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Negative impact of the pandemic on hospital admissions, morbidity and early mortality for acute cirrhosis decompensation

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ABSTRACT

Introduction The global pandemic has diverted resources away from management of chronic diseases, including cirrhosis. While there is increasing knowledge on COVID-19 infection in liver cirrhosis, little is described on the impact of the pandemic on decompensated cirrhosis admissions and outcomes, which was the aim of this study.

Methods A single-centre, retrospective study, evaluated decompensated cirrhosis admissions to a tertiary London hepatology and transplantation centre, from October 2018 to February 2021. Patients were included if they had an admission with cirrhosis decompensation defined as new-onset jaundice or ascites, infection, encephalopathy, portal hypertensive bleeding or renal dysfunction.

Results The average number of admissions stayed constant between the pre-COVID-19 (October 2018–February 2020) and COVID-19 periods (March 2020–February 2021). Patients transferred in from secondary centres had consistently higher severity scores during the COVID-19 period (UK Model for End-Stage Liver Disease 58 vs 54; p=0.007, Model for End-Stage Liver Disease-Sodium 22 vs 18; p=0.006, EF-CLIF Acute Decompensation (AD) score 55.0 vs 51.0; p=0.055). Of those admitted to the intensive care without acute-on-chronic liver failure, there was a significant increase in AD scores during the COVID-19 period (58 vs 48, p=0.009). In addition, there was a trend towards increased hospital readmission rates during the COVID-19 period (29.5% vs 21.5%, p=0.067). When censored at 30 days, early mortality postdischarge was significantly higher during the COVID-19 period (p<0.001) with a median time to death of 35 days compared with 62 days pre-COVID-19.

Discussion This study provides a unique perspective on the impact that the global pandemic had on decompensated cirrhosis admissions. The findings of increased early mortality and readmissions, and higher AD scores on ICU admission, highlight the need to maintain resourcing for high-level hepatology care and follow-up, in spite of other disease pressures.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is very little in the literature assessing the impact of the COVID-19 pandemic on the patients with decompensated cirrhosis. There is pressing need for this burden on cirrhosis care to be understood.

WHAT THIS STUDY ADDS

⇒ We demonstrate higher early mortality, as well as increased liver disease severity in some cirrhosis subpopulations during the COVID-19 pandemic. These novel findings have not previously been shown in the literature.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests alternative care pathways such as digital healthcare may need to play a more crucial role when face-to-face appointments are not possible during a pandemic.

INTRODUCTION

In the UK, liver cirrhosis is the third most common cause of premature death and has been increasing at a more rapid rate than the four most commonly diagnosed cancers; lung, breast, bowel and prostate.[1 2] The British Liver Trust indicates deaths from liver disease have increased by 400% since 1970, with 62000 years of working life lost per year, and National Health Service (NHS) care costs of over £3.5 billion.[3]

As cirrhosis progresses to decompensation, the median survival decreases sharply from greater than 10 years to 2–4 years.[4] At the most severe end, the distinct entity of acute-on-chronic liver failure (ACLF) has also been identified which is an acute deterioration of pre-existing chronic liver disease associated with extrahepatic organ failure (OF) and a short-term mortality of over 30% at 28 days.[5 6]

Patients with decompensated cirrhosis usually require a regular clinical assessment, within weeks of hospital discharge, and even despite optimal management have

readmission rates in excess of 30% at 30 days.[7] Moreover, data suggest that early readmissions are associated with reduced chance of independent living at 1 year.[8]

The COVID-19 pandemic has necessitated an unusual allocation of healthcare resources to acute respiratory presentations, which inevitably negatively impacts on resources available to care for patients with chronic diseases including liver disease. Such was the concern of the potential impact of the pandemic on cirrhosis care that the EASL-ESCMID position paper was produced to try and reduce predicted increased morbidity and mortality.[9] Moreover, there are an increasing numbers of publications addressing outcomes of those with chronic liver disease who develop COVID-19 infection .[10 11] While it has been speculated that the pandemic would have a negative impact on decompensated cirrhosis admissions and outcomes, there is very little data in the literature highlighting the real-world impact on this patient group.[12 13]

The aim of this study was to address whether there was a difference in the clinical course, characteristics and outcomes of decompensated liver cirrhosis patients admitted during the pandemic, when compared with cirrhosis patients admitted prior to the emergence of COVID-19, in a tertiary UK hepatology and transplantation centre.

