Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Low seroprevalence of SARS-CoV-2 antibodies in cirrhotic patients

Dear Editor,

Patients with underlying liver cirrhosis and coronavirus disease 2019 (COVID-19) seem to be at increased risk of adverse outcomes due to both hepatic decompensation and respiratory failure, as described in recent studies from all over the world [1–3]. Despite the efforts to promote two combined worldwide registries, the reported cumulative number of cirrhotic patients with an outcome in literature is far lower than 1000 individuals out of more than 27 million COVID-19 cases worldwide [4]. Cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with liver cirrhosis mainly come from hospitalized cohorts and suffer from reporting biases, thus cannot be extended to the whole population of cirrhotic patients. Evidence about asymptomatic and mildly symptomatic COVID-19 in patients with pre-existing liver cirrhosis is currently lacking.

Serology testing for SARS-CoV-2 antibodies has been recognized as a useful tool to diagnose previous or active infection in both symptomatic and asymptomatic individuals. According to the preliminary results of a study on SARS-CoV-2 seroprevalence performed by the Italian Institute of Statistics (ISTAT) between May 25th and July 15th 2020 [5], percentages in the Lazio region of Italy has been estimated to be as high as 1%. Despite such a high prevalence, none of the consecutive patients hospitalized for COVID-19 in our Center was affected by liver cirrhosis [6].

The aim of our study was to describe the seroprevalence of SARS-CoV-2 antibodies in a cohort of cirrhotic patients from the Lazio region of Italy after the first pandemic wave of early 2020.

Patients affected by liver cirrhosis attending the outpatient liver clinic of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS were consecutively enrolled starting from May 25th to August 10th 2020. All the study participants answered a questionnaire to assess the risk of social exposure as well as the occurrence of suggestive COVID-19 symptoms during the lockdown period in Italy (from March 12nd to May 4th 2020). The occurrence of liver-related clinical events (hepatic encephalopathy, ascites, gastrointestinal bleeding or newly diagnosed hepatocellular carcinoma) and the number of visits postponed were also recorded.

Serum SARS-CoV-2 antibodies were evaluated by a chemiluminescent immunoassay using the Atellica™ Solution instrument (Siemens).

Two-hundred-twenty-two cirrhotic patients were evaluated over the study period. Twenty of them refused to participate in the study; therefore 202 patients were finally included in the analysis (Table 1). Median age was 70.9 (61.0–77.7) years, with a prevalence of male gender (64.9%). Viral etiology was the most prevalent (51.5%), followed by nonalcoholic fatty liver disease (26.7%) and alcohol-related liver disease (29.7%). Fifty-three (26.2%) patients had a history of HCC, 56.6% of them with active disease. Liver cirrhosis was compensated in 75.24% of patients who were classified as Child-Pugh class A, while 19.8% were classified as Child-Pugh B and 2.5% as Child-Pugh C; the median model for end-stage liver disease (MELD) score was 9 (7–12). Signs of portal hypertension were present in 75.7% of the study participants.

Most patients (93.1%) lived in small family units (up to three cohabiting family members) and 33.7% of them received visits from non-cohabiting persons. More than one outing per week during the lockdown period was reported by 80 (39.6%) patients, and 83 (41.1%) attended at least one visit in hospitals or medical centers. Two patients reported SARS-CoV-2 infection among their family members and four among acquaintances, however only one had direct contacts with these subjects.

Ninety-seven (48%) patients received vaccination for influenza virus, 35 (17.3%) for Streptococcus pneumoniae, and 34 (16.8%) for both.

Overall, 45 (22.3%) patients presented any symptom compatible with SARS-CoV-2 infection. Fever and cough were the most common (11.9% each), followed by diarrhea (4.5%); a minority of patients reported also nausea/vomiting, conjunctivitis, or dysgeusia/anosmia. As shown in Table 1, the demographic and clinical features of patients in the asymptomatic group were similar to those of patients in the symptomatic group.

