Open Access
Full Length Article

ORIGINAL ARTICLE

Hepatocellular Carcinoma in Patients Suffering from Chronic Hepatitis B versus Co-Infection of Hepatitis B and D Virus

Riaz Hussain Khokhar [1], Anwar Ali Jamali [2], Shohabudin Rind [3]
[1] Postgraduate Department, Gastrointestinal & liver Diseases, Isra University Hospital at Hyderabad
[2] Assistant Professor, Department of Medicine, Peoples University of Medical and Health Sciences Nawabshah, Sind
[3] Postgraduate Department, Gastrointestinal & liver Diseases of Isra University Hospital at Hyderabad

ABSTRACT

Objective: To determine the frequency of hepatic cancer in subjects suffering from chronic liver disease due to hepatitis B versus hepatitis B with co-infection of viral hepatitis D.

Patients and Methods: This cross-sectional study was carried out in the Department of Medicine (Hepatology & Gastroenterology) at Isra University Hospital, Hyderabad Sindh, from March 2015 to February 2016. Both male and female patients, from 20-70 years of age either suffering from viral Hepatitis B alone or co-infected with viral hepatitis D were included in our research. Individuals having co-infection of Human Immunodeficiency virus, Viral hepatitis C, Wilson's disease, Hepatitis due to auto-immune diseases, alcoholic fatty liver disease, haemochromatosis, pregnant women and those patients who refused to give consent were excluded from study.

Results: Out of total 200 patients, 142(71%) were males while 58(29) were females. Mean age was 52.83±15.6 years. Total 173(86.5%) patients were suffering from viral hepatitis B alone, while 27(13.5%) were infected by co-infection of Viral hepatitis B and D. Total frequency of hepatocellular carcinoma was 45(22.5%) in all cases. HCC was more frequent (33.34%) in patients with co-infection of chronic hepatitis B and D, as compared to only chronic hepatitis B patients (20.80%) but the difference was non-significant (p-value 0.14).

Conclusion: Hepatocellular carcinoma was more frequent amongst patients co-infected with viral hepatitis D as compared to alone infection of hepatitis B virus.

Key words: Hepatocellular Carcinoma, Viral hepatitis B, Viral hepatitis D.

Author`s Contribution
[1] Conception, synthesis, planning of research and manuscript writing
[2] Interpretation and discussion Data analysis,
[3] Interpretation, manuscript writing and Active participation in data collection

Address of Correspondence
Anwar Ali Jamali
Email: dr.saeedarain786@gmail.com.

Article info.
Received: 2017
Accepted: 2017

Cite this article. *Khokhar RH, Jamali AA, Rind S. Hepatocellular Carcinoma in Patients Suffering from Chronic Hepatitis B Versus Co-Infection of Hepatitis B and D Virus. JIMDC.2017;6(4):*

Funding Source: *Nil.*
Conflict of Interest: *Nil*

Introduction

Hepatocellular carcinoma (HCC) is the commonest primary hepatic malignancy. It is also the leading cause of malignancy related mortality throughout the world. In the United States it is the ninth leading cause of mortality.[1] According to recent data, the rate of HCC is still rising globally, although it is variable throughout the world. Chronic viral hepatitis can lead to cirrhosis and HCC. Hepatitis B, C and D infections are the commonest reasons of chronic hepatitis worldwide. Hepatitis B virus is the double-stranded circular DNA and having 8 genotypes "A to H". Many epidemiological studies showed that hepatitis B infection is responsible for significant

