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Supplementary data

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High mortality rates for SARS-CoV-2 infection in patients with pre-existing chronic liver disease and cirrhosis: Preliminary results from an international registry

To the Editor:

Chronic liver disease (CLD) and cirrhosis are common conditions[1] associated with immune dysregulation,[2] leading to concerns that these patients are at increased risk of complications from COVID-19 resulting from infection with SARS-CoV-2.[3] However, the effects of COVID-19 among patients with pre-existing liver disease are currently undefined.

We report the outcomes of the first 152 consecutive submissions of clinician-reported cases of laboratory-confirmed COVID-19 in patients with CLD to two international reporting registries (COVID-Hep.net and COVIDCirrhosis.org) between 25 March 2020 and 20 April 2020. Our combined database includes 103 patients with cirrhosis and 49 with non-cirrhotic CLD from 21 countries across 4 continents (59.9% male, median age 61 years, aetiology: 22.4% non-alcoholic fatty liver disease, 19.7% alcohol, 11.8% hepatitis B, 10.5% hepatitis C, 35.6% other/combination).

Contributors were encouraged to enter data at the end of the patient's disease course. For patients admitted to hospital, cases were only included in the analysis if a definitive outcome of death or discharge was reported. 95.2% of patients with cirrhosis were hospitalised with a median length of hospital stay until discharge or death of 10 days (IQR 5–14 days). Outcomes for patients with cirrhosis included admission to intensive care unit (ICU) in 23.3%, invasive ventilation in 17.5%, non-invasive ventilatory support in 18.6%, renal replacement therapy in 4.9% and death in 39.8%. Mortality far exceeded that reported in

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Table 1. Characteristics of patients with laboratory-confirmed chronic liver disease and COVID-19 submitted to COVIDCirrhosis.org and COVID-Hep.net reporting registries between 25th March 2020 and 20th April 2020.

	Univariable analysis							Multivariable analysis	
	Total; n = 152		Survived; n = 105		Died; n = 47				
Variable	Median or n	IQR or %	Median or n	IQR or %	Median or n	IQR or %	*p* value[†]	OR (95%CI) for death	*p* value[§]
Age (years)	61	48–71	60	46–70	64	57–73	**0.025**	1.04 (1.00–1.09)	**0.048**
Sex (male)	91	59.9%	61	58.1%	30	63.8%	0.666	–	–
White ethnicity	86	56.6%	56	53.3%	30	63.8%	0.228	–	–
Smoker	9	5.9%	7	6.7%	2	4.3%	0.560	–	–
Obese (BMI >30 kg/m^2)	33	21.7%	18	17.1%	15	31.9%	**0.017**	3.59 (1.10–10.47)	**0.033**
Cardiovascular disease	33	21.7%	18	17.1%	15	31.9%	**0.041**	1.87 (0.57–6.15)	0.303
Diabetes mellitus	54	35.5%	30	28.6%	24	51.1%	**0.007**	2.86 (1.00–8.20)	0.051
Hypertension	60	39.5%	35	33.3%	25	53.2%	**0.021**	0.71 (0.22–2.24)	0.555
Liver disease severity									
CLD without cirrhosis	49	32.2%	43	41.0%	6	12.8%	**<0.001**	1.00	–
Child-Pugh A	46	30.3%	35	33.3%	11	23.4%	**<0.001**	1.21 (0.30–4.90)	0.789
Child-Pugh B	30	19.7%	17	16.2%	13	27.7%	**<0.001**	4.90 (1.16–20.61)	**0.030**
Child-Pugh C	27	17.8%	10	9.5%	17	36.2%	**<0.001**	28.07 (4.42–178.46)	**<0.001**
MELD score*	10	7–17	9	7–17	13	9–17	**0.014**	–	–
Laboratory (baseline)									
Sodium (mmol/L)	138	135–141	139	136–141	137	134–140	0.058	1.06 (0.93–1.22)	0.377
Prothrombin time (s)	13	12–17	13	12–15	15	13–18	**0.011**	–	–
Bilirubin (mg/dl)	1.1	0.6–1.9	0.9	0.5–1.5	1.4	0.8–2.0	**0.013**	–	–
Albumin (g/dl)	3.4	2.8–4	3.8	3.0–4.0	2.9	2.4–3.3	**<0.001**	–	–
Creatinine (mg/dl)	0.9	0.6–1.1	0.8	0.6–1.0	0.9	0.7–1.1	**0.010**	0.88 (0.53–1.47)	0.634
Events after diagnosis									
Any decompensation	39	25.7%	15	14.3%	24	51.1%	**<0.001**	–	–
New jaundice	27	17.8%	14	13.3%	13	27.7%	0.067	–	–

