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ORIGINAL ARTICLE

# Liver function test abnormalities are associated with a poorer prognosis in Covid-19 patients: Results of a French cohort

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**KEYWORDS**
COVID-19;
Liver function test abnormalities;
Prognosis

**Abstract**
*Aim:* To assess the impact of liver function test (LFT) abnormalities on the prognosis of patients with coronavirus disease 2019 (COVID-19) in a French cohort of hospitalized patients.
*Patients and method:* From March 13 to April 22, 2020, we collected on a computerized and anonymized database, medical records, laboratory data and clinical outcomes of patients hospitalized for confirmed cases of COVID-19 infection (RT—PCR and/or CT-scan). Patients were followed up until April 22, 2020 or until death or discharge. We have considered for statistical analysis, LFT abnormalities with levels greater than two times the upper limit of normal. Composite endpoint included admission to ICU, mechanical ventilation, severe radiologic injury and death to define disease severity.
*Results:* Among 281 patients (median age 60 years) with COVID-19, 102 (36.3%) had abnormal LFT. Hypertension (45.6%) and diabetes (29.5%) were the main comorbidities. 20.2% were taken liver-toxic drugs at the admission and 27.4% were given drugs known to induce hepatic cytolysis during hospitalization. Patients with elevated levels of ALT or AST were significantly more severe with a higher rate of admission to ICU (40.0% vs 6.0%, $p < 0.0001$), and global mortality (26.7% vs 12.1%, $p = 0.03$). In multivariate analysis, obesity and cytolytic profil were associated with the composite endpoint (respectively 2.37 [1.21; 4.64], $p = 0.01$ and OR 6.20, 95% confidence interval [1.84, 20.95], p-value 0.003)

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*Conclusion:* Most of liver injuries are mild and transient during COVID-19. LFT abnormalities are associated with a poorer prognosis and could be a relevant biomarker for early detection of severe infection.


## Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan (China) and has resulted in a pandemic, with 1,771,514 confirmed cases worldwide as of April 12, 2020.

The most common symptoms are fever, dry cough, shortness of breath, myalgia/fatigue. Potential complications include pneumonia, acute respiratory distress syndrome, multi-organ failure and death [1,2]. Potential gastrointestinal manifestations of COVID-19 have been reported, including nausea, vomiting, diarrhea and abnormal liver function test (LFT) [1,3].

One study has shown that 14—53% patients displayed abnormal levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) during disease progression, [4] and that liver abnormalities could be used to stratify patients' risk and monitoring illness severity [4]. Notably, these results were obtained in the Chinese population, and there is to date no data concerning clinical and liver function biological characteristics of European patients infected with SARS-CoV-2.

In this study, we retrospectively investigated the changes in LFTs in in-hospital infected patients from a single center in Montfermeil, France. We aimed to assess the impact of liver function parameters on the clinical outcome of patients with COVID-19.

## Methods

### Study population

From March 13, 2020 to April 22, 2020, a total of 281 consecutive patients were hospitalized and treated for COVID-19 infection in Montfermeil Hospital, located in the suburb of Paris (France). The study was performed in compliance with French legislation regarding non-interventional studies. The study protocol was submitted to the Comité de Protection des Personnes (CPP) Sud-Est 4 and was in compliance with ethical consideration. It was also approved by CER-U Paris (Université Paris Descartes, 13 March 2020). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Patients (or their family representative) were provided with written information and asked to give their oral consent before inclusion.

### Data collection

We collected on a computerized and anonymized database patients'medical records who were hospitalized for confirmed cases of COVID-19 infection. Patients were followed-up until April 22, 2020 or until death or discharge. Biological tests were performed in Montfermeil Hospital biomedical laboratory. Blood tests were performed at the investigator's discretion. Radiologic assessment was based on computed tomography (CT). Images were interpreted by experienced radiologists. The presence of radiologic abnormalities was determined on the basis of medical charts. Severity was defined as the extent of damaged lung tissue (<10%; 10—25%; 25—50 %; 50—70 %; >70 %).

