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Original Article

Hepatocellular Carcinoma (HCC) in HCV-Related Liver Cirrhosis After Sustained Viral Response (SVR)

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Abstract

Objective: Effectiveness of the direct-acting antivirals (DAAs) regarding the achievement of SVR post-treatment and its impact on the future occurrence of hepatocellular carcinoma (HCC) post-treatment of DAAs in Hepatitis C-related liver cirrhosis.

Methods: It was a cohort study that was done on 359 Hepatitis C patients who were given Ribavarin-Sofosfubuvir & Daclatasvir. We experienced 41.1% (158) lost follow-up. Only 86/201 (43.2%) completed follow-up. The study population was divided into two groups (SVR achieved vs didn't SVR achieve). Each group was further subdivided into two groups: developed HCC or did not develop HCC post-treatment of DAAs.

Results: 86 subjects who had median age of 50.6 ± 10.65 years who completed triple therapy regime and follow-up, were analyzed. The average follow-up period was 45 weeks (24-68 weeks). Out of 86 patients, 81 (94%) achieved SVR12 with triple therapy of Sofosbuvir-Daclasavir plus Ribavirin. Only 2(2.4%) patients out of 81 developed HCC after the achievement of SVR, while 3/5 (60%) of patients developed HCC who did not achieve SVR. The rate of achievement of SVR was quite lower in the group diagnosed with HCC than those who did not develop HCC post-treatment of DAAs (66.6% v 96.8%, p=0.023). HCC occurrence duration was 31-48 weeks after SVR achievement post-treatment of DAAs.

Conclusion: SVR achieved by Sofosbuvir-Daclasavir plus Ribavirin plus ribavirin decreases the occurrence of HCC but doesn't eliminate the chances of developing HCC (66.3 %- or 3.3 times lesser risk).

Keywords: Liver cirrhosis, sustained viral response, hepatocellular carcinoma (HCC)

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Introduction

There are more than 170 million patients in the world are suffering with Hepatitis C and relevant complications. Who says that about 3 to 5% of the world population has been infected with Hepatitis C.[1] According to WHO, there are as many as 10 million people suffering from chronic Hepatitis C in Pakistan. Given the extremely high prevalence of Hepatitis C in the Pakistani population, hepatitis eradication programs are at the government level to eliminate Hepatitis C by 2030.[2]

Main aim of chronic hepatitis C therapy is the elimination of the virus from the body and to gain SVR after 12 weeks of therapy. Conventionally, interferon especially peg-interferon alpha was most frequently used to eradicate Hepatitis C but their safety and efficacy were questionable. Also, they had an extremely large number of side effects including cytopenia, myalgias, headaches, and many others. In 2013, direct-acting antiviral regimens were introduced, especially sofosbuvir.[3] These antivirus has been approved to be highly effective in eradicating Hepatitis C with very fewer side effects and a wonderful safety profile. Sofosbuvir is a protease inhibitor that blocks the important protein synthesis required for the

transcription of the RNA of the Hepatitis C virus and inhibits the replication of the virus and effectively eliminates it from the body. These antivirals have been augmented in their action with Ribavarin, which is an immune modulatory drug that has been used in conjugation with each other. Also, Daclatsavir have same mechanism of action as being protease inhibitor of NS5A protein, and when used in conjugation with Sofosbuvir has shown to have sustained viral response as high as 99%.[4]

According to EASL Guidelines, the eradication therapy for Hepatitis C should be free of any interferons and this DAAs based therapy is currently the standard of care but some societies used to recommend the addition of Ribavirin to eradicate HCV virus. Patients with HCV genotype 1 or 4 which is quite prevalent in Pakistan, should be treated with two or more antivirals and have been proven to be highly effective in achieving SVR but we have very limited local data to determine their efficacy in either reducing the burden of hepatocellular carcinoma or modifying it in some other way.[5]

Achievement of SVR was speculated to bring down the HCV related complications in successfully treated patients i.e. those who achieve SVR post-treatment. In this cohort study, we evaluated the effectiveness of direct-acting antiviral-mediated SVR rate and its impact on future occurrence of hepatocellular carcinoma (HCC) post-treatment of DAAs in HCV-related liver cirrhosis.

Methods

This is a dual-center cohort study done at the PAQSJ Institute of Medical Sciences, Gambat, Pakistan and Lahore General Hospital, Lahore, Pakistan. In this study, medical reports and other health related records were studied to 359 subjects those met inclusion criteria. Their status was confirmed by quantitative HCV-RNA PCR and they have completed 12 weeks of triple therapy (Figure 01).