METHODS

Setting and study design

We conducted a single-centre retrospective cohort study evaluating admissions to the Royal Free Hospital London with acute decompensation (AD) of liver cirrhosis, from October 2018 to February 2021.

Admissions with decompensated cirrhosis were identified from inpatient records including ward lists, electronic patient records and hospital endoscopy reporting software (Unisoft). Data were collected using medical notes, laboratory, radiology and histology reports, clinic letters, discharge summaries and endoscopy reports. Data collected included patient demographics; aetiology of liver disease; precipitant of decompensation event; type of decompensation event; prior decompensation history; length of hospital stay; blood test results (admission, including admission to the intensive treatment unit (ITU) if applicable and discharge) and the presence of infection and/or spontaneous bacterial peritonitis (SBP) and COVID-19 status, which was determined by a PCR test on admission. In addition, physiological parameters and observations such as blood pressure, oxygen saturation by pulse oximetry (%) and fraction of inspired oxygen at admission were also recorded. For admissions involving stays in intensive care, data were collected on use of mechanical ventilation, inotropic support and haemofiltration Supplemental data were collected on patients requiring interventional procedures including abdominal paracentesis, endoscopy, liver biopsy and transhepatic portosystemic shunts (TIPSS). For patients requiring paracentesis between admissions, the frequency of paracentesis was recorded in intervals of weeks. Dates of death and/or liver transplantation were recorded for patients meeting these outcomes within the study period. Data were collected for all included patients throughout the study period with 6-month follow-up data obtained. Attempts were made to reduce the following sets of bias: information and selection bias by using multiple record systems to maximise data capture and minimise missing data, and confounding bias through multivariate analysis.

The following severity scores were calculated; UK Model for End-Stage Liver Disease, Model for End-Stage Liver Disease-Sodium and Child Pugh Score. Definitions from the European Association for the Study of the Liver Chronic Liver Failure Consortium (CLIF-C) were used to calculate CLIF-C OF scores and to establish the presence of ACLF. For patients without ACLF, CLIF-C AD scores on admission and discharge were recorded.[5]

Participants

Our cohort consisted of 388 patients, with a total of 591 admissions with decompensated cirrhosis. Patients were included if they had an admission with a decompensating event within the study period. Patients referred and transferred from external referral sites were identified and included in the cohort. Admissions were excluded if they lasted less than 24 hours, were planned elective admissions or if they occurred post liver transplant.

Definitions

Decompensated cirrhosis was defined as the presence of ascites, hepatic encephalopathy (HE), portal hypertension-related bleeding, infection or a combination of these, on a background of radiologically or histologically confirmed cirrhosis. Precipitants of decompensation were categorised as harmful drinking of alcohol, infection, gastrointestinal (GI) haemorrhage, hepatitis B reactivation, new portal vein thrombus, autoimmune hepatitis flare, drug-induced liver injury, new/progression of hepatocellular carcinoma or as unknown.

Alcoholic hepatitis was also recorded and defined using the National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition: history of heavy alcohol consumption (≥4 drinks per day), serum bilirubin >3 mg/dL (51.3 µmol/L), Aspartate Aminotransferase (AST) 50–400 U/L and AST: Alanine Aminotransferase (ALT) ratio >1.50.[14]

Confirmed infection was determined by blood, sputum and/or urine culture positivity and/or radiological evidence of chest infection on chest X-ray, or evidence of microbial growth from another source. Suspected infection was classified as cases where antimicrobials were prescribed based on clinical suspicion of infection, in the absence of positive culture results.