### Diagnosis

Inclusion criteria were confirmed cases of COVID-19 between March 13, 2020 and April 22, 2020 for all in-hospital patients over 18 years of age. Diagnosis was based on positive real-time reverse-transcriptase—PCR (RT—PCR) and/or typical aspect on non-contrast lung CT-scan, as defined by the Radiological Society of North America Expert Consensus Statement [5]. Confirmed cases were defined as a positive result on high-throughput sequencing or RT-PCR assay of nasal and pharyngeal swabs, on the basis of the World Health Organization (WHO) guidance. Patients whose molecular biology testing for the COVID-19 virus was inconclusive but who had typical injuries on lung CT scan were also included.

### Clinical characteristics

We collected clinical data on admission such as sex, age, body mass index (BMI) and comorbidities with a special attention to underlying liver disease. Drugs taken before and during hospitalization were also collected, especially those with liver toxicity. We additionnaly recorded the use of combined hydroxychloroquin-azithromycin administration.

### Biological data

Liver function was assessed through monitoring of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP). If more than one sample was collected, the highest value of each analyte was used. Abnormal liver function was defined as values greater than 2 times the upper limit of normal (ULN). Cytolytic profile refers to abnormal AST or ALT levels, and cholestatic profile refers to abnormal GGT levels. Patients with AST, ALT, ALP or GGT levels greater than 5 times the ULN were analyzed separately. Prothrombin, a reflect of liver function and coagulation, and CRP level at the day of admission, a marker of inflammatory response, were also recorded.

## Outcomes

Severity was determined through a composite outcome considering : (i) death, (ii) lung damaged extent >50% on CT-scan, (iii) respiratory failure requiring mechanical ventilation and (iv) admission to an intensive care unit (ICU). Criteria for intensive care admission in were: respiratory rate (RR) >30, requirement of oxygen flow >4 L/min in order to maintain an oxygen saturation >96%, a heart rate (HR) >90, systolic blood pressure <90 mmHg, consciousness disorders, respiratory failure and/or signs of shock.

## Statistical analyses

Summary statistics were medians and interquartile ranges for quantitative variables and percentages for categorical variables. Univariate analyses were performed using t-tests for quantitative variables and chi-squared test of independence or Fisher's exact tests for qualitative variables. Cyctolytic profile and variables with a *p*-value $\leq$0.20 in the univariate analyses were included in the multivariate model. A stepwise logistic regression analysis was performed to identify factors associated with cytolytic profile. The following variables were considered for multivariable logistic regression: gender, age, obesity, diabetes, hypertension, combine therapy (hydroxychloroquine-azithromycin) and hepatic cytolysis.

The odds ratio (OR) and 95% confidence interval (CI) were computed for each independent factor. p-values <0.05 were considered statistically significant. All statistical analyses was performed using soft ware SPSS (version 18.0).

## Results

358 patients were hospitalized for presumed COVID-19 infection from March 13 to April 22, 2020. 77 patients were excluded for negative PCR and no typical injuries on CT scan, when available.

## Characteristics of the population

Clinical and biological characteristics of the patients are shown in Table 1 and Table 2. Median age was 60 years (interquartile range (IQR), 46.5—73.5). Most patients were either overweight (39.5%) or obese (34.3%). In the overall cohort, hypertension (45.6%) and diabetes (29.5%) were the main coexisting comorbidities. No patients were being treated with non-steroidal anti-inflammatory drugs, 20.2% with liver-toxic drugs at the admission and 27.4% with therapy known to induce hepatic cytolysis during hospitalization (e.g., hydroxychloroquin and tocilizumab). Sixty point nine percent of confirmed COVID-19 cases had a positive RT-PCR test from nasal and pharyngeal swabs. Of 248 CT scans performed during the study period, 4.0% revealed >70% of lung damage. The median length of stay was 7.0 days (IQR [0—39]) and 11.0 days only in ICU. In total, 60.1% of patients suffered from severe disease, defined as ICU admission (15.3%), respiratory failure requiring mechanical ventilation (10.7%), >50 % of lung damage on CT scan (20.9%) or death (16.0%).