hepatocarcinogenicity.[1,2] Hepatitis B virus carriers have 10%–25% lifetime risk of HCC development. Unlike other reasons of hepatitis severity, hepatitis B virus is the unique and may develop HCC without cirrhotic evidence.[3] Persistent replication of hepatitis D virus and inflammation of liver may cause cirrhosis and development of hepatocellular carcinoma, while active replications of the both hepatitis B virus and hepatitis D virus may be responsible for high progression in disease, which leads to early liver cirrhosis and hepatic malignancy.[4] Several epidemiological studies controversially showed different role of hepatitis D virus infection in the rising HCC risk. Many previously published studies did not found elevated rates of HCC in cases having hepatitis D co-infection, but in recent literature, it is mentioned that co-infection may increase the tumor incidence.[4] Risk of the hepatocellular carcinoma should be reassessed according to the alteration of the natural history of hepatitis D chronic disease. However, burden of hepatitis D virus has decreased in several countries of the Western world, on other hand it is still prevalent still other countries, particularly in Asia Pacific Region.[5] Association of HCC with co-infection of hepatitis D virus and hepatitis B virus or with hepatitis B viral infection alone, is still unclear. As in many studies it is reported that the development hepatocellular carcinoma itself is the complex process concerning cumulative gain and the loss of functions and mutations affecting tumor suppressor and oncogenic products.[6,7] It has been reported that hepatitis B virus is more responsible for development of hepatocellular carcinoma, and hepatitis D virus seems to exert epigenetic control over HBV transcription and replication. A possible explanation may be that p24 and p27 both repress HBV enhancers, pIIE1 and PIIE2 inhibit replication, thus accounting for the low serum levels of HBV DNA in co-infected patients.[8] On other hand, Pakistan have recognized a huge difference in the occurrence and sharing of HCC between population, who are suffering from viral Hepatitis B virus alone and viral hepatitis B co-infected with viral hepatitis D in different areas.[9] The purpose of our study was to determine the frequency of HCC in subjects suffering from viral hepatitis B alone versus viral hepatitis B co-infected with viral hepatitis D virus.

Patients and Methods

This cross-sectional research study was carried out in the Department of Medicine (Hepatology & Gastroenterology) Isra University Hospital, Hyderabad Sindh from March 2015 to February 2016. Informed written consent was taken from patients or their relatives. Both male and female patients of chronic liver disease, either suffering from viral Hepatitis B alone or co-infected with viral hepatitis D, from 20-70 years of age were included in our research. Individuals having age less than 20 years or more than 70 years, Co-infection with Human Immunodeficiency Virus, viral hepatitis C, Wilson's disease, hepatitis due to auto-immune diseases, alcoholic fatty liver disease, haemochromatosis, pregnant women and those patients who refused to give consent were excluded from study. Complete clinical examination of all patients was carried out. All the patients were divided in two groups. Group 1 included chronic HBV mono-infection patients and group 2 comprised of patients having co-infection of chronic HBV and HDV. Viral hepatitis B was diagnosed on the basis of HBsAg positive on enzymatic assays analysis through ELISA. Viral hepatitis D was diagnosed in HBsAg positive cases on the basis of hepatitis D Virus antibodies on ELISA. The diagnosis of hepatocellular carcinoma was suggested in those patients who had the clinical features suggestive of hepatocellular carcinoma which was further confirmed by tri-phasic contrast enhanced CT scan / magnetic resonance imaging abdomen, typically showing hyper vascular solid hepatic mass with support of high levels (>100 ng/ml) of alpha-fetoprotein. Socioeconomic status according to monthly income was defined as upper >50,000 rupees/month, Middle 15,000- 49,000 rupees/month and lower <15,000 rupees/month. All data was recorded in the pre design performa. Data were entered and analyzed in SPSS 16. Mean and standard deviation (SD) were calculated for quantitative variables. Frequency and percentage were calculated for qualitative variables. Chi-square test was applied to compare the frequency of HCC in HBV mono infection versus HBV+HDV co-infection. p-value less the 0.05 was considered as statistically significant.

Results

Out of total 200 patients, 142(71%) were male while 58 (29%) were females. Mean age of subjects was 52.83±15.6 years (range was 20-70 years). Most of our patients (67%) belonged to middle age group. Regarding the education level, out of 200 subjects 115(57.5%) were un-educated. Majority of subjects (56.5%) in our study belonged to lower economic class (Table1).

Table 1: Demographic characteristics of participants (n=200)

Characteristics	n(%)
Age groups (years)	
20-40	44(22)
41-60	134(67)
>60	22(11)
Gender	
Male	142(71)
Female	58(29)
Educational status	
Un-educated	114(57)
Primary	57(28.5)
Middle-matric	13(6.5)
Intermediate	10(05)
Graduate	06(03)
Socioeconomic status	
lower	113(56.5)
Middle	70(35)
Upper	17(08.5)

Among these subjects, 173 were suffering from viral hepatitis B alone while 27 subjects were diagnosed to have viral hepatitis B and D co-infection (Figure 1).

