Liver damage in COVID-19 infected patients: A series of 299 cases: Mohammed VI Hospital University experience

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Abstract
COVID-19 infection is a viral infection with a particular tropism for lung tissue. However, organs involvement other than lung have been reported. Liver is also reported to be injured during infection by COVID-19 infection, which is most often revealed by an early elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST).

Involvement of liver could be explained by interaction of the virus with the hepatocytes directly through infecting them or through ischemia secondary to lung lesions. Drugs used in COVID-19 management have also been reported to be hepatotoxic.

Our work is a retrospective study that was about 299 COVID-19 infected patients. We aim through this study to report the occurrence of liver damage in COVID-19 infection. All subjects of our study have been admitted to the Oujda Mohammed VI university hospital of Morocco. All biological explorations in our series have been performed in the central laboratory of the same establishment.

Keywords: COVID-19, Liver injury, SARS-CoV-2, marker
Introduction
The 2019 novel coronavirus disease has posed a serious danger worldwide. The major damage induced during COVID-19 infection is lung damage. The liver has also been reported to be injured in terms of COVID-19 infection, especially in case of severe infections. [1] In one study in China, hepatic dysfunction has been reported in up to 50% of infected patients. The implicated pathophysiological factors are not yet fully understood and not enough evidence exists to prove if the COVID-19 virus is directly implicated in liver lesions. [2]
We aim through this work to report the incidence of liver damage in COVID-19 infected patients in a cohort of 299 patients who has been admitted to the reference hospital of the oriental region Mohammed VI University, during the second wave of the pandemic. We also will be discussing the physiopathology of liver involvement in COVID-19 infection and the impact of the virus on patients with chronic liver disease.

Materials and Methods
We report the result of a retrospective study about 299 patients who has been hospitalized for COVID-19 infection. A diagnosis of COVID-19 was based on SARS-CoV-2 real time reverse-transcriptase polymerase-chain-reaction (RT-qPCR) in respiratory samples in our laboratory. We have collected data from all hospitalized COVID-19 patients in a time period of four months from August to September 2021. Biological data have also been analyzed to report any alteration in levels of serum GOT, GPT, GGT, alkaline phosphatase, albumin and total bilirubin. All biological explorations in our series have been performed in the central laboratory of the Mohammed VI university hospital of Oujda, Morocco, those parameters are Inexpensive, available in all laboratories and measured by using atomic absorption spectrophotometry (ARCHITECT ci8200, Abbott Laboratories). Analytical method verification was performed; repeatability and intermediate precision were achieved.

Results (Table 1)
Our series contains 299 COVID-19 infected patients. They have been all admitted to the Mohammed VI university hospital for management of confirmed COVID-19 infection. There were 155 male patients (51,8%), and 144 female patients (48,2%). The sex ratio was calculated at 1,07. The age of our patients ranged from 1 to 101 years with an average of 64,32 years. The average duration of hospitalization was at 11,02 days ranging from 1 to 45days. 221 patients (73,9%) have recovered. 78 patients (26%) have however died.
Exploration of hepatic biological data have revealed variable alteration in regard of the different tested indices:
AST (aspartate aminotransferase) levels had values between 4 and 1479 UI/l with an average of 67.5UI/l. AST levels were found to be elevated in 224 cases (75%) ALT (alanine aminotransferase) levels had values between 6 and 1474UI/l with an average of 46,5UI/l. ALT levels were found to be elevated in 175 cases (58,5%) GGT (Gamma glutamyl-transferase) levels had values between 1.75 and 1192UI/l with an average of 87,99UI/l. GGT levels were found to be elevated in 174 cases (58,2%) Alkaline phosphatase levels had values between 4.9 and 1328UI/l with an average of 87,99UI/l. GGT levels were found to be elevated in 174 cases (58,2%) Total bilirubin levels had values between 19 and 1176mg/l with an average of 98,26mg/l. total bilirubin levels were found to be elevated in 293 cases (98%) Albumin levels had values between 20 and 47g/l with an average of 32,96g/l. Albumin was found to be decreased in 187 cases (62,5%).
Table 1. Characteristics of the patients (N=299) included in the study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>155 (51,8%)</td>
</tr>
<tr>
<td>Female sex</td>
<td>144 (48,2%)</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1,07</td>
</tr>
<tr>
<td>Age of patients</td>
<td>64,32 (1-101 years)</td>
</tr>
<tr>
<td>Duration of hospitalization</td>
<td>11,02 days(1-45 days)</td>
</tr>
<tr>
<td>Recovery rate</td>
<td>221 (73,9%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>78 (26%)</td>
</tr>
<tr>
<td>AST level</td>
<td>4 - 1479 UI/l (67.5UI/l)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>224 cases (75%)</td>
</tr>
<tr>
<td>ALT level</td>
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<td>ALT elevation</td>
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</tr>
<tr>
<td>GGT levels</td>
<td>1.75 -1192UI/l (87,99UI/l)</td>
</tr>
<tr>
<td>GGT elevation</td>
<td>174 (58,2%)</td>
</tr>
<tr>
<td>Alkaline phosphatase levels</td>
<td>4.9 -1328UI/l (94.4UI/l)</td>
</tr>
<tr>
<td>Alkaline phosphatase elevation</td>
<td>72(24,1%)</td>
</tr>
<tr>
<td>Total bilirubin levels</td>
<td>19- 1176mg/l (98,26mg/l)</td>
</tr>
<tr>
<td>Total bilirubin elevation</td>
<td>293 (98%)</td>
</tr>
<tr>
<td>Albumin levels</td>
<td>20 - 47g/l (32,96g/l)</td>
</tr>
<tr>
<td>Albumin decrease</td>
<td>187 (62,5%)</td>
</tr>
</tbody>
</table>

