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Pak J Med Res
Vol. 64, No. 3, 2025

Original Article

Biochemical and Demographic Factors Affecting Antiviral Treatment Failure in Hepatitis C Patients with Persistent Virologic Response Issues

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Abstract

Background: Worldwide, Hepatitis C virus (HCV) infection is a major public health concern. Twelve weeks following treatment completion, the persistent virologic response is known as SVR. The DAA (Direct-acting antiviral therapy) remains a challenge.
Objective: To determine the demographic and biochemical parameters responsible for the failure of antiviral therapy (sofosbuvir and daclatasvir) associated with hepatitis C sustained viral response.
Methods: This cross-sectional study is based on Electronic Medical records online through a portal provided by the Government of Punjab Pakistan between December 2023 and July 2024. Data of 50 Hepatitis C screened positive patients were registered after the approval from The University of Lahore's ethical review board. The Patients underwent biochemical Investigations and HCV RNA PCR. Patients were given three months of combined therapy of Daclatasvir 60 mg and Sofosbuvir 400 mg. Monthly follow-ups were taken and Sustained virology response (SVR12) was determined, whereby SVR is the sustained virologic response 12 weeks after completing treatment.
Results: Significant association has been found between DAA treatment and creatinine level, hemoglobin level and patient status. Demographically, mean age was 16.6±0.5 years, 19/50 (38.0%) were male and 31/50 (62.0%) were females. Concerning respondents, 66.0% were cured and 34.0% had a relapse. SVR was achieved in 66% cases. HCV patients responded well to a combined antiviral therapy.
Conclusion: A strong correlation existed between DAA treatment, patient status, hemoglobin level, and creatinine level. Combined antiviral therapy showed good results for achieving SVR rates.
Key words: Hepatitis C virus, DAA therapy, infection, daclatasvir, sofosbuvir.

Introduction

Despite widespread advocacy regarding the prevention of Hepatitis C and public health programs, the incidence of Hepatitis C is rising. HCV is a single-stranded RNA virus in the Flaviviridae family.[1] In adverse cases, HCV can cause permanent damage to the liver, including liver cirrhosis or hepatocellular carcinoma and sometimes even death.[2] The primary transmission route for HCV dissemination is exposure to contaminated blood products or blood, unsafe injection practices and occupational exposure.[3] Hepatitis C infection occurs all around the globe.[4,5] According to the WHO report, almost 3% of the total population of the world has been infected with hepatitis C and more than 180 million people are chronic carriers of HCV virus and at increased risk of developing hepatocellular carcinoma and liver cirrhosis.[4,5] Recently, the DAA use for HCV treatment has led to a significant improvement in the rates of SVR in patients with genotype 1 HCV infection.[6] However, it can lead to a resistant virus selection when DAA is used alone. The NS5A protein, the NS5B RNA-dependent RNA

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Received: 11 February 2025, **Accepted:** 09 September 2025
Published: 30 September 2025

Authors Contribution

SB & MM conceptualized the project. ML & SS did the data collection. MM* & FH did the literature search. SB & TM performed the statistical analysis. Drafting, revision & writing of manuscript were done by MM & MM*.

polymerase, and the NS3/4A protease are the three primary viral targets that are now the focus of HCV replication inhibition.[7] This rational combination have overcome the drug resistance challenge and improved the efficacy and safety profile with fewer adverse effect and drug-drug interaction.[8]

The government of Pakistan has started national and provincial hepatitis prevention and control initiatives, which include screening for and treating HCV-infected individuals. However, the frequency of HCV is higher in spite of all these measures.[9] However, data are lacking on the effectiveness of these interventions; therefore, our aim is to investigate the possible demographic and biochemical parameters responsible for the failure of antiviral therapy associated with hepatitis C sustained viral response.[9] In Pakistan, the first-line treatment has been changed to the new DAA comprises Daclatasvir and sofosbuvir with or without ribavirin. This has improved patient adherence and have a better safety profile.[10] Daclatasvir is an HCV NS5A replication complex inhibitor that is used in combination with sofosbuvir, with or without ribavirin. The 12-week regimen of sofosbuvir and daclatasvir in a patient with genotype 1 and 3 HCV infection has shown a high SVR, irrespective of prior treatment experience.[11]

The primary objective of this study is to identify the biochemical and demographic factors that contribute to the failure of antiviral treatment in relation to the sustained viral response in hepatitis C.

Methods

It was a cross-sectional study and Non-probability sampling technique was used to collect samples. The data of 50 Hepatitis C screened positive patients were registered on Electronic Medical records online through a portal provided by the Government of Punjab Pakistan between December 2023 and July 2024. Informed consent was taken from patients or patient attendants. Demographic data was taken on the questionnaire.

