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ORIGINAL ARTICLE

A global multicenter propensity-matched analysis of mortality risk and palliative care referral due to cirrhosis in hospitalized patients with COVID-19

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ABSTRACT

Background and Aim: A few recent studies identified cirrhosis as a risk factor for high mortality in patients with coronavirus disease-19 (COVID-19). Palliative care is less often involved in the management of cirrhosis. We analyzed a global multicenter database to study the risk of mortality and palliative care referrals in patients with COVID-19 and cirrhosis.
Methods: A federated cloud-based network (TriNetX) data from 50 health-care organizations across the globe were analyzed retrospectively. Patients with COVID-19 aged from 18 years to 90 years were identified between January 20, 2020, and November 16, 2020.
Results: A total of 1969 patients (Group A) with COVID-19 and cirrhosis and 169,257 patients with COVID-19 alone (Group B) were studied. The two groups had a similar occurrence of other comorbid diseases. In a propensity-matched analysis, the mortality rate in Group A (8.9%) was significantly higher than Group B (5.6%), hazard ratio (95% confidence interval) for mortality with cirrhosis was 1.59 (1.26–1.99) (P = 0.01). The occurrence of palliative care referrals in Group A (4.1%) was significantly higher than Group B (2.0%), hazard ratio (95% confidence interval) with cirrhosis was 2.02 (1.39–2.94) (P = 0.01).
Conclusion: Mortality rate and palliative care referrals were higher in patients with cirrhosis and COVID-19 compared to those with COVID-19 alone. This increased occurrence of palliative care referrals compared to the general trend in cirrhotic patients probably indicates increased awareness of COVID-19 as a life-threatening condition.
Relevance for Patients: Cirrhosis should be identified as a high-risk condition that may require palliative care referral in hospitalized patients with COVID-19. Hospital resource utilization and cost-analysis modeling should anticipate the need for palliative care referrals as a significant outcome in patients with cirrhosis who are hospitalized with COVID-19.

1. Introduction

As of mid-July 2022, the coronavirus disease-19 (COVID 19) pandemic has infected 448 million people globally, resulting in about 6.4 million deaths [1]. Advanced age, hypertension, coronary artery disease, diabetes mellitus, and chronic lung disease are known risk factors for severe illness [2]. COVID-19 results in a spectrum of liver diseases ranging from asymptomatic elevation of liver enzymes to acute-on-chronic liver failure or even acute liver failure. Elevation of liver enzymes is noted in up to 50% cases of COVID-19

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disease with greater increases in those with severe disease [2]. Chronic liver disease (CLD) is a major health problem affecting one-fourth of the world population and resulting in about 2 million deaths annually [3,4]. In a study from the UK, based on a large electronic database study of more than 17 million patients (>114,000 with CLD), CLD was identified as an independent predictor of hospitalization [5]. In a recent analysis of data of patients with CLD and COVID-19 from two international reporting registries (COVID-Hep.net and COVIDCirrhosis.org), authors reported 12.2% mortality in CLD without cirrhosis, 23.9% in Child-Turcotte-Pugh (CTP)-A cirrhosis, 43.3% in CTP-B cirrhosis, and 63.0% in CTP-C cirrhosis [6]. Hepatic decompensation occurred in 36.9% of patients with cirrhosis and was associated with 63.2% mortality (compared to 26.2% mortality in those without hepatic decompensation). In another study from North America, patients with cirrhosis and COVID-19 were reported to have higher mortality than patients with COVID-19 alone. However, in this study, authors found similar mortality in patients with cirrhosis and COVID-19 and cirrhosis alone [7]. The Charlson Comorbidity Index was the only independent mortality predictor in this entire matched cohort [7].