We excluded 172 patients who were non-cirrhotic. 86

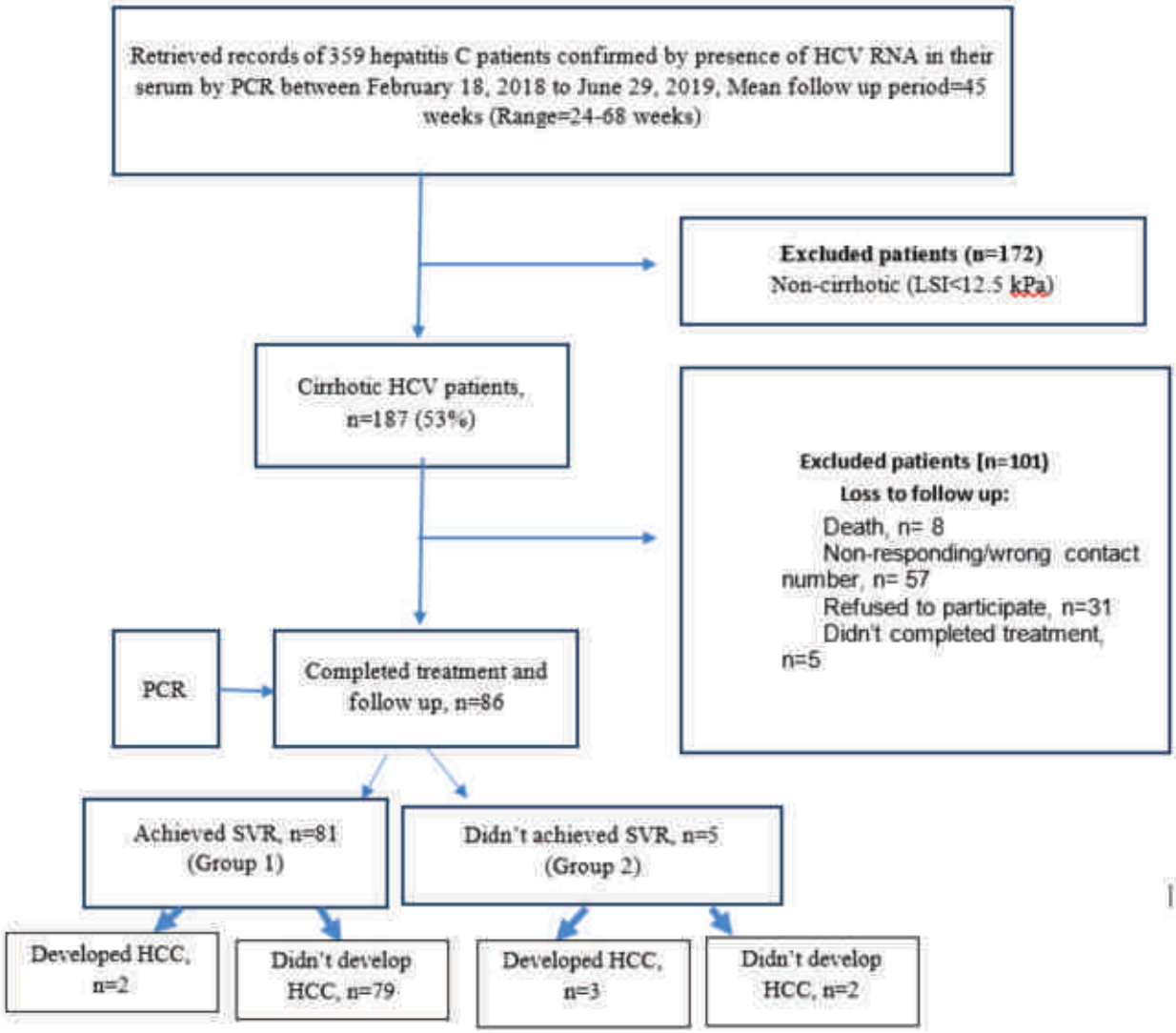

Figure 1. *Study Flow Diagram*

patients who completed the triple therapy regime and follow-up, were analyzed. Out of 86 patients, 81 (94%) achieved SVR12 with triple therapy of Sofosbuvir-Daclasavir plus Ribavirin. While five patients did not even complete therapy. The average follow-up period was 45 weeks (24-68 weeks). The patients were divided into groups, group 1: achieved SVR; group 2: did not achieve SVR.

On every 6 monthly follow-ups, these patients were advised to have an ultrasound abdomen and serum alpha-fetoprotein (AFP) done. When raised AFP with a suspected lesion on the USG abdomen was noted, a contrast-enhanced CT scan was performed to look for any lesion and characterize it radiologically. Based on the imaging reports, each group was subdivided into either "Developed HCC" or "Did not develop HCC". The study was approved by IRB board of PAQSJIMS (Ref./PAQSJIMS # 864). Informed and written consent was taken from the patients for the study.