Statistical analysis

Summary statistics were performed on patient demographics, aetiology of disease, precipitant of

decompensation, disease severity scores, symptoms of decompensation, interventions performed during admission, length of admission, intensive care admission, liver transplantation and mortality outcomes. A non-parametric assumption was used for all statistical tests. Any missing data were excluded from analysis. Data were grouped for analysis defined by admission date, with admission between October 2018 and February 2020 defined as pre-COVID-19 and admission from March 2020 to February 2021 as the COVID-19 period. The COVID-19 time period was defined by when healthcare systems at the Royal Free Hospital London were impacted by the COVID-19 pandemic, with all patients having mandatory COVID-19 PCR testing on admission. A Pearson's χ^2 test was used to test for statistically significant differences in nominal or ordinal data between pre-COVID-19 and COVID-19 groups, in addition to local and transferred patient groups. A Mann-Whitney U test was used to test for statistical significance in variables of continuous data between pre-COVID-19 and COVID-19 cohorts, and local and transferred patient groups. Survival analysis for mortality and transplant-free survival outcomes were performed using Kaplan-Meier procedure and log rank test with censoring to 30 or 90 days. In addition, a multivariate analysis was performed for mortality.

RESULTS

Summary demographics and characteristics of population

Data collected on patient admissions over 29 months were assessed. There were 388 patients with 591 admissions to the Royal Free Hospital London, with acute cirrhosis decompensation. The summary of demographics, comorbidities, aetiology of liver disease, precipitants of admission and liver disease severity scores for the entire cohort can be seen in table 1. The admissions were split between the pre-COVID-19 (October 2018–February 2020) time-period with 247 patients having 351 admissions, and the COVID-19 period (March 2020–February 2021) with 166 patients having 240 admissions. A total of 143 (86%) patients admitted during the COVID-19 period had no prior admissions in the pre-COVID-19 period. There was a median of 21 admissions per month over the total time (range 10–33) with some variations noted across the non-COVID-19 and COVID-19 time periods in figure 1. This included a relative reduction in winter cirrhosis admissions by 30% in the COVID-19 period, from December 2020 to February 2021, when compared with the two equivalent winter periods previously. In addition, other notable changes include times reflecting the UK national lockdown periods, and a notable spike in September 2020, after a major governmental initiative to reopen the hospitality sector.

During the COVID-19 period, four out of all patients tested at admission, were positive for COVID-19 on PCR (1.7% of admissions) of which three had symptoms consistent with infection, the other being asymptomatic. A further three patients had symptoms of COVID-19, however, had tested negative in hospital, and in two cases, COVID-19 was identified as the cause, or contributed to death.

Portal hypertension-driven complications were the most predominant cause of presentation, with 432 (73.1%) admissions with ascites noted either at presentation or during the admission, while 233 (39.4%) had HE. Moreover 210 patients (35.5%) had GI bleeding, of which 126 (60%) were found to have varices on endoscopic examination. Among 262 (44.3%) admissions with infection, 60 patients (23%) had suspected infection, while the remainder had confirmed infection with culture positivity or consolidation seen on chest X-ray examination, with 74 (12.5%) admissions requiring treatment for SBP.

As anticipated, AD admissions often required interventions, including: 75 (12.7%) patients requiring liver biopsy, 59 (10%) requiring an emergency TIPSS insertion and 277 (46.8%) required inpatient paracentesis at least once. Of those requiring TIPSS insertion, 38 (64.4%) had an indication of bleeding, 19 (32.2%) for ascites management and 1 for portal vein thrombus. The median length of stay per admission was 7 days (IQR: 11). Among the admissions, 102 (26.2%) of the index admissions during the recruitment period, required a further readmission, with a median number of admissions of 2 per patient. The median time from index admission to readmission was 40 days (IQR: 106.3).

Differences in patient characteristics between periods

Hospital admissions with cirrhosis AD were compared between the pre-COVID-19 and COVID-19 time periods. The average number of admissions per month did not differ between the two cohort periods (20.6 vs 20.0). In addition, there was no significant difference in the ratio of presentations or development of ACLF compared with AD (17% pre-COVID-19 and 16.6% during COVID-19). Of the 351 admissions during the pre-COVID-19 period, 152 (61.5%) had alcohol listed as their primary aetiology compared with 110 (65.9%) during the COVID-19 period (p=0.454). Patients presenting with alcohol as their precipitant for AD increased from 82 (23.5%) pre-COVID-19 to 59 (35.3%) during the COVID-19 period, although not reaching statistical significance (p=0.221). The number of admissions with alcoholic hepatitis according to NIAAA clinical criteria definition remained stable at 53 (15.1%) pre-COVID-19 and 39 (16.3%) during COVID-19.[14]

