DOI: https://doi.org/10.53350/pjmhs2023171830

ORIGINAL ARTICLE

Role of Non-Hepatotropic Viruses in Acute Sporadic Viral Hepatitis and Acute-on-Chronic Liver Failure in Adults

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ABSTRACT

Background and Aim: Viral infections, drugs, metabolic disorders, and autoimmune processes can cause hepatitis, which is a diffuse inflammatory condition of the liver. Hepatitis E (HEV) and hepatitis A (HAV) viruses are the most common causes of acute viral hepatitis (AVH). AVH and chronic liver failure (ACLF) patients were studied to determine whether they were infected with various hepatotropic and non-hepatotropic viruses.

Patients and Methods: This prospective study was conducted on 186 adult patients with ACLF and AVH in the Department of Gastroenterology, DHQ Teaching Hospital and Mufti Mahmood Memorial Hospital, Dera Ismail Khan from September 2020 to August 2022. Our study included consecutive patients with acute viral hepatitis who had a definite viral etiology, a fever or jaundice that developed after 3 weeks, and an ALT that was 2x the upper limit of normal. There were three serological tests performed for all the patients: hepatitis (A, B, C, D, and E), Epstein-Barr virus (EBV), and non-hepatitis (CMV). Data analysis was carried out in SPSS version 26.

Results: Of the total 186 samples investigated, the incidence of ACLF and AVH was 60 (32.3%) and 126 (67.7%) respectively. The prevalence of confirmed etiology such as HEV, HAV, HBV, and HCV was 98 (52.7%), 29 (15.6%), 20 (10.8%), and 2 (1.1%) respectively. The mixed viral etiology and Epstein-Barr virus was present in 18 (9.7%) and 19 (10.2%) respectively. The most prevalent cause of infection was HEV found in 76 (60.3%) AVH and 42 (70%) ACLF cases. The mortality rate among AVH patients was significantly lower 2.4% (n=3) than ACLF 23.3% (n=14). As compared to ACLF patients, AVH patients had significantly higher infections caused by non-hepatotropic viruses (24 vs. 3, p=0.001). There were significantly more mixed infections in AVH as opposed to ACLF (28 vs. 4, p<0.001).

Conclusion: The present study concluded that both AVH and ACLF patients were susceptible to HEV-associated hepatitis. There were significant numbers of patients with AVH being infected with non-hepatotropic viruses including CMV and EBV. These viruses are much less common in patients with ACLF.

Keywords: Epidemiology, Non-hepatotropic virus, Acute viral hepatitis, Acute chronic liver failure

INTRODUCTION

Acute liver failure (ALF) is a catastrophic clinical illness with a high death rate in the absence of specialized therapy, prompt high-level intensive care, and liver transplantation. The hepatic encephalopathy initial symptoms emerge within 8 weeks escorts acute liver failure [1, 2]. Prothrombin time should be assessed quickly in all patients with clinical or laboratory symptoms of acute hepatitis, as well as a complete screening for subtle changes in mentation [3]. The presence of poisons in the body is referred to as the presence of asbestos. ALF may arise due to a variety of reasons, including acetaminophen or other medication overdose, viral hepatitis, ischemia, and others. When ALF is not fatal, the liver has the unusual ability to recover entirely, however predicting death remains difficult [4, 5]. The principal causes of hepatitis include hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV), which are linked with high morbidity and death in developing countries [6, 7]. Liver inflammation is often caused by acute viral hepatitis leading to infectious consequences in terms of five different hepatitis viruses such as HEV, HAV, HDV, HBV, and HCV. These hepatitis can strike rapidly, with 8 weeks typical recovery. In contrast, HDV, HBV, and HCV can induce persistent infections that culminate in liver cirrhosis and chronic hepatitis [8, 9].

Hepatitis caused by viruses other than A to E account for approximately 15 % to 60 % of cases [10, 11]. Few investigations have been conducted to determine the precise pathological etiologies in the non-viral hepatitis patients. Specific infectious etiology is required to determine therapy choices and evaluate the patient's outcome. There is a scarcity of research on non-hepatotropic viruses' role, particularly EBV and CMV, in acute-on-chronic liver failure (ACLF) and acute sporadic viral hepatitis. The current study was conducted to determine the prevalence of several viruses (hepatotropic and non-hepatotropic) in AVH and ACLF patients.

METHODOLOGY

This prospective study was conducted on 186 adult patients with ACLF and AVH in the Department of Gastroenterology, DHQ Teaching Hospital and Mufti Mahmood Memorial Hospital, Dera Ismail Khan from September 2020 to August 2022. Our study included consecutive patients with acute viral hepatitis who had a definite viral etiology, a fever or jaundice that developed after 3 weeks, and an ALT that was 2x the upper limit of normal. There were three serological tests performed for all the patients: hepatitis (A, B, C, D, and E), Epstein-Barr virus (EBV), and non-hepatitis (CMV). Based on chemiluminescent assay (CMIA), HAV and CMV with antibody IgM, HBsAg, HCV, and HBV core antigen (anti-HBc IgM) were carried out for screening of the patients. Eligible patients were classified as having AVH or ACLF. Blood samples positive for HAV or HEV were analyzed for the investigation of virological features of HEV and HAV infections. The institutional ethics committee accepted the protocol. HAV and HEV RNA were detected and quantified in plasma samples using q RT-PCR. Viral RNA Mini Kit was used to extract RNA from 200 L of plasma.