Statistical analysis: SPSS version 25 was the software through which data refinement and analysis were performed. Dichotomous variables were compared Chi-square test while quantitative continuous variables were compared using an independent student T-test. We performed binary logistic regression analysis to predict the true odds of SVR as an independent predictor of HCC by controlling confounders like the history of smoking, and family history of hepatocellular carcinoma.

Results

86 patients who had median age of 50.6 ± 10.65 years who completed the triple therapy regime and follow-up, were analyzed. The average follow-up period was 45 weeks (24-68 weeks). Out of 86 patients, 81 (94%) achieved SVR12 with triple therapy of Sofosbuvir-Daclasavir plus Ribavirin. The average fibroscan score was 24.20+12.45. The population characteristics, demographics, and other clinical parameters of study population have been elaborated in Table 01. SVR was not achieved in 5 (5.81%) patients.

The SVR achievement rate was significantly associated with history of HCC in family ($p<0.05$), though rest of the patient-related parameters such as type of sex, history of smoking, diabetes mellitus, alcohol consumption, and history of Hepatitis B infection were not statistically significantly related to SVR achievement rate (Table 02). Getting SVR with direct-acting antivirals was statistically associated with serum albumin, serum total bilirubin and total serum platelet count ($p<0.05$) while it was not associated to rest of the lab parameters like PT, APTT, AST, and ALT ($P>0.05$) (Table 03).

Only 2(2.4%) out of 81 patients who achieved SVR developed HCC in our follow-up. In contrast, 3/5 (60%) of patients who did not achieve SVR developed HCC in our follow-up. The relationship between SVR status and the development of HCC was observed to be statistically significant, with $p<0.001$ (Table 04).

To predict the true odds of SVR status as an independent predictor of HCC by controlling confounders like family history of HCC, history of smoking, platelet count, total bilirubin, and albumin, we applied Binary Logistic Regression Analysis which concluded that those patients who did not achieve SVR have 3.28 times greater odds of developing HCC than those who achieve SVR in 1.5 years of follow up. Cox & Snell R Squared value suggested that those patients who achieved SVR

Table 1: *Descriptive statistics of study population (n=86)*

Variable	Mean	Std. Deviation
Age (years)	50.6279	10.65728
Height (cm)	156.6582	9.62753
Weight (kg)	61.2716	15.00917
FibroScan Score (kPa)	24.2035	12.45713
Hb (g/dL)	13.1347	4.12192
RBCs (*10^6 cells/mm^3)	4.9499	.84505
Hct	39.0567	6.88922
MCV (fl)	79.6789	7.39504
MCH(pg)	27.5986	9.17513
TLC (* 10^3 cells/mm^3)	8.2824	3.13760
Neutrophils (%cells/mm^3)	58.7794	13.14678
Lymphocytes (%cells/mm^3)	31.3154	10.69520
Monocytes (%cells/mm^3)	3.8270	2.94280
Platelets (× 10^{11} /unit)	184.3784	93.70161
PT (seconds)	16.9543	3.57564
APTT (seconds)	35.6842	8.11440
INR	1.2108	.30414
ALT (units/L)	97.2462	68.04296
AST (units/L)	87.4308	49.24840
ALP (units/L)	330.9885	166.37542
Total Bilirubin (mg/dL)	1.1508	.80161
Serum Albumin (g/dL)	3.5517	.88090

Abbreviations: Hb: Hemoglobin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, RBCs: Red blood cells, Hct: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular heamoglobin, TLC: Total lecukocyte count, PT: Prothrombin time, APTT: Activated partial prothrombin time, ALP: Alkaline phosphatase.

had 66.3% fewer chances of developing HCC than those who did not achieve SVR (Table 05).

Table 2: *Relationship of various patient related factors and achievement of SVR (n=86)*

	SVR achieved (n=81)	SVR not achieved (n=5)	*p value*
Gender			
Male (37)	36	1	0.35
Female (49)	45	4	
History of smoking			
Yes	27	3	0.337
No	54	2	
Diabetes		4	
Yes	34	1	0.165
No	47		
Alcohol Drinking		0	
Yes	3	5	0.231
No	78		
Hepatitis B Infection			
Yes	16	0	0.578
No	63	5	
Family History of HCV Related Hepatocellular carcinoma			0.012
Yes	2	2	
No	84	3	

Table 4: *Incidence of HCC in subgroups of study population (n=86)*

		Developed HCC		Total	p-value
		Yes	No		
SVR	Yes	2	79	81	
	No	3	2	5	0.001
Total		5	81	86	

Table 3: *Relationship of various disease related factors and achievement of SVR (n=86)*

