Direct-acting antiviral agents in the treatment of chronic Hepatitis C – Real-life experience from clinical practices in Pakistan

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Saima Mushtaq
National University of Sciences and Technology

Atika Mansoor
Institute of Biomedical and Genetic Engineering

Saima Siddiqi
Institute of Biomedical and Genetic Engineering

Amjad Khan
Quaid-i-Azam University

Sobia Manzoor
National University of Sciences and Technology

lcianunique@yahoo.com

Corresponding Author

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Abstract
Background: This study aims to evaluate the clinical effectiveness in terms of sustained virological response (SVR), predictors of SVR and safety of available second generation generic direct-acting antivirals in Pakistani chronic Hepatitis C patients.

Methods: This is a retrospective study conducted in multiple centers of Pakistan from January 2015 to January 2019. The samples include patients infected with chronic hepatitis C virus, regardless of virus genotype, cirrhosis, or prior treatment. Statistical analysis was performed to compare the effectiveness among the direct-acting antiviral agents (DAAs) based treatments and also to reveal the factors influencing the achievement of SVR.

Results: A total of 993 patients were included in the present study, with the majority receiving sofosbuvir with daclatasvir (95%), sofosbuvir with daclatasvir and ribavirin (4%) and sofosbuvir with ribavirin (1%). There were 96% cases of chronic hepatitis, 3% cases compensated cirrhosis and 1% cases of decompensated cirrhosis. Genotype 3 (99.6%) was the most common genotype. Overall SVR after 12 weeks was 98% for all treatment regimens. High SVR12 was observed with sofosbuvir in combination with daclatasvir (98.5%), then sofosbuvir in combination with daclatasvir and ribavirin (90.2%) and sofosbuvir in combination with ribavirin (75%). SVR rates were high in CHC patients (98.2%) as compared to cirrhotic patients (92.1%) and it was high in treatment naive (98.8%) then IFN experienced patients (90.1%). In multivariate binary logistic regression analysis, patients’ education status, treatment strategy, viral load and ALT had statistically significant association with SVR at 12 weeks. No major adverse events occurred which required treatment discontinuation.

Conclusion: Generic oral DAAs (sofosbuvir with daclatasvir) achieved higher SVR12 rates and were well tolerated in this large real-world cohort of genotype 3 infected patients.

Introduction
Chronic hepatitis C virus (HCV) infection is the main cause of liver pathologies and hepatocellular carcinoma (HCC) worldwide (1). Globally, 71 million people infected with chronic hepatitis C (CHC) infection, with estimated 3.5–5 million die annually (2). According to recent estimates Pakistan has the second-largest HCV burden in the world, with of 4.5–8.2% HCV sero-prevalence (3, 4). Out of the
seven major HCV genotypes (5), the majority of HCV infections in Pakistan are GT3a (69.1%), followed by GT1 (7.1%), 2 (4.2%), and 4 (2.2%) (4, 6). In Pakistan, HCV is transmitted by many risk factors, such as health care practices i.e. injections and blood transfusion in health care professionals (27-42.3%) and in the general population (7.8-68%), community-based activities i.e. ear and nose piercing, barbering, and injecting drug use (4, 7, 8).

Before the introduction of DAAs, the HCV treatment was interferon (IFN)-based that had many side effects i.e. poorly tolerated and low SVR rate (50%) (9). Inspite of “Chief Minister’s Program for Hepatitis B and C Control in Pakistan”, the IFN-based treatment was only effective in 67%-74% of the infected population (10, 11).

Hepatitis C treatment has been transformed by the development of DAAs. HCV replication cycle is inhibited by these drugs mainly interfering with the activity of non-structural proteins of HCV (12). Three drug classes (inhibitors of the NS3/NS4A protease, inhibitors of the NS5A complex and inhibitors of the NS5B polymerase) have been developed and approved by the FDA. Combinations of two or more drugs from three classes achieve high (> 90%) SVR rates and are well tolerated (12).

In Pakistan, the treatment for CHC infection is changing to the new DAAs. Since November 2014, sofosbuvir and ribavirin was the registered and widely available DAAs in Pakistan (13, 14). Sofosbuvir (SOF) inhibits the NS5B region of HCV which encodes RNA-dependent RNA polymerase enzyme for viral replication. SOF has pangenotypic action with less side effects as compare to IFN-based therapy (15). Pakistan is among the high-burden countries for HCV where majority of the HCV infected population fall in lower income category. They are unable to buy high priced branded SOF for their treatment. Therefore, the government of Pakistan and the pharmaceutical companies started manufacturing SOF generics at a low prices to control the HCV prevalence (16).

