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ORIGINAL ARTICLE

The impact of the COVID-19 pandemic on patients with chronic liver disease: Results from the Global Liver Registry

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Abstract

Patients with preexisting chronic liver disease (CLD) may experience a substantial burden from both coronavirus 2019 (COVID-19) infection and pandemic-related life disruption. We assessed the impact of the COVID-19 pandemic on patients with CLD. Patients enrolled in our Global Liver Registry were invited to complete a COVID-19 survey. As of June 2021, 2500 patients (mean age \pm SD, 49 \pm 13 years; 53% men) from seven countries completed the survey. Of all survey completers, 9.3% had COVID-19. Of these patients, 19% were hospitalized, 13% needed oxygen support, but none required mechanical ventilation. Of all patients including those not infected with COVID-19, 11.3% reported that the pandemic had an impact on their liver disease, with 73% of those reporting delays in follow-up care. The Life Disruption Event Perception questionnaire confirmed worsening in at least one area (food/nutrition, exercise, social life, vocation/education, financial situation, housing,

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or health care) in 81% and 69% of patients with and without a history of COVID-19, respectively ($p = 0.0001$). On a self-assessed Likert health score scale (range, 1–10; 10 indicates perfect health), patients with a COVID-19 history scored lower (mean \pm SD, 6.7 ± 2.2 vs. 7.4 ± 2.2 , respectively; $p < 0.0001$) despite reporting similar health scores if there was no pandemic (mean \pm SD, 8.5 ± 1.4 vs. 8.4 ± 1.6 , respectively; $p = 0.59$). After adjustment for country of enrollment, liver disease etiology and severity, age, sex, body mass index, diabetes, and history of psychiatric comorbidities, COVID-19 was found to be independently associated with lower self-assessed health scores (beta = -0.71 ± 0.14 ; $p < 0.0001$). The COVID-19 pandemic resulted in a substantial burden on the daily life of patients with CLD.

INTRODUCTION

Chronic liver disease (CLD) is a major cause of mortality, morbidity, and resource utilization worldwide.^[1,2] At present, liver cirrhosis with its related complications is the ninth most common cause of death globally.^[3] The most common etiologies of CLD include alcohol-related liver disease (ALD), viral hepatitis B (HBV) and C (HCV), and nonalcoholic fatty liver disease (NAFLD).^[2]

Since its first description in early 2020, we have learned that coronavirus 2019 (COVID-19) does not spare any organ system.^[3–9] In fact, it has been reported that up to 50% of patients with COVID-19 can develop some form of hepatic dysfunction that may eventually result in poor outcomes.^[3,7,9] Additionally, patients with NAFLD who were hospitalized with COVID-19 were reported to be sicker on admission and require more hospital resource utilization than those without liver disease. Higher fibrosis-4 (FIB-4) and multimorbidity scores, morbid obesity, older age, and hypoxemia on admission have been identified as independent predictors of mortality in patients with CLD who developed COVID-19.^[8]

In addition to severe clinical outcomes, once infected, patients with CLD may experience pandemic-related life disruption. This could include difficulties in accessing routine care and disruption of personal support networks, daily routines, habits, and mental stress. The aim of this study was to characterize the impact of COVID-19 on patients with CLD by using data from the preexisting Global Liver Registry (GLR).

MATERIALS AND METHODS

Patient population

For the purpose of this study, patients enrolled in our GLR^[10] were invited between May 2020 and May 2021 to complete a specifically designed survey. The GLR

was established in 2016, enrolling patients with three common types of CLD: chronic hepatitis B (CHB), chronic hepatitis C (CHC), and NAFLD/nonalcoholic steatohepatitis (NASH). As of 2022, the GLR enrolled patients with CLD from 18 countries from all continents. Patients were not enrolled if they had CLD etiology other than the three listed above, decompensated cirrhosis, hepatocellular carcinoma (HCC) and other liver malignancies, or liver transplantation. Clinicodemographic data (age, sex, race, site of enrollment) were collected following inclusion in the GLR, along with most recent height and weight used to calculate body mass index (BMI), relevant elements of the patient's past medical history, and laboratory data needed to calculate FIB-4 scores (liver enzymes and platelet count). The study was approved by the Western Institutional Review Board and by institutional review boards or similar supervisory institutions from each participating site. All patients provided informed consent before being enrolled in the GLR.

