

Predictive Factors in the Incidence of Liver Cirrhosis in Chronic Hepatitis B Mono-Infection in Comparison With HBV/HDV Co-Infection

Anwar Hussain Abbasi¹, Amna Riaz MBBS², Hina Andaleeb³, Muhammad Omar Qureshi⁴, Nadeem Yousuf³, Khawaja Ashfaq Ahmed³

1 Department of Gastroenterology, Rawal Institute of Health Sciences, Islamabad, Pakistan;

2 Postgraduate Trainee (Internal Medicine), Rawal Institute of Health Sciences, Islamabad, Pakistan;

3 Department of Medicine, Rawal Institute of Health Sciences, Islamabad, Pakistan;

4 Consultant Gastroenterologist, Ali Medical Private Centre, Islamabad.

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Correspondence to: Anwar Hussain Abbasi, Assistant Professor, Department of Gastroenterology, Rawal Institute of Health Sciences, Islamabad, Pakistan.
Email: anwar30pk@gmail.com

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ABSTRACT

AIM: The aim of this study was to investigate the virological and biochemical characteristics of patients infected with HBV mono-infection and HDV/HBV co-infection; and to determine risk factors associated with development of liver cirrhosis.

METHODS: Cross-sectional study in which 586 HBV patients were identified based on testing on ELISA. Important characteristics were extracted. Patients with anti-HDV positive status were also identified. Liver cirrhosis was based on APRI (≥ 1.5) or/and FIB4 (≥ 1.45);

or/and Fibroscan (F4). HBV-DNA level $\leq 2,000$ IU and $\geq 20,000$ IU were categorized to label patients with low and high viral load, respectively. HB surface Ag (HBsAg) was categorized as low when titer was ≤ 10 IU/mL.

RESULTS: Among all, mono-infected HBsAg patients was higher (52.04%) as compared to patients co-infected with HDV (11.77%). Patients with HDV coinfection had higher risk of having liver cirrhosis as compared to patients with HBV mono-infection, 33 (23.74%) vs. 39 (28.05%), respectively. Most of the risk predictors such as increasing age, raised AST, APRI, and FIB4 scores, and low platelet counts were similar in both groups but surprisingly liver cirrhosis may occur irrespective of raised bilirubin, AST, and HBV DNA levels in coinfecting HBV/HDV patients, $p < 0.05$.

CONCLUSION: Liver cirrhosis and hepatocellular carcinoma in patients with HBV/HDV co-infection appears to be more prevalent compared to HBV mono-infection. Liver cirrhosis occurs at younger age in patients with HBV/HDV co-infection as compared to HBV mono-infection. Among HBV/HDV co-infected patients cirrhosis status was independent of HBV viral load.

Key words: Liver cirrhosis; Predictive factors; Viral hepatitis; Hepatitis B virus; Hepatitis Delta co-infection; Pakistan

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INTRODUCTION

Cirrhosis of the liver is the end-stage-liver disease caused by many liver diseases including viral hepatitis B, C, and D also. Worldwide, liver cirrhosis become an important public health concern and a significant source of morbidity and mortality^[1]. The prevalence of liver cirrhosis in developed countries is almost similar and estimated between 0.27% in United States^[2] and 0.3-0.6% in France^[3]. In

Pakistan, more than 75% of the cases with liver cirrhosis and hepatocellular carcinoma are caused by viral hepatitis with a prevalence rate of HCV and HBV mono-infection associated liver cirrhosis was 55.8% and 32.6%, respectively^[4]. Previously conducted an epidemiological study has shown higher prevalence of liver cirrhosis in co-infected HBV/HCV patients as compared to mono-infected HBV patients, 44% vs. 21%, respectively^[5]. While, the prevalence of HBV/HDV induced liver cirrhosis is comparatively low and accounts for 18% of the cases^[6].

Multiple factors can play an important role in predicting liver cirrhosis in patients with HBV mono-infection. In a study conducted by Wong GLH and colleagues^[7] has shown increased risk of advanced liver fibrosis in HBeAg-positive patients older than 35 years of age with an alanine transaminase (ALT) level greater than 0.5 x ULN. Another recent study conducted by Lakaho S has shown increased prevalence of liver cirrhosis in patients with raised total bilirubin and direct bilirubin levels but none among them reached statistical significance level^[8].