Proper utilization of palliative care specialty services (PC) in the management of patients with cirrhosis and end-stage liver disease (ESLD) is critical. PC focuses on quality of life by optimizing symptom management and providing psychosocial, spiritual, and practical support for patients and their caregivers. PC has been integrated into chronic disease states such as end-stage COPD, heart failure, and renal failure. However, PC has been underutilized and underevaluated for patients with cirrhosis. Most studies do not evaluate the requirement for PC as an outcome measure in cirrhosis. With the current pandemic, patients with combined cirrhosis and COVID-19 pose a unique challenge with risk of worsening COVID-19 and/or decompensation from underlying cirrhosis. It is unclear if utilization of PC services changed with onset of the pandemic, especially among hospitalized COVID-19-infected cirrhotic patients. Considering this ongoing concern, we aimed to retrospectively evaluate the mortality risk and PC referrals in patients with cirrhosis and COVID-19 as compared to those with only COVID-19 in a global multicenter database.

2. Methods

We utilized a federated cloud-based network (TriNetX), which provides access to anonymized data of electronic medical records from 50 health-care organizations across the globe. The TriNetX search was performed on September 8, 2020, and a deidentified dataset of patients with COVID-19 aged from 18 years to 90 years was identified as having received care between January 20, 2020, and November 16, 2020 (details provided in the supplementary material [8,9]).

2.1. Study outcomes

Outcomes of the study include referral for palliative care and mortality. The outcomes were measured before and after 1:1 propensity matching of the groups based on the baseline demographics and comorbidities.

2.2. Statistical analysis

All statistical analyses were performed on the TriNetX online platform. To safeguard the PHI, TriNetX conceals patient counts by rounding patient counts in analyses up to the nearest 10. Descriptive measures such as means with standard deviations and proportions were used to describe patient characteristics. For each outcome, the risk ratio was calculated to estimate the risk of cirrhosis on the outcomes. A priori defined two-sided alpha value of <0.05 was used for statistical significance. Propensity Score Matching: To account for confounding variables, we performed a 1:1 propensity score matching with a caliper of 0.1 pooled standard deviations based on the following variables: Age, gender, race, hypertension, diabetes mellitus, obesity, chronic kidney disease (CKD), ischemic heart diseases, and chronic obstructive pulmonary disease.

3. Results

Among all the patients (n = 171,226), there were 1969 patients (Group A, 1.13%) with COVID-19 and cirrhosis and 169,257 (Group B, 98.87%) with COVID-19 alone. Mean age, gender ratio, ethnicity, and comorbid conditions were comparable in both groups (Table 1). The comorbid diseases studied include hypertension, diabetes mellitus, chronic kidney disease, chronic obstructive pulmonary disease, ischemic heart disease, mental and behavioral disorders secondary to psychoactive drug use, and obesity. The occurrence of comorbid conditions (other than cirrhosis and related conditions) was comparable in both study groups. Non-alcoholic fatty liver disease, alcohol, and chronic hepatitis C accounted for cirrhosis in 45.3%, 27.5%, and 23.9% of patients, respectively. Mean Model for ESLD-Sodium (MELD-Na) score in Group B was 18. Ascites was present in 11.8% and esophageal varices 25.0% of patients in the cirrhosis group. Hepatocellular carcinoma was reported in 2.6% of patients with cirrhosis.

After propensity-matched analysis of data, the overall mortality in Group A was 8.9% and Group B was 5.6% with a hazard ratio (95% confidence interval) of mortality with coexisting cirrhosis being 1.59 (1.26–1.99) (P = 0.01). Similarly, the requirement for palliative care referrals in Group A was 4.1% and Group B was 2.0% with a hazard ratio (95% confidence interval) of palliative care referrals with coexisting cirrhosis being 2.02 (1.39–2.94) (P = 0.01). In propensity-matched subgroup analysis, we analyzed patients who had early (within 7 days of hospital admission) PC referral, the hazard ratio of morality for cirrhosis and COVID-19 was comparable to the whole group, namely, 1.59 (1.12–2.26). In another subgroup analysis, the hazard ratio of mortality for COVID-19 and cirrhosis and ascites (compared to COVID-19 without cirrhosis or ascites) was 2.28 (1.59–3.27) (P < 0.01) and of PC referral as 2.5 (RR 2.50 [1.46–4.27]) (P < 0.01).

