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Recommended Citation

Perisetti, Abhilash MD; Kaur, Randeep; and Thandassery, Ragesh, "Increased Diagnosis of Hepatocellular Carcinoma in Hospitalized Patients with Alcohol Related Hepatitis after the Covid-19 Outbreak: A Global Multi-Center Propensity Matched Analysis." (2021). *PCI Publications and Projects*. 58.

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LETTER TO THE EDITOR

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Increased Diagnosis of Hepatocellular Carcinoma in Hospitalized Patients with Alcohol Related Hepatitis after the Covid-19 Outbreak: A Global Multi-Center Propensity Matched Analysis

We have read the recent article by Kim et al¹ with interest. We extended our study into the course of hepatocellular carcinoma (HCC) in patients with alcohol-related hepatitis post COVID-19 pandemic. The Coronavirus 2019 (COVID-19) pandemic has posed significant challenges in the management of chronic liver disease. Missed or delayed diagnosis of HCC is anticipated due to temporary interruption in standard surveillance protocols during the pandemic, although no large studies have documented these results. We attempted to study the baseline characteristics and outcomes in patients hospitalized with alcohol-related hepatitis, before and after the COVID-19 outbreak, and analyze the impact on outcomes including the diagnosis of HCC and inpatient mortality. A federated cloud-based network (TriNetX) data from fifty health care organizations across the globe was analyzed retrospectively.² Patients admitted with alcohol-related hepatitis between January 2019 and December 2020 were studied. They were categorized into 2 groups including post-COVID outbreak (group 1, January 1, 2020 to December 1, 2020) and pre-COVID outbreak (group 2, January 1, 2019 to December 1, 2019). Patient characteristics and outcomes related to hospitalization were compared between these groups.

Of 23,201 patients studied, 4383 patients were included in post-COVID, and 18,818 pre-COVID group. The 2 groups had comparable demographic features and occurrence of other comorbid diseases (Table 1), none of which had a COVID-19 diagnosis. After propensity matched analysis, we found that post-COVID group had a tendency to have higher total bilirubin levels ($P = .05$) during hospitalization. Similarly, the post-COVID group had a higher proportion of patients with underlying cirrhosis ($P = 0.02$). Patients had a similar course during hospitalization including most of the variables compared among the 2 groups except the occurrence of hepatorenal syndrome (higher in the post-COVID group;

$P < .001$). Among the outcome variables studied, the post-COVID group had an increased occurrence of HCC (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.08–1.32; $P < .001$), however occurrence of ascites (OR, 0.72; 95% CI, 0.45–1.17; $P = .18$), hepatic encephalopathy (OR, 0.74; CI, 0.49–1.11; $P = .15$), need for steroid use (OR, 1.13; CI, 0.91–1.41; $P = .24$) and inpatient death (OR, 0.93; CI, 0.72–1.20; $P = .59$) were comparable among both groups.

These results might indicate decreased outpatient diagnosis of HCC, likely from delay or discontinuity in standard HCC surveillance as a result of the COVID-19 outbreak. We may infer that higher bilirubin levels and higher diagnosis of cirrhosis in the post-COVID group are consequent to general patient behavior of seeking medical care only with increased symptoms during the pandemic, however this did not translate to increased mortality. HCC is a slow growing tumor with a tumor doubling time of 6 months and we anticipate that the clinical impact of a missed diagnosis will be more remarkable in long term follow up in the post pandemic phase, and our results probably indicate only the tip of an iceberg. A larger study including the hospitalized and outpatient population might address this issue more appropriately. Tapper et al described 3 waves of the impact of COVID-19 on cirrhosis care; (1) an early high acuity phase with delayed routine care, (2) a challenging 'return to normal' phase, and (3) a final phase of missed diagnoses and progressive disease.¹ Our study testifies these predictions, and we recommend a greater caution as we encounter patients at risk for HCC in clinics, to confirm that they have not missed their scheduled ultrasound surveillance.

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Table 1. Propensity Matched Comparison of Groups With Alcohol-Related Hepatitis After and Before COVID-19 Outbreak