**Table 1 Clinical characteristics of 281 patients infected with SARS-CoV-2.** Quantitative variables are summarized as median (interquartile range) and categorical variables as number/total number (percentages).

| | All (281) |
|---|---|
| Age (year) | 60.0 (46.5—73.5) |
| **Sex** | |
| Female | 132/281 (47.0%) |
| Male | 149/281 (53.0%) |
| **BMI (kg/m$^2$)** | 28.0 (24.8—32.8) |
| <19 | 10/233 (4.3%) |
| 19—25 | 51/233 (22.0%) |
| 25—30 | 93/233 (39.5%) |
| >30 | 80/233 (34.3%) |
| **Comorbidities** | |
| Diabetes | 83/281 (29.5%) |
| Hypertension | |
| Heart Failure | 128/281 (45.6%) |
| COPD | 32/281 (11.4%) |
| Documented liver | 2/281 (0.7%) |
| disease | 2/281 (0.01%) |
| **Treatments** | |
| NSAIDs | 0/281 (0.0%) |
| Immunosupressants | 4/281 (1.4%) |
| Corticoids | 4/281 (1.4%) |
| **Liver-toxic drugs** | |
| At admission | 57/281 (20.2%) |
| During hospitalization● | 77/281 (27.4%) |
| Onset of symptoms to admission¶ in days | 7,0 (3.0—9.5) |
| Positive RT-PCR test from nasal and pharyngeal swabs | 171/281 (60.9%) |
| **Severity outcome** | |
| Admission to ICU | 43/281 (15.3%) |
| Mecanical ventilation | 30/269 (10.7%) |
| Death | 45/281 (16.0%) |
| **CT-scan Injury** | |
| <10% | 33/248 (13.3%) |
| 10—25% | 81/248 (32.7%) |
| 25—50% | 82/248 (33.1%) |
| 50—70% | 42/248 (16.9%) |
| >70% | 10/248 (4.0%) |
| **Length of stay (days)** | |
| All | 7.0 (0—39) |
| ICU | 11.0 (2—24) |
| Specific treatments | |
| Hydroxychloroquin—azithromycine | 72/277 (26.0%) |

*other liver toxic drugs : statine, febuxostat, fenofibrate, amlodipine, allopurinol, risedronate, mycophenolate mofetil, tacrolimus, ciclosporin, verapamil, diltiazem, rovamycine, ceftriaxon, rifampicin, valproate, carbamazepine, levetiracetam, amiodarone, pregabaline, econazole, apixaban,rivaroxaban, levodopa, gemcitabine.
●during hospitalization refers to patients who received either PQL/AZT combination or Tocilizumab therapy during.
¶Data regarding the onset symptom to admission (day) were missing for 24 patients (8,5%).

**Table 2** Biological characteristics of 281 patients infected with SARS-CoV2.

| | All |
|---|---|
| Laboratory tests | |
| Liver function — Median (*extremes*) [U/liter] | |
| AST (male or female [15—37] (1) | 51 (12—2056) |
| ALT (female [13—56] ; male [16—61]) (2) | 46 (8—1148) |
| GGT (female [5—55] ; male [15—85]) (3) | 79 (12—1186) |
| ALP (female - male) (4) | 73 (21—744) |
| PT (%) | 94 (11—100) |

(1) Data regarding AST were missing for 74 patients (26.3%).
(2) Data regarding ALT were missing for 38 patients (13.5%).
(3) Data regarding GGT were missing for 68 patients (24.2%).
(4) Data regarding ALP were missing for 46 patients (16.4%).

Median CRP (IQR 25—75) was 41.6 mg/L (7.5—76.8) in the non-severe group and 90 (65—171) in the severe group.

## Liver dysfunction

### Descriptive analysis

Of the 281 patients included, 102 (36.3 %) had liver dysfunctions. High level of GGT was the most common perturbation (25.3%), followed by elevated AST (24.3%) and ALT (12.8%) levels (Table 1). Only a minority of patients (6.4%) had perturbations above 5 times the ULN.