The Covid-Global Registry Questionnaire survey

The Covid-Global Registry Questionnaire (Covid-GRQ) survey consisted of 23 items ([Supporting Material 1](#)). Questions included whether patients had been infected with COVID-19 and the characteristics of their illness if they had been infected (duration of illness in days, symptoms, diagnostics, and treatment received). In addition, all GLR enrollees, regardless of whether they had been infected with COVID-19, were asked to answer questions about the overall effect of the pandemic. Specifically, patients were asked whether the COVID-19 pandemic had any impact on their liver disease condition, whether they had difficulties in accessing medical care during the pandemic, and whether supportive care was needed in order to cope with the COVID-19 pandemic. All patients were also asked to

rate their overall health given the pandemic situation and, separately, if there were no pandemic, both on a 1–10 Likert scale (with 10 indicating perfect health). Finally, the Covid-GRQ included a Life Disruption Event Perception (LDEP) questionnaire with two multidomain questions that asked about the degree of change in the patient's life and habits (scored on a Likert scale from 0 “Not at all changed” to 6 “Completely changed”) and how the patient viewed the changes compared to before the pandemic (scored on a scale from –3 “Much worse” to +3 “Much better”).^[11] Both questions covered the following seven aspects of daily life: Food & Nutrition, Exercise & Movement, Social & Interpersonal, Vocational & Educational, Financial Stability, Housing, and Health Care. The scores across all the categories were averaged to yield the LDEP change and LDEP trend scores, respectively.

Statistical analysis

Demographic and relevant clinical parameters as well as Covid-GRQ responses and LDEP scores were summarized as means \pm SDs or frequencies (percentages) and were compared between patients who did and did not report having had COVID-19 and other comparison groups, using Wilcoxon rank-sum nonparametric test (continuous parameters) or Pearson's chi-square test (categorical parameters). Independent predictors of the self-reported health score were assessed using a generalized linear regression. All analyses were run in SAS 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was determined by two-tailed $p < 0.05$.

RESULTS

As of June 2021, the GLR included 10,500 enrollees. Of these, 2500 patients with CLD (mean \pm SD age, 49 ± 13 years; 53% men) from seven countries (Turkey, India, Egypt, United States, Mexico, Malaysia, and Pakistan) completed the Covid-GRQ survey. Of these patients, 20% had CHB, 14% CHC, and 66% NAFLD. The general characteristics of the study participants are shown in Table 1.

Of all survey completers, 232 (9.3%) reported having had COVID-19 (Table 1). Of those infected, 86% reported being diagnosed by a laboratory test, 93% had at least one symptom, and 75% received treatment for their symptoms. The mean duration of illness was 12.5 ± 10.5 days; 64% reported receiving antiviral treatment, 19% were hospitalized, 13% needed oxygen support, but none required mechanical ventilation (Table 2).

Regardless of their personal COVID-19 history, 11.3% of all survey completers reported that the pandemic had an impact on their liver disease ($p = 0.37$, between those who were and were not infected); the

majority of those (73%) reported delays in follow-up care (Table 2). The LDEP questionnaire included in the survey confirmed that 81% of patients infected with COVID-19 versus 69% of patients without a history of COVID-19 infection ($p = 0.0001$) experienced worsening in at least one aspect of their life (Table 2). The most substantial worsening was observed for social life (74% infected vs. 61% not infected), exercise (51% vs. 42%), and financial situation (37% vs. 30%) (all $p < 0.025$; Figure 1). In addition, self-assessed health scores were lower in patients with a history of COVID-19 than in those without (mean \pm SD, 6.7 ± 2.2 vs. 7.4 ± 2.2 , respectively; $p < 0.0001$) despite similar scores reported if there were no pandemic (mean \pm SD, 8.5 ± 1.4 vs. 8.4 ± 1.6 , respectively; $p = 0.59$; Table 2). In both groups, current health scores were lower in comparison to patients' own assessments if there were no pandemic (both $p < 0.0001$).

Comparison across the seven countries of origin for the survey completers showed that the highest rate of COVID-19 infection was observed in Turkey (12%) while the lowest rate was seen among GLR participants from Egypt (<1%; Table S1). Among all survey completers regardless of their COVID-19 history, patients from Mexico and Pakistan reported the greatest impact of the pandemic on their liver disease (38%), primarily owing to limited access to routine care. The same patients also reported the highest rate of needing supportive care during the pandemic (defined as specialized care to support the patient and their family members cope with the situation and help improve symptoms and quality of life) (range, 18%–21%; Table S1). Patients from Pakistan also had the lowest self-reported health scores (mean, 4.2 on a 1–10 scale).