The inclusion of SOF-based DAAs in the “National Guidelines for HCV Treatment in Pakistan” has increased its use by clinicians. Recently, Daclatasvir (DCV; HCV NS5A replication complex inhibitor) new DAAs are also available in Pakistan and added in the national treatment program with combination of SOF against GT3. Such additions will certainly offer better safety profile with improving patient compliance to treatment (15, 17).
However, these DAAs are designed on the bases of proteins structure of GT1HCV. Also, the registration trials for these drugs contained few patients infected with GT3HCV, which is highly prevalent in Pakistan. This raises a concern about the effectiveness of these drugs on Pakistani patients. Given the limited data on treatment of chronic GT3 HCV infection with DAAs and the above concerns, this study was conducted to gather data on the antiviral efficacy of generic DAAs with respect to treatment outcome in chronic HCV Pakistani patients. The predictors of SVR at 12 weeks and safety profile of DAAs were also determined in this cohort.

Materials And Methods

Study design

This was a retrospective cohort study of 1200 CHC patients, who were treated with different sofosbuvir based DAAs between January 2015 to January 2019. The patient records were collected from Centre for Liver and Digestive Diseases, Holyfamily Hospital, Rawalpindi and outdoor patient department of General Teaching Hospital, Islamabad. Both hospitals are tertiary care hospitals. Out of 1200 patients, 993 patients completed the therapy while 207 patients were lost of follow-ups and missing data. The ethical committee of Holyfamily hospital, Institute of Biomedical and Genetic Engineering and National University of Science and Technology approved this study. Those CHC patients which are having (≥18 years) of age and concluded or make withdrawal of second generation DAA treatment before January 2019 were included in this study. Patients were included in this cohort regardless of comorbidities, co-infection, liver cirrhosis, prior treatment or genotype. Treatment and management of patients at study centers were as per national guidelines. Treatment Naive or Interferon experienced patients were offered generic sofosbuvir 400 mg and daclatasvir 60 mg once daily for 12 weeks. Ribavirin 1000 mg (in patients < 75 kg) or 1200 mg (in patients > 75 kg) was added to the regimen (Fig.1).

Study assessments

Pretreatment baseline demographics, laboratory findings, baseline Hepatitis C virus viral load, treatment efficacy at 12–24 weeks, different DAAs combination, prior treatment experience and comorbidities were recorded. For the determination of cirrhosis status, some non-invasive measures were used like Fibroscan, ultrasound and child class before the initiation of therapy. Pretreatment PCR
≥ 80000 IU mL−1 was considered as high viral load whereas PCR < 80000 IU mL−1 was considered as low viral load (18).

Treatment response was assessed with HCV RNA viral load (IU/ml) at 4 weeks after initiation of treatment (RVR; defined as undetectable HCV RNA after four weeks of therapy), at the end of treatment (EOTr; defined as undetectable HCV RNA at treatment completion), and 12 weeks after completion of treatment (SVR12; defined as undetectable viral load at 12 weeks after the end of treatment). Tests were performed using Artus HCV RT-PCR Kit (Qiagen) or Hepatitis C Viral RNA Quantitative/Qualitative Fluorescence Diagnostic Kit (PCR Fluorescence Probing) by Sansure Biotech. The lower limit of detection of HCV RNA was 34 IU/ml Artus HCV RT-PCR Kit and 50 IU/ml for Sansure Biotech kit. Patients that completed the therapy but did not have any SVR results (i.e., missing data or lost to follow up) were excluded from the analysis.

Statistical analysis
Statistical Package for Social Sciences (SPSS) version 21 was used for the analysis of data. One-way ANOVA was used for the calculation of means and standard deviations of continuous variables. Categorical data is presented in the form of frequencies and percentages. For observing significance between categorical variables, we used a chi-squared test. Relevant variables with a p-value < 0.25 in the univariate analysis were included in the multivariate analysis (19). For obtaining a final model, Multivariate logistic regression analysis with the Wald statistical criteria was considered and used. A p-value of < 0.05 was considered statistically significant. Correlations assessed among those variables which were included in multivariate analysis. The results of multivariate analysis were presented as P-value, adjusted odds ratio and 95% confidence interval. The fit of the model was assessed by Hosmer Lemeshow and overall classification percentage.

Results
Characteristics of patients at baseline
Demographic and clinical characteristics of patients at baseline are shown in Table 1. Mean age of the cohort was 45.6 ranging from 18 to 90 years with females in majority than males (55%). Comorbidities at baseline included diabetes (26.1%), hypertension (11.5%), chronic kidney disease (6.3%), ischemic heart disease (4.3%), HIV (0.4%) and HBV (1.8%). Significant differences were
observed in age groups (p-value = 0.054), gender (p-value = 0.016), ethnicity (p-value = 0.004) and HCV genotype (p-value = <0.001). Socioeconomic status with lower and middle classes more affected than the upper class (p-value = 0.030), marital status (p-value = <0.001), diabetes mellitus (p-value = 0.013), viral load (p-value = 0.051), AST (p-value = 0.012) and ALT (p-value = 0.015) also showed significant differences.

Treatment regimens
Among the 993 patients with chronic HCV infection, 944 (95.1%) patients were in SOF+DCV group, 41(4.1%) patients in SOF+DCV+RBV group, and 8 (28.1%) patients in SOF+RBV group (Fig 1).