Identification of risk factors associated with liver cirrhosis among patients infected with HBV alone or co-infected with HBV/HDV infection is a need of time to around the world because data is lacking not only in Pakistan but also in majority of the developed countries. Further, this study will also help gastroentero-hepatologists and policy makers to design better management strategies and policies to improve patient's quality of life and reduce economic burden caused by this disease.

METHODS

This was a descriptive cross-sectional hospital based study was conducted on a group of 586 patients who were diagnosed with HBsAg over a period of longer than six months. The cases were

selected from the hepatitis centers, Islamabad & Rawalpindi over a period of six months i.e. from February 2021 to July 2021. The inclusion criteria for this study was positive and treatment naïve HBsAg patients, both males and females, age ≥ 18 years and ≥ 60 years, and patients with autoimmune hepatitis, hepatocellular carcinoma, chronic kidney disease, pregnant women, immunocompromised status, concomitant HIV infection, and refusal to participate in this study. Consent was taken from every patient and/or their attendant after briefing them the objectives of the study. The Hospital Ethical Committee approved the study.

Senior laboratory technologist drew 5mL venous blood sample using a sterilized disposable syringe, and then the sample was used for the detection of hepatitis B and hepatitis D viruses by enzyme linked immunosorbent assay (ELISA).

A standard method was used in our study to calculate the degree of liver cirrhosis, the APRI score, which is calculated by including the baseline upper limit levels of AST (IU/L) and then divide them by with platelet counts (10⁹/L) and all values multiple with 100. And as per guidelines recommendations, we set cutoff values of APRI score for liver cirrhosis as ≥ 1.5^[9]. The FIB-4 index is calculated using the formula: FIB-4 = Age (years) × AST (U/L) / [PLT(10⁹/L) × ALT^{1/2} (U/L)]. The theoretical basis for this index has been previously described^[10].

The variables studied were age, gender, area of residence, marital status, comorbid conditions, baseline laboratory and clinical parameters, co-infection with HDV, presence of hepatocellular carcinoma (HCC) & liver cirrhosis, and clinical manifestations. We used Statistical package for social science (SPSS) version 26 for data entry and final analysis. The collected data were analyzed for frequency with percentage and distribution. All the baseline and clinical variables were used as a risk factor for liver cirrhosis by comparing the data using chi-square test/fisher's exact test and independent *t*-test, where appropriate with a significance level of *p* < 0.05.

Table 1 Baseline and clinical characteristics of study subjects.

Baseline Variables	Overall (n = 586)	Cirrhotics (n = 139)	Noncirrhotics (n = 447)	p value
	Number (%) or mean ± SD			
Age - years	37.07 ± 13.87	42.97 ± 12.69	35.24 ± 13.73	<0.001
Gender				
Male	368 (62.79)	86 (61.87)	282 (63.08)	0.43
Female	218 (37.20)	53 (38.12)	165 (36.91)	
Area of residence				
Urban	392 (66.89)	92 (66.18)	301 (67.33)	0.55
Rural	194 (33.10)	47 (33.81)	146 (32.66)	
Laboratory parameters				
ALT - IU/L	64.22 ± 71.24	97.21 ± 84.70	53.97 ± 49.21	<0.001
AST - IU/L	44.12 ± 28.78	84.72 ± 70.62	53.97 ± 49.21	<0.001
Total bilirubin - mg/dL	0.8.10 ± 1.32	0.987 ± 1.36	0.636 ± 0.437	<0.001
Platelet count - × 10 ⁹ /L	223.78 ± 69.53	164.64 ± 70.82	242.27 ± 57.88	<0.001
Serum creatinine - mg/dL	0.86 ± 0.56	0.89 ± 0.14	0.88 ± 0.55	0.14
Clinical variables				
HBsAg level	2660.78 ± 4527.39	2099.12 ± 1822.82	2834.56 ± 5069.79	0.09
HBV DNA level	4721246.52 ± 43104102.33	7054444 ± 68946500	4022874 ± 31590322	0.47
APRI score	0.80 ± 1.08	1.77 ± 1.40	0.504 ± 0.739	<0.001
FIB4 score	1.24 ± 1.50	2.67 ± 2.18	0.789 ± 0.788	<0.001
Ascites	14 (2.38)	14 (10.07)	0 (0)	<0.001
GI bleed	14 (2.38)	11 (7.91)	3 (0.67)	<0.001
Encephalitis	2 (0.34)	2 (1.43)	0 (0)	0.056
Comorbid				
Hepatocellular carcinoma	12 (2.04)	10 (7.19)	2 (0.44)	<0.001
HBV mono-infection	305 (52.04)	33 (23.74)	272 (60.85)	<0.001
HBV/HDV co-infection	69 (11.77)	39 (28.05)	30 (6.71)	<0.001

Table 2 Predictors of Liver cirrhosis among patients monoinfected with HBV.

