

Hepatocellular Carcinoma in Hepatitis C-Associated Cirrhotic Patients Treated with Different Combinations of Direct-Acting Antiviral Agents Available in Pakistan: A Prospective Observational Study

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ABSTRACT

Background: The hepatitis C virus (HCV) is a leading cause of chronic liver disease, including hepatic cirrhosis and hepatocellular cancer (HCC). Drugs that act directly on the virus, like as direct-acting antivirals (DAAs), are associated with improved long-term virologic responses and reduced treatment time. Pakistani patients with HCV-related cirrhosis receiving DAA medication were studied to see if they had an increased risk of hepatocellular carcinoma (HCC).

Material and Methods: We conducted a prospective observational study at Isra University Hospital Hyderabad from July 2019 to August 2020. Three hundred fourteen patients met the inclusion criteria and were included. We recorded baseline demographic characteristics, Child-Pugh class, model for end-stage liver disease (MELD) score, alpha-fetoprotein level, and abdominal ultrasound/computed tomography (CT) scan before and after treatment.

Results: Three hundred-fourteen individuals took part in the research. The average age of participant with hepatocellular carcinoma was 46.7 years. Twenty (sixty-nine) of the participants developing hepatocellular carcinoma were men, while nine (thirty-one percent) were women ($p=0.221$). Five (17.2%) of the HCC participants were diabetics, and seventeen (58.6%) were tobacco users ($p=0.001$). Twenty individuals (69%) developed HCC after receiving a combination of sofosbuvir and daclatasvir. A sofosbuvir/velpatasvir combination led to the development of HCC in nine (31%) of individuals ($p=0.1$). HCC was diagnosed in eight individuals under the age of forty (27.6%), but in 21 patients beyond the age of forty (72.6%) ($p=0.55$). HCC was found in 65.6 percent of Child-Turcotte-Pugh class A participants.

Conclusion: DAAs have been linked to a higher risk of HCC. Participants receiving a combo of sofosbuvir/daclatasvir were more likely to develop HCC than those who received sofosbuvir/velpatasvir alone.

Keywords: Velpatasvir, Hepatocellular carcinoma, Sofosbuvir, Cirrhosis,

INTRODUCTION

The hepatitis C virus (HCV) may play a substantial role in hepatic disease, as there are around 170 million people infections. HCV is a Flaviviridae virus that was first identified in late twentieth century. It is an enveloped RNA virus [1]. After two decades, HCV causes cirrhosis in about 16% of people. Every year, up to 5% of cirrhotic patients develop hepatocellular carcinoma (HCC). Furthermore, hepatic decompensation patients have a 20% probability of dying within a year [2].

The most frequent form of hepatic cancer, HCC, is the second leading cause of cancer-related death worldwide. Cirrhosis, diabetes, old age, especially genotype 3 all increase the risk of HCC [3].

Knowledge of the structure of HCV proteins i.e. polymerase and proteases has paved the way for new drug discovery and development. With regard to medication development for the HCV, enzymes such as NS2-3a and other HCV proteases are essential. DAAs that bind proteins have been developed as a result. When opposed to sustained response from interferon, which only produced response in 40-50 percent of patients, DAAs allow approximately 100 percent of patients to have a sustained virologic response (SVR) [4-6]. Elimination of the hepatitis

C virus (HCV) is critical in preventing serious consequences from chronic hepatitis C [7-10].

When individuals are treated with DAAs, recent investigations revealed an overall rise in hepatocellular carcinoma. When HCV participants were managed with DAAs after local therapy of hepatoma, Reigh et al. discovered an unexpected rise of 27.6% in hepatoma recurrence [11]. Kozbial et al. discovered a 6.6 percent rise in the prevalence of HCC after using such DAAs for the first year [12], while Cardoso et al. found a 7.4 percent increase in the incidence of HCC [13]. According to Conti et al. and colleagues, cirrhotic with hepatitis C treated with DAAs had a 3.16 percent incidence of HCC and a 28.81 percent recurrence of HCC [14].

Others, on the other hand, claimed that HCV-infected people had lower HCC. Different results were found in a Chinese study by Zeng et al., who found a small drop in the estimated prevalence of hepatoma [15]. After using DAAs, Kanwal et al. found a 1% reduction in the incidence of HCC [16].

Due to contradictory reports in the literature on the prevalence of HCC following therapy with DAAs and a lack of data on patients in Pakistan, we conducted this study in Pakistan.