	SVR	Mean	Std. Deviation	p value
RBCs	Yes	4.9598	.85349	0.648
(*10^6 cells/mm^3)	No	4.7300	.72746	
Platelets	Yes	190.0000	94.55499	0.0001
(× 10^{11} /unit)	No	106.8000	13.25519	
PT	Yes	17.0452	3.70676	0.582
(seconds)	No	16.0000	1.63299	
APTT	Yes	36.2353	8.22066	0.227
(seconds)	No	31.0000	6.00000	
INR	Yes	1.2143	.31047	0.776
	No	1.1500	.21213	
ALT	Yes	95.1667	67.98658	0.398
(units/L)	No	122.2000	71.11399	
AST	Yes	84.5833	48.75546	0.107
(units/L)	No	121.6000	46.51129	
ALP	Yes	325.9161	146.71304	0.706
(units/L)	No	387.8000	338.89851	
Total Bilirubin	Yes	1.0183	.66501	0.0001
(mg/dL)	No	2.7400	.58138	
Albumin	Yes	3.7260	.84056	0.013
(g/dL)	No	2.6800	.49699	

Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, RBCs: Red blood cells, ALP: Alkaline phosphatase,

Discussion

Main aim of chronic hepatitis C therapy is the elimination of the virus from the body and to gain SVR after 12 weeks of therapy. Conventionally, interferon especially peg-interferon alpha was most frequently used to eradicate Hepatitis C but their safety and efficacy were questionable. Literature from western world have demonstrated intimidating evidence regarding effectiveness of the direct-acting antivirals (DAAs) regarding the achievement of SVR post-treatment and its impact on the future occurrence of hepatocellular carcinoma (HCC) post-treatment of DAAs in Hepatitis C-related liver cirrhosis. As hepatitis C is a silent killer and it takes almost more than 20 years to develop liver cirrhosis and relevant complications that is most of the time is the first symptomatic presentation of the infection. It gives us the leerage to utilize this window period to curb this infection and eradicate virus before it does irreversible damage to the liver parenchyma.[6]

First, SVR rate with triple therapy was observed to be

Table 5: *Binary Logistic Regression Analysis for predicting true odds of SVR as an independent predictor of HCC by controlling confounders (n=86)*

		B	S.E.	Wald	df	Sig.	Exp(B)	Cox & Snell R Square
Step 1	Cont.	1.190	0.432	7.594	1	0.006	3.286	0.663

94% in our local population of hepatitis c with liver cirrhosis and our findings are concurrent with rest of the literature body published from India and some other centers in Pakistan.[7,8] Second, the SVR achievement rate was significantly associated with history of HCC in family, though rest of the patient-related parameters such as type of sex, history of smoking, diabetes mellitus, alcohol consumption, and Hepatitis B infection were not statistically significantly related to SVR achievement rate. Getting SVR with direct-acting antivirals was statistically associated with serum albumin, serum total bilirubin and total serum platelet count while it was not associated to rest of the lab parameters like PT, APTT, AST, and ALT and these findings were aligned with other published studies and established literature related to HCV-related liver cirrhosis and HCV-related HCC.[9-13]

Thirdly, our data from the Pakistani side indicate that SVR achievement is associated with 66.6% decreased chances of development of HCC in 1.5 years of follow-up. Still, it is not confirmed that SVR achievement is linked with the complete prevention of future HCC development in 1.5 years of follow-up post-treatment of DAAs. On the contrary, those who did not achieve SVR were 3 times more likely to develop viral hepatitis-induced HCC than those who achieved SVR. Similar findings have been reported by other studies.[14,15]

Fourthly, our data revealed the importance of follow-up of those cirrhotic patients who did not achieve SVR as those who did not achieve SVR are significantly more likely to develop viral hepatitis-induced HCC. So, we recommend that non-responders or relapsers should be treated aggressively, and strict follow-up should be maintained till and beyond the achievement of SVR to curb and manage any incident of HCC at early stages and effectively decrease morbidity and mortality associated with HCV and HCC prospectively.

Conclusion

1. SVR rate with triple therapy was observed to be 94% in our local population of hepatitis C with liver cirrhosis.
2. SVR achieved by new direct-acting antivirals (DAAs) plus ribavirin does decrease the occurrence of HCC but doesn't eliminate the chances of developing HCC.
3. HCV-infected patients who don't achieve SVR are at 66.3%- or 3.3 times greater risk of developing HCC than those who achieve SVR in 1.5 years of follow-up.
4. We suggest a close surveillance program for cirrhotic patients who do not achieve SVR in Pakistan.

Author's contribution: AH designed the study. SHA and AH collected and arranged data. HFU and MS compiled data. TKB, AH, UI, MU, MF, and MM contributed to the statistical analysis of data and writing manuscripts. AH provided supervision in the improvement of study design, data analysis, and manuscript writing.

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