Three patients who did not report any symptom were tested positive for SARS-CoV-2 antibodies (overall prevalence 1.5%; considering asymptomatic patients only 1.9%). As summarized in Table 2, all of them presented compensated liver cirrhosis (Child-Pugh score A5, MELD 7). Working habits, visits from relatives and medical centers attendance during the lockdown period were identified as possible causes of viral transmission. The course of SARS-CoV-2 infection was uneventful for both COVID-19 symptoms or liver-related clinical events.

During the lockdown period, at least one scheduled hepatology visit was postponed for 109 (54%) patients, whereas two or more visits were postponed for 37 (33.9%). Twenty-four (11.9%) participants experienced liver-related clinical events; the most frequent ones were hepatic encephalopathy (37.5%) or ascites (33.3%), followed by gastrointestinal bleeding (16.7%). One patient had a new diagnosis of hepatocellular carcinoma. Eight of the 101 patients (7.3%) whose visit was postponed experienced a liver-related event, compared with 16 of the 93 patients (17.2%) whose visit was not postponed (0.38).

To our knowledge, this is the first report on the prevalence of asymptomatic or mildly symptomatic SARS-CoV-2 infection in patients with liver cirrhosis.

Although previously published studies [1–3] raised concerns about a more severe clinical course and worse COVID-19 outcomes in patients with pre-existing liver cirrhosis, it should be noticed

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Table 1
Demographic and clinical characteristics of cirrhotic patients included in the study. Continuous variables are reported as median and interquartile range, categorical ones as frequencies and percentages.

	Overall (202)	Asymptomatic patients (154)	Symptomatic patients (48)	p-value
Male gender	131 (64.9)	97 (63)	34 (70.8)	0.05
Age	70.9 (61–77.7)	71.1 (60.8–78)	69.6 (62.8–76.3)	0.74
Etiology of liver disease				
– Viral	104 (51.5)	80 (51.9)	24 (50)	0.87
– Non-alcoholic fatty liver disease	54 (26.7)	37 (24)	17 (35.4)	0.14
– Alcohol	60 (29.7)	42 (27.3)	18 (37.5)	0.21
– Other	22 (10.9)	21 (13.6)	1 (2.1)	0.03
Hepatocarcinoma	53 (26.2)	42 (27.3)	11 (22.9)	0.70
– Active HCC	30 (56.6)	23 (54.8)	7 (63.6)	1
Child-Pugh score				
– A class	157 (77.7)	121 (78.6)	36 (75)	0.81
– B class	40 (19.8)	29 (18.8)	11 (22.9)	
– C class	5 (2.5)	4 (2.6)	1 (2.1)	
MELD score	9 (7–12)	9 (7–11)	9 (7–12)	0.41
Portal hypertension	153 (75.7)	114 (74.0)	39 (81.3)	0.34
– Splenomegaly	124 (61.4)	88 (57.1)	36 (75)	0.03
– Low platelet count (≤100,000/mmc)	80 (39.6)	57 (37)	23 (47.9)	0.18
– Esophageal or gastric varices	101 (50)	73 (54.1)	28 (58.3)	0.25
Weekly outings during lockdown period				
– None	90 (44.6)	70 (45.5)	20 (41.7)	0.73
– ≤1	32 (15.8)	25 (16.2)	7 (14.6)	
– 2–4	43 (21.3)	32 (20.8)	11 (22.9)	
– 5–7	37 (18.3)	27 (17.5)	12 (25)	
Living in small family units (up to 3 cohabiting members)	188 (93.1)	12 (7.8)	2 (4.2)	0.53
Attended medical centers	83 (41.1)	60 (39)	23 (47.9)	0.31
Visits from non-cohabiting persons	68 (33.7)	53 (34.4)	15 (31.2)	0.73
Reported social contact with known SARS-CoV-2 positive individuals	1 (0.005)	1 (0.006)	–	–
Vaccination				
– Influenza	97 (48)	77 (50)	20 (41.7)	0.33
– *Streptococcus pneumoniae*	35 (17.3)	29 (18.8)	6 (12.5)	0.39
– Both	34 (16.8)	28 (18.2)	6 (12.5)	0.51
Liver-related complications during lockdown period	24 (11.9)	15 (9.7)	9 (18.8)	0.12
– New-onset or worsened ascites	8 (33.3)	5 (33.3)	3 (33.3)	0.35
– Hepatic encephalopathy	9 (37.5)	4 (26.7)	5 (55.6)	
– Gastrointestinal bleeding	4 (16.7)	4 (26.7)	–	
– Hepatocellular carcinoma	1 (0.5)	–	1 (2.1)	
Scheduled visits postponed during lockdown period	109 (54)	87 (56.5)	22 (45.8)	0.25
– Two or more	37 (33.9)	32 (36.8)	5 (22.7)	0.14