The study included patients 18 to 60 years of age who were Seropositive for HCV antibodies, HCV genotype 1 or 2 or 3 infections, patients with prior treatment and who will be confirmed failure during or after treatment with Daclatasvir and Sofosbuvir, patients having AST to Platelet ratio index (APRI) of ≤2, and who were diagnosed Cases of Chronic liver disease. Patients having chronic liver disease other than HCV infection, critically ill patients and those having co-infection with HIV or Hepatitis B virus were excluded from this study.

A total of 80 HCV patients were referred patients from Hospital OPD and were screened under supervision on Rapid Diagnostic Kits (RDT). Hepatitis C screened positive patients were registered on Electronic Medical records online through a Portal provided by the Government of Punjab Pakistan. The Patients underwent biochemical Investigations like Hemoglobin, Liver function tests, Renal function tests, PT, and APTT. The patient's sample for HCV RNA PCR was taken and sent to Government Punjab Head office Lab. Following the collection of PCR reports, the patients were given three (3) months of DAA (Direct Antiviral Agents) which will include Daclatasvir 60 mg and Sofosbuvir 400 mg. Monthly follow-ups was taken which include General body response and biochemical tests like CBC and LFT. PCR will be taken after three months of End Treatment response (SVR12).

The data was analyzed using Statistical package for social sciences (SPSS) version 23.0. Quantitative variables were expressed as mean ± standard error of the mean (S.E.M). The statistically significant value accepted with p <0.05. Relative results of all three groups were obtained and subject to t-test, and anova as per requirement.

Results

In this study, a data of 50 participants have been analysed. Frequency distribution of respondents regarding different demographic characteristics is given in Table-1. Mean age was 16.6±0.5 years. 17 (34.0%) respondents were of age less than or equal to 40 years, 18 (36.0%) were from 41 years to 50 years and 15 (30.0%) were of age greater than 50 years. Out of 50 respondents, 19 (38.0%) were male and 31 (62.0%) were females. Among respondents, 33 (66.0%) were cured and 17 (34.0%) were relapse. The SVR test showed that out of 50 patients, SVR was achieved in 66% cases.

Table 1: Frequency distribution of demographic variables.

Variables	*Categories*	*Frequency (%)*
Age group (years)	≤40	17 (34.0)
	41 – 50	18 (36.0)
	51+	15 (30.0)
Gender	Male	19 (38.0)
	Female	31 (62.0)
Patient Stage	Cured	33 (66.0)
	Relapse	17 (34.0)
Socio-economic Status	Low	37 (74.0)
	Middle	13 (26.0)
Marital status	Single	1 (2.0)
	Married	48 (96.0)
	Divorced	1 (2.0)
SVR	Not-Detected	33 (66.0)
	Detected	17 (34.0)

The association between SVR and demographic variables has been determined by using the Pearson Chi square test. No significant association has been found between age of the participant and SVR (p =0.198). This means that there is no effect of age in SVR detection. No significant relationship was found between SVR and gender of the patient (p =0.806). This shows that SVR (detected or not detected) and gender of the respondents were independent. Significant association has been found between SVR and patient status (<0.001). Overall, no significant relationships have been found between age, socioeconomic status, gender, marital status and SVR (Table-2).

Table 2: Association of SVR with different demographic variables.

Demographic Variables	*Categories*	*SVR*		*p value*
		Not Detected	*Detected*	
Age	<=40	13	4	0.198
	41-50	9	9	
	>50	11	4	
Gender	Male	14	5	0.369
	Female	19	12	
Patient Status	Cured	33	0	0.000
	Relapse	0	17	
Socioeconomic Status	Low	23	14	0.334
	Middle	10	3	
Marital Status	Single	1	0	0.585
	Married	31	17	
	Divorced	1	0	

Two sample T test was applied to check the difference between patients where SVR was detected or not detected. In 33 patients SVR was not detected and in 17 patients SVR was detected. With respect to urea in the patients, it can be concluded that the mean difference between SVR not-detected and SVR detected patients is non-significant. Hb value for patients where SVR was not-detected found higher. As p-value >0.05, therefore, we concluded that the PCR value in both groups was statistically non-significant (Table-3).

According to the study's findings, HCV patients responded effectively to combination therapy consisting of sofosbuvir and daclatasvir. Sixty-six percent of the participants in this trial had eradication of HCV successfully.