Treatment response and SVR predictors
The overall SVR12 was 98% (973/993). In univariate analysis, it was identified that patients who achieved SVR12 when compared with those who did not achieve SVR12 showed statistically significant differences at various parameters. These included relationship in age, socioeconomic status, education, race, marital status, hypertension, cirrhosis, child-Pugh score, treatment given, RVR, ETR, prior treatment, viral load, AST and ALT. However, in multivariate binary logistic regression analysis, patients’ education status, treatment, viral load and ALT had statistically significant association with sustained viral response at 12 weeks (SVR12). Educated patients were more likely to achieve SVR than non-educated as shown in table 2. Furthermore, combination therapy to achieved SVR 12 (Sofosbuvir + daclatasvir) showed significant results compared to other treatment regimens (OR = 31.23, 95% CI: 2.179-447.813, p-value = 0.011). Similarly, patients with lower viral loads, that is less than 800,000 IU mL$^{-1}$ showed good response to treatment as compared to higher viral loads (SVR12 OR = 20.31 95%CI: 1.549-266.519, p-value = 0.022). Higher ALT levels were also less likely to achieve SVR12 (OR = 0.093, 95%CI: 0.014-0.611, p-value: 0.013). This model fit was based on non-significant Hosmer Lemeshow test (p-value = 1) and an overall classification percentage of 98.7% from the classification table. SVR12 was not affected by HIV or HBV status, the presence of comorbidities, cirrhosis or previous treatment (Table 2).

Comparison of different treatment regimens
In Sofosbuvir+Daclatasvir group, 98.5% patients achieved SVR. In multivariate binary logistic regression analysis, education status (OR = 42.037, 95%CI = 1.596-1107.522, p-value = 0.025) and
elevated ALT (OR = 0.003, 95% CI = 0.000–0.252, p-value = 0.010) had statistically significant association with SVR12 (Table 3).

**Sofosbuvir + Daclatasvir + Ribavirin group** achieved 90.2% SVR rate as depicted in Table (Supplementary file). Presence of cirrhosis, prior treatment experience, elevated liver enzymes and other comorbid conditions did not exhibit significant association with SVR12 in multivariate binary logistic regression analysis. However viral load, employment and education status were significant factors in univariate analysis but not in multivariate analysis.

**Sofosbuvir + Ribavirin group** overall SVR 12 rate was reported as 75% as shown in Table (Supplementary file). In this group, no significant association was observed between SVR12 and any variable in multivariate analysis.

**Rates of sustained virological response in chronic and cirrhotic HCV patients**
The SVR rates were higher in chronic HCV patients (98.2%) as compare to cirrhotic patients (CC = 93.8%, DC = 83%). Sofosbuvir in combination with ribavirin was not as effective as the other combinations in chronic HCV patients with SVR rate 75%. However, only decompensated cirrhosis was difficult to treat group achieving 83% SVR rates than the rest of the patient groups. A highest SVR rate in all patient groups was achieved by sofosbuvir and daclatasvir combination (Table 4).

**Adverse events reported by treatment regimen**
Table 5 describes the association between treatment regimens and adverse events (AEs) reported during the study. Statistically significant association was observed between treatment regimens and skin rash (43.8%), Insomnia (33%), Oral ulcers (30.2%) and fatigue (16.6%).

**Discussion**

Development of direct acting antiviral agents (DAAs) is the landmark in treatment of HCV infection. This Interferon-free treatment provides high SVR rates and tends to prevent liver disease progression. Availability of DAA regimens replaced interferon treatment for HCV therapy across the globe (12). A notable decline was observed in the prices of DAAs by the DAAs generics availability in 101 developing countries (20), but scientific assessment is required for the efficacy of these generics. However, to design and to implement strategies regarding the treatment of HCV on large scale, it is necessary to review the existing experience with DAAs in Pakistani population.
In the current study, we reported the effects of DAA-based regimens for the treatment of chronic hepatitis C infection. We observed 989/993 HCV patients of GT3. The clinical effectiveness (SVR12) of SOF+DCV (±RBV) was 98%. These findings are comparable with Indian study where SVR12 rate was 96% in GT3 by DCV+SOF (±) RBV (21). Belperio et al. reported 94.5% SVR12 with SOF+DCV and 88.1% SVR12 with DCV + SOF + RBV combination (22), However, we noticed little higher SVR12 rates i.e. 98.8% in SOF+DCV group and 90.2% in DCV + SOF + RBV group. Our study found similar SVR12 rates as reported in other studies (21, 23–25).

In the current study, we observed 75% SVR12 rate in CHC patients with SOF + RBV, which is in agreement to the results of the study conducted by Jacobson et al. where they reported 78% sustained virologic response with SOF + RBV (26). This shows only SOF is less effective than other combinational therapies. Thus, a longer period of therapy is required to remove remaining viral reservoirs or the addition of other DAAs to the treatment.