SPSS version 26 was used for statistical analysis. Numerical variables were presented as a mean and standard deviation, and continuous variables as a frequency and percentage. As applicable, the Chi-squared test was employed to compare results between HAV and HEV positive groups. All descriptive statistics were done by taking 95% confidence interval and 5% level of significance.

RESULTS

Of the total 186 samples investigated, the incidence of ACLF and AVH was 60 (32.3%) and 126 (67.7%) respectively. The prevalence of confirmed etiology such as HEV, HAV, HBV, and HCV was 98 (52.7%), 29 (15.6%), 20 (10.8%), and 2 (1.1%) respectively. The mixed viral etiology and Epstein-Barr virus was present in 18 (9.7%) and 19 (10.2%) respectively. The most

prevalent cause of infection was HEV found in 76 (60.3%) AVH and 42 (70%) ACLF cases. The mortality rate among AVH patients was significantly lower 2.4% (n=3) than ACLF 23.3% (n=14). As compared to ACLF patients, AVH patients had significantly higher infections caused by non-hepatotropic viruses (24 vs. 3, p=0.001). There were significantly more mixed infections in AVH as opposed to ACLF (28 vs. 4, p<0.001). Table-I shows the baseline details and laboratory findings. Figure-1 depicts the prevalence of AVH and ACLF among total patients. Clinical manifestations are shown in Figure-2. The virological etiology of AVH and ACLF patients are demonstrated in Figure-3. Table-II compared the acute viral hepatitis with acute-on chronic liver failure groups.

Table-1: Baseline details and laboratory findings of the studied population (n=186)

Parameters	Value
Age (yrs.)	38±4.0 (16-60)
Gender N (%) Male Female	 121 (65.1) 65 (34.9)
Laboratory findings Total bilirubin (mg/dL) ALT (IU/L) AST (IU/L)	 8.6 (1.1–101.9) 1582 (840–2334) 1365 (726–1806)

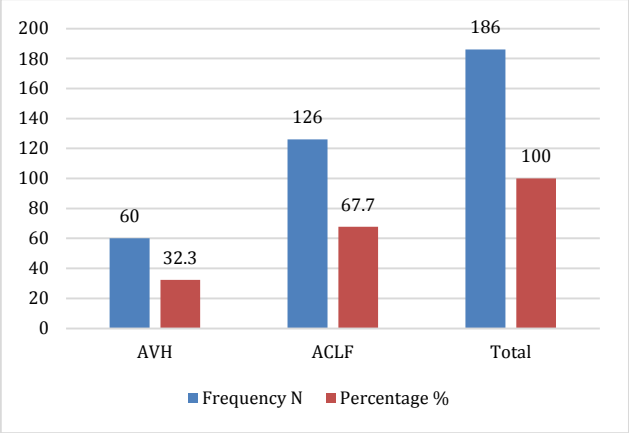

Figure-1: prevalence of AVH and ACLF (n=186)

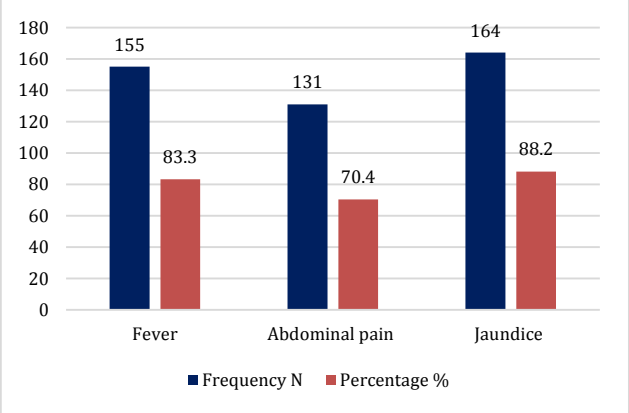

Figure-2: Clinical manifestations of studied population (n=186)

Table-2: comparison of the AVH with ACLF

Features	AVH N=126	ACLF N=60	P-value
Age (years)	31 (16–60)	45 (18–60)	0.003
Gender N (%) Male	 90 (74.4)	 31 (25.6)	0.03
ALT (IU/L) mean	934.8	348	0.05
Total Bilirubin (mg/dL)	9.64	15.24	0.06
Mortality N (%)	3 (2.4)	14 (23.3)	0.001