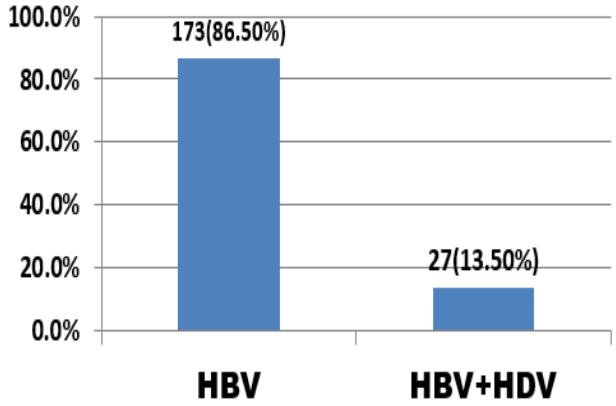

Figure 1: Patient's distribution according to HBV and HBV+HDV Co-infection (n=200).

Out of all study participants, 45 were diagnosed with HCC and 155 were without hepatocellular carcinoma. Thus, total HCC frequency was 22.5% (Figure 2).

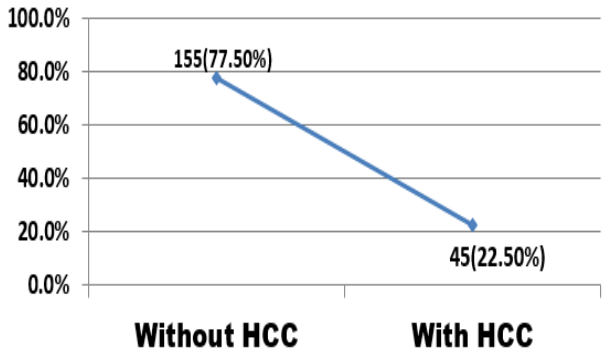

Figure 2: Patient's distribution according to frequency of HCC (n=200).

Ultrasound abdomen revealed that 127(63.5%) subjects had evidence of chronic liver disease without decompensation and remaining 73(36.5%) subjects were present with decompensation indicated by ascites, dilated portal vein, splenomegaly and malignant change / growth /mass. These suspected cases of HCC were stepped up for alpha-feto protein level, CT-scan abdomen. After performing these investigations, 45(22.5%) individuals were diagnosed as having hepatic cancer. All the suspected cases of HCC were also confirmed on biopsy. Mean alpha fetoprotein level in our study was 5322.44 ±2779.82 ng/ml. HCC was more frequent (33.34%) in patients with co-infection of chronic hepatitis B and D, as compared to patients having only chronic hepatitis B (20.80%) but difference was not significant p-value 0.14 (Table.2).

Table 2: Association of HCC with HBV & HBV+HDV co-infection (n=200)

Parameter	HCC		Total	p-value
	With HCC n (%)	Without HCC n (%)		
HBV	36(20.80)	137(88.20)	173	0.14
HBV+HDV	09(33.34)	18(66.66)	27	

Discussion

Hepatic carcinoma is the fifth most frequent cancer and 3rd common reason of mortality. It is documented that the

hepatitis B virus is one of the commonest oncogenic virus in human.[10] Prevalence of HCC is high in population infected by hepatitis B virus. Additionally, increased risk of HCC is reported in HDV infected cases.[10] Present study has been carried out to determine the proportional frequency of HCC in patients affected by chronic hepatitis B or chronic co-infection of hepatitis B and hepatitis D. The mean age of subjects was 52.83±15.6 years with minimum of 20 years and maximum 70 years. Similarly, study of Abbas Z et al[10] reported that patient's mean age was 54.6 ± 11.1 years. Another study of Kim HS et al[11] also indicated that mean age was 48 years, with range of 18 years-94 years and male predominance (64.5%). These gender findings are also comparable to our study, as out of 200 patients, 142(71%) were male, while 58(29%) were females.