In the current study, SVR12 was very high in treatment-naive patients (99%) as compare to treatment-experienced (90%). These findings are comparable with a study conducted by Nelson and colleagues where SVR12 rates were 90% and 86% in treatment-naive and treatment-experienced patients with SOF+DCV and an overall SVR rate was 96% which is almost similar to our findings (24).

The stage of disease like presence or absence of cirrhosis influence on SVR rate is also very important. We observed lower effectiveness of SOF+DCV in patients with cirrhosis (92% SVR12) as compared to non-cirrhotic patients (98% SVR12). In compliance to our study findings, SVR12 rates greater than 90% in cirrhotic patients was reported in respective studies conducted elsewhere (21, 23–25, 27, 28).

Cure rates above 90% have been reported using different combinations of all-oral DAAs in CHC patients treated in several clinical trials (29, 30). Initial real-world results support these findings but the efficacy tends to be lower mainly due to predictors of lower SVR rate in registration trials.

Furthermore doctor’s limited expertise using these new DAAs led to the impairment of their success (29–36).

Given the high SVR rates with DAAs, treatment failure studies is comparatively low and largely
influenced by treatment strategies explored and drugs combination (35, 37, 38). Furthermore, predictors of SVR rates are not uniform in different trials making it difficult to make comparisons. Baseline variables associated with a lower SVR rate include the presence of natural polymorphisms at the viral non-structural genes that reduce drug susceptibility, infection with HCV GT1 and GT3, liver cirrhosis, prior treatment experience and elevated viral load (5, 37, 38).

In the current study, we observed patients’ education status, treatment strategy, viral load and elevated ALT as predictors of SVR12. Educated patients achieved higher rate of SVR12 than with no education. As during therapy, recurrent missing doses or premature drug cessation by uneducated people can lead to adverse events and treatment failure. Limited information is available to explain this finding.

Furthermore, those patients who were treated with SOF+DCV significantly achieved higher SVR12 (p = 0.011) than those who were treated with other treatments like SOF+DCV+RBV and SOF + RBV. Studies conducted so far did not find this correlation neither as a predictor of SVR12. Patients with viral load <800,000 IU mL−1 significantly achieved higher SVR12 (p = 0.022) then viral load ≥800,000 IU mL−1. These findings are comparable with Brazilian study (18) and Lourianne study (15). The negative predictor of SVR was elevated alanine transaminase (ALT) level. Those patients who had elevated ALT levels were less likely to achieved higher SVR12 (p = 0.013). Our findings are supported by a study conducted by Huynh et al. (39).

As the treatment with generic DAAs is safe and effective alternative towards the elimination of HCV (40). The safety profile of these generic DAAs in our study was well tolerated. The most common AEs were skin rash, Insomnia, oral ulcers and fatigue which is comparable with a study findings conducted by Leroy et al. where fatigue and insomnia were major side effects. (41). In our study apart from these major AEs, patient also complained of skin rash (43.8%) and Oral ulcers (30.2%). A study from Egypt reported skin rash up to 9.8% of the patients using generic sofosbuvir and daclatasvir (20). Oral ulcers have been found 8.8% with this combination in Pakistani population (42).

Conclusions
The findings of the current study confirmed that second generation generic DAAs (sofosbuvir with
daclatasvir) are highly effective for CHC patients treatment in Pakistan, particularly for genotype 3. Current SVR rates with sofosbuvir based DAAs were higher as compared with previous therapies. Host factors like education level, treatment strategy, viral load and Alanine aminotransferase (ALT) were seemed to be the predictors of SVR rate. The safety profile of these DAAs was well tolerated and safe. A large multi-center prospective study is recommended to confirm the present findings.

**Study limitations**
This study was limited to only three months follow-up. A multicenter study with longer follow-up of six months is recommended. Furthermore, only host factors being assessed in this study, the viral factors (resistance associated substitutions; RAS) need to be assessed for the efficacy of the therapeutic regimens.

**Abbreviations**
DAA, Direct Acting Antivirals; SOF, Sofosbuvir; DCV, Daclatasvir; RBV, Ribavirin; BMI: Body mass index; HCV, Hepatitis C virus; DM, Diabetes Mellitus; HTN, Hypertension; CKD, Chronic kidney disease; IHD, Ischemic heart disease; HIV, Human immunodeficiency viruses; HBV, Hepatitis B virus; RVR, Rapid virological response; ETR, End-of-treatment response; SVR, Sustained virological response; IFN, Interferon; HB, Hemoglobin; WBCs, White blood cells; PLT, Platelets; TBR, Total bilirubin; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

**Declarations**

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**Availability of data and materials**
All data generated or analyzed during this study are included in this current article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors’ contributions**
SM conceived and designed this study under guidance and supervision of SM. AK and SM made
substantial contributions to the acquisition and analysis of the data. SM drafted the manuscript and AM, SS, and SM were involved in critical revision for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the ethical review board of Rawalpindi Medical University, Holyfamily, Institute of Biomedical and Genetic Engineering and National University of Science and Technology (IRB–130). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication
Not applicable.