After adjustment for country of enrollment, liver disease etiology and severity (FIB-4 score), age, sex, BMI, diabetes, and history of psychiatric comorbidities in multivariable analysis, having had COVID-19 was found to be independently associated with lower self-reported health scores (beta = -0.71 ± 0.14 on a 1–10 scale, $p < 0.0001$).

DISCUSSION

In this global study in which 2500 patients with CLD completed a survey about their experience with COVID-19, we found that approximately one in 10 had contracted COVID-19 by the time of completion and, of those, almost 20% were hospitalized but none required mechanical ventilation. The most common form of CLD in this study was NAFLD or NASH and, as such, patients with these diseases represented the majority of patients from the GLR who contracted COVID-19.

Of particular interest was that 93% of those infected with COVID-19 reported having at least one symptom and 75% received some type of treatment, with 64%

TABLE 1 Comparison of Global Liver Registry patients who reported having versus not having had COVID-19

	Positive history of COVID-19	Negative history of COVID-19	p value	All participants
Number	232	2268		2500
Chronic liver disease etiology				
Chronic hepatitis B	59 (25.4%)	430 (19.0%)	0.0179	489 (19.6%)
Chronic hepatitis C	10 (4.3%)	347 (15.3%)	<0.0001	357 (14.3%)
NAFLD or NASH	163 (70.3%)	1491 (65.7%)	0.17	1654 (66.2%)
Country				
Turkey	181 (78.0%)	1299 (57.3%)	<0.0001	1480 (59.2%)
India	13 (5.6%)	134 (5.9%)	0.85	147 (5.9%)
Egypt	1 (0.4%)	267 (11.8%)	<0.0001	268 (10.7%)
United States	22 (9.5%)	387 (17.1%)	0.0029	409 (16.4%)
Mexico	4 (1.7%)	46 (2.0%)	0.75	50 (2.0%)
Malaysia	1 (0.4%)	25 (1.1%)	0.34	26 (1.0%)
Pakistan	10 (4.3%)	110 (4.9%)	0.71	120 (4.8%)
Age, years	47.4±10.7	49.1±12.7	0.0497	48.9±12.6
Male sex	115 (52.5%)	1121 (52.7%)	0.96	1236 (52.7%)
Employed	91 (47.4%)	731 (43.9%)	0.35	822 (44.2%)
Baseline medical history:				
Cirrhosis by biopsy or elastography	27 (13.8%)	280 (16.8%)	0.30	307 (16.5%)
Body mass index, kg/m ²	32.4±7.3	31.1±6.7	0.0337	31.2±6.8
Type 2 diabetes	82 (37.6%)	750 (36.5%)	0.75	832 (36.6%)
Anxiety or panic disorder	75 (34.4%)	610 (29.6%)	0.14	685 (30.0%)
Depression or mood disorder	40 (18.5%)	272 (13.6%)	0.05	312 (14.1%)
Clinically overt fatigue	106 (48.8%)	783 (38.0%)	0.0019	889 (39.0%)
Total FACIT-F score (0–160)	116.6±27.0	117.3±26.8	0.76	117.3±26.9

Note: Data show numbers (percentage) or mean ± SD.

Abbreviations: COVID-19, coronavirus 2019; FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

treated with antiviral drugs (e.g., remdesivir, oseltamivir/tamiflu, avigan/favipiravir, lopinavir–ritonavir) and 13% requiring oxygen support. Notably, 77% patients enrolled in Turkey and 80% in Pakistan reported having received antiviral treatment versus less than 10% in the United States ($p < 0.0001$). This may reflect regional differences in COVID-19 management or changes in treatment over time occurring along with local surges of infections in specific geographic areas.

In addition to clinical data, we also gathered self-reported health scores from the survey completers. In fact, in our multivariable regression analysis, having had COVID-19 infection was independently associated with lower self-reported health scores. Furthermore, nearly 60% of those who had COVID-19 reported that they had at least some difficulty performing daily activities. These findings about patients with CLD included in this study are in line with what is known about COVID-19 in the general population.