BMI, body mass index; CLD, chronic liver disease; MELD, model for end-stage liver disease (2016 revision); OR, odds ratio.
*MELD score presented is as calculated for all patients; when restricted to patients with cirrhosis, MELD was 11 (IQR 7–19) in those who survived and 14 (9–17) in those who died, $p = 0.136$. To explore the relationship of MELD with death, multiple logistic regression was repeated with death as the dependent variable and age, baseline MELD, obesity, cardiovascular disease, diabetes mellitus, hypertension, and baseline albumin as independent variables; here the OR for death for MELD was 1.05 (0.98–1.11) $p = 0.204$; other variables with $p < 0.05$ were age 1.05 (1.00–1.08) $p = 0.038$, obesity 3.61 (1.36–9.60) $p = 0.010$, and baseline albumin 0.97 (0.93–1.00) $p = 0.029$. Any decompensation defined as one or more of worsening ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal haemorrhage.
[†]*p* values for univariable analyses calculated using chi-squared or Wilcoxon ranksum tests as appropriate. *p* values <0.05 in bold.
[§]*p* values for multivariable analysis calculated by multiple logistic regression with the dependent variable as death and the following independent variables: age, obesity, cardiovascular disease, diabetes mellitus, hypertension, chronic liver disease status as Child-Pugh class, baseline serum sodium, and baseline serum creatinine. *p* values <0.05 in bold.

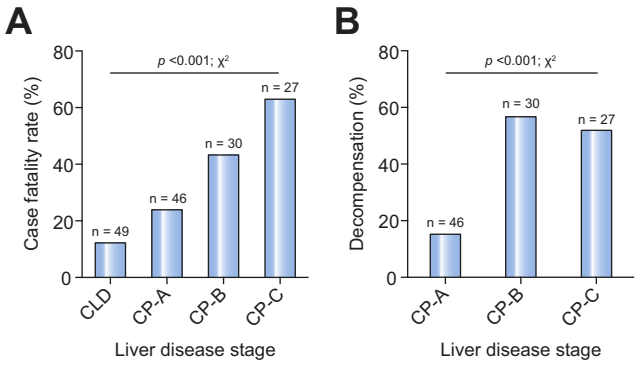

Fig. 1. Outcome in patients with non-cirrhotic chronic liver disease or cirrhosis with COVID-19. Graphs depict data from 152 submissions to COVID-Hep.net and COVIDCirrhosis.org registries between 25th March 2020 and 20th April 2020. (A) Case fatality rate by liver disease stage. (B) Rates of hepatic decompensation by stage of cirrhosis (defined as one or more of new or worsened ascites, spontaneous bacterial peritonitis, new or worsened hepatic encephalopathy, or variceal haemorrhage). *p* values derived using chi-squared test. CLD, chronic liver disease without cirrhosis; CP, Child-Pugh.

unselected populations,[4] hospitalised patients with cirrhosis in the era preceding COVID-19,[5] and in patients with cirrhosis admitted with influenza.[6] In patients not admitted to ICU, 59.5% had non-severe disease, 27.8% had severe disease but escalation of care was deemed inappropriate, and 3.7% were considered to require ICU but were not admitted due to lack of availability. Targeted antiviral therapy was used in 38.1% of total cases. The most frequently used treatments were chloroquine/hydroxychloroquine (23.0%), lopinovir/ritonavir (6.6%), tocilizumab (3.3%), and interferon-alpha (3.3%).

Cause of death in patients with cirrhosis was reported as COVID-19 lung disease in 78.7%, cardiac-related in 4.3%, and liver-related in 12.2%. Risk factors for poor COVID-19 outcomes in the general population, including advanced age, obesity, renal impairment, heart disease, and diabetes mellitus, were over-represented among those who died, although male sex and non-white ethnicity were not.[7] Mortality correlated strongly with baseline Child-Pugh class and model for end-stage liver disease (MELD) score (Table 1). Deaths occurred in 12.2% of patients with CLD without cirrhosis, 23.9% with Child-Pugh class A cirrhosis, 43.3% with Child-Pugh class B cirrhosis, and

63.0% with Child-Pugh class C cirrhosis (Fig. 1A). Child-Pugh class B and C cirrhosis remained associated with death after adjusting for baseline characteristics including comorbidities (Table 1). Child-Pugh class B and C cirrhosis remained significant predictors of mortality when analysis was restricted to those with cirrhosis.

Hepatic decompensation occurred in 36.9% and was associated with baseline Child-Pugh class (Fig. 1B). Decompensation events included worsening ascites (27.2%), spontaneous bacterial peritonitis (2.9%), hepatic encephalopathy (16.5%), and variceal haemorrhage (1%). Hepatic decompensation during COVID-19 was strongly associated with a subsequent risk of death: 63.2% of those with new decompensation died compared to 26.2% of those without new decompensation. Notably, 24.3% of those with new hepatic decompensation had no respiratory symptoms of COVID-19 at the time of diagnosis.