Informed consent
Informed consent was obtained from all individual participants included in the study.

Competing interests
The authors declare that they have no competing interests.

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Tables

Table 1: Demographic and clinical characteristics of patients at baseline with treatment regimens

| Treatment regimens | Total (n = 993) | P value |
|--------------------|----------------|---------|
| SOF + DCV 12W (n = 944) | 45.57(18-90) | 0.288 |
| SOF + DCV + RBV 12W (n = 41) | 45.44(19-75) |
| SOF + RBV 12W (n = 8) | 52.63(33-62) |
| Total (n = 993) | 45.62(18-90) |
| P value | 0.054 |
| rs | 875 (88%) |
| 832 (88.1%) | 118 (12%) |
| 38 (92.7%) | 3 (3.7%) |
| 5 (62.5%) | 118 (12%) |
| 523 (88%) | 118 (12%) |
| 10 (2.2%) | 3 (3.7%) |
| 31 (75.6%) | 448 (45%) |
| 511 (54.1%) | 545 (55%) |
| 31 (75.6%) | 545 (55%) |
| 59.22 (12.2-124) | 153.06 (32-182) |
| 59.55 (12.2-124) | 25.18 (2-51.6) |
| 25.05 (2-51.6) | 27.96 (19.71-38.86) |
| 604 (60.8%) | 314 (31.6%) |
| 581 (61.5%) | 32 (1.3%) |
| 19 (46.3%) | 1 (12.5%) |
| Status          | 42(4.4%) | 5(12.2%) | 2(25.0%) | 49(4.9%) |
|-----------------|---------|---------|---------|---------|
| 25(2.6%)        | -       | -       | 1(12.5%)| 26(2.6%)|
| 1(0.1%)         | 1(2.4%) | 1(12.5%)| -       | 2(0.2%) |
| 1(0.1%)         | 40(97.6%)| 7(87.5%)| 989(99.6%)|
| 942(99.8%)      | -       | -       | -       | -       |

<0.001

| tatus           | 391(41.4%)| 26(63.4%)| 15(36.6%)| 553(58.6%)|
|-----------------|-----------|---------|---------|-----------|
| 25(2.6%)        | 1(0.1%)   | -       | 1(12.5%)| -         |
| 1(0.1%)         | 40(97.6%)| 7(87.5%)| 989(99.6%)|
| 942(99.8%)      | -       | -       | -       | -       |

0.809

| Status          | 307(32.5%)| 17(41.5%)| 15(36.6%)| 478(50.6%)|
|-----------------|-----------|---------|---------|-----------|
| 159(16.8%)      | 9(22%)    | -       | 1(12.5%)| -         |
| 17(41.5%)       | 4(50%)    | 4(50%)  | 324(32.6%)|
| 15(36.6%)       | -       | -       | 497(50.1%)|
| 9(22%)          | -       | -       | 172(17.3%)|

0.030

| Status          | 203(21.5%)| 10(24.4%)| 15(34.1%)| 478(50.6%)|
|-----------------|-----------|---------|---------|-----------|
| 291(30.8%)      | 13(31.7%)| 3(7.3%) | -       | 60(6.4%)  |
| 17(41.5%)       | 4(50%)    | 4(50%)  | 324(32.6%)|
| 15(34.1%)       | 4(50%)   | 4(50%)  | 497(50.1%)|
| 9(22%)          | -       | -       | 172(17.3%)|

0.153

| Status          | 383(40.6%)| 24(58.5%)| 3(7.3%) | 561(59.4%)|
|-----------------|-----------|---------|---------|-----------|
| 38(3.3%)        | 4(9.8%)   | 1(12.5%)| -       | -         |
| 3(7.3%)         | 4(9.8%)   | -       | -       | -         |
| 24(58.5%)       | 3(7.3%)  | 1(12.5%)| -       | -         |
| 17(41.5%)       | 3(7.3%)  | 1(12.5%)| -       | -         |

<0.001

| Status          | 255(27.0%)| 3(7.3%) | 2(25.0%)| 563(59.6%)|
|-----------------|-----------|---------|---------|-----------|
| 110(11.7%)      | 4(9.8%)   | 1(12.5%)| -       | -         |
| 61(6.5%)        | 1(2.4%)   | 1(12.5%)| -       | -         |
| 39(4.1%)        | 4(9.8%)   | -       | -       | -         |
| 4(0.4%)         | -       | -       | -       | -         |
| 18(1.7%)        | -       | -       | -       | -         |

0.013

| Status          | 906(96%)  | 41(100%)| 3(7.3%) | 38(4%)|
|-----------------|----------|---------|---------|------|
| 38(4%)          | -       | -       | -       | -    |
| 41(100%)        | -       | -       | -       | -    |
| 8(100%)         | -       | -       | -       | -    |
| 955(96%)        | -       | -       | -       | -    |