Discussion:
The COVID-19 infection manifests most often in form of respiratory symptoms with reported non-respiratory symptoms such as abdominal pain, vomiting, nausea and diarrhea. [3]
Evidence that the COVID-19 virus is not limited to the respiratory system have been reported in some recent studies proving presence of COVID-19 viral particles in the stool in over half of cases. Biopsies of the gastrointestinal tract have also shown mucosal alterations in the stomach, duodenum and rectum in form of oedema and lympho-plasmocytic inflammatory infiltrates. [4]
This presence of COVID-19 virus in the stool raises the possibility of an oro-fecal transmission. This was further demonstrated by identifying COVID-19 RNA in the stool in 20% patients, especially in the hospitalized individuals. [4]
Liver is also reported to be injured during infection by COVID-19 infection. This injury is most often revealed by an early elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). [5]
Decrease of Albumin serum level and increase of bilirubin levels have also been reported. [5]
In severely infected patients, the liver injury tends to be also severe when compared to patients presenting with mild respiratory symptoms. [1,6].
Many theories exist to explain the involvement of liver during the COVID-19 infection. One of the theories is tending to explain the hepatic lesion through involvement of liver immune cells such as the intrahepatic cytotoxic T cells and Kupffer cells. [7]
On the pathological level, analysis of liver biopsies from patients who have died from COVID-19 infection showed mild lobular and portal activity with microvascular steatosis. These data suggest 2 possible factors inducing liver lesions: the virus it self and toxicity of drugs used against it. [8]
The direct interaction of the virus with the hepatocytes is explained by the abundant presence of ACE2 receptors in the live which suggests the possible infection of hepatocytes by the virus. [9]
Hepatic ischemia secondary to respiratory manifestations could also contribute the inflammatory
response in the liver. [10]
Among the drugs used in the management of COVID-19 infection, lopinavir/ritonavir are the most implicated ones in the genesis of liver lesions. [11]
Many studies have shown that patients with history of B or C chronic hepatitis have no increased risk or COVID-19 infection. However, the infection in these patients, most often presenting other comorbidities, tend to have more severe forms of this infection. [12]
When patients with chronic liver disease are infected, they could present decompensation or a viral reactivation in cases of B or C chronic hepatitis. [18]
In case of patients with history of nonalcoholic fatty liver disease (NAFLD), a higher risk of severe COVID-19 infection has been reported in recent studies. [13]
In many studies, and although many hepatic biological indices were elevated in severely infected patients, no correlation was found between liver biological alteration during COVID-19 infection and the severity of infection. That would be explained by the fact that the liver is not the target organ of COVID-19 virus. [14]
After recovery, hepatic function returns to its normal or anterior state meaning that hepatic alterations during COVID-19 infection are temporary and do disappear without any special therapy. [15]
In the literature, recent studies have identified an incidence of 14.8 to 53% for the occurrence of liver injury during COVID-19 infection. The most relevant biological findings were abnormal ALT/AST levels, a slight elevation of bilirubin levels [16,17].
In a recent study in China, about approximately 1100 patients, a difference was identified between patients with severe COVID-19 infection when compared to those with a non-severe form in terms of occurrence of liver injury. The incidence was at about 56% in patients with severe infection and 18% in patients with non-severe infection. [18]
In this same study, the difference was not very remarkable when it comes to ALT levels since this latter was elevated in 20% of patients with non-severe COVID-19 infection and in 28% in patients suffering from the severe form. [18]
In cases of deaths complicating COVID-19 infections, the ALT and AST level have been also reported to be elevated and could reach in one case values of 7590 and 1445U/L for ALT and AST respectively. [19]
The decrease in Albumin levels was identified especially in severe cases and the reported values was between 26.3 and 30.9g/L [19].

Conclusion:
Our study showed a significant elevation of aminotransferase levels and a decrease in albumin with an increase in bilirubin in patients infected with COVID-19. These findings are probably due to two factors that can induce liver damage: the virus and the drugs used to treat it. After recovery, liver function returns to normal or previous levels, meaning that liver damage during COVID-19 infection is temporary and disappears without special treatment. Despite the elevation of many liver biologic parameters in severely infected patients, no correlation is found between liver biologic alteration during COVID-19 infection and severity of infection. This could be explained by the fact that the liver is not the target organ of COVID-19.
References:


