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ABOUT COVER

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ORIGINAL ARTICLE

Retrospective Cohort Study

Association between alcohol-associated cirrhosis and inpatient complications among COVID-19 patients: A propensity-matched analysis from the United States

Faisal Inayat, Hassam Ali, Pratik Patel, Rubaid Dhillon, Arslan Afzal, Attiq Ur Rehman, Muhammad Sohaib Afzal, Laraib Zulfiqar, Gul Nawaz, Muhammad Hassan Naeem Goraya, Subanandhini Subramanium, Saurabh Agrawal, Sanjaya K Satapathy

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Abstract

BACKGROUND

Alcohol-associated cirrhosis (AC) contributes to significant liver-related mortality

in the United States. It is known to cause immune dysfunction and coagulation abnormalities. Patients with comorbid conditions like AC are at risk of worse clinical outcomes from coronavirus disease 2019 (COVID-19). The specific association between AC and COVID-19 mortality remains inconclusive, given the lack of robust clinical evi-dence from prior studies.

AIM

To study the predictors of mortality and the outcomes of AC in patients hospitalized with COVID-19 in the United States.

METHODS

We conducted a retrospective cohort study using the National Inpatient Sample (NIS) database 2020. Patients were identified with primary COVID-19 hospitalizations based on an underlying diagnosis of AC. A matched comparison cohort of COVID-19 patients without AC was identified after 1:N propensity score matching based on baseline sociodemographic characteristics and Elixhauser comorbidities. Primary outcomes included median length of stay, median inpatient charges, and in-hospital mortality. Secondary outcomes included a prevalence of systemic complications.

RESULTS

A total of 1325 COVID-19 patients with AC were matched to 1135 patients without AC. There was no difference in median length of stay and hospital charges in COVID-19 patients with AC compared to non-AC ($P > 0.05$). There was an increased prevalence of septic shock (5.7% *vs* 4.1%), ventricular fibrillation/ventricular flutter (0.4% *vs* 0%), atrial fibrillation (13.2% *vs* 8.8%), atrial flutter (8.7% *vs* 4.4%), first-degree atrioventricular nodal block (0.8% *vs* 0%), upper extremity venous thromboembolism (1.5% *vs* 0%), and variceal bleeding (3.8% *vs* 0%) in the AC cohort compared to the non-AC cohort ($P < 0.05$). There was no difference in inpatient mortality in COVID-19 patients with non-AC compared to AC, with an odds ratio of 0.97 (95% confidence interval: 0.78-1.22, $P = 0.85$). Predictors of mortality included advanced age, cardiac arrhythmias, coagulopathy, protein-calorie malnutrition, fluid and electrolyte disorders, septic shock, and upper extremity venous thromboembolism.

CONCLUSION

AC does not increase mortality in patients hospitalized with COVID-19. There is an increased association between inpatient complications among COVID-19 patients with AC compared to non-AC.

Key Words: Alcoholic cirrhosis; COVID-19; Chronic liver disease; Mortality predictors; Inpatient complications

Core Tip: High-risk comorbid conditions significantly increase the mortality linked to coronavirus disease 2019 (COVID-19). In this large National Inpatient Sample-based retrospective cohort study, we aimed to evaluate the specific clinical impact of alcohol-associated cirrhosis (AC) on patients hospitalized with COVID-19. We analyzed the patient outcomes based on comorbidities, mechanical ventilation, intensive care unit admission, and mortality predictors. Our findings show that AC does not increase mortality in patients hospitalized with COVID-19. Pertinently, there is an increased association between inpatient complications and COVID-19 patients with AC compared to non-AC. Predictors of mortality included advanced age, cardiac arrhythmias, coagulopathy, protein-calorie malnutrition, fluid and electrolyte disorders, septic shock, and upper extremity venous thromboembolism.

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INTRODUCTION

The global pandemic of coronavirus disease 2019 (COVID-19) has profoundly affected patients with pre-existing comorbidities. The World Health Organization reported that there were 768 million confirmed cases and 6.9 million fatalities as of June 21, 2023[1]. The disease presents a broad range of clinical features, from asymptomatic respiratory infection to severe pneumonia, thromboembolism, and even death. Initial reports from Wuhan indicated elevated serum liver biochemistry panels and associated liver injury in COVID-19 patients[2]. Previous research has demonstrated that patients with chronic liver disease (CLD) had a longer disease duration and higher mortality after contracting COVID-19[3,4]. CLD is a sig-

nificant public health concern, with an estimated global burden of 1.5 billion patients and 2 million annual deaths[5]. It is notable that viral hepatitis remains the leading cause of cirrhosis worldwide[6]. However, obesity and alcohol use have emerged as critical risk factors following advances in the prevention and treatment of viral hepatitis[6]. This etiological shift is expected to shape the future epidemiology of CLD[6]. It can potentially make the hepatic involvement of COVID-19 particularly troubling for patients with underlying alcohol-associated cirrhosis (AC)[7].

Patients with cirrhosis often develop immunological perturbations, leading to systemic inflammation and immune deficiency[8]. This immune dysfunction could potentially make it more difficult for cirrhotics to fight COVID-19. Numerous studies have identified an increased risk of COVID-19 severity and death in cirrhotic patients[9-11]. However, the literature offers conflicting results regarding the clinical impact of underlying cirrhosis on COVID-19 outcomes. For instance, Bajaj *et al*[12] reported similar mortality rates between cirrhotics with and without COVID-19, yet highlighted higher mortality in cirrhotics compared to patients suffering from COVID-19 alone. Moreover, the COVID-19-associated mortality rates in patients with CLD and cirrhosis varied from 8.9% to 39.8%[13,14].

Based on available clinical epidemiologic studies, there is a limited understanding of the etiologic basis of the clinical outcomes of cirrhosis in patients with COVID-19. However, several studies have investigated this subject. For example, in a single-center retrospective analysis of a cohort of patients hospitalized for COVID-19 with a prevailing alcoholic CLD, liver cirrhosis was linked to a fourfold increase in 30-d mortality[15]. A Korean study suggested that people with underlying nonalcoholic fatty liver disease may be more likely to test positive for severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) and experience severe infection[16]. In addition, Kim *et al*[17] conducted a multicenter, observational cohort study demonstrating increased overall mortality in patients with CLD and COVID-19 due to alcohol-associated liver disease, decompensated cirrhosis, and hepatocellular carcinoma.

Our objective is to assess the impact of AC on outcomes and mortality in patients hospitalized with COVID-19 using a large, multicenter database. We also seek to identify mortality predictors in COVID-19 patients with AC. To our knowledge, this is the first study to examine the specific clinical influence of AC on COVID-19 by assessing substantial epidemiological trends in hospitalized patients in the United States.

MATERIALS AND METHODS

Design and data source

This retrospective cohort study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[18]. We utilized the recently released National Inpatient Sample (NIS) database 2020. It is designed by the Agency for Healthcare Research and Quality[19]. NIS is the largest inpatient database in the United States healthcare system[19]. The design of this database enables the calculation of national estimates using sampling weights and a 20% stratified sample of hospitals[19]. Detailed information on the design of NIS and sampling methods is available at https://www.hcup-us.ahrq.gov. NIS 2020 utilized the International Classification of Diseases (ICD) 10 coding system to store and report data. We identified hospitalizations with a primary diagnosis (DX1) of COVID-19 using the "U07.1" ICD-10 code, which was introduced in March 2020[20]. Hospitalizations were excluded if the patient age was < 18 years, individuals were transferred, and/or COVID-19 was listed as a secondary diagnosis. Furthermore, patients were excluded if there was any history of cirrhosis due to nonalcoholic and other causes (viral, autoimmune, or non-specified), hepatocellular carcinoma, malignant neoplasm, end-stage renal disease requiring dialysis, quadriplegia, lymphoma, renal transplant, or liver transplant, as these were deemed high-risk conditions that could confound our analysis.

Outcome measures

Primary outcomes included median length of stay, median inpatient charges, and in-hospital mortality. Secondary outcomes included a prevalence of respiratory, cardiac, circulatory, neurological, and renal complications.

Statistical analysis

Statistical analysis was performed using Statistical Software for Data Science (StataCorp LLC, College Station, TX, United States) version 16.0. Two cohorts were created based on the presence or absence of a secondary diagnosis of AC using ICD-10 codes employed in the published literature[21]. We developed matched cohorts using propensity score matching (PSM) to minimize the effect of comorbid imbalances between comparison cohorts. Each case was assigned a propensity score using a multivariable logistic regression that included baseline sociodemographic characteristics (age, sex, race, socioeconomic status, and Elixhauser comorbidities). Propensity scores between the two cohorts were matched in a 1:N fashion using the nearest-neighbor method within 0.01 standard deviations of the calculated score[22]. The covariate balance was then visualized using the two-way plot (Figure 1). A two-sample Wilcoxon rank-sum (Mann-Whitney) test was utilized for continuous variables. The Chi-square test was used to compare categorical variables. The significance threshold was set at $P < 0.05$. For logistic regression, hierarchical models were designed using any unbalanced variables in PSM (race). The positive mortality predictors were then used to build a final multivariate model. Only significant positive predictors of mortality were reported as odds ratios (OR) with 95% confidence intervals (CI) and P values.

Ethical considerations

The NIS is a de-identified hospital-level, third-party database. The privacy of patients, clinicians, and medical centers is protected by its design. Patient consent was waived as the hospitalization data were stripped of any patient identifiers. The approval of the institutional review board (IRB) was not required for this study.

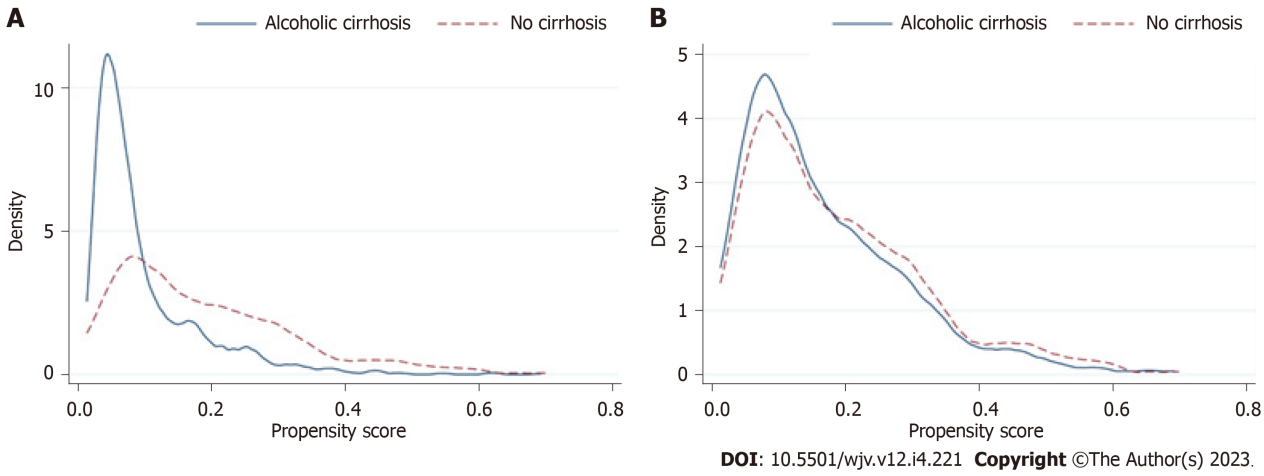

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Figure 1 Two-way plot visualizing the covariate balance in our study. A: Before matching; B: After matching.

RESULTS

A total of 738010 primary COVID-19 hospitalizations fulfilled the selection criteria and were included in the study. A total of 1325 hospitalizations with AC were matched to 1135 without AC using nearest-neighbor matching (Table 1). The age group 50-64 years had a higher prevalence in the AC cohort than the non-AC cohort ($P < 0.001$). The median age was 60 years, with an interquartile range (IQR) of 54-67 in the AC cohort and 61 years (IQR: 54-67) in the non-AC cohort. There was no disparity based on gender ($P = 0.31$). Hispanics (33.2% *vs* 26.0%) and Native Americans (4.9% *vs* 4.8%) had a higher prevalence in the AC cohort compared to the non-AC cohort ($P < 0.001$). There was a higher prevalence of an Elixhauser Comorbidity Index (ECI) score ≥ 3 (98.9% *vs* 2.2%) in the AC group compared to the non-AC group ($P < 0.001$). Mortality was significantly higher in hospitalizations with non-AC compared to AC (15.0% *vs* 14.7%, $P = 0.024$). Disposition was more likely to be against medical advice if there was a secondary diagnosis of AC compared to non-AC (3.8% *vs* 3.5%, $P = 0.024$). There was no difference in intensive care unit (ICU)-level care (10.6% each, $P = 1.00$). There was no significant difference in median length of stay or median hospital charges between the AC and non-AC groups ($P > 0.05$).

There was an increased prevalence of septic shock (5.7% *vs* 4.1%), ventricular fibrillation/ventricular flutter (0.4% *vs* 0%), atrial fibrillation (13.2% *vs* 8.8%), atrial flutter (8.7% *vs* 4.4%), first-degree atrioventricular nodal block (0.8% *vs* 0%), upper extremity venous thromboembolism (VTE) (1.5% *vs* 0%), variceal bleeding (3.8% *vs* 0%), and pulmonary hypertension (21.1% *vs* 6.6%) in the AC cohort compared to the non-AC cohort ($P < 0.05$) (Table 2). The additional comorbidity burden in the matched cohort is outlined in Supplementary Table 1. AC had no significant association with acute kidney injury (OR 0.89, 95%CI 0.74–1.07, $P = 0.23$) or acute liver failure (OR = 0.97, 95%CI: 0.21-4.34, $P = 0.91$).

On multivariate regression, significant predictors of mortality for the matched cohort included cardiac arrhythmias (OR = 2.34, 95%CI: 1.38-3.97, $P = 0.002$), coagulopathy (OR = 1.87, 95%CI: 1.28-2.73, $P = 0.001$), protein-calorie malnutrition (OR = 5.96, 95%CI: 3.67-9.68, $P < 0.001$), fluid and electrolyte disorders (OR = 1.56, 95%CI: 1.05-2.32, $P = 0.027$), septic shock (OR = 18.77, 95%CI: 10.02-35.13, $P < 0.001$), atrial fibrillation (OR = 2.01, 95%CI: 1.11-3.63, $P = 0.020$), upper extremity VTE (OR = 11.38, 95%CI: 3.65-35.46, $P < 0.001$), and increasing age (OR = 1.06, 95%CI: 1.04-1.07, $P < 0.001$) (Table 3).

DISCUSSION

This national population-based study evaluated hospitalized COVID-19 patients with and without AC according to age, gender, and race to identify high-risk individuals. Our findings indicate that AC does not significantly increase mortality among patients hospitalized with COVID-19. However, it is associated with a higher prevalence of inpatient complications, particularly in certain demographic groups and people with higher ECI scores. Interestingly, despite these complications, there was no significant difference in the need for ICU-level care, length of stay, or hospital charges between the AC and non-AC groups.

Alcohol consumption increased during the COVID-19 pandemic due to isolation and social distancing protocols[23]. A study conducted in the United States analyzed changes in adult alcohol consumption during the pandemic[24]. It reported a 14% increase in the frequency of alcohol use[24]. The median age group in their analysis that saw increased alcohol consumption was similar to the median age in our AC cohort (IQR: 54-67). The increase in alcohol intake during the COVID-19 pandemic in this age group might have aggravated the disease burden of AC[24]. A multicenter study in the United States reported that Hispanic ethnicity and decompensated cirrhosis were associated with a higher risk for severe COVID-19[17]. In our data, we also observed a higher prevalence of Hispanics in the AC cohort than in the non-AC cohort. It is known that increasing age reduces the ability to metabolize alcohol due to decreased mitochondrial function [25]. Upon multivariate analysis of our data, we identified increasing age as a mortality predictor among COVID-19

Table 1 Baseline biodemographic characteristics of hospitalized coronavirus disease 2019 patients with and without alcohol-associated cirrhosis, *n* (%)

Factor	Alcoholic cirrhosis	No alcoholic cirrhosis (before matching)	*P* value	No alcoholic cirrhosis (after matching)	*P* value
Total hospitalizations	1325	736685		1135	
Age groups (yr)			< 0.001		< 0.001
18-34	30 (2.3)	36860 (5.0)		60 (5.3)	
34-49	195 (14.7)	105475 (14.3)		205 (18.1)	
50-64	625 (47.2)	213325 (29.0)		435 (38.3)	
65-79	375 (28.3)	242015 (32.9)		350 (30.8)	
≥ 80	100 (7.5)	139010 (18.9)		85 (7.5)	
Gender			< 0.001		0.31
Male	930 (70.2)	380300 (51.6)		775 (68.3)	
Female	395 (29.8)	356385 (48.4)		360 (31.7)	
Race			< 0.001		< 0.001
White	580 (43.8)	388810 (52.8)		515 (45.4)	
Black	145 (10.9)	129635 (17.6)		180 (15.9)	
Hispanic	440 (33.2)	156285 (21.2)		295 (26.0)	
Asian	25 (1.9)	25065 (3.4)		35 (3.1)	
Native American	65 (4.9)	6500 (0.9)		55 (4.8)	
Other	70 (5.3)	30390 (4.1)		55 (4.8)	
Elixhauser Comorbidity Index score			< 0.001		< 0.001
0	0 (0.0)	44530 (6.0)		25 (2.2)	
1	0 (0.0)	98560 (13.4)		70 (6.2)	
2	15 (1.1)	141150 (19.2)		1040 (91.6)	
≥ 3	1310 (98.9)	452445 (61.4)		25 (2.2)	
Region of hospital			< 0.001		0.008
Northeast	280 (21.1)	133450 (18.1)		245 (21.6)	
Midwest	250 (18.9)	168480 (22.9)		275 (24.2)	
South	430 (32.5)	309115 (42.0)		335 (29.5)	
West	365 (27.5)	125640 (17.1)		280 (24.7)	
Location/teaching status of hospital			< 0.001		0.009
Rural	65 (4.9)	88910 (12.1)		75 (6.6)	
Urban nonteaching	180 (13.6)	147560 (20.0)		115 (10.1)	
Urban teaching	1080 (81.5)	500215 (67.9)		945 (83.3)	
Primary payer			< 0.001		0.030
Medicare	570 (43.0)	369155 (50.1)		455 (40.1)	
Medicaid	420 (31.7)	93610 (12.7)		385 (33.9)	
Private	250 (18.9)	243440 (33.0)		245 (21.6)	
Other	85 (6.4)	30480 (4.1)		50 (4.4)	
Median household income national quartile for patient ZIP code			0.074		0.31
1st (0-25th)	480 (36.2)	249205 (33.8)		445 (39.2)	
2nd (26th-50th)	335 (25.3)	203325 (27.6)		280 (24.7)	

3rd (51st-75th)	310 (23.4)	163695 (22.2)		235 (20.7)	
4th (76th-100th)	200 (15.1)	120460 (16.4)		175 (15.4)	
Disposition of patient			< 0.001		0.024
Discharged to home or self-care (routine discharge)	685 (51.7)	445390 (60.5)		555 (48.9)	
Transfer to short-term hospital	40 (3.0)	21910 (3.0)		20 (1.8)	
Transfer other: Skilled nursing facility, intermediate care facility, or another type of facility	235 (17.7)	98350 (13.4)		205 (18.1)	
Home health care	120 (9.1)	99700 (13.5)		145 (12.8)	
Against medical advice	50 (3.8)	7535 (1.0)		40 (3.5)	
Died during hospitalization	195 (14.7)	63625 (8.6)		170 (15.0)	
Day of admission			0.43		0.27
Weekday	990 (74.7)	543410 (73.8)		870 (76.7)	
Weekend	335 (25.3)	193275 (26.2)		265 (23.3)	
Mechanical ventilation	130 (9.8)	43865 (6.0)	< 0.001	140 (12.3)	0.046
ICU admission	140 (10.6)	43120 (5.9)	< 0.001	120 (10.6)	1.00
Vasopressor requirement	30 (2.3)	9345 (1.3)	< 0.001	30 (2.6)	0.54
Age in years at admission, median (IQR)	60.0 (54.0, 67.0)	65.0 (53.0, 77.0)	< 0.001	61.0 (51.0, 72.0)	0.65
Length of stay in days, median (IQR)	5.0 (3.0, 9.0)	5.0 (3.0, 8.0)	0.016	6.0 (3.0, 11.0)	0.1
Total hospital charges in USD, median (IQR)	44739.0 (24963.0, 80405.0)	39061.0 (22215.0, 71177.0)	< 0.001	49862.0 (25884.0, 90286.0)	0.098

ICU: Intensive care unit; IQR: Interquartile range.

patients with AC. The clinical symptoms between the younger and older age groups might be similar in the presence of AC. However, the elderly tend to develop more complications due to a decline in the robustness of the immune system. In a study conducted at the Johns Hopkins Health System, Krishnan *et al*[26] showed that increasing age and hepatic decompensation were associated with all-cause mortality among COVID-19 patients with CLD.

In our analysis, the mortality rates were comparable in both the AC and non-AC cohorts. One potential explanation could be that during the COVID-19 pandemic, only the most critically ill cirrhotic patients were admitted, rendering the presence of infection negligible in impacting the clinical outcome. Moreover, comorbidities among AC patients with higher ECI scores could affect the mortality rate. This might have resulted in similar ICU admission rates in both AC and non-AC cohorts. Intriguingly, our data showed that more non-AC patients received mechanical ventilation than AC patients. This is noteworthy because it may indicate an attempt to avoid mechanical ventilation, which is commonly regarded as a predictor of death in cirrhosis[10]. Shalimar *et al*[27] showed in their study that the need for mechanical ven -tilation independently predicted mortality in CLD patients with COVID-19.

Cirrhosis-associated immune dysfunction is characterized by systemic inflammation and impaired immunocom-petence[28]. The dysregulated complement factors, immunoglobulins, and acute-phase proteins may correlate with cirr-hosis severity and can serve as biomarkers of immune alterations in these patients[28]. These dysregulations expose cirrhotics to an increased risk of infections and liver-related death[28]. Bolarín *et al*[29] revealed that sepsis was the leading cause of non-sudden death in patients with AC ten years after liver transplantation. Guerra Veloz *et al*[30] showed that hospitalized COVID-19 patients with CLD required almost four times more antibiotic therapy compared to those without CLD. Similar findings were observed in another study, which demonstrated that cirrhotics had an increased risk of mortality, organ dysfunction syndrome, superinfections, and greater influenza severity compared to non-cirrhotics[31]. These observations may explain why a higher prevalence of *Hemophilus* pneumonia, septic shock, and spontaneous bacterial peritonitis was observed among AC patients in our study.

Patients with cirrhosis often develop portal hypertension. It frequently leads to upregulation of angiotensin-converting enzyme 2 (ACE-2) to counteract this major complication of cirrhosis[32]. This makes patients with AC more susceptible to COVID-19 infection, as ACE-2 is the critical functional receptor for SARS-CoV-2[33,34]. Therefore, it could possibly be associated with inpatient complications and a poor prognosis. During the pandemic, hospital stays for patients with cirrhosis were shorter, and more of these patients were discharged to go home compared to the pre-COVID era. Similarly, we observed a higher proportion of AC patients discharged home than non-AC patients in our study. This trend reflects the drive to conserve inpatient resources and promote home isolation unless the patient requires urgent medical treatment. However, it might have increased the risk of early post-hospital discharge mortality in patients with decompensated cirrhosis during the COVID-19 period[35]. A United States national cohort study using data from the Veterans Health Administration reported a decrease in hospitalizations of cirrhotic patients during the pandemic from January to April 2020[36]. Contrarily, in line with the increase in alcohol consumption during the early phase of the

Table 2 Inpatient outcomes of coronavirus disease 2019 patients with and without alcohol-associated cirrhosis, *n* (%)

Variables	Alcoholic cirrhosis	No alcoholic cirrhosis (before matching)	*P* value	No alcoholic cirrhosis (after matching)	*P* value
n	1325	736685		1135	
Asthma exacerbation	5 (0.4)	13170 (1.8)	< 0.001	5 (0.4)	0.81
ARDS	80 (6.0)	31970 (4.3)	0.002	100 (8.8)	0.008
Type I respiratory failure	545 (41.1)	379975 (51.6)	< 0.001	475 (41.9)	0.72
Type II respiratory failure	15 (1.1)	7640 (1.0)	0.73	15 (1.3)	0.67
Bacterial pneumonia	10 (0.8)	6005 (0.8)	0.81	10 (0.9)	0.73
Klebsiella pneumonia	0 (0.0)	1425 (0.2)	0.11	0 (0.0)	-
Streptococcus pneumonia	0 (0.0)	805 (0.1)	0.23	0 (0.0)	-
Staphylococcus pneumonia	5 (0.4)	3850 (0.5)	0.46	10 (0.9)	0.11
Hemophilus pneumonia	5 (0.4)	300 (< 1)	< 0.001	0 (0.0)	-
Anosmia	0 (0.0)	1240 (0.2)	0.14	0 (0.0)	-
Hemorrhagic CVA	0 (0.0)	615 (0.1)	0.29	0 (0.0)	-
Ischemic CVA	0 (0.0)	475 (0.1)	0.36	0 (0.0)	-
Dysgeusia	0 (0.0)	695 (0.1)	0.26	0 (0.0)	-
Diarrhea	80 (6.0)	44110 (6.0)	0.94	65 (5.7)	0.74
Septic shock	75 (5.7)	21780 (3.0)	< 0.001	47 (4.1)	0.007
SVT	30 (2.3)	9375 (1.3)	0.001	25 (2.2)	0.92
VT	20 (1.5)	10065 (1.4)	0.65	40 (3.5)	0.001
Vfib/Vflutter	5 (0.4)	1315 (0.2)	0.087	0 (0.0)	0.038
Afib	175 (13.2)	77340 (10.5)	0.001	100 (8.8)	< 0.001
Aflutter	115 (8.7)	47410 (6.4)	< 0.001	50 (4.4)	< 0.001
First-degree AV nodal block	10 (0.8)	3250 (0.4)	0.086	0 (0.0)	0.003
Second-degree AV nodal block	0 (0.0)	1515 (0.2)	0.098	0 (0.0)	-
Complete AV nodal block	0 (0.0)	1375 (0.2)	0.12	10 (0.9)	< 0.001
ECMO	0 (0.0)	120 (< 1)	0.64	0 (0.0)	-
Total acute VTE	50 (3.8)	26120 (3.5)	0.65	75 (6.6)	0.001
Portal venous thrombosis	5 (0.4)	190 (< 1)	< 0.001	15 (1.3)	0.009
Budd Chiari	0 (0.0)	35 (< 1)	0.80	0 (0.0)	-
Upper extremity VTE	20 (1.5)	1960 (0.3)	< 0.001	0 (0.0)	< 0.001
Lower extremity VTE	10 (0.8)	8050 (1.1)	0.24	10 (0.9)	0.73
Other VTE	10 (0.8)	1285 (0.2)	< 0.001	5 (0.4)	0.32
Pulmonary embolism	20 (1.5)	18055 (2.5)	0.027	50 (4.4)	< 0.001
Variceal bleeding	50 (3.8)	100 (< 1)	< 0.001	0 (0.0)	< 0.001
Hepatorenal syndrome	5 (0.4)	140 (< 1)	< 0.001	15 (1.3)	0.009
Hyponatremia	325 (24.5)	123080 (16.7)	< 0.001	285 (25.1)	0.74
Pulmonary hypertension	280 (21.1)	1210 (0.2)	< 0.001	75 (6.6)	< 0.001
Spontaneous bacterial peritonitis	15 (1.1)	35 (< 1)	< 0.001	5 (0.4)	0.057
Acute liver failure	4 (0.34)	303 (0.45)	< 0.001	4 (0.30)	0.82
New HD	2 (0.15)	750 (0.11)	< 0.001	0 (0)	0.1

ARDS: Acute respiratory distress syndrome; CVA: Cerebrovascular accident; SVT: Supraventricular tachycardia; VT: Ventricular tachycardia; Vfib: Ventricular fibrillation; Vflutter: Ventricular flutter; Afib: Atrial fibrillation; AV: Atrioventricular; ECMO: Extracorporeal membrane oxygenation; VTE: Venous thromboembolism; HD: Hemodialysis.

Table 3 Inpatient mortality predictors for coronavirus disease 2019 patients with alcohol-associated cirrhosis (after matching)

Variables	Odds ratios	*P* value
Alcohol-associated cirrhosis	0.82 (0.64-1.05)	0.12
Cardiac arrhythmias	2.34 (1.38-3.97)	0.002
Coagulopathy	1.87 (1.28-2.73)	0.001
Protein-calorie malnutrition	5.96 (3.67-9.68)	< 0.001
Fluid and electrolyte disorders	1.56 (1.05-2.32)	0.027
Septic shock	18.77 (10.02-35.13)	< 0.001
Atrial fibrillation	2.01 (1.11-3.63)	0.020
Spontaneous bacterial peritonitis	4.28 (0.91-20.1)	0.065
Upper extremity venous thromboembolism	11.38 (3.65-35.46)	< 0.001
Increasing age	1.06 (1.04-1.07)	< 0.001

pandemic, we might foresee a rise in long-term morbidity and mortality related to alcohol-associated liver disease[37]. Therefore, AC hospitalizations may increase in the future, requiring high-level hepatology care and follow-up.

In patients with cirrhosis, the risk of developing VTE is significantly increased due to the reduced ability to synthesize anticoagulation factors[38]. In line with these findings, we also noted a higher prevalence of VTE in the AC cohort. In addition, the presence of VTE was identified as a mortality predictor. Therefore, cirrhotic patients should undergo a case-by-case consideration of thromboprophylaxis for deep vein thrombosis[39]. Another significant variable observed in our data was the higher prevalence of atrial fibrillation among the AC cohort. A nationwide study conducted in Korea demonstrated a 46% increased risk of developing atrial fibrillation in cirrhotic patients compared to the non-cirrhotic control group[40]. Furthermore, with COVID-19 in these patients, there is a higher chance of observing electrocardiographic abnormalities. In a systematic review, a fourfold higher risk of death was reported among COVID-19 patients with atrial fibrillation[41]. This finding overlaps with our data, where atrial fibrillation was also identified as a mortality predictor. Upon multivariate analysis, we also identified cardiac arrhythmias and coagulopathy as mortality predictors for the AC cohort. Therefore, cirrhotic patients must be carefully monitored before being discharged home to prevent such serious complications. Notably, the clinical management of cirrhotics with COVID-19 is complicated because most pharmacological agents are metabolized by cytochrome P450 monooxygenases in the liver[42]. Therefore, patients with COVID-19 may have a higher risk of developing hepatotoxicity in the presence of CLD due to drug-drug interactions [42]. This might have contributed to the overall ICU admission rate reported in the AC cohort in our study.

Recent research revealed several associations between SARS-CoV-2 infection and medical conditions that may lead to liver dysfunction[43]. Moreover, studies have demonstrated that there is an increased risk of decompensation and mortality in COVID-19 patients with pre-existing cirrhosis[44]. This can possibly be attributed to cirrhosis-related immunological modulation, insufficient physiological reserves, and an increased risk of severe COVID-19 disease[43,44]. The underlying mechanism of liver injury secondary to COVID-19 is multifactorial. SARS-CoV-2 may induce direct hepatotoxicity *via* cholangiocytes, translocation from the gut to the liver, or indirect liver damage from systemic inflammation, hypoxia, ischemic insult, or drug-induced liver injury[44]. While the expression of ACE-2 receptors on hepatocytes has been reported, a substantial contribution from indirect causes of liver injury has been described in COVID-19 patients [44]. Furthermore, treating severe COVID-19 infection with certain antiviral agents, immunomodulators, and supportive agents may also cause hepatotoxicity[44]. Large registries report a case fatality rate of 38%, rising to 70% in the Child-Pugh C category[7,44]. These findings highlight the need for vigilant pharmacological management. Further research is warranted to evaluate the pathological interplay between AC and COVID-19. It is particularly important to understand the mecha-nisms of liver injury and the impact of COVID-19 on pre-existing liver disease.

Our retrospective study is one of the largest to evaluate the specific clinical impact of AC on COVID-19 hospitalizations. We analyzed the patient outcomes based on comorbidities, mechanical ventilation, ICU admission, and mortality predictors. Given the critical nature of the disease association, a multidisciplinary approach is required to manage hospitalized COVID-19 patients with AC. This study will provide invaluable information with regard to identifying high-risk patients and monitoring the factors associated with the rising prevalence of AC. One of the major strengths of this study is the detailed comparison between COVID-19 patients with and without AC. This allows for a better understanding of the variables associated with mortality among the two cohorts.

Limitations

We acknowledge certain limitations to our study. The ICD-10 coding system may present inaccurate data when utilizing a large database like NIS, which may potentially skew the analysis. In addition, the NIS data might only be representative of those hospitals participating in the Healthcare Cost and Utilization Project[45]. The information regarding severity of the disease or treatment is not provided in the NIS database. The COVID-19 waves varied from state to state within the United States. Hence, some areas were more heavily impacted than others. Upon analysis of geographical regions in our data, urban teaching hospitals had a greater number of patients with AC. A nationwide study of hospitalized patients in the United States identified urban hospitals as being associated with a greater risk of infection in cirrhotic patients[46]. These infections included sepsis, pneumonia, and spontaneous bacterial peritonitis[46]. Therefore, the mortality rate might be higher, especially in urban hospitals. Moreover, it can be difficult to diagnose chronic non-AC as COVID-19 may lead to abnormalities in liver function testing in hospitalized patients[47,48].

CONCLUSION

This study has thoroughly analyzed the influence of AC on COVID-19 hospitalizations. Our results indicate that the presence of AC does not significantly impact mortality in COVID-19 patients, warranting further evaluation in a larger cohort. Interestingly, despite the higher ECI scores among the AC cohort, the length of stay and ICU admission rates were comparatively similar across the non-AC cohort. Advanced age was found to be a predictor of death in patients with AC, along with other variables like cardiac arrhythmias, coagulopathy, protein-calorie malnutrition, fluid and electrolyte disorders, septic shock, and upper extremity VTE. Due to the multifactorial nature of hepatic injury in COVID-19, further research will be required to evaluate effective pharmacological treatments in COVID-19 patients with AC. Despite the fact that COVID-19 transmission has slowed down, identifying high-risk groups early on is important. It will make it more convenient for hospitalized COVID-19 patients with AC to receive a tailored medical treatment that could improve their prognosis.

ARTICLE HIGHLIGHTS

Research background

Patients with chronic liver disease (CLD) may be at risk of adverse outcomes following coronavirus disease 2019 (COVID-19). Initial findings from Wuhan indicated potential liver injury in COVID-19 patients. With the growing role of obesity and alcohol, understanding the specific implications of alcohol-associated cirrhosis (AC) for patients with COVID-19 is of paramount clinical importance for prognostication and appropriate therapeutic strategy.

Research motivation

Cirrhosis is typically associated with immune system impairments, which might hinder the ability of patients to combat COVID-19. While several studies have indicated an increased risk of COVID-19 severity in cirrhotic patients, the specific impact of AC on inpatient outcomes remains incompletely defined.

Research objectives

This study primarily aims to assess the impact of AC on inpatient outcomes and mortality rates in patients hospitalized with COVID-19 compared to those without AC. Furthermore, we intend to identify predictors of mortality within the COVID-19 patient cohort with AC.

Research methods

A retrospective cohort study was conducted using the National Inpatient Sample database 2020, focusing on hospitalizations with a primary diagnosis of COVID-19. Two cohorts were established based on the presence or absence of AC. Propensity score matching was used to compare the cohorts and a range of statistical analyses were applied to the data.

Research results

Of the 738010 patients hospitalized with COVID-19 that fulfilled the selection criteria, 1325 with AC were compared to 1135 without AC. It was found that AC did not significantly increase mortality in COVID-19 patients. However, it was linked to a higher prevalence of inpatient complications, especially in certain demographics and those with higher Elixhauser Comorbidity Index scores.

Research conclusions

AC does not increase mortality rates in the context of COVID-19 hospitalizations. However, it is associated with a heightened prevalence of certain inpatient complications. Despite these systemic complications, there was no noticeable difference in intensive care unit requirements, length of stay, or hospital charges between AC and non-AC groups.

Research perspectives

This research provides valuable insights into the implications of AC for COVID-19 patients. It prompts clinicians to conduct future research and delve deeper into understanding the exact mechanisms leading to these complications in COVID-19 patients with AC. Exploring preventive measures or pharmacological treatment adjustments for this vulnerable population may improve patient outcomes.

FOOTNOTES

Author contributions: Inayat F, Ali H, Patel P, Dhillon R, and Afzal A concepted and designed the study, participated in the acquisition of data, interpretation of results, writing of the original draft, and critical revisions of the important intellectual content of the final manuscript; Rehman AU, Afzal MS, Zulfiqar L, Nawaz G, Goraya MHN, Subramanium S, and Agrawal S contributed to the analysis and interpretation of results and drafting of the manuscript; Satapathy SK reviewed, revised, and improved the manuscript by suggesting pertinent modifications; and all authors critically assessed, edited, and approved the final manuscript and are accountable for all aspects of the work.

Institutional review board statement: The data of patients was not acquired from any specific institution but rather open-access United States National Inpatient Sample (NIS) database. The NIS contains de-identified information, protecting the privacy of patients, physicians, and hospitals. Therefore, it was deemed exempt from the institutional review board.

Informed consent statement: Participants were not required to give informed consent for this retrospective cohort study since the analysis of baseline characteristics used anonymized clinical data.

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ORIGINAL ARTICLE

Retrospective Study

Performance evaluation of NeuMoDx 96 system for hepatitis B and C viral load

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Abstract

BACKGROUND

Hepatitis B virus (HBV) and hepatitis C virus (HCV) viral load (VL) estimation is essential for the management of both HBV and HCV infections. Due to a longer turnaround time for VL estimation, many patients drop out from the cascade of care. To achieve the global goals of reducing morbidity and mortality due to HBV/HCV and moving towards their elimination by 2030, molecular diagnostic platforms with faster and random (*i.e.* single sample) access are needed.

AIM

To evaluate the performance of the recently launched NeuMoDx 96 random access system with the conventional COBAS®AmpliPrep/COBAS TaqMan system for HBV and HCV VL estimation.

METHODS

Archived once-thawed plasma samples were retrieved and tested on both platforms. Correlation between the assays was determined by linear regression and Bland-Altman analysis. The study included samples from 186 patients, 99 for HBV of which 49 were true infected HBV cases (hepatitis B surface antigen, anti-hepatitis B core antibody, and HBV DNA-positive) and 87 for HCV assay in which

39 were true positives for HCV infection (anti-HCV and HCV RNA-positive).

RESULTS

The median VL detected by NeuMoDx for HBV was 2.9 (interquartile range [IQR]: 2.0-4.3) $\log_{10}$ IU/mL and by COBAS it was 3.70 (IQR: 2.28-4.56) $\log_{10}$ IU/mL, with excellent correlation (R^2 = 0.98). In HCV, the median VL detected by NeuMoDx was 4.9 (IQR: 4.2-5.4) $\log_{10}$ IU/mL and by COBAS it was 5.10 (IQR: 4.07-5.80) $\log_{10}$ IU/mL with good correlation (R^2 = 0.96).

CONCLUSION

The overall concordance between both the systems was 100% for both HBV and HCV VL estimation. Moreover, no genotype-specific bias for HBV/HCV VL quantification was seen in both the systems. Our findings reveal that NeuMoDx HBV and HCV quantitative assays have shown overall good clinical performance and provide faster results with 100% sensitivity and specificity compared to the COBAS AmpliPrep/COBAS TaqMan system.

Key Words: Hepatitis B; Hepatitis C; NeuMoDx; Random access; Viral load; COBAS AmpliPrep

Core Tip: In this study, the clinical performance of the NeuMoDx 96 random access system for hepatitis B virus (HBV) and hepatitis C virus (HCV) viral load (VL) quantification was evaluated and compared to the routinely used COBAS AmpliPrep/COBAS TaqMan system. Good concordance was observed between both systems for the HBV and HCV VL assays. Due to its random access (*i.e.* single sample access) characteristics and shorter turnaround, the NeuMoDx 96 can be considered a faster and effortless molecular testing system.

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INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the most common causes of chronic liver diseases worldwide. This underscores its public health significance, with more than 250 million HBV carriers and about 70 million people with chronic HCV infection[1]. As a result of HBV vaccination programs[2,3] and direct-acting antiviral treatment against HCV[4], the prevalence of these infections has significantly decreased but both are still major risk factors for the development of cirrhosis and hepatocellular carcinoma. In resource-poor nations, gaps in HBV and HCV screening, treatment, and monitoring, as well as a lack of efficient therapeutic management choices for HBV/HCV-related liver cancer, have resulted in a low survival rate among infected persons. In response to this significant worldwide public health burden, the World Health Organization launched a worldwide Health Sector Strategy on Hepatitis 2016-2021 in 2016, with the objective of eliminating viral hepatitis as a public health issue by 2030[5]. Moreover, HBV and HCV account for about 96% of all viral hepatitis deaths in low- and middle-income countries[1]. The complete burden of disease includes not just death but also decreased quality of life for patients (due to cirrhosis and associated comorbidities), financial expenses of care for people and health care systems alike, and social economic costs[6]. Serological assays to detect antigens/antibodies to HBV/HCV do not differentiate between an active and past infection; thus, an active ongoing infection must be confirmed by the detection of viral DNA/RNA[7]. This two-step process for diagnosing active HBV & HCV infection, *i.e.* first a serological test to screen for exposure, followed by a nucleic acid test (NAT) to confirm viremia often takes a longer time and leads to patient loss to follow-up[6].

Therefore, to prevent loss to follow-up of a patient from the cascade of care, it is important to have molecular assays that are fully automated with high throughput and short turnaround (TAT), particularly in low-income countries[8].

At present, batch-based closed molecular testing platforms are routinely being used but recently fully automated random access (*i.e.* single sample) closed systems are coming up and have demonstrated good potential[9,10]. The NeuMoDx 96 molecular system (QIAGEN Sciences, Waltham, MA, United States) is one such recent fully automated random access closed system. Therefore, the present study compared and evaluated the clinical performance of the NeuMoDx 96 molecular system (referred to as assay 1) for HBV and HCV viral load (VL) testing with the routinely used COBAS®AmpliPrep/COBAS® TaqMan®, v2.0 (Roche Diagnostics, GmbH, Mannheim, Germany) system (referred to as assay 2).

MATERIALS AND METHODS

Study population

This was a retrospective study conducted in a tertiary care liver center in Delhi, India. A total of 186 archived once-thawed plasma samples with pre-existing test results from initial routine lab testing were used. Among these, 99 samples for the HBV assay and 87 samples for the HCV assay were simultaneously tested on both platforms from the same freeze-thaw cycle. Of the 99 samples, 49 were HBV true positive (hepatitis B surface antigen [HBsAg], anti-hepatitis B core antibody [anti-HBc] total, and HBV DNA-positive; VL range: 1 to > 10^6 $\log_{10}$ IU/mL), and the remaining 50 were confirmed negatives for HBV (HBsAg, anti-HBc and HBV DNA-negative). In the HCV assay, of the 87 samples, 39 were true positives for HCV infection (anti-HCV antibody and HCV RNA-positive; VL range: 1 to > 10^6 $\log_{10}$ IU/mL), and the remaining 48 were confirmed negatives for HCV infection (anti-HCV antibody and HCV RNA negative).

The clinical details along with other virological parameters were obtained from our Hospital Information System. Samples from patients with other co-infections, such as human immunodeficiency virus and hepatitis delta virus, on immunosuppressants and samples with insufficient available volume were excluded. This study was approved by the Institutional Ethics Board (Approval No. IEC/2023/102/MA06) and conducted as per the principles of the Declaration of Helsinki. The study was performed on deidentified, anonymous, archived once-thawed clinical plasma samples. Therefore, the requirement of individual patient consent was waived.

NeuMoDx 96 molecular system (assay 1)

In the NeuMoDx 96, 550 µL plasma was used in the instrument as per the manufacturer's instructions. The results of the test were automatically displayed on the system approximately within 1 h for HBV DNA and approximately within 1.25 h for HCV RNA. The results are expressed as IU/mL. The lower limit of detection (LOD) and lower limit of quantification (LLOQ) for both HBV and HCV assays provided by the manufacturer are 8.0 IU/mL and 0.9 $\log_{10}$ IU/mL, respectively (Table 1).

COBAS®AmpliPrep/COBAS® TaqMan® (assay 2)

In the COBAS®AmpliPrep/COBAS® TaqMan®, v2.0, 650 µL plasma sample was used in the instrument. The results of the test were automatically displayed on the system within 5 h for HBV DNA and about 5 h 45 min for HCV RNA. For the HBV assay, the LOD and LLOQ claimed by the manufacturer are 20 IU/mL and 1.3 $\log_{10}$ IU/mL, respectively. For the HCV assay, the LOD and LLOQ are ≥ 15 IU/mL and 1.5 $\log_{10}$ IU/mL, respectively (Table 1).

Statistical analyses

The HBV and HCV VLs are expressed in $\log_{10}$ format. Continuous variables were summarized using the mean ± SD or median with interquartile range (IQR), as applicable. Categorical variables are presented as percentages. Linear regression and Pearson's correlation coefficient were determined for VL results between assay 1 and assay 2. The Bland-Altman plot was used to determine the level of agreement between the assays, in which the difference in HBV VLs measured by the two assays was plotted against the mean of the assays. All analyses were done using Statistical Package for the Social Sciences software version 22 (SPSS Inc., Chicago, IL, United States).

RESULTS

Characteristics of the study population

The baseline demographic and clinical characteristics of the study population are described in Table 2. The male:female ratio was 2.5:1.0. The overall mean age was 45 years ± 15 years. The median VL detected for the HBV DNA-positive samples was 2.9 (IQR 2.0-4.3) $\log_{10}$ IU/mL and 3.7 (IQR: 2.28-4.56) $\log_{10}$ IU/mL for assay 1 and assay 2, respectively. For HCV RNA, the median VL detected was 4.9 (IQR: 4.2-5.4) $\log_{10}$ IU/mL and 5.1 (IQR: 4.07-5.80) $\log_{10}$ IU/mL for assay 1 and assay 2, respectively. Further, for the HBV assay, genotyping data were available for 24 plasma samples with the following information: GTD (n = 10 as D1 and n = 8 as D2), GTA (n = 4, all as A1) and GTC (n = 2, all as C1). For the HCV assay, genotype results were available for 34 plasma samples with the following distribution: GT3 (n = 20 as 3a and n = 4 as 3b), GT1 (n = 6, all were GT1a), and GT4 (n = 4, all were GT4c).

Clinical performance of assay 1 for HBV VL

A total of 99 samples were analyzed, of which 49 were true HBV positives and 50 were true negatives for HBV infection. A 100% concordance was observed for both positive and negative samples. Therefore, the sensitivity (95% confidence interval [CI]: 92.75-100.00) and the specificity (95%CI: 92.89-100.00) were found to be 100%. Assay 1 showed no difference in quantification of HBV VL across different genotypes compared to assay 2.

Correlation and agreement analyses of HBV VL measurement

A total of 49 confirmed HBV DNA-positive samples were used with VL ranging from 1.0 to 7.7 $\log_{10}$ IU/mL (Table 3). Linear regression analysis of the quantifiable VLs obtained by both assays demonstrated a good correlation (Pearson's correlation coefficient; r^2 = 0.991) (Figure 1A). The Bland-Altman plot was used to determine the level of agreement between the assays (Figure 1B). The mean difference between assay 1 and assay 2 was 0.05 $\log_{10}$ IU/mL, with agreement limits ranging from -0.458 to 0.694 $\log_{10}$ IU/mL. With an intraclass correlation coefficient (ICC) of 0.995 (95%CI: 0.990-

Table 1 Comparison of characteristics between assay 1 and assay 2

Parameter	HBV		HCV	
	Assay 1	Assay 2	Assay 1	Assay 2
Sample volume	550 µL plasma	650 µL plasma	550 µL plasma	650 µL plasma
Turnaround time	Approximately 1.00 h	Approximately 5.00 h	Approximately 1.25 h	Approximately 5.45 h
LOD in IU/mL	8.0	20	8.0	≥ 15
LLOQ as $\log_{10}$ IU/mL	0.9	1.3	0.9	1.5
Linear range quantification as $\log_{10}$ IU/mL	1-9	1.3-8.2	1-9	1.5

HBV: Hepatitis B virus; HCV: Hepatitis C virus; IU: International unit; LLOQ: Lower limit of quantitation; LOD: Limit of detection.

Table 2 Baseline demographic and clinical characteristics of the study population

Characteristic	HBV patient group	HCV patient group
Patients, *n*	99	87
Sex as M/F ratio	3.34:1.00	1.71:1.00
Age in yr, mean ± SD	44.0 ± 14.6	46.0 ± 14.9
Total bilirubin in mg/dL, median (IQR)	0.83 (0.59-0.83)	0.95 (0.58-2.15)
Direct bilirubin in mg/dL, median (IQR)	0.18 (0.10-0.47)	0.25 (0.10-0.62)
ALT values in IU/mL, median (IQR)	32.5 (23.2-60.1)	33 (17.0-59.7)
AST values in IU/mL, median (IQR)	36 (28.00-62.75)	46 (27.0-99.2)
NeuMoDx viral load as $\log_{10}$ IU/mL, median (IQR)	2.9 (2.0-4.3)	4.9 (4.2-5.4)
COBAS viral load as $\log_{10}$ IU/mL, median (IQR)	3.7 (2.28-4.56)	5.1 (4.07-5.80)

ALT: Alanine transaminase, AST: Aspartate aminotransferase; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IQR: Interquartile range; IU: International unit; M: Male; SD: Standard deviation.

Table 3 Comparison of hepatitis B virus viral load results between assay 1 and assay 2

Range of viral load as $\log_{10}$ IU/mL	HBV	
	Assay 1, *n* = 49	Assay 2, *n* = 49
10^1-10^3	*n* = 25 (51.0%)	*n* = 19 (38.7%)
10^3-10^6	*n* = 18 (36.7%)	*n* = 25 (51.0%)
> 10^6	*n* = 6 (12.2%)	*n* = 5 (10.2%)

HBV: Hepatitis B virus.

0.997; P = 0.001), the two systems agreed well (Figure 1B).

Clinical performance of assay 1 for HCV VL

A total of 87 samples were analyzed, of which 39 were true HCV positives and 48 were confirmed negatives for HCV infection. A 100% concordance was observed for both the positive and negative samples. Therefore, the sensitivity (95%CI: 90.97-100.00) and specificity (95%CI: 92.6-100.0) were found to be 100% compared to assay 2. No difference was seen in VL quantification among the different HCV genotypes between assay 1 and assay 2.

Correlation and agreement analyses of HCV VL measurement

A total of 39 confirmed HCV RNA-positive samples were used with VL ranging from 1.26 to 7.09 $\log_{10}$ IU/mL (Table 4). Linear regression analysis of the quantifiable VLs obtained by both assays demonstrated a good correlation (Pearson's correlation coefficient; r^2 = 0.978) (Figure 1C). The Bland-Altman plot was used to determine the level of agreement between the assays (Figure 1C). The mean difference between assay 1 and assay 2 was 0.06 $\log_{10}$ IU/mL, with agreement

Table 4 Comparison of hepatitis C virus viral load results between assay 1 and assay 2

Range of viral load (log_{10} IU/mL)	HCV	
	Assay 1 (*n* = 39)	Assay 2 (*n* = 39)
10^1-10^3	*n* = 4 (10.2%)	*n* = 2 (5.1%)
10^3-10^6	*n* = 32 (82.0%)	*n* = 28 (71.7%)
> 10^6	*n* = 3 (7.69%)	*n* = 9 (23.07%)

HCV: Hepatitis C virus.

limits ranging from -0.987 to 1.182 log_{10} IU/mL. With an ICC of 0.988 (95%CI: 0.981-0.992; *P* = 0.001), the two systems agreed well (Figure 1D).

DISCUSSION

In this study, the performance of a random access system (NeuMoDx 96) was compared with the currently used batch system (COBAS AmpliPrep/COBAS TaqMan) for the detection of HBV DNA and HCV RNA from clinical samples. A concordance of 100% was observed between both systems for both HBV DNA and HCV RNA analyses. Moreover, both assays demonstrated a good correlation with respect to the VL estimation. Such systems with random access to samples are the need of the hour, so that results are provided in a shorter TAT to the clinicians[11]. In the cascade of care for both HBV DNA and HCV RNA, patients screened initially through serological tests often are lost to follow-up for VL testing due to either non-availability of the assays or a high TAT. The use of existing batch testing platforms across most of the diagnostic labs results in longer "sample-to-result" time[12-15].

At present, for conventional real-time PCR, closed systems are commonly used[16]. Though the analytical sensitivity or LOD of these assays is good and lies between 5 and 15 IU/mL, these available assays typically run on batch testing to justify and minimize the cost of the test. This further leads to an increase in TAT, which eventually delays the test results, and augments the total number of visits of the patients to the health care facility, and dropouts from the care process[17]. Another important aspect is that if viremic patients are not identified earlier, they pose a significant risk of transmission of active infection to their family members and close contacts due to the nature of transmission of both HBV and HCV infections.

Almost near point-of-care molecular testing platforms that are available at present for HBV/HCV VL are very limited (GeneXpert, TrueNAT)[9,18]. These systems provide random access to samples but are useful in diagnostic sites with low sample throughput such as in peripheral settings or remote areas, whereas systems such as NeuMoDx can cater to large numbers of samples and be placed easily in a high-throughput laboratory. Molecular testing platforms such as NeuMoDx can provide faster results with a very short TAT in a cost-effective manner. Limited studies regarding the evaluation of the NeuMoDx platform are available. Our study focused on its real-life evaluation on clinical samples[19-21].

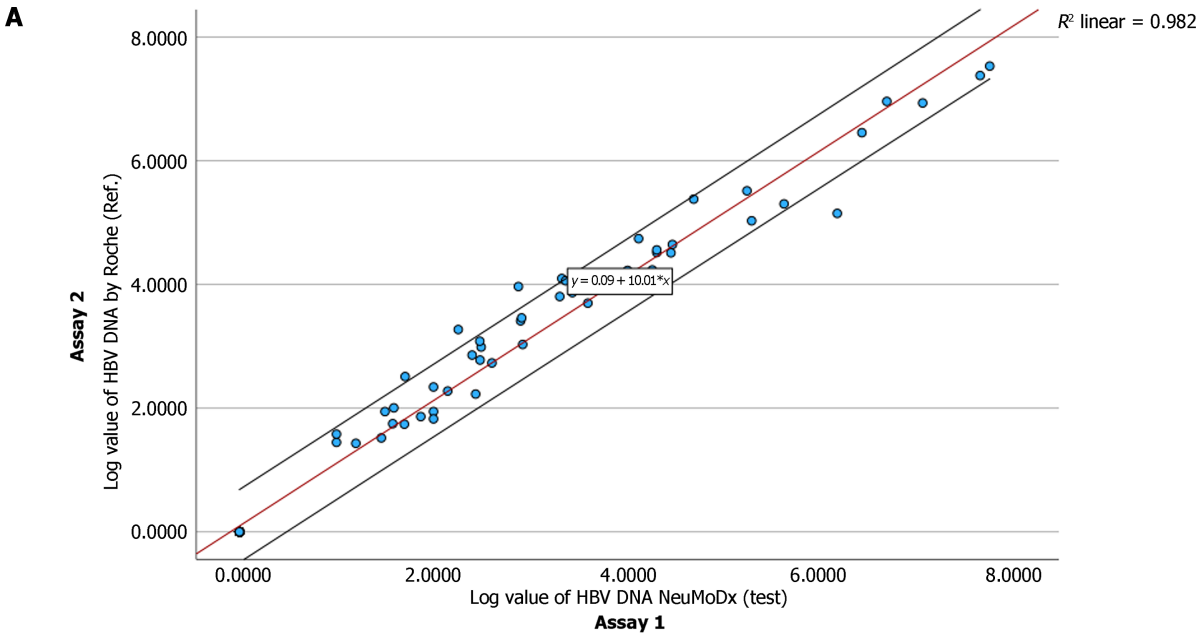
We found good correlation of HBV DNA and HCV RNA levels, especially when the VL in the sample was higher (> 10^6 log_{10} IU/mL). However, in VL 10^1-10^3 log_{10} IU/mL, despite good concordance, only satisfactory correlation was seen. This could be because very low VLs in clinical samples are often difficult to quantitate in terms of their exact values.

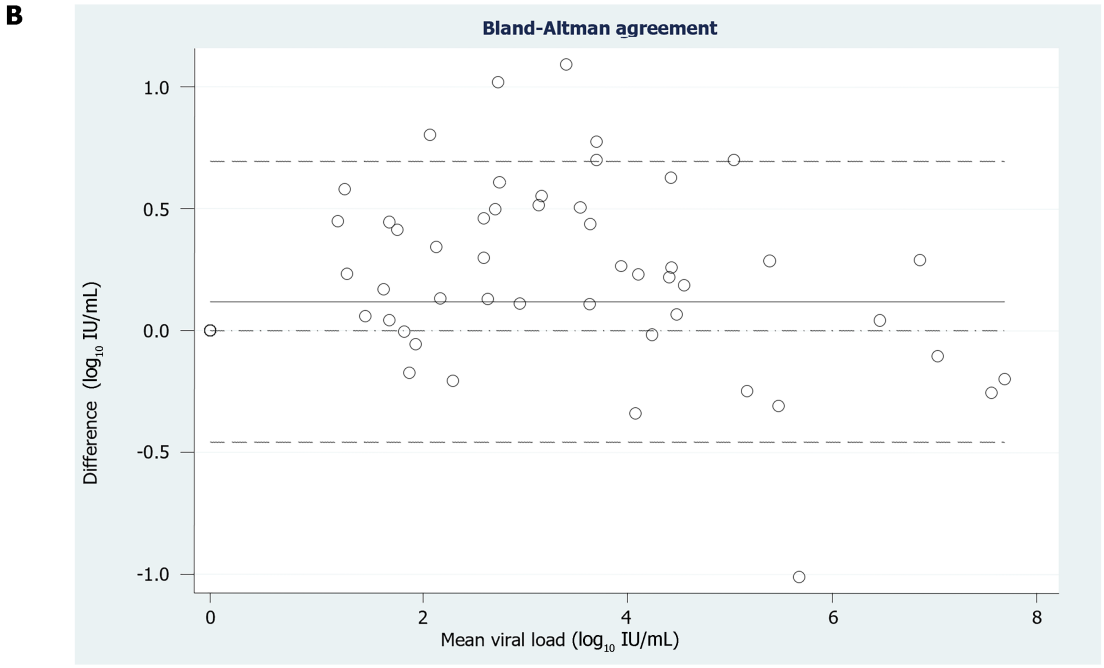
This system includes various functions including specimen preparation, nucleic acid extraction, real-time PCR set-up, amplification, and detection, all integrated within a single platform. Notably, this system provides numerous advantages, including high-throughput capacity, complete traceability, minimal risk of cross-contamination, and stringent safety standards for end users. The assay holds all of the reagents required for up to 20 different assays on board and works at room temperature. Therefore, this automated assay can be used in resource-limited settings, particularly in areas where refrigeration could be a problem. This can be used just like chemiluminescence platforms used for serological testing and would not require specialized molecular testing facilities or separate infra-structure requirements[22], which are extremely expensive to design and require specialized trained manpower to perform such assays. The expertise needed to perform testing on this platform and subsequent manual steps are greatly reduced and a single person can operate on the machine and perform multiple assays together.

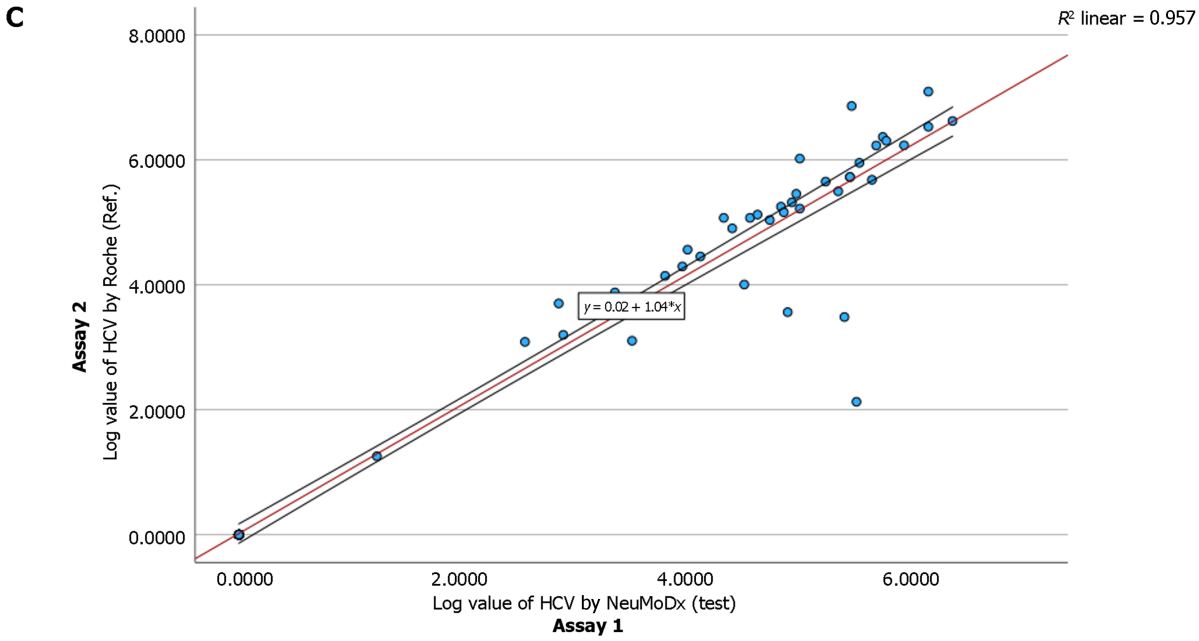
An important limitation of our study is that it was a retrospective, single-center study done on already archived tested samples; thus, large-scale prospective studies in real time are needed to further evaluate their reproducibility, stability, and cost-effectiveness.

CONCLUSION

The findings of the study demonstrated excellent clinical performance (100% concordance) of the random access system compared to the conventional routinely used batch system. With a short TAT and user-friendly operation, it is a reliable assay for HBV and HCV VL assessment. These promising preliminary results indicate that the NeuMoDx 96 system holds great potential as a novel VL measurement solution in effective patient care and management.


A
R² linear = 0.982
y = 0.09 + 10.01*x
Log value of HBV DNA by Roche (Ref.)
Assay 2
Log value of HBV DNA NeuMoDx (test)
Assay 1
0.0000
2.0000
4.0000
6.0000
8.0000


B
Bland-Altman agreement
Difference (log10 IU/mL)
Mean viral load (log10 IU/mL)
1.0
0.5
0.0
-0.5
-1.0
0
2
4
6
8


C
R² linear = 0.957
y = 0.02 + 1.04*x
Log value of HCV by Roche (Ref.)
Assay 2
Log value of HCV by NeuMoDx (test)
Assay 1
0.0000
2.0000
4.0000
6.0000
8.0000

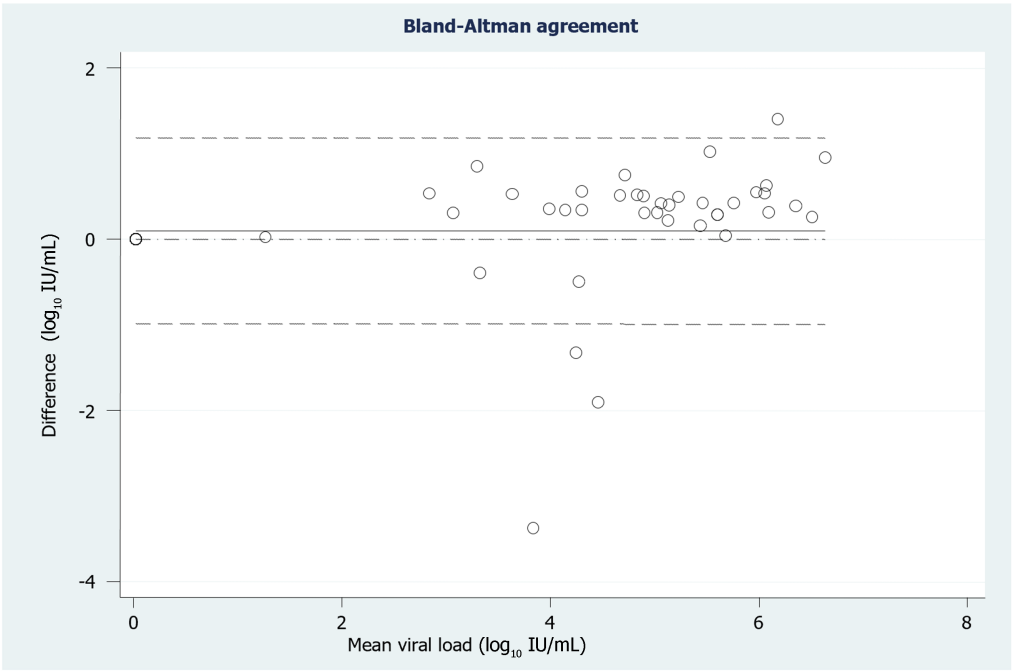


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Figure 1 Linear regression analysis and Bland-Altman plot. A: Linear regression analysis for correlation of hepatitis B virus (HBV) viral load between assay 1 and assay 2; B: Bland-Altman plot for comparison of HBV viral load between assay 1 and assay 2; C: Linear regression analysis for correlation of hepatitis C virus (HCV) viral load between assay 1 and assay 2; D: Bland-Altman plot for comparison of HCV viral load between assay 1 and assay 2.

ARTICLE HIGHLIGHTS

Research background

Large-scale prospective studies are needed to evaluate the overall analytical, clinical performance, and reproducibility of the NeuMoDx 96 system.

Research motivation

The findings of this study demonstrated excellent clinical performance (100% concordance) of the random access system compared to the conventional commercially available batch system. With a short turnaround time (TAT) and user-friendly operation, it is a reliable assay for hepatitis B virus (HBV) and hepatitis C virus (HCV) viral load (VL) assessment.

Research objectives

In this study, overall a good correlation (100% concordance) and agreement were found between the two systems for HBV DNA and HCV RNA VL quantification. The sensitivity and specificity of the NeuMoDx 96 for both HBV and HCV assays were found to be 100%. Moreover, no difference was found in the quantification of HBV/HCV VL across different genotypes.

Research methods

A total of 186 archived once-thawed plasma samples with pre-existing test results from initial routine lab testing were used. The overall concordance, correlation, and agreement were evaluated among all samples for HBV and HCV VL estimation using both systems.

Research results

The objectives of the study were: (1) Comparison of a random access system with conventional routinely used real-time PCR for quantifying HBV and HCV VL in plasma samples; (2) to estimate the overall concordance and agreement of VL quantification of clinical samples between the two systems; and (3) to evaluate genotype-based comparison of HBV and HCV VL between both systems.

Research conclusions

To date, most routinely used assays for HBV/HCV VL estimation typically run on batch testing. The use of such platforms across most of the diagnostic lab results in longer "sample-to-result" time, leading to loss to follow-up. Therefore, a reliable random access system with a shorter TAT is the need of the hour for all clinicians.

Research perspectives

HBV and HCV pose a significant health burden in low- and middle-income countries. The TAT for VL quantification (from receiving samples to giving out results) is longer for the conventional routinely used batch system-based real-time PCR assays. Therefore, to prevent loss to follow-up of a patient from the cascade of care, it is important to have molecular assays that are fully automated with high throughput and short TAT.

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FOOTNOTES

Author contributions: Chooramani G contributed to the original manuscript draft writing and data curation; Samal J contributed to the data analyses and manuscript writing; Rani N contributed to the validation and data compilation; Singh G contributed to the validation and data compilation; Agarwal R contributed to the manuscript editing; Bajpai M contributed to the manuscript editing; Kumar M contributed to the clinical investigations; Prasad M contributed to the statistical analyses; Gupta E contributed to the conceptualization, supervision, and final manuscript editing; All authors read and approved the manuscript.

Institutional review board statement: The study was reviewed and approved by the Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) of Institute of Liver and Biliary Sciences (Approval No. IEC/2023/102/MA06).

Informed consent statement: This was a retrospective study, so patient informed consent was waived.

Conflict-of-interest statement: The authors declare having no conflict of interest that pertains to this work.

Data sharing statement: No additional data are available.

Country/Territory of origin: India

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