0.359

| Status          | 938(99.4%)| 41(100%)| 3(7.3%) | 6(0.6%)|
|-----------------|---------|---------|---------|------|
| 938(99.4%)      | -       | -       | -       | -    |
| 41(100%)        | -       | -       | -       | -    |
| 32(78%)         | -       | -       | -       | -    |
| 828(87.7%)      | -       | -       | -       | -    |

0.548

| Status          | 116(12.3%)| 9(22%) | 3(7.3%) | 913(96.7%)|
|-----------------|---------|-------|---------|-----------|
| 828(87.7%)      | 32(78%) | 4(50%)| 957(96%)|
| 9(22%)          | 4(50%)  | 3(7.3%)| 957(96%)|
| 3(7.3%)         | 1(2.4%) | 1(2.4%)| 36(4%)  |
| 38(92.7%)       | 38(92.7%)| 2(25%)| 36(4%)  |

0.001

| Status          | 31(3.3%) | 2(25%) | 4(9.8%) | 930(98.5%)|
|-----------------|---------|-------|---------|-----------|
| 913(96.7%)      | 38(92.7%)| 6(75%)| 973(98%)|
| 31(3.3%)        | 3(7.3%) | 2(25%)| 973(98%)|
| 2(25%)          | 2(25%)  | 4(9.8%)| 902(91%)|
| 4(9.8%)         | 2(25%)  | 37(90.2%)| 91(9%)|

<0.001

| Status          | 20(2%)  | 3(37.5%)| 14(1.5%)| 864(91.5%)|
|-----------------|--------|--------|--------|-----------|
| 930(98.5%)      | 37(90.2%)| 6(75%)| 973(98%)|
| 80(8.5%)        | 8(19.5%)| 5(62.5%)| 902(91%)|
| 14(1.5%)        | 2(25%) | 4(9.8%)| 91(9%) |
| 1(0.1%)         | 1(2.4%)| 1(12.5%)| -         |

0.001

| Status          | 2(25%)  | 3(37.5%)| 864(91.5%)| 80(8.5%)|
|-----------------|--------|--------|-----------|--------|
| 913(96.7%)      | 38(92.7%)| 6(75%)| 973(98%)|
| 31(3.3%)        | 3(7.3%) | 2(25%)| 973(98%)|
| 31(3.3%)        | 3(7.3%) | 2(25%)| 902(91%)|
| 1(0.1%)         | 1(2.4%)| 1(12.5%)| -         |

0.051
Table 2. Demographic and clinical characteristics of patients at baseline by treatment response

| Variables               | SVR12 (No. %) | Univariate analysis | P-value | Multivariate analysis |
|-------------------------|---------------|---------------------|---------|-----------------------|
|                         | Yes           | No                  | OR (95% CI) |                        | OR (95% CI) |
| **Gender**              |               |                     |          |                       |             |
| Male                    | 440 (98.2)    | 8 (1.8)             | Reference | 1.238 (0.502-3.056)    |              |
| Female                  | 553 (97.8)    | 12 (2.2)            |          |                       | NA          |
| **Age (years)**         |               |                     |          |                       |             |
| 18-60                   | 862 (98.5)    | 13 (1.5)            | Reference | 4.182 (1.634-10.703)   | 0.003       |
| >60                     | 111 (94.1)    | 7 (5.9)             |          |                       | Reference   | 1.420 (0.112-18.1) |
| **HCV Genotype**        |               |                     |          |                       |             |
| 1                       | 2 (100)       | -                   | Non-computable |                       | Reference |
| 2                       | 2 (100)       | -                   |          |                       | Reference   | 2.441 (0.271-21.1) |
| 3                       | 969 (98)      | 20 (2)              |          |                       | Reference   | 36.425 (1.487-892.175) |
| **Socioeconomic Status**|               |                     |          |                       |             |
| Low                     | 319 (98.5)    | 5 (1.5)             | Reference |                       | Reference   | 0.296 (0.022-3.219) |
| Middle                  | 489 (98.4)    | 8 (1.6)             | 1.044 (0.338-3.219) | 0.941      | 0.224 (0.016-3.1 |
| High                    | 165 (95.9)    | 7 (4.1)             | 2.707 (0.846-8.659) | 0.093      | 0.576 (0.037-8.5) |
| **Education**           |               |                     |          |                       |             |
| No                      | 205 (94)      | 13 (6)              | Reference |                       | Reference   | 36.425 (1.487-892.175) |
| Primary                 | 404 (99.5)    | 2 (0.5)             | 0.078 (0.017-0.349) | 0.001      | 0.224 (0.016-3.1 |
| Secondary               | 303 (99.3)    | 2 (0.7)             | 0.104 (0.023-0.466) | 0.003      | 12.268 (1.237-121 |
| Tertiary                | 61 (95.3)     | 3 (4.7)             | 0.776 (0.214-2.810) | 0.699      | 0.576 (0.037-8.5 |
| **Race**                |               |                     |          |                       |             |
| Punjabi                 | 595 (98.2)    | 9 (1.8)             | Reference |                       | Reference   | 2.441 (0.271-21.1) |
| Pathan                  | 310 (99)      | 4 (1)               | 0.853 (0.261-2.792) | 0.793      | Reference   | 2.441 (0.271-21.1) |