MATERIAL AND METHODS

We did a prospective observational study at the Isra tertiary-care Hospital in Hyderabad, Pakistan. Based on prior findings of HCC (7.6%)²⁴, sample size was estimated using online OpenEpi, with an error margin of 3% and a ninety-five percent confidence level. As a result, a sample size of three hundred participants was determined, but 314 individuals were enrolled in total over the course of a year. HCV-associated liver cirrhosis individuals of whatever gender from eighteen to seventy years have been included in the investigation. Before beginning the study, it was necessary to obtain approval from the institutional review board. After getting written agreement, participants who fulfilled the inclusion criteria were involved in this study. Depending on their financial situation, the participants were given a combo of sofosbuvir/daclatasvir and ribavirin or a combo of sofosbuvir/velpatasvir and ribavirin. We kept track of baseline demographics, Child-Turcotte-Pugh class (CTP), MELD score, abdominal radiological findings and alpha-fetoprotein results. Participants were excluded out from research if they had been diagnosed with hepatoma before enrollment, or if they had co-infecting with other hepatitis viruses (B or D) and had hepatic cirrhosis due to other reasons, such as hemochromatosis or Wilson’s illness, or if they refused to participate. Patients who obtained sustained response within 24 weeks of completion of therapy had their data collected. We also kept track of the length and type of DAA used. The presence of HCC was determined based on characteristic imaging abnormalities.

Statistical Analysis: For data entry and analysis, statistical package for social sciences 26.0 was used. For age, CTP class, α-fetoprotein levels, MELD score, and length of DAAs therapy, we determined mean and standard deviation. For cirrhosis, gender and HCC presence, frequency and percentage were calculated. Through stratification, confounders such as age, gender, MELD score, and length of DAA therapy, CTP score, tobacco use, diabetes mellitus, and the existence of hepatic cirrhosis were controlled. The findings were considered significant if the p-value was less than 0.05.

RESULTS

Three hundred fourteen participants were enrolled in the research. Demographic characteristics are shown in table-1. Twenty-nine individuals (20 males, 9 women) had HCC (9.2%), with an average age of 46.7 years.

Abbreviations: HCC, hepatocellular carcinoma; CTP; Child-Turcotte-Pugh; MELD, model for end-stage liver disease; DAA, direct-acting antiviral agent; SD, standard deviation.

Five (17.2%) of individuals who developed HCC had concomitant diabetes (p=0.174), whereas Seventeen (58.6%) were cigarette smoker (p=0.001). Twenty participants with HCC were given with a sofosbuvir/daclatasvir combo (69%) and nine participants with HCC were administered with just a sofosbuvir/velpatasvir combo (31%) (p=0.1).

Eight participants (27.6%) under the age of 40 developed HCC, while 21 patients (72.6%) beyond the age of 40 got HCC (p=0.55). CTP class A (n=19; 65.6 percent) had the highest rate of HCC, with no statistical significance

from those other groups. With the MELD score of 9, twenty-three individuals (79.3%) developed HCC.

Table 1: Demographic characteristics

	HCC	No HCC	P-value
Gender			
Male	20 (69%)	163 (57%)	0.221
Female	9 (31%)	122 (42.8%)	
α-fetoprotein (Mean ± SD)	876.5 ± 142.9	22 ± 90	<0.0001
Age (Mean ± SD)	46.7 ± 10.3	44.4 ± 11.5	0.301
Smoker	17 (58.6%)	12 (4.2%)	0.001
Diabetes	5 (17.2%)	28 (9.8%)	0.174
DAA			
Sofosbuvir/Velpatasvir	9 (31%)	134 (47%)	0.1
Sofosbuvir/Daclatasvir	20 (69%)	151 (53%)	
Age (years)			
≥40 years	21 (72.4%)	191 (67%)	0.55
<40 years	8 (27.6%)	94 (33%)	
CTP class			
Class C	1 (3.4%)	19 (6.7%)	0.77
Class B	9 (31%)	91 (31.9%)	
Class A	19 (65.6%)	175 (61.4%)	
MELD-score			
≥10	6 (20.7%)	56 (19.6%)	0.89
<9	23 (79.3%)	229 (80.4%)	

Figure 1 shows the percentages of hepatocellular carcinoma based on the length of therapy. Participants who got sofosbuvir/daclatasvir developed hepatocellular carcinoma in eight percent at 12 weeks, while fifteen percent at twenty-four weeks. While at 12 weeks, 4% of participants receiving sofosbuvir/velpatasvir combo ultimately developed hepatocellular carcinoma, while at 24 weeks, 9% had hepatocellular carcinoma. Five patients exhibited elevated amounts of alpha-fetoprotein but have not been identified with HCC.