### Univariate analysis

Factors associated to cytolytic injury were male (73.7% vs 44.7%, $p < 0.0001$), liver toxic treatments (54.7% vs 35.0%, $p < 0.0001$), in particular statins, antiepileptics and hydroxychloroquin (45.9% vs 18.7%, $p < 0.0001$) (Table 3). Patients with high transaminase levels were significantly more severe with a higher rate of admission to ICU (40.0% vs 6.0%, $p < 0.0001$), CT-scan injury >50% (71.6% vs 39.7%, $p < 0.0001$) and global mortality (26.7% vs 12.1%, $p = 0.03$). Similar results were obtained for patients with cholestatic liver injury (Table 4) except for sex, liver toxic drug and global mortality (with respective *p*-values of 0.77, 0.13 and 0.38).

### Multivariate analysis

Table 5 shows the association of factors with the composite severity endpoint (admission to ICU, respiratory failure requiring mechanical ventilation, CT scan injury >50% and global mortality). Elevated levels of AST or ALT (6.20 [1.84; 20.95], $p = 0.003$) and obesity were associated with severe disease (2.37 [1.21; 4.64], $p = 0.01$). Age, gender, diabetes, hypertension and hydroxychloroquin were not associated with disease severity.

Table 6 shows descriptive and univariate analyses comparing CRP levels between the severe and non-severe group of patients. Median CRP was 41.6 mg/L (IQR 7.50—76.75) in non-severe group and 90.0 mg/L (IQR 65.0—171) in severe patients. CRP level was significantly higher in severe than in non-severe group ($p = 0.011$)

## Discussion

While the association between COVID-19 and liver function abnormalities have been studied in Chinese cohorts, data from the European pandemic is lacking. Here, we present the results of a monocentric French cohort of 281 patients consecutively hospitalized for COVID-19, and show that high ALT or AST levels are associated with disease severity.

Characteristics of our study population are in line with prior studies, with a slightly male predominance (53.0%) and a median age of 60.0 years. Main comorbidities were diabetes (29.5%) and hypertension (45.6%). Notably, Chinese cohorts displayed lower prevalence of diabetes (<10%) and obesity (with a median BMI of 22.6 $kg/m^2$) than this cohort [1,6]. Primary liver diseases were more frequent among Chinese patients, with a reported prevalence of 2.0% [1,6]; this discrepancy may be explained by the higher rate of chronic hepatitis B in China.

Severe infection is known to be more frequent among those patients, but they had mostly imbalanced diabetes or hypertension, which was not the case in our study Global mortality was also similar (16.0%), yet the number of admissions to ICU (15.3%) was higher than previously reported [1].

Thirty-six point three percent of patients showed liver abnormalities, in agreement with Chinese data, reporting liver impairment in 14—53% of cases of COVID-19 infections [4]. Notably, abnormalities were mild and transient in this cohort; in particular, <10% of patients had levels greater than 5 times the ULN at admission or during hospitalization.

Multivariate analysis showed that elevated levels of ALT or AST, as well as obesity, were associated with more severe disease. Obesity has already been identified as a predictive factor of severity [7]. Abnormal liver test could be an interesting tool for early detection of severe COVID-19 infection.

Liver abnormalities (especially cytolytic profile) is more frequent among male patients, for reasons that remain unclear. We found no significant difference in prevalence of comorbidities such as underlying liver disease, diabetes or hypertension and for liver toxic drugs intake between men and women. Further studies will be required to confirm and better understand the association between gender and cytolytic liver injury.

Liver injury in COVID-19 infection can be due to several mechanisms. It may be directly caused by the virus: recent studies showed that the key receptor for SARS-CoV-2 cell entry, (ACE2 receptor) was expressed in respiratory tract but also in other tissues, especially kidneys, enterocytes and cholangiocytes [8,9]. Future work will be needed to determine the exact mechanism of liver damage.

In this study, high level of GGT was the most frequent injury reported (25.3%), while ALP was not always substantially elevated. It is known that GGT and ALP are a reflect of the cholangiocyte function, even though it can be increased in injuries of other tissues. Pathological studies of liver tissues from patients with SARS-CoV2 confirmed the presence of virus, although viral inclusions were not observed, suggesting that viral titers are relatively low, and that liver damage in SARS-CoV-2 infection is likely to be mediated by apoptosis [10].