Baseline Variables	Liver Disease Status		p value
	Cirrhotics (n = 33)	Noncirrhotics (n = 272)	
Age - years	42.93 ± 15.58	34.36 ± 14.35	0.001
Gender			
Male	21 (63.63)	178 (65.44)	0.1
Female	12 (36.36)	94 (34.55)	
Area of residence			
Urban	24 (72.72)	188 (69.11)	0.76
Rural	9 (27.27)	84 (30.88)	
Laboratory parameters			
ALT - IU/L	76.30 ± 62.28	48.29 ± 51.23	<0.001
AST - IU/L	62.78 ± 43.32	30.77 ± 19.36	<0.001
Total bilirubin - mg/dL	0.9 ± 1.16	0.62 ± 0.41	0.008
Platelet count - × 10	202.36 ± 75.91	243.86 ± 58.08	<0.001
Serum creatinine - mg/dL	1.0 ± 0.19	0.86 ± 0.48	0.08
Clinical variables			
HBsAg level	2720 ± 1456	3340 ± 5341	0.51
HBV DNA level			
<1000	12 (36.36)	120 (44.11)	0.001
≥1000 - 2000	0 (0)	15 (5.51)	
2000 - 20000	0 (0)	57 (20.95)	
≥20000	12 (36.36)	32 (11.76)	
APRI score	1.20 ± 0.95	0.40 ± 0.30	<0.001
FIB4 score	1.84 ± 1.24	0.68 ± 0.47	<0.001
Ascites	2 (6.06)	0 (0)	<0.001
GI bleed	1 (3.03)	0 (0)	<0.001
Comorbids			
Hepatocellular carcinoma	2 (6.06)	0 (0)	0.003

RESULTS

Among all 586 HBsAg positive treatment naive patients, most of them were males ($n = 368$, 62.79%), belongs to younger age group (37.07 ± 13.87 years) and 66.89% ($n = 392$) were urban dwellers. The frequency of mono-infected HBsAg patients was higher ($n = 305$, 52.04%) as compared to patients co-infected with HDV (69, 11.77%). Frequency of liver cirrhosis was 23.72% ($n = 139$) while non-cirrhotics were more common and represent 76.27% ($n = 447$) of the cases among all. Surprisingly, patients with HDV coinfection had higher risk of having liver cirrhosis as compared to patients with HBV mono-infection, 33 (23.74%) vs. 39 (28.05%), respectively (Table 1).

The risk factors associated with liver cirrhosis in patients mono-infected with HBsAg were increasing age (42.93 ± 15.58 years), raised mean alanine transaminase (76.30 ± 62.28 IU/L), aspartate aminotransferase (62.78 ± 43.32 IU/L), and total bilirubin (0.9 ± 1.16 mg/dL) levels, low platelet count ($202.36 \pm 75.91 \times 10^9/L$), increased APRI (1.77 ± 1.40) & FIB4 (2.67 ± 2.18) scores, and HBsAg levels $\geq 20,000$, p value < 0.05 (Table 2).

The risk factors associated with liver cirrhosis in patients coinfecting with HBV/HDV were increasing age (37.51 ± 11.89 years), raised mean aspartate aminotransferase (113.51 ± 89.32 IU/L), low platelet count ($160.52 \pm 87.24 \times 10^9/L$), and increased APRI (2.39 ± 1.88) & FIB4 (1.88 ± 1.31) scores, p value < 0.05 (Table 3).

Table 3 Predictors of Liver cirrhosis among patients coinfecting with HBV/HDV.