Model for end-stage liver disease (MELD); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

that these studies included only hospitalized patients. Moreover, as the pandemic wave of early 2020 overwhelmed the power of the healthcare systems of diagnosing patients with mild or asymptomatic disease [7], previously published reports may suffer of possible selection biases.

Our study showed a prevalence of positive SARS-CoV-2 antibodies as high as 1.5% in a large population of consecutively evaluated cirrhotic outpatients, raising to 1.9% when only asymptomatic participants were considered. This is in line with that reported in the general population from our region in Italy after the first pandemic wave (1%) [5]. Overall, study participants declared a good adherence to the prescription of shelter-in-place measures, with 60% of them reporting outing frequencies of once a week or less during the lockdown period, probably due to the awareness of their frailty.

As suggested by the clinical features of the three patients who tested positive for SARS-CoV-2 antibodies, risk factors for the infection were related to hospital visits, working habits, and contacts with relatives. Interestingly, two seropositive patients showed the typical risk factors for severe COVID-19, i.e. old age (Patient 1) and morbid obesity (Patient 3), but this did not influence the clinical course of the infection, which was uneventful for both COVID-19- or liver-related complications.

This study also provides a picture of the impact that SARS-CoV-2 pandemic exerted on the clinical practice of our hepatology outpatient clinic. Indeed, more than half of the participants got their scheduled visit postponed due to the emergency, and for one third of them the visit was postponed for twice or more. We also registered more than 10% of liver-related events during the lockdown period. Despite the implementation of telemedicine, the encouragement of off-site laboratory testing and the maintenance of on-site care only for patients with liver tumors and decompensated disease, as suggested by international recommendations [8,9], the drastic reduction of all non-urgent outpatient services and elective hospitalizations could have caused detrimental effects. Nonetheless, this may have increased the collateral costs of the pandemic, because delayed diagnoses and treatments could enhance disease burden in the coming months [10]. However, the rate of patients who experienced liver disease complications was higher among those whose visit was not delayed. This could be a measure of the efficacy of our telemedicine surveillance program, which allowed us to carefully select patients for whom visits could be delayed.

This study shows some limitations. As already discussed, we do not have a control group of non-cirrhotic patients available, although recent data of the National Institute of Statistics (ISTAT) from the general Italian population were used as comparison.

In conclusion, our study reports a prevalence of positive SARS-CoV-2 antibodies as high as 1.5% in a sample of consecutive asymptomatic or mildly symptomatic patients with liver cirrhosis. This integrates the previously published reports of unfavorable

Table 2
Demographic and clinical features of the three cirrhotic patients tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies.

	Gender	Age	Comorbidities	Etiology of liver disease	Child-Pugh	MELD	Portal hypertension	Suggestive symptoms of COVID-19	Reported contacts with known SARS-CoV-2+ individuals	Possible sources of contagion	Vaccination	Liver-related clinical events during lockdown period
Patient 1	M	91	past history of prostate cancer	HCV	A5	7	no	none	no	frequent visits from sons	influenza and *s. pneumoniae*	none
Patient 2	M	54	obesity	NAFLD, HFE	A5	7	yes (splenomegaly)	none	no	working 7 days/week	none	none
Patient 3	F	70	type 2 diabetes, hypertension, history of melanoma	HCV	A5	7	yes (splenomegaly, low-platelet count)	none	no	attended medical centers	influenza	none

Model for end-stage liver disease (MELD); coronavirus disease (COVID).

outcomes of COVID-19 in hospitalized cirrhotic patients, and suggests that data collected in more heterogeneous clinical settings are warranted to better understand the course of the infection in liver cirrhosis.

Declaration of Competing Interest

The Authors declare no conflict of interest.

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