**Table 3** Characteristics of patients with COVID-19 and cytolytic liver injury.

| | AST or ALT ≥ 2 x ULN (n = 76) | AST or ALT < 2 x ULN (n = 206) | p-value | OR; (IC 95%) | |
|---|---|---|---|---|---|
| F/M | | 20/56 (26.3%) | 114/92 (55.3%) | < 0.0001 | 0.28 [0.16; 0.51] |
| BMI (kg/$m^2$) | >25 | 27 (37.0%) | 61 (30.7%) | 0.3 | 1.33 [0.76; 2.33] |
| | >30 | 30 (39.5%) | 88 (42.7%) | 0.65 | 0.88 [0.51; 1.51] |
| Diabetes | | 20 (26.3 %) | 63 (30.6%) | 0.53 | 0.83 [0.46; 1.49] |
| Hypertension | | 34 (45.3%) | 94 (45.6%) | 0.97 | 0.99 [0.58; 1.68] |
| Heart Failure | | 8 (10.7 %) | 24 (11.7%) | 0.82 | 0.91 [0.38; 2.11] |
| COPD | | 1 (1.3%) | 1 (0.5%) | 0.46 | 2.77 [0.17; 44.9] |
| >1 comorbidity | | 19 (28.2%) | 58 (25.3%) | 0.64 | 0.87 [0.47; 1.58] |
| Treatments | NSAIDs | 0 (0.0%) | 0 (0.0%) | — | — |
| | Immunosuppressant | 5 (6.7%) | 6 (2.9%) | 0.15 | 2.8 [0.71; 8.05] |
| | Liver toxic drugs | 41 (54.7%) | 72 (35.0%) | 0.003 | 2.24 [1.31; 3.84] |
| | Hydroxychloroquin | 34 (45.9%) | 38 (18.7%) | < 0.0001 | 3.68 [2.07; 6.58] |
| Admission in ICU | | 30 (40.0%) | 13 (6.3%) | < 0.0001 | 9.90 [4.78; 20.48] |
| CT scan injury > *50*% | | 53 (71.6%) | 81 (39.7%) | < 0.0001 | 3.83 [2.15; 6.83] |
| Death | | 20 (26.7%) | 25 (12.1%) | 0.003 | 2.63 [1.36; 5.10] |

**Table 4** Characteristics of patients with COVID-19 and cholestatic liver injury.

| | GGT ≥ 2 x ULN (n = 71) | GGT< 2 x ULN (n = 210) | p-value | OR; (IC 95%) | |
|---|---|---|---|---|---|
| Sex ration (F/M) | | 32/39 (45.1%) | 97/109 (47.1%) | 0.77 | 0.92 [0.54; 1.59] |
| BMI (kg/$m^2$) | >25 | 25 (37.3%) | 63 (30.7%) | 0.3 | 1.34 [0.75; 2.39] |
| | >30 | 26 (38.8%) | 92 (44.9%) | 0.78 | 0.88 [0.44; 1.37 |
| Diabetes | | 21 (29.6 %) | 62 (29.5%) | 0.99 | 0.83 [0.56; 1.81] |
| Hypertension | | 31 (43.7%) | 97 (46.2%) | 0.71 | 0.90 [0.53; 1.55] |
| Heart Failure | | 6 (8.5 %) | 26 (12.4%) | 0.37 | 0.65 [0.26; 1.66] |
| COPD | | 1 (1.4%) | 1 (0.5%) | 0.42 | 2.99 [0.18; 48.4] |
| >1 comorbidity | | 20 (28.2%) | 57 (27.1%) | 0.87 | 1.05 [0.58; 1.92] |
| Treatments | NSAIDs | 0 (0.0%) | 0 (0.0%) | — | — |
| | Corticoids | 1 (1.4%) | 3 (1.4%) | 0.99 | 0.99 [0.10; 9.63] |
| | Immunosuppressant | 5 (7.0%) | 6 (2.9%) | 0.12 | 2.58 [0.76; 8.71] |
| | Liver toxic drugs | 34 (47.9%) | 79 (37.6%) | 0.13 | 1.52 [0.89; 2.62] |
| | Hydroxychloroquin | 26 (36.6%) | 46 (22.3%) | 0.018 | 2.01 [1.12; 3.60] |
| Admission in ICU | | 22 (31.0%) | 21 (10.0%) | < 0.0001 | 4.04 [2.06; 7.94] |
| CT scan injury > *50*% | | 46 (65.7%) | 88 (42.3%) | 0.001 | 2.61 [1.49; 4.60] |
| Death | | 9 (12.7%) | 36 (17.1%) | 0.38 | 0.70 [0.32; 1.54] |