This large, multicentre, international cohort of patients with chronic liver disease and cirrhosis allows for in-depth assessment of the clinical factors associated with poor outcomes from COVID-19. Accepting that data from registries are subject to selection bias, preliminary findings suggest that baseline liver disease severity is strongly associated with COVID-19-related morbidity and mortality. Furthermore, many SARS-CoV-2-infected patients with cirrhosis experienced hepatic decompensation even in the absence of respiratory symptoms. These findings have important implications for clinicians regarding risk stratification and prognostication for patients with cirrhosis and COVID-19 and suggest the need to maintain a low threshold for SARS-CoV-2 testing in the presence of new hepatic decompensation.

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Conflicts of interest

The authors have no conflicts of interest or competing interests to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Concept and Design: TM, AMM, EB, ASB, GW, TWJ. Acquistion of data: CA, MJA, TC, RD, JG, USG, TWJ, PDJ, AM, GM, PVP, XQ, FS, NNU. Statistical analysis: TM, AMM, GW. Interpretation of data: TM, AMM, EB, ASB, GW. Drafting and critical revision of manuscript: TM, AMM, EB, ASB, GW.

Supplementary data

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A local response to COVID-19 for advanced liver disease: Current model of care, challenges and opportunities

To the Editor:
We read with great interest the work by Tapper and Asrani in the recent issue of the *Journal of Hepatology*.[1] While we share the authors' concerns about care disruptions and the long-term negative consequences for cirrhosis care, we posit that the future of cirrhosis care need not be painted in such stark colors. In fact, the pandemic has created an unprecedented natural experiment, teaching us valuable lessons about patient care that can be both long-lasting and life-saving. Herein, we provide an example of local coordinated response to COVID-19 from the University of Pennsylvania (UPENN), a large, diverse, tertiary-care center and liver transplant program in the US with a catchment area extending up to 160 km.

Changes in clinical care

Major shifts in clinical care due to COVID-19 began on 16 March 2020. Prior to this date, our multi-disciplinary team worked with health-system leaders on a coordinated response based on prioritizing lifesaving therapies for the sickest, deferring elective care in cases where it was safe to do so, and altering care delivery models to telemedicine and remote monitoring to maintain contact and routine care activities for our active population of patients with advanced liver disease.

Telemedicine use, remote monitoring, and current management

At the beginning of the COVID-19 response, we leveraged the electronic health record's (EHR) online portal to routinely communicate with patients about COVID-19 symptoms, appropriate behavior, and how to contact the medical team with questions and concerns. We have also leveraged the EHR to proactively generate reports on cancelled patient visits. From 1 March 2020 to 26 April 2020, 910 individual patients with advanced liver disease or post-transplant were originally scheduled in outpatient clinics. Of those, 505 (56%) appointments were kept as scheduled, 334 (37%) were rapidly rescheduled and, 12 (1.3%) are scheduled in the future, and 60 (6.6%) have yet to be rescheduled. Building on our previous experience, we shifted up to 69% of our visits to telemedicine within a 6-week period (Fig. 1).[2] We have initiated home-based, remote monitoring for decompensated cirrhosis using UPENN's online portal[3] that interfaces with patients' or caregivers' cellphones to monitor symptoms, enrolling 35 patients in the first week of program initiation.

We have postponed elective variceal surveillance, however, we use guideline-recommended beta blocker prophylaxis in newly identified cases of clinically significant portal hypertension.[4,5] To conserve healthcare resources, we have maintained limited but essential endoscopy for serial banding in those who recently bled from varices, facilitated new clinical evaluations in those with severe clinical situations of recent onset of jaundice, severe hepatitis, new hepatic decompensation, while hepatocellular carcinoma (HCC) case assessment and therapy has continued in an uninterrupted manner. While surveillance for HCC could be delayed for a couple of months until we achieve re-entry and "the new normal", those patients currently willing to accept HCC surveillance are undergoing imaging studies. Further, patients with high model for end-stage liver disease scores continue to be transplanted at our center as these procedures are clearly nonelective.[6] We have been quite judicious, but uncompromising by limiting outpatient laboratory exposure for our patients with cirrhosis and after liver transplant, while recently transplanted patients have been provided home nurse or mobile laboratory blood drawing to follow essential care parameters.

Ongoing challenges, future uncertainty, and areas of opportunity

Despite active population management, use of technology, and close communication between our physicians and community-based providers, multiple challenges remain. In order to reserve resources to battle COVID-19, our health system initially limited hospitalizations and inpatient transfers to severe, life-threatening cases or in situations where the need for transplantation was imminent, although within a short period of time re-entry strategies that include elective surgeries are being implemented. It is not yet clear how many needed hospitalizations were deferred in the community or what long-term sequelae this may have. We also recognize that patient perceptions alter their willingness to accept routine blood tests and imaging studies that could also negatively impact quality of care.

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