Another interesting finding of our study comes from the perceived impact of the COVID-19 pandemic on patients' lives regardless of their personal infection

history. In this context, we found that almost 70% of our study population stated that at least one aspect of their life worsened because of COVID-19 and over 60% reported detrimental consequences on their social and interpersonal interactions. We also attempted to quantify the impact of COVID-19 on the delivery of routine care, which is essential for patients with CLD. As such, we found that 11.3% reported that the pandemic had a negative impact on their liver disease, and the vast majority of those reported delays in follow-up care; notably, there was no difference between those with and without a history of actual infection. This is a disturbing finding that, however, is in accordance with a recent study that reported a 40% reduction in the routine monitoring of CLD to include HCC surveillance during the pandemic.^[12] It is important to note that the latter can lead to a rise in adverse and lethal outcomes given that the doubling time for HCC tumor volume is less than 90 days.^[13] In addition, delayed care has been shown to increase liver-related mortality even without developing HCC.^[14] These findings could help policy makers plan for future public health emergencies when determining

TABLE 2 Responses to Covid-GRQ by Global Liver Registry participants who reported having versus not having had COVID-19 infection

Covid-GRQ item	Positive history of COVID-19	Negative history of COVID-19	p value	All participants
COVID-19 pandemic had any impact on liver disease (yes/no)	21 (9.1%)	260 (11.6%)	0.25	281 (11.3%)
Had difficulty in access to medical care	10 (4.3%)	88 (3.9%)	0.77	98 (4.0%)
Delayed follow-up care	16 (6.9%)	189 (8.4%)	0.42	205 (8.3%)
Had difficulty in access to laboratory tests	8 (3.4%)	110 (4.9%)	0.32	118 (4.8%)
Needed supportive care during the pandemic	36 (15.7%)	210 (9.5%)	0.0027	246 (10.0%)
Self-reported overall health given the pandemic situation (1–10)	6.73±2.15	7.36±2.17	<0.0001	7.30±2.17
Self-reported overall health if there were no pandemic (1–10)	8.47±1.42	8.37±1.59	0.59	8.38±1.57
LDEP				
LDEP change score (0–6)	2.28±1.31	2.13±1.32	0.20	2.15±1.32
LDEP trend score (–3 to +3)	–0.26±1.05	–0.11±0.94	<0.0001	–0.13±0.95
LDEP trend: food/nutrition got worse	48 (20.7%)	369 (16.3%)	0.09	417 (16.7%)
LDEP trend: exercise got worse	118 (50.9%)	952 (42.2%)	0.0113	1070 (43.0%)
LDEP trend: social got worse	172 (74.1%)	1363 (60.5%)	<0.0001	1535 (61.8%)
LDEP trend: vocation/education got worse	37 (15.9%)	258 (11.5%)	0.0438	295 (11.9%)
LDEP trend: financial got worse	86 (37.2%)	674 (30.0%)	0.0229	760 (30.7%)
LDEP trend: housing got worse	13 (5.6%)	113 (5.0%)	0.70	126 (5.1%)
LDEP trend: health care got worse	65 (28.1%)	606 (26.9%)	0.69	671 (27.0%)
LDEP: at least one aspect got worse	188 (81.0%)	1553 (68.8%)	0.0001	1741 (69.9%)
COVID-19-specific items:				
Had at least one COVID-19 symptom	216 (93.1%)	NA		
Received treatment for COVID-19	156 (75.0%)	NA		
Was diagnosed based on a positive test	174 (86.1%)	NA		
Duration of illness, days	12.5±10.6	NA		
Received treatment with antivirals	145 (64.4%)	NA		
Was hospitalized	42 (18.5%)	NA		
Required oxygen support	30 (13.2%)	NA		
Had no difficulty performing daily activities	98 (43.2%)	NA		
Received supportive care while ill	96 (41.6%)	NA		

Note: Data show numbers (percentage) or mean ± SD.

Abbreviations: COVID-19, coronavirus 2019; Covid-GRQ, corona virus disease-Global Registry Questionnaire; LDEP, Life Disruption Event Perception; NA, not applicable.

how to keep access to health care open for all while also dealing with the emergency rather than trading one disease for another.