**Table 5** Multivariate analysis: predictive factors associated with severity composite endpoint.

| Predictive Factor | p-value | OR; CI (95%) |
|---|---|---|
| Sex | 0.10 | 060 [0.329; 1.10] |
| Age | 0.35 | 1.01 [0.99; 103] |
| obesity | 0.01 | 2.37 [1.21; 4.64] |
| Diabetes | 0.26 | 0.67 [0.34; 1.34] |
| Hypertension | 0.66 | 0.85 [0.42; 1.74] |
| Hydroxychloroquin | 0.77 | 1.13 [0.51; 2.49] |
| Hepatic cytolysis | 0.003 | 6.20 [1.84; 20.95] |

**Table 6** CRP level at the day of admission in severe and non-severe groups.

| CRP (mg/L) | Non-severe | Severe |
|---|---|---|
| Median (IQR) | 41.6 [7.5; 76.8] | 90.0 [65.0; 171.0] |

An other possibility is that liver damage is induced by hepatotoxic drugs. In our study, 20.4% of patients had liver-toxic treatments on admission (mainly statins, antiepileptics and oral anticoagulants). Twenty-seven point four percent of patients were treated by hydroxychloroquine during hospitalization. Elevation of liver transaminases is a frequent secondary effect and has been a cause of early interruption.

Last, it is also possible that liver abnormalities are due to sepsis and tissue hypoxemia. Levels of CRP, a good marker of inflammation, were significantly higher in severe group ($p$ = 0.011). Histological examination showed apoptotic injuries

such as vesicular steatosis and watery degeneration which may be due to hypoxemia [6]. COVID-19 infection is characterized by an important inflammatory response, resulting in cytokine storm and pneumonia-associated hypoxia. It might contribute to liver injury and even liver failure in patients who are critically ill.

Several limitations of this study should be noted. As a monocentric study, it may be difficult to generalize results to other regions of varying epidemiological characteristics. Still, Seine Saint-Denis, the suburb where Montfermeil Hospital is located, is one of the most affected region in France with a high level of hospitalization and death rate.

Because of the retrospective study design, only a few patients were known to have underlying liver disease. It is hard to know if LFT abnormalities reflect their baseline liver function or a real effect of COVID-19 infection. In this study, we mainly focused on the peak-value. Future work with regular and standardized follow-up at the beginning and during and hospitalization period would be interesting to precisely explore the kinetics of liver dysfunction. It would help to determine if elevated LFT are a risk factor of severe disease or if severe disease induces liver dysfunction.

Comorbidities such as balanced diabetes and hypertension were not associated to the composite endpoint. Combination therapy using hydroxychloroquin and azithromycin was also not associated with severe disease. A possible explanation is the lack of standardized criteria to begin a combination therapy: in Montfermeil Hospital, respiratory failure requiring oxygenotherapy greater than 4 L per minutes associated with a respiratory rate greater than 28 per minute were one of those criteria, which differs from the definition of severe disease in our study.

In conclusion: 36.3% of patients with COVID-19 infection had abnormal liver test during the study period. Liver tests abnormalities were associated with a poorer prognosis and could be a crucial biomarker for early detection of severe infection

## Conflicts of interest

Stéphane Nahon reports lecturer or advisory board fees from AbbVie, MSD, Vifor Pharma, Pfizer, Janssen and Ferring.

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