4. Discussion

Our study in a propensity-matched analysis of the outcomes of hospitalized patients with COVID-19, with and without cirrhosis,

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Table 1. Baseline characteristics and clinical outcomes in COVID-19 patients with and without cirrhosis

Characteristic name	COVID with cirrhosis (*n*=1969) (Group A)	COVID without cirrhosis (*n*=169,257) (Group B)	*P*	COVID with cirrhosis (*n*=1968) (Group A)	COVID without cirrhosis (*n*=1968) (Group B)	*P*
	Before matching			After matching		
Age (SD)	60.746063 (12.89)	48.409695 (19.07)	0.00	60.74238 (12.89)	62.506096 (13.82)	0.06
Male (%)	1150 (58.41)	75,506 (44.61)	0.0000	1149 (58.38)	1127 (57.27)	0.4777
Female (%)	819 (41.60)	93,328 (55.14)	0.0000	819 (41.62)	840 (42.68)	0.4979
Caucasian (%)	1142 (58.00)	79,704 (47.09)	0.0000	1141 (57.98)	1165 (59.20)	0.4374
African-American (%)	340 (17.27)	25,674 (15.17)	0.0099	340 (17.28)	334 (16.97)	0.7996
Comorbidities						
Essential hypertension (%)	1288 (65.41)	41,742 (24.66)	0.0000	1287 (65.40)	1324 (67.28)	0.2120
Diabetes mellitus (%)	925 (46.98)	22,192 (13.11)	0.0000	924 (46.95)	946 (48.07)	0.4826
COPD (%)	369 (18.74)	7080 (4.18)	0.0000	369 (18.75)	358 (18.19)	0.6514
Obesity (%)	646 (32.81)	23,911 (14.13)	0.0000	645 (32.77)	651 (33.08)	0.8387
Ischemic heart diseases (%)	638 (32.40)	13,532 (8.00)	0.0000	637 (32.37)	623 (31.66)	0.6324
Chronic kidney disease (%)	618 (31.39)	9993 (5.90)	0.0000	617 (31.35)	555 (28.20)	0.307
Cerebrovascular diseases (%)	384 (19.50)	8799 (5.20)	0.0000	383 (19.46)	358 (18.19)	0.3080
Mental and behavioral disorders due to psychoactive substance use (%)	814 (41.34)	15,083 (8.91)	0.0000	813 (41.31)	798 (40.55)	0.6268
Esophageal varices (%)	494 (25.09)	66 (0.04)	0.0000	493 (25.05)	10 (0.51)	0.0000
Ascites (%)	233 (11.83)	149 (0.09)	0.0000	233 (11.84)	10 (0.51)	0.0000
HE (%)	23 (1.17)	25 (0.01)	0.0000	23 (1.17)	10 (0.51)	0.0000
Hepatopulmonary syndrome (%)	10 (0.51)	0	0.0000	10 (0.51)	0	0.0015
HCC (%)	52 (2.64)	0	0.0000	52 (2.64)	0	0.0000
Etiology of cirrhosis (NAFLD/alcohol/HCV/HBV, %)				45.3/27.5/23.9/3.5		
Labs						
Hemoglobin (SD)	11.75 (2.54)	13.26 (2.05)	<0.0001	11.75 (2.54)	12.89 (2.32)	<0.0001
Platelets (SD)	162.86 (99.31)	250.66 (82.48)	<0.0001	162.86 (99.35)	237.40 (85.63)	<0.0001
Bilirubin total (SD)	1.58 (3.26)	0.56 (0.50)	<0.0001	1.58 (3.26)	0.60 (0.51)	<0.0001
Creatinine (SD)	1.59 (4.01)	1.02 (1.64)	<0.0001	1.59 (4.01)	1.43 (3.40)	0.2157
INR (SD)	1.32 (0.58)	1.15 (0.63)	<0.0001	1.32 (0.58)	1.18 (0.42)	<0.0001
Hemoglobin A1c (SD)	6.39 (1.88)	6.33 (1.69)	0.3100	6.39 (1.88)	6.77 (1.83)	<0.0001
Prothrombin time (SD)	15.22 (5.91)	13.26 (5.44)	<0.0001	15.23 (5.91)	13.57 (4.33)	<0.0001
Leukocytes (SD)	6.57 (4.34)	7.96 (35.25)	0.1200	6.57 (4.34)	7.96 (5.83)	<0.0001
Sodium (SD)	137.39 (4.53)	138.96 (3.48)	<0.0001	137.39 (4.53)	138.59 (4.12)	<0.0001
Alanine aminotransferase (SD)	40.49 (112.82)	29.66 (71.02)	<0.0001	40.50 (112.85)	31.13 (67.91)	0.0058
Aspartate aminotransferase (SD)	60.93 (259.09)	30.42 (137.74)	<0.0001	60.95 (259.17)	34.64 (144.95)	0.0006
Albumin (SD)	3.45 (0.79)	3.99 (0.66)	<0.0001	3.45 (0.79)	3.83 (0.66)	<0.0001
Protein (SD)	6.76 (1.41)	7.06 (1.14)	<0.0001	6.76 (1.41)	6.89 (1.22)	0.0074
Outcome			HR			HR
Palliative care (%)	81 (4.11)	1583 (0.94)	4.40 (3.53–5.47)	81 (4.12)	40 (2.03)	2.02 (1.39–2.94)
Mortality (%)	176 (8.94)	4484 (2.65)	3.37 (2.92–3.90)	176 (8.94)	111 (5.64)	1.59 (1.26–1.99)