Several caveats of our investigation need to be considered. First, our study is only representative of those patients who chose to respond to the survey so our findings may not be representative of all patients with CLD, particularly those who died or remained too disabled post-COVID-19 infection to respond to our survey invitation. There was only a small number of participating sites from a few countries with inherent enrollment biases and varying COVID-19 burden across regions. This poses a limitation regarding the ability to generalize our conclusions. However, the information we have

provided here is beneficial in understanding the impact of an acute and potentially severe disease among those who suffer with a chronic disease as well as providing the impact of COVID-19 among patients from around the world. The study also did not cover periods of universal availability of COVID-19 vaccines and of the spread of more contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants that left larger proportions of most populations with a history of the infection or vaccine-induced immunity or both; either of those could have affected patients' experience with the infection. We also acknowledge that because this study was cross-sectional in design, we were unable to determine long-term outcomes from COVID-19,

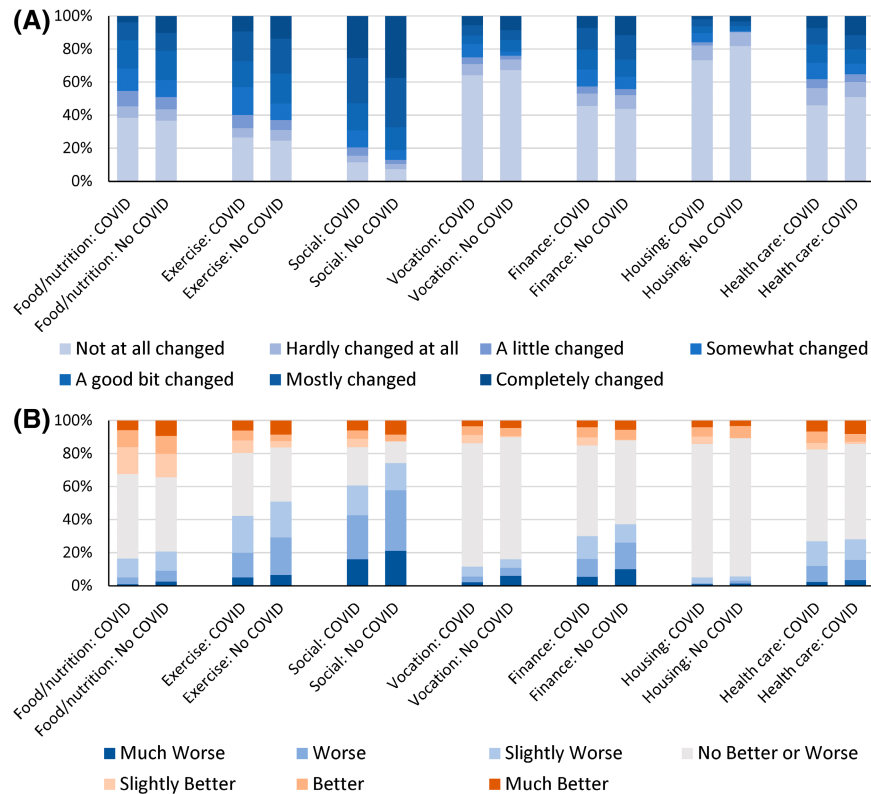


FIGURE 1 Life Disruption Event Perception scores by history of COVID-19 among Global Liver Registry participants. (A) To what degree have your life and habits changed in each of these categories since the beginning of the pandemic? (B) Compared to before the pandemic, how do you view the changes to each life category? COVID-19, coronavirus 2019.

especially among those who reported a significant negative impact from the infection. Thus, we believe that further research is warranted, but this study has provided a basis from which further comparisons can be made. Finally, the survey was all self-reported and, as such, the responses are biased toward a patient's ability to recall their experience.

In summary, we have described the impact of the COVID-19 pandemic on patients with CLD from seven different countries around the world. We found that over half of all patients reported that the COVID-19 pandemic had a detrimental effect on their ability to be socially active, although a higher percentage was noted among those who had a COVID-19 infection. Perhaps most disturbing was that some patients reported that COVID-19 negatively impacted their CLD care, primarily through delays in follow-up care. Given that timely access to both routine and urgent health care is essential for patients with CLD, policy-maker efforts must focus on how to effectively continue to deliver care even during a public health emergency.

CONFLICTS OF INTEREST

Zobair Younossi consults for Gilead, Merck, and Intercept. Yusuf Yilmaz is on the speakers' bureau of NovoNordisk, AbbVie, Abdi Ibrahim, Bimillah Pharmaceutical, and Echasens and received grants from Biocodex; he is on the speakers' bureau of and

received grants from Gilead. The other authors have nothing to report.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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