Those presenting with GI bleeding on admission non-significantly reduced from 73 (20.9%) pre-COVID-19 to 37 (15.4%) during COVID-19 (p=0.327), of which 47 (64.4%) and 28 (75.7%), respectively, were found to have varices. There was also a significant reduction in TIPSS procedures performed during the COVID-19 period, down from 45 (12.9%) to 14 (5.8%) (p=0.006), however, the proportion of TIPSS inserted for bleed indication remained at a comparable proportion (64% vs 69%). The number of admissions with documented

Table 1 Table showing demographics, aetiology, precipitant and disease severity scores of decompensated cirrhosis admissions

	Total	Pre-COVID-19	COVID-19	P value
Male	264 (67.7%)	161 (65.2%)	117 (70.1%)	0.186
Female	126 (32.3%)	86 (34.8%)	50 (29.9%)	
Age				
Median (IQR)	58 (16)	59 (17)	57 (15.5)	0.314
<30	10	6 (1.7%)	4 (1.7%)	
30–50	136	71 (20.3%)	65 (27%)	
50–70	316	192 (54.9%)	123 (51%)	
>70	100	59 (16.9%)	41 (17%)	
Ethnicity				
White	247 (63.3%)	149 (60.3%)	113 (67.7%)	0.146
Asian	37 (9.5%)	27 (10.9%)	11 (6.6%)	
Black	17 (4.4%)	13 (5.3%)	5 (3%)	
Other	81 (20.8%)	50 (20.2%)	38 (22.8%)	
Mixed	1 (0.3%)	1 (0.4%)	0	
Not stated	7 (1.8%)	7 (2.8%)	0	
Comorbidities				
Diabetes	87 (22.3%)	61 (24.7%)	32 (19.2%)	0.135
Cardiac	48 (12.3%)	31 (12.6%)	21 (12.6%)	0.845
Respiratory	52 (13.3%)	33 (13.4%)	20 (12%)	0.98
Chronic kidney disease	24 (6.2%)	16 (6.5%)	11 (6.6%)	0.724
Neurological	26 (6.7%)	18 (7.3%)	13 (7.8%)	0.516
Malignancy	33 (8.5%)	25 (10.1%)	9 (5.4%)	0.121
Other	81 (20.8%)	61 (24.47%)	24 (14.4%)	0.03
Aetiology				
Alcohol	246 (63.1%)	152 (61.5%)	110 (65.9%)	0.401
Nonalcoholic steatohepatitis (NASH)	55 (14.1%)	40 (16.2%)	23 (13.8%)	
Hepatitis C	49 (12.6%)	33 (13.4%)	18 (10.8%)	
Hepatitis B	19 (4.9%)	13 (5.3%)	6 (3.6%)	
Autoimmune hepatitis	25 (6.4%)	13 (5.3%)	12 (7.2%)	
Primary biliary cirrhosis	8 (2.1%)	7 (2.8%)	1 (0.6%)	
Primary sclerosing cholangitis	11 (2.8%)	8 (3.2%)	3 (1.8%)	
Cryptogenic cirrhosis	11 (2.8%)	9 (3.6%)	3 (1.8%)	
Wilson's disease	3 (0.8%)	2 (0.8%)	2 (1.2%)	
Other	9 (2.3%)	5 (2%)	4 (2.4%)	
Precipitant				
Alcohol	150 (25.4%)	82 (23.5%)	59 (35.3%)	0.301
Infection	131 (22.2%)	79 (22.6%)	31 (18.6%)	
Gastrointestinal haemorrhage	111 (18.8%)	73 (20.9%)	37 (15.4%)	
Varices	75 (67.6%)	47 (64.4%)	28 (75.7%)	
Hepatitis B reactivation	2 (0.3%)	2 (0.6%)	0	
New portal vein thrombosis	1 (0.2%)	0	1 (0.6%)	
Hepatocellular carcinoma	5 (0.8%)	2 (0.6%)	3 (1.8%)	
Autoimmune flare	3 (0.5%)	1 (0.3%)	2 (1.2%)	
Drug-induced liver injury	2 (0.3%)	2 (0.6%)	0	

