 2020 May 27. PMID: 32459524; PMCID: PMC7322508. doi: 10.1152/ajpendo.00198.2020.

[24] Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev 2020;21(6):e13034. JunEpub 2020 Apr 13.PMID: 32281287; PMCID: PMC7235532. doi: 10.1111/obr.13034.

[25] Docherty AB, Harrison EM, Green CA, ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. BMJ 2020;369: m1985. May 22PMID: 32444460; PMCID: PMC7243036. doi: 10.1136/bmj.m1985.

[26] Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology 2020;158:1611–25.

[27] Targher G, Mantovani A, Byrne CD, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. Gut 2020;69(8):1545–7 AugEpub 2020 May 15.PMID: 32414813. doi: 10.1136/gutjnl-2020-321611.