[€]A 1:1 propensity score matching was done based on the following variables: Age, gender, race, hypertension, diabetes mellitus, obesity, CKD, ischemic heart diseases, COPD, and cirrhosis of liver. *P*-values in bold are statistically signi f cant. Data represent mean values. Cells marked green indicate signi f cant increase in parameter value relative to Group B, and cells marked red indicate signi f cant decrease in parameter value compared to Group B. COPD: Chronic obstructive pulmonary disease, INR: International normalized ratio, HE: Hepatic encephalopathy, HCC: Hepatocellular carcinoma, SD: Standard deviation, CKD: Chronic kidney disease, HR: Hazard ratio, HCV: Hepatitis C virus, HBV: Hepatitis B virus, NAFLD: Nonalcoholic fatty liver disease

shows that there is signi f cantly increased risk of mortality and PC referrals in patients with cirrhosis and COVID-19. Cirrhosis increases the risk of mortality and PC referral by about 100% and 50%, respectively, after matching for age, gender, ethnicity, body mass index, and non-liver-related comorbidities. The risk was even higher in COVID-19 patients with cirrhosis and ascites. Another multicenter study from the US reported 14% mortality in patients with CLD and COVID-19, identifying alcohol-related liver disease, decompensated liver disease, and Hispanic origin as independent predictors of mortality [11]. Our results are in

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concordance with similar studies which reported higher mortality in patients with cirrhosis and COVID-19 [5,6,10,11].

In cirrhosis, frailty and sarcopenia are closely related, both are closely correlated with PC referrals and mortality [12-14]. Frailty, a "syndrome of decreased reserve and resistance to stressors, resulting in declines across multiple systems" is often reported in a large proportion of patients with cirrhosis [12,15]. The PC provides symptom management, psychosocial, spiritual, and practical support for patients with life-limiting and life-threatening illnesses. PC is often sought in patients with clear features of terminal illness, along with other active therapies that are intended to prolong life. PC is integrated into the management of other chronic diseases, including advanced heart failure, respiratory diseases, and renal failure, the inclusion of cirrhotic patients has been low, unless there is a concurrent diagnosis of hepatocellular carcinoma or metastatic cancer [14]. PC referral rate in cirrhosis is variable and can range from 1% in 2006 to 7% in 2012, and the referral rates depend on geographic area and national or regional institutional policies [16,17]. A recent study has shown that patients with ESLD and low socioeconomic status, Hispanic ethnicity, those who live in the northeastern part of the United States, and those treated in small and nonteaching hospitals were less likely to receive a PC evaluation [17]. Our study shows that PC referral was 10% in COVID-19 alone group and 15% in COVID-19 with cirrhosis group, which may be indicative of increased awareness and identification of severe COVID-19 as a life-threatening condition.