Continued

Table 1 Continued

	Total	Pre-COVID-19	COVID-19	P value
Unknown	185 (31.3%)	108 (30.9%)	47 (28.1%)	
Disease severity scores on admission (median, IQR)				
UKELD	56 (10)	56 (10)	57 (10)	0.392
MELD Na	21 (10)	20 (9)	21 (11)	0.684
Child Pugh Score	10 (3)	9 (3)	10 (3)	0.82
AD Score	54.3 (12.9)	54 (13)	55 (13)	0.69

Data have been shown for the total cohort, as well as a breakdown of the pre-COVID-19 and COVID-19 time periods.
AD, acute decompensation; MELD Na, Model for End-Stage Liver Disease-Sodium; UKELD, UK Model for End-Stage Liver Disease.

infection remained similar between the pre-COVID-19 and COVID-19 periods (43.1%–46.5%, p=0.376). However, the proportion of patients with SBP increased significantly from 32 (9.1%) to 42 (17.4%) (p=0.005).

Liver disease severity at admission and impact of tertiary transfers

Of the 591 total admissions, 170 (28.9%) were external hospital tertiary referrals for specialist intervention with a breakdown seen in table 2. The liver disease severity scores on admission of locally admitted patients had little variation between the pre-COVID-19 and COVID-19 period (table 2). However, the liver disease severity scores of tertiary transferred patients during COVID-19 were consistently higher than pre-COVID-19 transfers, with the Child Pugh and MELD-Na scores both showing statistically significant increases (p=0.032 and p=0.006). There was a significant decrease in the number of transferred patients presenting with a GI bleed (pre-COVID-19 43.3% to COVID-19 16.4%, p<0.001) and a non-significant increase in presentations with new decompensation events including ascites (62%–75%), HE (33%–44%) and infections (45%–59%).

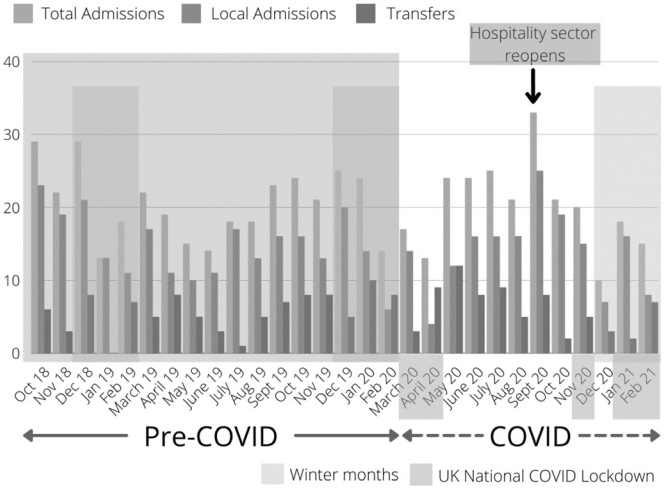

Figure 1 Graph showing admissions per month as a total number, as well as the split between local admissions and external referrals transferred to the unit from other hospitals.

The length of stay per admission between pre-COVID-19 and COVID-19 time periods remained at a median of 7 days. However, there was a rising trend in readmission rates from 21.5% to 29.5%, p=0.067, from pre-COVID-19 to COVID-19 periods, although the median time to first readmission during the COVID-19 period was 57 days, compared with 33 days pre-COVID-19 (p=0.056).

ITU support requirements

During the COVID-19 period, there was no significant change in the number of ITU admissions, length of stay, organ support requirements nor mortality. The proportion of patients with all grades of ACLF on admission to intensive care non-significantly increased from 63.8% pre-COVID-19 to 73.9% during the COVID-19 period (p=0.241). Importantly, of the patients admitted to intensive care without OFs, the median AD score increased significantly from 48 (IQR: 12) pre-COVID-19 to 57.5 (IQR: 17.5) during the COVID-19 period, (p=0.009). The proportion of patients with an AD score over 60 increased from 7.4% to 50% in the COVID-19 period (p=0.002), with an equal number of these being local versus transferred patients.

Outcomes and mortality data

The proportion of patients who received a liver transplant within 90 days of follow-up during the COVID-19 and pre-COVID-19 periods was comparable (3.5% vs 4.8%, p=0.535). However, the median time to transplantation non-significantly increased from 28 days pre-COVID-19 to 70 days during COVID-19 (p=0.328).