Discussion

Chronic hepatitis C infection is a major public health issue in Pakistan. It is one of the leading causes of mortality and morbidity associated with liver disease. It is believed that HCV-infected patients are more prone to failure of treatment. While the issue related to the efficacy of DAA treatment in HCV-infected patients has been explored extensively. Identifying the predictors of HCV treatment outcomes before the DAA treatment initiation is important in finding high-risk patients and alerting healthcare personnel to form a strategy to address treatment barriers. Identifying predictors of treatment outcomes help in reducing healthcare cost by preventing unnecessary retreatment and public health outcomes related to unattained SVR. A few studies only found the factors that affect the treatment outcome. In this study, 50 patients with genotype 1, 2 and 3 were enrolled and were treated with daclatasvir and sofosbuvir. The treatment duration was 12 weeks in treatment-experienced patients. The findings of this study reveal that sofosbuvir and Daclatasvir combination therapy worked well for HCV patients. In this study, 66% of patients have achieved successful HCV eradication. These findings are in accordance with the study carried out by Fontaine et al, in which a high SVR rate have been achieved in a patient given combination therapy of sofosbuvir and daclatasvir. In another study carried out in Egypt, more than 18000 patients suffering from HCV infection have achieved the SVR-12 rate of 95%.[12]

An important finding of this study is that host-related factors that affect treatment outcomes, such as gender, age, marital status, and socioeconomic status were significant in this study cohort. Regarding age, only a few previous studies have shown the association between age and SVR rates in DAA regimens. The similar findings have been found in a study in which albumin level, age and gender are independent factors with DAA treatment.[13] In some studies, very little association between age and SVR rates has been observed.[14] This study failed to determine any significant difference between SVR and AST, ALT, albumin level, urea, prothrombin time and APRI score. This is inconsistent with the findings of yet another study whereby a significant difference has been found between platelet counts and SVR.[15] This comes in the same line with previous studies but different from the findings in which no significant difference has been found between platelet count and SVR.[16]

The study shows that the sofosbuvir and daclatasvir combined therapy provided high rates of cure. This finding is consistent with the study conducted in which the DAA regimen proves to be effective with high cure rates and adverse effect with low incidence.[17] This finding is also in line with the study carried out by Pol et al. in which it is demonstrated that sofosbuvir and daclatasvir combination therapy had high antiviral potency.[18]

Table 3: Comparison between variables and SVR detected/not detected.

Demographic Variable	*Detected/Not Detected*	*N*	*Mean*	*SD*	*p-value*
Age	Not-Detected	33	43.70	9.48	0.634
	Detected	17	44.94	6.91	
Weight	Not-Detected	33	67.06	16.23	0.141
	Detected	17	74.47	17.23	
ALT	Not-Detected	33	74.18	40.79	0.473
	Detected	17	83.41	46.35	
AST	Not-Detected	33	89.12	52.58	0.093
	Detected	17	64.53	37.39	
Albumin	Not-Detected	33	3.41	0.87	0.085
	Detected	17	3.81	0.51	
Urea	Not-Detected	33	38.58	14.07	0.224
	Detected	17	33.94	9.00	
Creatinine	Not-Detected	33	0.65	0.38	0.031
	Detected	17	0.95	0.55	
Prothrombin time	Not-Detected	33	11.99	0.83	0.428
	Detected	17	11.81	0.70	
Hb	Not-Detected	33	11.68	2.01	0.039
	Detected	17	10.39	2.10	
PLT	Not-Detected	33	262.94	88.43	0.000
	Detected	17	149.65	51.08	
APRI Score	Not-Detected	33	1.25	1.00	0.506
	Detected	17	1.44	0.82	
Diagnostic PCR (IU/ML)	Not-Detected	33	856775	1043022	0.394
	Detected	17	1248320	2188653	

The finding shows that a significant difference is found between creatinine and SVR. Previous studies also show that creatinine levels are significantly lower in individuals who show treatment failure. This finding is consistent with the previous studies' findings that haemoglobin is an important predictor of DAA regimen.[22] For example, in one retrospective study carried out on 152 patients with HCV infection, almost 15% experienced anemia.[19] The findings have shown that Hb level before the treatment of DAA has no impact on virologic response but is associated with increased serum creatinine.[23] The finding of this study shows no significant difference between albumin level and SVR rate. This finding is not in line with the previous studies in which it was found that higher albumin is related to the achievement of SVR.[20] Another important finding of this study is that Sofosbuvir and daclatasvir combination therapy has found to be effective in patients with genotype 3 HCV infection.[21]

There were few limitations to this research study. First, this study uses the secondary data from the hospital department, and thus, not all variables were available for analysis. Another limitation of this study is the small sample size. More comprehensive data should be obtained for in depth mechanism and making clear interpretation regarding the current association.

Conclusion

Age, gender, marital status and socioeconomic status have been found to be independent factors in achieving SVR rate. The combined daclatasvir and sofosbuvir regimen are recommended in treating genotype 1, 2 and 3 HCV-infected patients. Based on the findings of this study, combined sofosbuvir and daclatasvir treatment found to have favorable outcomes of achieving SVR rates in patients with chronic HCV infection.

Funding: None.

Availability of Data: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval: The ethical review board of University of Lahore's approved the study via letter no. IMBB/BBBC/22/11.

Conflict of Interest: None declared

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