In this study, 27(12.5%) subjects were suffering from viral hepatitis B and D co-infection. Similarly, a national study of Shaikh MA et al[12] reported that anti-HDV was positive in (23.6%) patients with HBV positive. In some other international studies, the sero-prevalence of anti-HDV in HBV was reported as 11.5% in Iran and 10.6% in India.[13,14] In Turkey, the prevalence of anti-HDV serological markers were observed as 27.5% in HBV related chronic hepatitis.[15]

In this current analysis, HCC was more frequent in patients with co-infection of chronic hepatitis B and D as 09(33.34%) out of 27 cases, as compared to only chronic hepatitis B patients as 20.80% out of 173 cases. Amougou MA et al[16] reported that in HCC-cases found, hepatitis Delta antibody (Anti-HDV) co-infection was present in 41.4 %. Studies had also shown that extravagant reproduction of virus particles by HBV in combination with HDV leading to massive necro-inflammation results in HCC.[17]

Cases infected by combination of HBV and HDV also develop HCC earlier as compared to those having HBV infection only.[18,19] Saravanan S et al[20] researches showed the subjects of chronic hepatitis group, suffering from viral hepatitis B and are chronically ill, antibodies against hepatitis D Virus were present in approximately 5.7% of diseased persons. This generally leads to chronic liver disease (Cirrhosis) in about 5.9% patients. Co-infection including hepatitis D virus is linked to diverse patterns of the reciprocal inhibitions of the replication of virus.[21] In literature it has been reported that HDV suppresses HBV replication with most cases being HBeAg -ve and with decreased HBV DNA level as compared to cases having HBV monoinfection.[22-24] Potential mechanisms of virology of HBV suppression by HDV as inhibitions of HBV enhancers may include proteins of HDV (p24 and p27).[25] Consistently previous studies reported that HBV/HDV co-infection has higher level of ALT and AST and decreased PLT and PTA levels.[23,26] As well as patients infected by HBV/HDV co-infection are estimated, 1.43 times more likely to progress to ESLD (end stage liver disease) as compared to those cases having HBV infection only. It is suggested that HBV/HDV co-infection leads to more rapid progression in hepatic disease as compared to those only infected by mono-infection of HBV.[16] It is suggested that studies should also be conducted in other centers, to find out association of HCC with chronic HBV mono-infection and chronic co-infection of hepatitis B virus and hepatitis D virus and to find out the mechanisms of their oncognesis.

Conclusion

This study accomplished that HCC was more frequent amongst patients having co-infection with viral hepatitis D as compared to infection of hepatitis B virus alone. Mono infected viral hepatitis B or all HBV infected patients should be screened for HDV, because early recognition and treatment of co-infected HBV and HDV, may reduce the burden of associated morbidity and mortality.

Reference

1. Balogh J, David Victor III EH, Burroughs SG, Boktour M, Saharia A, Li X, Ghobrial RM, Monsour Jr HP. Hepatocellular carcinoma: a review. Journal of hepatocellular carcinoma. 2016; 3:41-53.
2. International Agency for Research on Cancer (IARC) Monographs on the evaluation of carcinogenic risks to humans. Hepatitis Viruses. 1994; 59:182–221
3. Crissien AM, Frenette C. Current Management of hepatocellular carcinoma. Gastroenterol Hepatol. 2014;10(3):153–161
4. Abbas Z, Abbas M, Abbas S, Shazi L. Hepatitis D and hepatocellular carcinoma. World journal of hepatology. 2015 Apr 18;7(5):777-86
5. Abbas Z, Jafri W, Raza S. Hepatitis D: Scenario in the Asia-Pacific region. World J Gastroenterol. 2010;16(5):554–562