Overall mortality did not change throughout the study period with pre-COVID-19 inpatient mortality at 12.2% compared with 14.8% during COVID-19 (p=0.466). However, patients who died post hospital discharge during the COVID-19 period (and without COVID-19 infection), did so over a significantly shorter time with a median time to death of 35 days, compared with 62 days in pre-COVID-19 times (p=0.005). Figure 2 shows the Kaplan-Meier survival analysis for time to early deaths postdischarge after first admission, censored at 30 days, with those in the COVID-19 period having a significantly shorter survival (p<0.001). When analysing the whole

Table 2 Table showing severity scores and symptoms comparing the pre-COVID-19 and COVID-19 periods with a breakdown of admissions between local admissions and external referrals

		Pre-COVID-19		COVID-19	
		Domestic (n=255)	Transferred (n=97)	Domestic (n=167)	Transferred (n=73)
Severity Scores Median (IQR)	MELD Na	21 (9)	18 (11)	21 (9)	22 (11.5)
	CPS	9.42 (3)	10 (3)	10 (3)	10 (2)
	AD score	55.4 (12.8)	51.9 (10.9)	55.0 (11.7)	55.0 (15.7)
Symptoms	Ascites	192 (75.3%)	60 (61.9%)	125 (74.9%)	55 (75.3%)
	HE	102 (40%)	32 (33%)	68 (40.7%)	32 (43.8%)
	Infection	107 (42%)	44 (45.4%)	69 (41.3%)	43 (58.9%)
	Gastrointestinal bleeding	32 (12.5%)	42 (43.3%)	25 (15%)	12 (16.4%)

AD, acute decompensation; CPS, Child Pugh Score; HE, hepatic encephalopathy; MELD Na, Model for End-Stage Liver Disease-Sodium.

cohort, a multivariate analysis demonstrated that bilirubin, CRP and HE could independently predict 30-day mortality with a trend to significance with creatinine, International Normalised Ratio (INR) and infection (table 3).

DISCUSSION

COVID-19 has clearly impacted on the ability of healthcare providers to deliver care to patients with cirrhosis but the actual consequences on patient morbidity, outcomes, hospital and ITU utilisation, in decompensated cirrhosis patients, not directly infected by the virus, remains unclear.

The key findings of our study included higher liver disease severity scores at presentation in patients externally transferred during COVID-19 compared with pre-COVID-19, with notably higher CLIF-C AD scores in those not developing ACLF, when admitted to the ITU. A trend was also observed towards increased readmission rates during the COVID-19 period and increased early mortality (median <10 days post discharge).

While the average number of admissions did not differ between the two periods, monthly admissions did fall during national lockdown periods. Consequently, the seasonal spike common for winter was not seen in 2020 but instead higher peaks in early Summer and Autumn 2020 were observed, between the first and second lockdowns in the UK. This is consistent with the literature with some studies showing reduced cirrhosis admissions during the pandemic and others demonstrating no significant difference.[15–17]

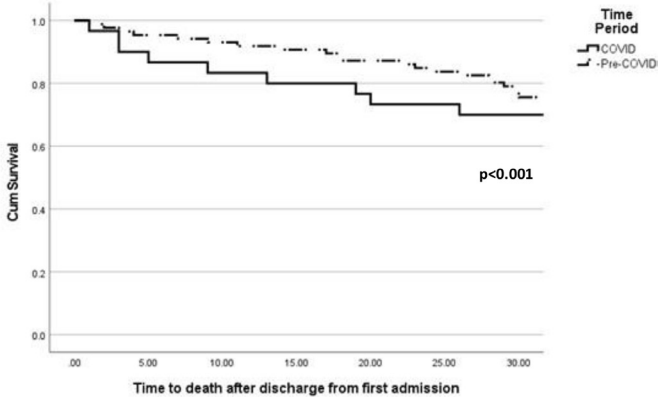

Figure 2 Kaplan-Meier survival curve for time to death post discharge after first admission censored to 30 days comparing the pre-COVID-19 and COVID-19 periods.