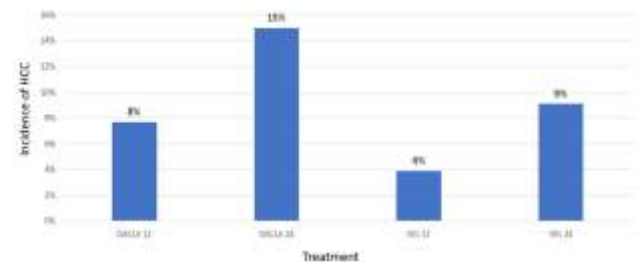


Figure 1. Hepatocellular carcinoma with length of therapy

Abbreviations: DACLA 12/24, sofosbuvir/daclatasvir for 12/24 weeks; HCC, hepatocellular carcinoma; VEL 12/24, sofosbuvir/velpatasvir for 12/24.

DISCUSSION

HCC develops slowly and is influenced by the length of the sickness and also the viral strain [17]. The goal of HCV therapy is to halt the progression of the illness, minimize

spread, and lower the risk of HCC. [18]. DAAs had already grown in importance as a management option with a high SVR [19]. Although what appears to be a very good treatment, HCC is still a concern. According to studies, up to eight percent of people with HCV related hepatic cirrhosis develops hepatoma each year [20].

The incidence of hepatoma had increased somewhat after DAA therapy, according to our findings. However, this finding contradicts Zeng et al and colleagues [15], concluding that DAAs therapy reduced the incidence of HCC. Our observations also contradicted those of Kanwal et al., which claimed that DAA therapy reduced the incidence of HCC [16]. Our observations are in agreement with that of the Ravi et al., Kozbial et al., and Cardoso et al., who found an elevated chances of hepatoma after DAAs therapy [12, 13, 21].

We discovered that patients treated with sofosbuvir/daclatasvir had a higher risk of HCC than those treated with sofosbuvir/velpatasvir that opposes the current literature, which claims that use of DAA reduces, or has no impact on development of hepatocellular carcinoma [22-24]. Moreover, one research concluded that sofosbuvir-only protocols with ribavirin were linked to a five-fold increase in HCV risk compared to other combos [25]. One meta-analysis of numerous studies found no evidence of a difference in HCC incidence between those who received DAAs and those who received interferon therapy [26].

Hepatocarcinogenesis linked to DAA has been documented. Yang et al. discovered that hepatocellular carcinoma relapsed sooner if participants received DAA's for HCV [27]. An elevated likelihood of HCC post DAA administration was found in those who had previously received many HCC treatments, according to another research investigation [28]. We discovered a higher incidence of HCC in CTP A participants, which contradicts previous research. Calvaruso et al. investigated the occurrence of hepatocellular carcinoma in participants with HCV-related hepatic cirrhotics managed with DAAs and discovered that hepatocellular carcinoma occurred in 2.1% of CTP A patients, 7.8 percent of CTP B patients, and 12.4 percent of CTP C patients [29]. Romano et al. also found an increased occurrence in participants with CTP B [30]. Because six percent of the participants in this research were in CTP C, therefore, the true prevalence cannot be estimated due to the study's tiny sample.

There were a couple significant limitations to our research. First, it used an observational design using a non-randomized methodology from a single hospital experience. Furthermore, this research had a tiny sample size and was restricted to a single region of the country. In terms of disease frequency, the findings may not be generalizable. Second, variables such as age, length of DAA therapy, tobacco use, and diabetes were kept in the study which may be important confounders. Furthermore, we only examined two DAA combinations available in Pakistan, limiting the generalizability of our findings to other DAA combos widely available worldwide. We were unable to collect genotypes in our patients due to a lack of resources. The use of successive sampling, which was appropriate for our study design, was one of our study's strengths. To the best of our knowledge, this was the first

study on the subject in South Asia, and we ruled out all potential HCC risk factors.

CONCLUSION

During the twenty-four week follow-up, HCV-related hepatic cirrhosis participants managed with DAAs had a higher chances of hepatocellular carcinoma, according to our findings. Participants who got a combo of sofosbuvir with daclatasvir were more likely to develop HCC. Additional bigger sample sizes and extended follow-up are needed to confirm these observations.

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