	Before matching		<i>P</i> value ^a	After matching		<i>P</i> value
	Post-COVID (group 1) n = 4383	Pre-COVID (group 2) n = 18,818		Post-COVID (group 1) n = 4383	Pre-COVID (group 2) n = 4383	
Age, y (± SD)	49.7 ± 12.3	50.2 ± 12.3	.01	49.7 ± 12.3	49.7 ± 12.2	.09
Gender, male, %	63.9	64.7	.33	63.9	63.7	.82
BMI, kg/m ² (± SD)	28.1 ± 5.9	27.7 ± 5.8	.02	28.2 ± 5.9	27.7 ± 5.8	.09
Comorbid diseases, %						
Hypertension	65.5	65.6	.89	66.5	66.6	.26
Diabetes mellitus	21.5	22.5	.14	21.5	20.9	.56
Obesity	27.3	23.9	< .001	27.3	26.7	.58
Chronic kidney disease	11.1	10.5	.25	11.1	9.9	.08
Coronary artery disease	18.1	18.3	.75	18.1	17.8	.73
COPD	18.9	20.3	.39	18.9	18.7	.80
Cerebrovascular disease	11.0	12.7	.003	11.0	10.8	.68
Laboratory values						
HbA _{1c} (± SD)	6.3 ± 2.3	6.3 ± 2.2	.71	6.3 ± 2.3	6.2 ± 1.9	.89
Hemoglobin, g/dL (± SD)	13.1 ± 2.1	11.4 ± 2.6	.01 ^a			
Platelet count, per mL (± SD)	214.5 ± 123.2	214.2 ± 100.8	.96	214.5 ± 123.2	213.7 ± 104.2	.94
Serum sodium, mEq/dL (± SD)	138.4 ± 3.6	138.5 ± 3.8	.66	138.4 ± 3.6	138.4 ± 4.1	.54
Creatinine, mg/dL (± SD)	2.08 ± 10.1	1.98 ± 10.5	.89	2.08 ± 10.1	1.2 ± 4.4	.33
Bilirubin, total, mg/dL (± SD)	1.4 ± 2.9	1.5 ± 3.8	.72	0.71 ± 0.3	1.4 ± 2.9	.05
Alanine transaminase, U/L (± SD)	56.5 ± 53.0	57.8 ± 101.5	.86	56.5 ± 53.0	54.5 ± 56.0	.72
Aspartate transaminase, U/L (± SD)	77.2 ± 81.3	82.4 ± 207.6	.74	66.5 ± 69.5	82.3 ± 207.6	.21
Albumin, g/dL (± SD)	3.8 ± 0.8	3.9 ± 0.8	.29	3.8 ± 0.8	3.8 ± 0.8	.79
INR (± SD)	1.2 ± 0.2	1.4 ± 0.7	.94	1.2 ± 0.24	1.2 ± 0.4	.60
Prothombin time, s (± SD)	13.8 ± 3.3	13.5 ± 4.5	.69	13.8 ± 3.3	13.2 ± 4.9	.47
Course of illness, %						
Underlying cirrhosis	33.8	30.8	< .001	33.8	31.5	.02
Esophageal varices	14.3	13.4	.11	14.3	13.7	.40
Hepatorenal syndrome	3.8	2.7	< .001	3.8	2.2	< .001
Steroid therapy	21.7	20.3	.04	21.7	21.0	.48

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HbA_{1c}, hemoglobin A_{1c}; INR, international normalized ratio; SD, standard deviation.

^aPropensity matched analysis was performed and *P* < .05 was significant.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2021.05.010>.

References

- Kim D, et al. Clin Gastroenterol Hepatol. 2020 ;S1542-3565(20) 31288-X. <https://doi.org/10.1016/j.cgh.2020.09.027>
- <https://www.trinetx.com/>.

Conflicts of interest

The authors disclose no conflicts.

<https://doi.org/10.1016/j.cgh.2021.05.010>

Supplementary Material

Data on TriNetX network were obtained from academic medical centers, specialty physician services, and community hospitals. The data used is acquired from TriNetX (<https://www.trinetx.com/>). TriNetX has received a waiver from the institutional review board because 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 1 or more of the following International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modifications (ICD-10-CM) codes in the electronic medical records: U07.1 COVID-19; B34.2 coronavirus infection, unspecified; and B97.29 other coronavirus as the cause of disease classified elsewhere.¹ 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 2 groups: COVID-19 patients without cirrhosis (group A), and COVID-19 with cirrhosis (group B). Comorbidities were identified using codes I10 (essential hypertension), I20-25 (ischemic heart disease), N18 (chronic kidney disease), E08-13 (diabetes mellitus), J44.9 (chronic obstructive pulmonary disease, unspecified), and E65-E68 (overweight, obesity, and hyperalimentation).^{1,2} 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 HCOs because of privacy restriction. Recording of ICD codes in administrative data may vary in comorbidities, severity of illness, length of hospitalization, and whether in-hospital death occurred.³ However, the data collection errors are minimized because 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

Cirrhosis, Moon et al.⁴

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

K71 Toxic liver disease

K75.81: NASH

K76.9 Fatty liver not elsewhere specified

B18 Chronic viral hepatitis

B19.1 unspecific viral hepatitis

K73. Chronic hepatitis not elsewhere classified

K75.3 Granulomatous hepatitis

K75.4 autoimmune hepatitis

K75.89 other specified inflammatory liver disease

K76.81- HPS

K76.7- HRS

Other comorbidities

CV diseases ICD 10

I60-69

Substance abuse

F10-F19

Supplementary References

1. Harrison SL, et al. *PLoS Med* 2020;17:e1003321.
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4. Moon AM, et al. *J Hepatol* 2020;73:705-708.