Looking at the overall data, alcohol was the most predominant aetiology with NASH second, which is consistent with European data.[18 19] In terms of precipitants for decompensation, the proportion of patients presenting with infection and GI bleeding are consistent with larger observational studies such as the CANONIC study, from non-COVID-19 times.[5] No significant difference was noted in alcohol as precipitant between the COVID-19 and pre-COVID-19 time periods, despite some of the highest levels of alcohol consumption in the world reported in the UK as well as Nordic countries.[20] We speculate that this perhaps was due to reluctance of patients to attend hospital due to concerns regarding COVID-19 infection, as well as a lack of power due to insufficient sample size.

While the purpose of this study was not to address the direct impact of COVID-19 infection in patients with established cirrhosis, given all patients were tested on arrival to the hospital during the COVID-19 period, interestingly we show that only four admissions among this tested cohort were positive for the infection, of which two were symptomatic. This is consistent with large scale studies which demonstrate no significant increased risk of acquiring COVID-19 with chronic liver disease.[21]

We noted a non-significant reduction in GI bleeding during the COVID-19 period, especially among tertiary referrals, which correlated with a significant reduction in TIPSS insertions that were performed (p=0.006). This is likely due to reduced availability of bed resource, especially ventilated ITU beds in our tertiary bleeding referral centre, for external transfers requiring airway protection prior to salvage TIPSS consideration, and also in part, through overall reduced endoscopic services activity during the COVID-19 period.

Table 3 A univariate and multivariate analysis of variables predicting 30-day mortality

	Univariate analysis			Multivariate analysis	
Variables	Mortality within 30 days (n=81) Mean (SD)	Survival beyond 30 days (n=307) Mean (SD)	P value	OR (95% CI)	P value
Age	55.9 (12.5)	56.9 (13.6)	0.564		
Sex (male) N (%)	58 (71.6)	204 (66.4)	0.379		
Sodium (mmol/L)	**131.6 (8.6)**	**134.5 (6.8)**	**0.001**	0.98 (0.94 to 1.01)	0.181
Creatinine (µmol/L)	**143.3 (121.1)**	**98.3 (92.0)**	**<0.001**	1.00 (1.00 to 1.00)	0.096
Bilirubin (µmol/L)	**194.1 (179.6)**	**100.67 (135.1)**	**<0.001**	**1.00 (1.00 to 1.00)**	**0.011**
ALT (U/L)	**99.0 (172.9)**	**60.2 (108.8)**	**0.013**	1.00 (1.00 to 1.01)	0.573
AST (U/L)	**197.1 (305.2)**	**111.8 (166.4)**	**<0.001**	1.00 (1.00 to 1.00)	0.465
Albumin (g/L)	**28.3 (5.1)**	**30.2 (5.8)**	**0.007**	0.96 (0.91 to 1.01)	0.076
INR	**1.9 (1.0)**	**1.5 (0.6)**	**<0.001**	1.38 (0.95 to 2.00)	0.095
Platelets ($\times 10^9$/L)	127.5 (80.7)	127.0 (71.8)	0.956		
WCC ($\times 10^9$/L)	**12.4 (7.5)**	**8.8 (7.5)**	**<0.001**	1.02 (0.99 to 1.04)	0.209
CRP (mg/L)	**57.3 (57.4)**	**30.3 (39.1)**	**<0.001**	**1.01 (1.00 to 1.01)**	**0.017**
Ascites N (%)	66 (81.5)	217 (70.7)	0.052		
Hepatic encephalopathy N(%)	**48 (59.3)**	**96 (31.3)**	**<0.001**	**1.70 (1.00 to 2.87)**	**0.049**
GI bleeding N (%)	36 (44.4)	111 (36.2)	0.172		
Infection N (%)	**57 (70.4)**	**125 (40.7)**	**0.007**	1.75 (0.97 to 3.15)	0.063
SBP N (%)	**20 (24.7)**	**26 (8.5)**	**<0.001**	1.14 (0.55 to 2.37)	0.725
First admission during COVID-19 time period N (%)	30 (37.0)	112 (36.5)	0.927		
Transferred from another centre N (%)	35 (43.2)	110 (35.8)	0.193		

Values that are statistically significant are displayed in bold.
CRP, C reactive protein; GI, gastrointestinal; SBP, spontaneous bacterial peritonitis; WCC, white cell count.