Baseline Variables	Liver Disease Status		p value
	Cirrhotics (n = 39)	Noncirrhotics (n = 30)	
Age - years	37.51 ± 11.89	28.82 ± 12.00	0.005
Gender			
Male	21 (63.63)	178 (65.44)	0.1
Female	12 (36.36)	94 (34.55)	
Area of residence			
Urban	24 (72.72)	188 (69.11)	0.76
Rural	9 (27.27)	84 (30.88)	
Laboratory parameters			
ALT - IU/L	143.42 ± 95.43	72.31 ± 43.81	0.06
AST - IU/L	113.51 ± 89.32	49.93 ± 23.69	<0.001
Total bilirubin - mg/dL	1.3 ± 2.2	0.67 ± 0.39	0.153
Platelet count - × 10	160.52 ± 87.24	243.86 ± 58.08	0.003
Serum creatinine - mg/dL	1.2.03 ± 01.19	0.91 ± 0.68=3	0.02
Clinical variables			
HBsAg level	1533 ± 1732	1238 ± 1655	0.491
HBV DNA level			
<1000	20 (51.28)	16 (53.33)	0.639
≥1000 - 2000	1 (2.56)	0 (0)	
2000 - 20000	2 (5.12)	4 (13.33)	
≥20000	7 (17.94)	6 (20.0)	
APRI score	2.39 ± 1.88	1.07 ± 1.92	0.008
FIB4 score	1.88 ± 1.31	0.86 ± 0.52	<0.001
Ascites	4 (10.25)	0 (0)	0.025
GI bleed	2 (5.12)	1 (3.33)	0.666
Comorbids			
Hepatocellular carcinoma	4 (10.25)	0 (0)	0.025

DISCUSSION

Viral hepatitis B and coinfection with HBV/HDV are the most important causes of end-stage liver disease and hepatocellular carcinoma in developing countries like Pakistan^[4]. In our study the overall prevalence of liver cirrhosis was 23.72%, in which most of them had coinfection with HBV/HDV (28.05%) as compared with mono-infection with HBV infection (23.74%). Similar findings were observed in a previously conducted study in Pakistan by Khan AU *et al.* in which they observed more than 80% progression of chronic liver disease in patients coinfecting with HBV/HDV^[11]. Another recent study conducted by JH Bockmann and colleagues also observed higher prevalence of liver cirrhosis among coinfecting patients as compared to mono-infected HBV and HCV patients^[12]. Rapid progressive nature and severe aggression of HDV infection could be the underlying reason for the development of liver cirrhosis. Risk predictors of liver cirrhosis in patients mono-infected with HBV and coinfecting with HBV/HDV sometimes different. Identification of such risk predictors are crucial to prevent patients from further progressive end-stage liver disease like liver cirrhosis and hepatocellular carcinoma. These risk predictors may vary from one region to another region depending upon non-modifiable, partially modifiable, or modifiable factors such as genetics, dietary habits, environmental factors, availability of treatment facilities, response to treatment, and conditions which may compromise their immunity. However, in our study we evaluated baseline and clinical

characteristics to identify risk predictors of liver cirrhosis in mono-infected HBV and coinfecting HBV/HDV. Increasing age, elevated AST levels, low platelets count, and raised APRI & FIB4 scores were common risk predictors of liver cirrhosis among both groups with significant association. While, certain risk factors are exclusively present in both groups, risk predictors of liver cirrhosis in patients with mono-infected HBV infection were elevated AST, bilirubin, and HBV DNA levels ($p < 0.05$) and surprisingly these factors have no significant association in prediction of liver cirrhosis in patients coinfecting with HBV/HDV infections.

Multiple studies have been conducted in this regard some studies are consistent with our findings^[13-15] and some studies showed disagreement^[16,17]. Data from Pakistan also shows high prevalence of liver cirrhosis among HBV/HDV patients but risk factors associated with increased prevalence is still not studied that is why this study will provide a baseline ground for future studies.

Study limitations

This study was conducted in private centers from single city of Punjab where mostly people come from educated class and urban areas. We also missed certain important predictors of liver cirrhosis such as diabetes mellitus, hypertension, and cigarette smoking (which we found in international studies). Last and most important was determination and comparison of HBV genotypes among cirrhotic patients. Besides these limitations, our study provides important observations which will definitely help clinicians in the management of such patients and also, future studies should address these limitations to publish more robust data.

CONCLUSION

Liver cirrhosis and hepatocellular carcinoma in patients with HBV/HDV co-infection appears to be more prevalent compared to HBV mono-infection. Liver cirrhosis occurs at younger age in patients with HBV/HDV co-infection as compared to HBV mono-infection. Among HBV/HDV co-infected patients cirrhosis status was independent of HBV viral load.

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LIMITATION OF STUDY

Our study has certain limitations which should be addressed in further studies such as, our study was a single center study and data collected from this center cannot reflect whole Pakistani population. Secondly, we are unaware of the chronic dyspeptic symptoms underlying cause like, whether these symptoms are due to chronic NSAIDs usage or due to positive *H. pylori* infection, that should be evaluated separately in future studies.

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