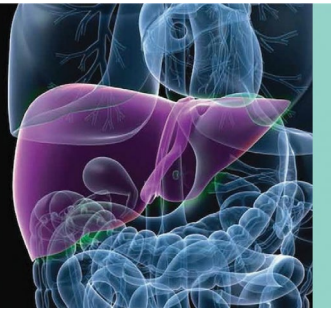


# The Liver and COVID-19 in Mexico

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## BACKGROUND

Coronavirus disease 2019 (COVID-19) has been since its origins a highly contagious disease. The virus spread rapidly across the planet, and by May 2021, it had infected more than 168 million people in 191 countries.<sup>1</sup> After Asia and Europe, America was severely affected by the pandemic. The first case in Latin America was reported in Brazil on February 26, 2020, and the first death on March 7 in Argentina.<sup>2</sup> In Mexico (the 13th-largest country in the world in size and the 10th most populous with 128,649,565 inhabitants), the first case was reported on February 25 and the first death on March 18, and by May 2021, 2.5 million Mexicans have been infected, with a mortality close to 10% (224,000).<sup>3</sup>

The Mexican government declared a national health emergency on March 30 and implemented restrictions in the public, private, and social sectors which include: voluntary quarantine (lock-down), school closings, social distancing, and limitation of non-essential activities. Simultaneously, the number of cases (especially severe cases) increased, and as in other parts of the world, it was reported that between up to 30% of Mexican patients infected by severe acute respiratory syndrome coronavirus-2

(SARS-CoV-2) developed gastrointestinal and liver manifestations (Fig. 1).<sup>4,5</sup>

Immediately, medical associations dedicated to gastroenterology and hepatology in Mexico issued recommendations and guidelines for the identification, management, and treatment of patients with liver manifestations associated with SARS-CoV-2, as well as for patients with pre-existing liver disease and liver transplant.<sup>7,8</sup> Also, the groups dedicated to the research of liver diseases in Mexico in collaboration with national and international partners undertook the task of describing the first series of cases, risk factors, and mortality associated with COVID-19 in Mexicans (Table 1).

## LIVER DAMAGE DUE TO SARS-COV-2

Liver injury in COVID-19 patients is related to several factors, including direct cytopathic effect of the virus, immune-mediated collateral damage, or an exacerbation of preexisting liver disease.<sup>6</sup> As in other cases series, abnormal liver functions tests (LFT) was a common finding in Mexican patients with COVID-19. In the first cohort reported in our country in May 2020, abnormal liver enzyme

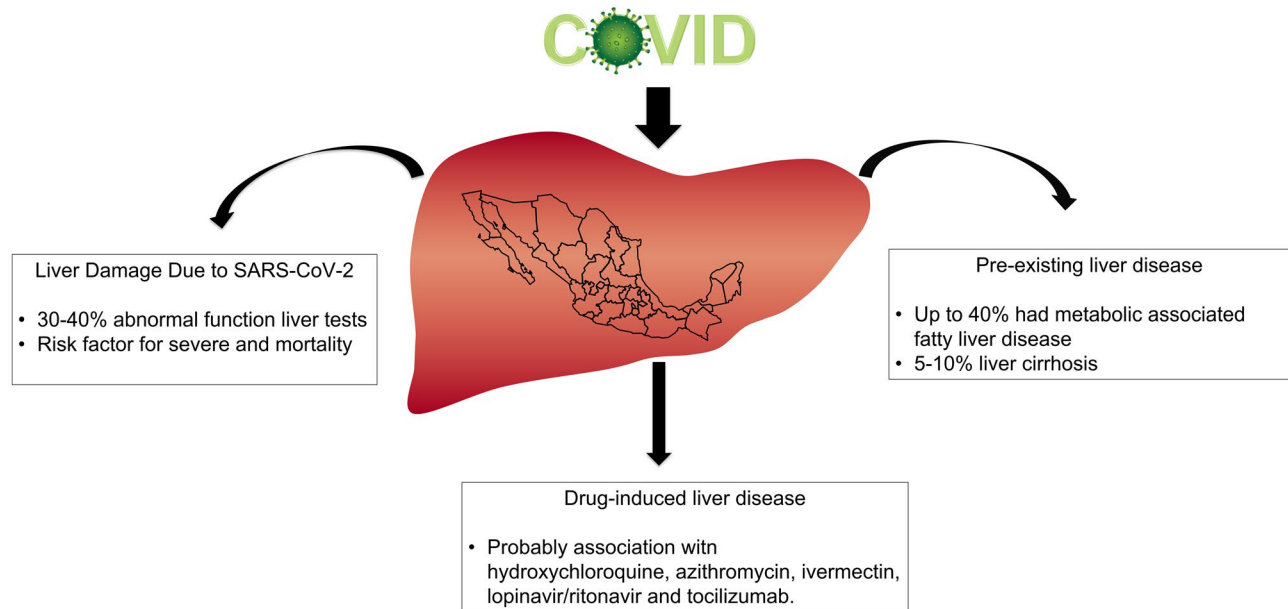
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**FIG 1** The liver and COVID-19 in Mexico.