Data are presented as mean (range) or n (%). P-value for continuous variables is calculated by one-way ANOVA, p-value for categorical variables is calculated by Pearson chi-square test by comparing three groups. Abbreviations: DAA, direct acting antivirals; SOF, Sofosbuvir; DCV, daclatasvir; RBV, ribavirin; BMI: body mass index; HCV, hepatitis C virus; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; IHD, ischemic heart disease; HIV, human immunodeficiency viruses; HBV, Hepatitis B virus; Rapid virological response (RVR); End-of-treatment response (ETR); Sustained virological response (SVR12); IFN, interferon; HB, Hemoglobin; WBCs, white blood cells; PLT, platelets; TBR, total bilirubin; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.
| **Resident** | Balochi | Sindhi | Viral load (IU/mL) | *p* Value | Viral load (IU/mL) | *p* Value |
|--------------|---------|--------|--------------------|-----------|--------------------|-----------|
| Rural        | 46(93.9)| 3(6.1) | 4.312(1.128-16.476)| 0.033     | 3.523(0.041-305)  | 0.001     |
| Urban        | 22(88) | 4(12)  | 12.02(3.436-42.051)| <0.001    | 3.209(0.024-425)  | 0.001     |
| **Marital status** |        |        |                    |           |                    |           |
| Single       | 402(98.3)| 7(1.7)| Reference          |           | NA                 |           |
| Married      | 571(97.8)| 13(2.2)| 1.307(0.543-3.306) | 0.571     |                   |           |
| **Employment** |        |        |                    |           |                    |           |
| Employed     | 381(99.5)| 2(0.5)| Reference          |           | Reference          |           |
| Unemployed   | 592(97) | 18(3)  | 5.792(1.336-25.105)| 0.019     | 0.276(0.019-3.5)  |           |
| **Diabetes Mellitus** |        |        |                    |           |                    |           |
| No           | 718(97.8)| 16(2.2)| Reference          |           | Reference          |           |
| Yes          | 255(98.5)| 4(1.5) | 0.704(0.233-2.125) |           | NA                 |           |
| **Hypertension** |        |        |                    |           |                    |           |
| No           | 863(98.2)| 16(1.8)| Reference          |           | Reference          |           |
| Yes          | 110(96.5)| 4(3.5) | 1.961(0.644-5.972) | 0.236     | Reference          |           |
| **Chronic kidney disease** |        |        |                    |           |                    |           |
| No           | 911(98) | 19(2)  | Reference          |           | NA                 |           |
| Yes          | 62(98.4)| 1(1.6)  | 0.773(0.102-5.872) | 0.804     |                   |           |
| **Ischemic heart disease** |        |        |                    |           |                    |           |
| No           | 931(98) | 19(2)  | Reference          |           | NA                 |           |
| Yes          | 42(97.7)| 1(2.3)  | 1.167(0.153-8.923) | 0.882     |                   |           |
| **HIV** |        |        |                    |           |                    |           |
| No           | 973(98.4)| 16(1.6)| Non-computable    |           | NA                 |           |
| Yes          | -       | 4(100)  |                    |           |                    |           |
| **HBV** |        |        |                    |           |                    |           |
| No           | 955(97.9)| 20(2.1)| Non-computable    |           | NA                 |           |
| Yes          | 18(100) | -       |                    |           |                    |           |
| **Cirrhosis** |        |        |                    |           |                    |           |
| Absent       | 938(98.2)| 17(1.8)| Reference          |           | Reference          |           |
| Present      | 35(92.1)| 3(7.9)  | 0.211(0.059-0.755) | 0.017     | 0.103(0.009-1.1)  |           |
| **Child-Pugh score** |        |        |                    |           |                    |           |
| Class A      | 968(98.1)| 19(1.9)| Reference          |           | Reference          |           |
| Class B      | 5(83.3)| 16(1.7)  | 0.098(0.011-0.881) | 0.038     | 1.171(0.003-540)  |           |
| **Treatment** |        |        |                    |           |                    |           |
| SOF +DCV +RBV | 37(90.2)| 4(9.8)  | Reference          |           | Reference          |           |
| SOF +DCV     | 930(98.5)| 14(1.5)| 7.181(2.254-22.880)| 0.001     | 31.239(2.179-44'8)|           |
| SOF + RBV    | 6(75)  | 2(25)   | 0.324(0.048-2.177) | 0.246     | 12.032(0.185-780)|           |
| **RVR** |        |        |                    |           |                    |           |
| No           | 117(90.7)| 12(9.3)| Reference          |           | Non-computable    |           |
| Yes          | 856(99.1)| 8(0.9)  | 10.974(4.394-27.406)| <0.001    |                    |           |
| **ETR** |        |        |                    |           |                    |           |
| No           | 24(66.7)| 12(33.3)| Reference        |           | Non-computable    |           |
| Yes          | 949(99.2)| 8(0.8)  | 59.312(22.215-154.359)| <0.001    |                    |           |
| **Prior Treatment** |        |        |                    |           |                    |           |
| Treatment Naive | 891(98.8)| 11(1.2)| Reference        |           | Reference          |           |
| Pretreated with IFN | 82(90.1) | 9(9.9) | 8.890(3.580-22.075)| <0.001    | 0.119(0.012-1.1)  |           |
| **Viral load** |        |        |                    |           |                    |           |
| ≥ 800,000 IU mL−1 | 273(94.8)| 15(5.2)| Reference        |           | Reference          |           |
| <800,000 IU mL−1 | 700(99.3)| 5(0.7)  | 0.130(0.047-0.361) | <0.001    | 20.319(1.549-26f) |           |
| Responses | SVR12 rate | Univariate P value | Multivariate P value |
|-----------|------------|--------------------|----------------------|
| Overall   | 930/944 (98.5) |                     |                      |
| **Age groups (years)** | | | |
| Adults (18–60) | 823/832 (98.9) | Reference | Reference |
| Elders (> 60) | 107/112 (95.5) | 0.010 | 0.685 |
| **Gender** | | | |
| Male | 426/433 (98.4) | Reference | 0.755 |
| Female | 504/511 (98.6) | | |
| **Ethnicity** | | | |
| Punjabi | 574/582 (98.6) | Reference | Reference |
| Pathan | 296/296 (100) | 0.994 | 0.992 |
| Balochi | 39/42 (92.9) | 0.014 | 0.791 |
| Sindhi | 21/24 (87.5) | 0.001 | 0.954 |
| **HCV genotype** | | | |
| 1 | 1/1 (100) | Reference | 1.000 |
| 2 | 1/1 (100) | 1.000 | 1.000 |
| 3 | 928/942 (98.5) | | |
| **Resident** | | | |
| Rural | 386/391 (98.7) | Reference | 0.663 |
| Urban | 544/553 (98.4) | | |
| **Socioeconomic status** | | | |
| Low | 302/307 (98.4) | Reference | 0.665 |
| Middle | 472/478 (98.7) | 0.665 | 0.839 |
| High | 156/159 (98.1) | | |
| **Education** | | | |
| No | 194/203 (95.6) | Reference | Reference |
| Primary | 390/390 (100) | 0.993 | 0.989 |
| Secondary | 289/211 (99.3) | 0.016 | 0.025 |
| Tertiary | 57/60 (95) | 0.854 | 0.832 |