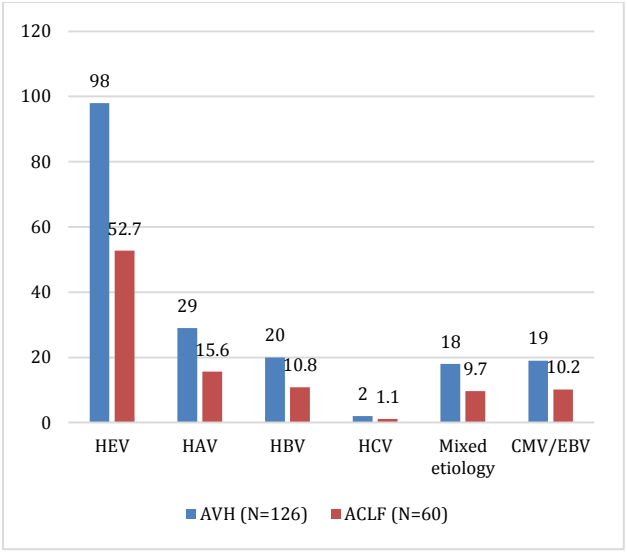

Figure-3: virological etiology of AVH and ACLF patients

DISCUSSION

The present study mainly focused on the role of numerous viruses (hepatotropic and non-hepatotropic) in patients with AVH and ACLF and found that ALF is a very uncommon condition, particularly in the industrialized world [12]. The causes of ALF are many and may differ from one country to the next. Hepatitis B was once thought to be the most prevalent cause of ALF [13]. Patients with AVH and ACLF were both vulnerable to HEV-associated hepatitis. A considerable percentage of AVH patients were infected with non-hepatotropic viruses such as CMV and EBV. These viruses are substantially less prevalent in ACLF patients. There have been numerous investigations carried out on the hepatotropic viruses frequency in AVH [14, 15], while data for ACLF are limited [16, 17]. In the current investigation, we discovered AVH group had greater incidence of non-hepatotropic viruses over the ACLF group. The limitations of the study were that only patients with proven viral origin were enrolled, and the non-hepatotropic group was assessed for EBV and CMV. In healthy adults, CMV or EBV causing hepatitis is typically limited, although it can occasionally be linked with substantial morbidity and death [18, 19].

Immunocompromised people with HIV, chemotherapy patients, transplant recipients, and burn patients are among those most at risk of infection and catastrophic illness. EBV or CMV primary infection in immunocompetent people normally had no illness symptoms, although it may lead to mononucleosis syndrome. There have been rare reports of immunocompetent individuals with induced hepatitis CMV or EBV [20, 21]. In the current investigation, we discovered that CMV and EBV both have a role in the etiology of AVH and ACLF. As a result, even in immunocompetent individuals, acute sporadic hepatitis differential diagnosis might include non-hepatotropic viruses.

HEV was the supreme prevalent infectious source in both ACLF and the AVH groups in the current investigation, followed by HAV. Sporadic hepatitis is caused by HEV, accounting for > 25% of acute sporadic hepatitis in endemic countries. The prevalence of HEV varies from 30% to 70% in acute sporadic hepatitis [22]. Most underdeveloped nations, including Pakistan, have a high prevalence of HAV infection. HAV infection, on the other hand, is connected with the establishment of protective immunity. Furthermore, HAV infection in children is typically moderate and asymptomatic. Our findings demonstrate that adults had a greater infectious HAV incidence. With improvements in community socioeconomic situations, the age of getting HAV infection has shifted from infancy to older age groups in Pakistan [23-25] and internationally [26, 27].

The majority of patients were men, might indicate increased vulnerability to infection, or a sophisticated prospect of developing infectious symptoms. Hepatitis E patients reported greater bilirubin levels as compared to HAV-infected individuals. The mortality rate in E infection was much greater, and it was linked with underlying chronic liver disease decompensation. HEV or HAV serological testing using IgM antibody detection is the most accurate way for determining acute sporadic hepatitis caused by a virus.

In the present study, when AVH patients were compared to ACLF cases, HEV infection was clearly higher in the ACLF group than in the HAV group. Furthermore, HEV infection was the leading cause of mortality in ACLF. The ACLF associated mortality rate was 28% lower than stated in previous studies [28, 29], most likely because viral origin of ACLF was evaluated. According to Zhang et al., [30] HEV, HAV, HBV, and HCV had higher prevalence of 53%, 39%, 19%, and 13% respectively. Remarkably, the frequency of HAV was 100% among children aged 6 years. HEV infection, on the other hand, has been observed to be greater in adults than in children. Alternative research utilizing sera from 74 adult patients obtained at several found simultaneous infection with more than one kind of hepatitis virus in 28 patients [31, 32].

CONCLUSION

The present study concluded that both AVH and ACLF patients were susceptible to HEV-associated hepatitis. There were significant numbers of patients with AVH being infected with non-hepatotropic viruses including CMV and EBV. These viruses are much less common in patients with ACLF.

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