levels were abnormal in 33% of cases and this finding was associated with mortality.<sup>4</sup> In a prospective study coordinated by the Latin American Association for the Study of the Liver (ALEH) in 1,611 hospitalized patients, abnormal LFT on admission were present on 45.2% of the cohort and mortality was 15.1%.<sup>9</sup> Patients with abnormal LFT on admission presented higher mortality 18.7% compared to those with normal liver biochemistries 12.2% ( $P < 0.0001$ ). After excluding patients with history of chronic liver disease, abnormal LFT on admission were independently associated with death and severe COVID-19, both adjusted by age, gender, diabetes, pneumonia, and body mass index  $>30$ . Similar results have shown in recent prospective multicenter international cohort among 829 hospitalized patients (203 from Mexico), in whom hypertransaminasemia was present in 267 patients (32.3%) and liver injury during hospitalization was associated with a higher hospital stay ( $>10$  days) and worst outcome.<sup>5</sup> Further studies in our population have shown consistently that abnormal LFT, in particular alanine aminotransferase and aspartate aminotransferase, were associated with a higher in-hospital mortality risk (Table 1).<sup>10,11</sup>

## PREEXISTING LIVER DISEASE AND COVID-19

Although initial data reported that previous liver disease was not associated with severity, later studies shown an important association between preexisting liver disease (such

as nonalcoholic fatty liver disease [NAFLD]) and COVID-19. As expected, due to high prevalence of overweight and obesity in our population, studies in Mexican COVID-19 patients have found a high prevalence of metabolic comorbidities, which included hypertension, NAFLD and type 2 diabetes. In a retrospective study in 155 hospitalized Mexican patients, abnormal LFT were present in 96.8%, prevalence of steatosis was 42.6% and of significative liver fibrosis was 44.5%.<sup>12</sup> Liver fibrosis by FIB-4 was associated with risk of intensive care unit (ICU) admission (odds ratio [OR] 1.74;  $P = 0.023$ ) and mortality (OR 6.45,  $P = 0.002$ ); but no independent associations were found. In a more recent study Campos-Murgía et al.<sup>13</sup> found in 432 hospitalized patients with COVID-19 that 40.6% fulfilled criteria for metabolic associated fatty liver disease (MAFLD). Although the authors did not find significant differences in the outcomes of hospitalized patients with MAFLD and those without MAFLD, a significant increase in the risk of mechanical ventilation requirement, acute kidney injury, and mortality in patients with MAFLD and advanced liver was found. The role of MAFLD in the outcomes of patients with COVID-19 is still controversial.

## DRUG-INDUCED LIVER INJURY AND SARS-CoV-2

Drug-induced liver injury (DILI) should be considered among the important differentials of liver injury in

**TABLE 1 . PUBLICATIONS ON THE IMPACT OF SARS COV-2 INFECTION AND THE LIVER IN THE MEXICAN POPULATION**

Author	Journal	Setting	n	Abnormal liver function tests (%)	Pre-existing liver diseases (%)	Outcome
Remes-Troche JM, et al. <sup>4</sup>	Gastroenterology	Retrospective, single center Veracruz, Mexico (Southeast Mexico)	112	33%	Not know	Liver abnormalities were associated to mortality
Sánchez-Luna SA, et al. <sup>5</sup>	Gastroenterology	Prospective, multicenter, international Mexico, Spain, Chile and Poland	829	32.3%	Steatosis (2.4%)	Liver injury during hospitalization was associated with a higher hospital stay (>10 days) and worst outcome
Mendizabal M, et al. <sup>9</sup>	Annals of hepatology	Prospective multicenter evaluation	1,611	45.2%	Overall, 8.5% had chronic liver disease and 3.4% had cirrhosis.	Mortality was 15.1%. (9) Patients with abnormal LFT on admission presented higher mortality 18.7% compared to those with normal liver biochemistries 12.2% ( $P < 0.0001$ ).
		11 Latin American countries			The most common etiologies of chronic liver disease were metabolic-associated fatty liver disease, alcohol, chronic hepatitis C and cholestatic diseases.	
Vidal-Cevallos et al. <sup>10</sup>	Annals of Hepatology	Retrospective multicenter (3 centers) México City	377	Not reported	Not reported	An alanine aminotransferase > 61 U/L, C-reactive protein > 231 mg/l and lactate-dehydrogenase > 561 U/l were associated with higher odds for in-hospital death.
Higuera-de la Tijera, et al. <sup>11</sup>	Liver Research	Observational case control study México city	166	Not reported	10.2% had chronic liver disease (liver cirrhosis, non-alcoholic fatty liver, autoimmune hepatitis, hepatitis C related cirrhosis)	Multivariate analysis showed that important factors at admission predicting the requirement for mechanical ventilation aspartate aminotransferase $\geq 250$ IU/L and D-dimer $\geq 3500$ ng/mL).
López-Méndez et al. <sup>12</sup>	Annals of hepatology	Retrospective, single center México City	155	96.8%	Liver steatosis 42.6% and significant liver fibrosis 44%	Liver fibrosis by FIB-4 was associated with risk of ICU admission and mortality.
Campos-Murguía A, et al. <sup>13</sup>	Digestive Liver Diseases	Retrospective, single center México City	432	Not reported	40.6% had fatty liver by CT scan assessment	The presence of fibrosis rather than the presence of metabolic associated fatty liver disease was associated with increased risk for mechanical ventilation, development of kidney failure, and higher

COVID-19 patients. In Mexico, as in other parts of the world, the desperation for effective therapy at the beginning of the pandemic led to the indiscriminate and irrational use of drugs that could potentially trigger DILI. It is probable that many of the abnormal LFT in our Mexican patients were associated with the following drugs: hydroxychloroquine, azithromycin, lopinavir/ritonavir, ivermectin, baricitinib, tocilizumab, and remdesivir.

## CONCLUSIONS

In summary, despite the high prevalence of metabolic diseases and chronic alcohol consumption in Mexico, the impact of the SARS-CoV-2 on the liver in Mexican patients was similar to that described in other parts of the world. The long-term effects and sequelae of liver function in Mexican patients with pre-existing liver disease are yet to be determined.

## CORRESPONDENCE

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