6. Gao C, Fang L, Zhao HC, Li JT, Yao SK. Potential role of diabetes mellitus in the progression of cirrhosis to hepatocellular carcinoma: a cross-sectional case-control study from Chinese patients with HBV infection. Hepatobiliary Pancreat Dis Int. 2013;12(4):385–393.
7. Levrero M. Viral hepatitis and liver cancer: the case of hepatitis C. Oncogene. 2006; 25(27):3834–3847.
8. Wedemeyer H, Manns MP. Epidemiology, pathogenesis and management of hepatitis D: update and challenges ahead. Nat Rev Gastroenterol Hepatol. 2010;7(1):31–40
9. Zaidi G, Idrees M, Malik FA, Amin I, Shahid M, Younas S, Hussain R, Awan Z, Tariq A, Parveen K. Prevalence of hepatitis delta virus infection among hepatitis B virus surface antigen positive patients circulating in the largest province of Pakistan. Virol J. 2010; 7(1):283.
10. Abbas Z, Qureshi M, Hamid S, Jafri W. Hepatocellular carcinoma in hepatitis D: does it differ from hepatitis B monoinfection? Saudi J Gastroenterol. 2012; 18(1):18-22.
11. Kim HS, Kim SJ, Park HW, Shin WG, Kim KH, Lee JH, Kim HY, Jang MK. Prevalence and clinical significance of hepatitis D virus co-infection in patients with chronic hepatitis B in Korea. Journal of medical virology. 2011 ;83(7):1172-7.
12. Shaikh MA, Shaikh WM, Solangi GA, Shaikh BA, Soomro MA. Frequency of hepatitis D virus infection in hepatitis B surface antigen-positive liver diseases. J Coll Physicians Surg Pak. 2011; 21(1):23-5.
13. Roshandel G, Semnani S, Abdolahi N, Besharat S, Keshtkar AA, Joshaqani H, et al. Prevalence of hepatitis D virus infection in hepatitis B surface antigen-positive subjects in Golestan Province, Northeast Iran. J Microbiol Immunol Infect 2008; 41(3): 227-30.
14. Chakraborty P, Kailash U, Jain A, Goyal R, Gupta RK, Das BC, et al. Seroprevalence of hepatitis D virus in patients with hepatitis B virus-related liver diseases. Indian J Med Res 2005; 122(3):254-7.
15. Celen MK, Ayaz C, Hosoglu S, Geyik MF, Ulug M. Anti-hepatitis delta virus seroprevalence and risk factors in patients with hepatitis B in Southeast Turkey. Saudi Med J 2006; 27(5):617-20.
16. Amougou MA, Noah DN, Moundipa PF, Pineau P, Njouom R. A prominent role of Hepatitis D Virus in liver cancers documented in Central Africa. BMC infectious diseases. 2016; 16(1):647.
17. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012; 30(12):2212-9.
18. Verme G, Brunetto MR, Oliveri F, Baldi M, Forzani B, Piantino P, et al. Role of hepatitis delta virus infection in hepatocellular carcinoma. Dig Dis Sci. 1991; 36(8):1134–6.
19. Brunetto MR, Oliveri F, Colombatto P, Bonino F. Hepatocellular carcinoma and infections with multiple hepatitis viruses. Princess Takamatsu Symp. 1995; 25:61–6.
20. Saravanan S1, Velu V, Kumarasamy N, Shankar EM, Nandakumar S, Murugavel KG et al. Seroprevalence of hepatitis delta virus infection among subjects with underlying hepatic diseases in Chennai, southern India. Trans R Soc Trop Med Hyg. 2008; 102(8):793-6.
21. Schaper M, Rodriguez-Frias F, Jardi R, Tabernero D, Homs M, et al. Quantitative longitudinal evaluations of hepatitis delta virus RNA and hepatitis B virus DNA shows a dynamic, complex replicative profile in chronic hepatitis B and D. J Hepatol 2010;52(5): 658–664.
22. Cross TJ, Rizzi P, Horner M, Jolly A, Hussain MJ, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. J Med Virol 2008; 80(2):277–282.
23. Zachou K, Yurdaydin C, Drebber U, Dalekos GN, Erhardt A, et al. Quantitative HBsAg and HDV-RNA levels in chronic delta hepatitis. Liver Int 2010;30(3): 430–437.
24. Heidrich B, Deterding K, Tillmann HL, Raupach R, Manns MP, et al. Virological and clinical characteristics of delta hepatitis in Central Europe. J Viral Hepat 2009;16(12):883–894.
25. Williams V, Brichler S, Radjef N, Lebon P, Goffard A, et al. Hepatitis delta virus proteins repress hepatitis B virus enhancers and activate the alpha/beta interferon-inducible MxA gene. J Gen Virol 2009; 90(11): 2759–276
26. Mumtaz K, Ahmed US, Memon S, Khawaja A, Usmani MT, et al. Virological and clinical characteristics of hepatitis delta virus in South Asia. Virol 2011; 8(1): 312.