Interestingly, there was a statistically significant increase in the rate of SBP during the COVID-19 period. This is unexplained, though given that admissions during the COVID-19 period had higher CLIF-C AD scores and more frequently met ACLF criteria, one might expect such patients to have higher risk for developing SBP, with higher portal pressures driving bacterial translocation. Another potential explanation for greater SBP during COVID-19 could be suboptimal ascites management and patient compliance with or access to appropriate antibiotic prophylaxis, although this is speculative, as our study design could not avail information on medication compliance or oversight of patients being managed at home.

Although not significant, an increasing trend in cirrhosis decompensation hospital readmission rates (p=0.067) was noted in the COVID-19 period. This is likely to have a multifactorial basis which includes: lack of ease of access to early, postdischarge follow-up; diminished community/primary care access to support, and potential for expedited premature hospital discharges, reflecting pressure on healthcare systems consequent on the pandemic. Of note, there was also, a trend towards increased time to first readmission during the COVID-19 period, which may have been due to a reluctance of patients to attend hospital until they were more unwell, compounded by pressures on secondary care beds leading to reduced access, which is supported by our data showing higher liver disease severity scores, particularly in patients accepted as transfers in from secondary care sites.

While there was no difference in overall survival between the time periods, the median time to death post index hospital discharge, was significantly shorter (35 vs 62 days) in the COVID-19 cohort compared with non-COVID-19 times. This is at variance with some of the published literature, although in smaller cohorts, which have shown mortality increases of 52%.[22] Increased mortality has also been reported in other conditions such as respiratory, cancer and sepsis admissions.[23] This has been thought to be as a consequence of: (1) patients presenting late, in an attempt to avoid hospital presentation for fear of acquiring COVID-19; (2) impact of redistribution of clinical resources to acute medical care and away from supporting standard hepatology care pathways, most likely to impact on secondary care units, faced with more general medical case loads; (3) increased numbers with more advanced disease

(CLIF-AD score or ACLF progression) and (4) reduced availability of liver transplantation.[22] The concept of patients presenting with more advanced disease during the pandemic is supported by the multivariate analysis showing that markers of liver disease severity such as bilirubin as well as presence of HE independently predicted 30-day mortality.

Consistent with the early mortality data, we show an increase in cirrhosis decompensation severity scores on admission to the ITU during the COVID-19 period, especially noted in externally transferred patients. This is again consistent with patients presenting with more advanced disease which has been suggested in the literature.[10] The fact that overall mortality was not significantly different during the COVID-19 period compared with pre-COVID-19 times, despite higher liver-disease severity scores, is a testament of the ability of units to continue to provide high-quality supportive hepatology care, despite the constraints of the pandemic.

Our data show CLIF-C AD scores of those admitted to ITU without meeting OF criteria, were significantly higher during the COVID-19 period, especially in patients with AD scores over 60, who have been shown to have a higher risk of mortality and are more likely to progress to ACLF and thereby, requirement for organ support.[6 19] This may be in part attributable to patients being transferred in from secondary care, who had consistently higher AD disease severity scores during COVID-19 period, compared with local patients, who had similar scores across both time periods. A possible explanation is likely to reflect the lack of specialist hepatology input within secondary care sites in the UK which has been described, and patients being referred to tertiary care centres when they were more advanced in their decompensation.[24]

The key limitations of this observational study include that it is a single centre study and is retrospective in nature. Factors influencing hospital readmissions rates and mortality in the community were also not easy to discern in the data accessible and warrant further investigation in prospective studies. Outcome data for secondary care transferred patients were not always possible to verify once the patients returned to their local units for further follow-up and this may have introduced information bias. In addition, the cohort size may have limited the possibility to detect potential statistically significant differences in some of the outcomes measured.

In conclusion, this study provides useful insight into the effects that the COVID-19 pandemic has had on hospital admissions with decompensated cirrhosis, in a large UK tertiary liver centre. In particular, this study shows increased cirrhosis decompensation severity and early mortality, highlighting the need to focus on maintaining high-level specialist hepatology care, even after the patient is discharged from the hospital. Given that the effects of the pandemic will continue to impact Hepatology service provision for years to come, this necessitates considerations for alternative care pathways that mitigate reduced access for direct clinical review, especially early posthospital discharge, such as considering remote monitoring in this vulnerable patient population.

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