Our results validate the recommendations to avoid possible exposure to COVID-19 by strictly following appropriate health-care advisories, particularly in high-risk subjects [18]. Judicious utilization of telehealth facilities and avoiding hospital visits, unless strongly indicated, could possibly be an important step toward reducing risk of exposure. Similar studies have shown that the mortality risk increases with severity of underlying liver disease [5-7]. Our study is limited by its retrospective electronic records review method. Furthermore, PC referrals are sometimes subjective in nature, so a lack of a consensus and policy with regard to palliative care utilization could result in non-homogeneity in the data collected. We were unable to stratify severity of cirrhosis based on CTP and MELD-Na scores by nature of the dataset. However, our observations concur with similar studies, and in addition, this analysis shows that the palliative care referrals are significantly higher in patients with cirrhosis and COVID-19.

5. Conclusion

Mortality rate and palliative care referrals were higher in patients with cirrhosis and COVID-19 compared to those with COVID-19 alone. Mortality rate and palliative care referrals were even higher in COVID-19 patients with cirrhosis and ascites. The increased occurrence of palliative care referrals compared to the general trend in cirrhotic patients probably indicates increased awareness of COVID-19 as a life-threatening condition.

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Conflicts of Interest

None.

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Supplementary File

Data on TriNetX network are obtained from academic medical centers, specialty physician services and community hospitals. The used is acquired from the TriNetX (https://www.trinetx.com/). TriNetX has received a waiver from IRB since it does not contain any protected health information or the HCO Information. It only includes aggregated counts and statistical summaries of deidentified information. Using TriNetX analytics platform, COVID-19 patients were identified based on Centers for Disease Control and Prevention coding guidelines. Patients were included if they had one or more of the following International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modifcations (ICD-10-CM) codes in the EMR's: U07.1 COVID-19; B34.2 Coronavirus infection, unspecified; B97.29 Other coronavirus as the cause of disease classified elsewhere.[8] ICD-10 codes K74.60 (unspecified cirrhosis of liver), K74.69 (other cirrhosis of liver), and K74.6 (other and unspecified cirrhosis of liver) were included to identify patients with cirrhosis of the liver. These COVID-19 patients with cirrhosis were divided into two groups – COVID-19 patients without cirrhosis (Group A); and COVID-19 with cirrhosis (Group B). Comorbidites were identified using codes I10 (essential hypertension), I20-25 (Ischemic heart disease), N18 (CKD), E08-13 (Diabetes Mellitus), J44.9 (Chronic obstructive pulmonary disease, unspecified), and E65-E68 (Overweight, obesity, and hyperalimentation).[8,9] The data are susceptible to coding or data entry errors when patient information is translated into the ICD-10 codes. Only age of death was available. Date of death is not available. Underreporting of the data could be possible from HCO's. We could not report the influence of different HCO's due to privacy restriction. Recording of ICD codes in administrative data may vary in cormorbidites, severity of illness, length of hospitalization, and whether in hospital death occurred.[10] However, the data collection errors are minimized since TriNetx aggregates the data directly from the electronic medical records.

ICD 10 codes used:

Corona virus

- U07.1, B34.2, B97.29, J12.81
- Exclusion: B34.2, B97.2.

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- K70.30, K70.31, K74.60, K74.69, K74.3, K74.4, K74.5 cirrhosis
- Varices: I85.0, I 85.01, I85.10, I85.11, 86.4
- Ascites: K70.31, K70.11, R18.8, K65.2
- HE: K70.41, K72.11, K72.91, B15, B16, B17.11, B19.0, B19.11, B19.21
- HCC: C22.0, C22.8, C22.9.

Cause of liver disease

- K83.1 PSC
- 76.9 other specified diseases of liver
- K76.89 other specified diseases of liver
- K76.9 liver disease unspecified
- K72.9 Hepatic failure

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- K71 Toxic liver disease
- K75.81: NASH
- K76.9 Fatty liver not elsewhere specifed
- B18 Chronic viral hepatitis
- B19.1 unspecifc viral hepatitis
- K73. Chronic hepatitis not elsewhere classifed
- K75.3 Granulomatous hepatitis
- K75.4 autoimmune hepatitis
- K75.89 other specifed infammatory liver disease
- K76.81- HPS
- K76.7- HRS.

Other comorbidities

- CV diseases ICD 10
- I60-69.

Substance abuse

- F10-F19.

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