All variables with p-value < 0.25 were included in the multivariate analysis.

Abbreviations: OR, odds ratio; CI, confidence interval; SOF, Sofosbuvir; DCV, daclatasvir; RBV, ribavirin; HCV, hepatitis C virus; HIV, human immunodeficiency viruses; HBV, Hepatitis B virus; Rapid virological response (RVR); End-of-treatment response (ETR); Sustained virological response (SVR12); IFN, interferon; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.
| Single-Married | 381/383 (99.5) | Reference | 0.063 | Reference | 0.231 |
|----------------|----------------|-----------|--------|-----------|-------|
| | 549/561 (97.9) | Reference | 0.848 | | |

| Employment | 375/381 (98.4) | Reference | 0.895 | 0.261 |
|------------|----------------|-----------|--------|-------|
| Employed   | 555/563 (98.6) | Reference | 0.997 | 0.574 |

| Co-morbidities | 251/255 (98.4) | Reference | 0.999 | 0.999 |
|----------------|----------------|-----------|--------|-------|
| DM             | 107/110 (97.3) | Reference | 0.848 | 0.231 |
| HTN            | 61/61 (100)    | Reference | 0.895 | 0.261 |
| CKD            | 38/39 (97.4)   | Reference | 0.997 | 0.574 |
| IHD            | 0/4 (0)        | Reference | 0.999 | 0.999 |
| HIV            | 18/18 (100)    | Reference | 0.848 | 0.231 |
| HBV            | 0/4 (0)        | Reference | 0.848 | 0.231 |

| Cirrhosis | Absent | 895/906 (98.2) | Reference | 0.143 | Reference | 0.091 |
|-----------|--------|----------------|-----------|--------|-----------|-------|
| Present   | 35/38 (92.1) | Reference | 0.143 | 0.091 |

| Child-Pugh score | 925/938 (98.6) | Reference | 0.019 | Reference | 0.980 |
|------------------|----------------|-----------|--------|-----------|-------|
| Class A          | 5/6 (83.3)     | Reference | 0.019 | Reference | 0.980 |

| RVR | No | 106/116 (91.4) | Reference | <0.001 | Reference | 0.997 |
|-----|----|----------------|-----------|--------|-----------|-------|
| Yes | 824/828 (99.5) | Reference | <0.001 | Reference | 0.997 |

| ETR | No | 21/31 (67.7) | Reference | <0.001 | Reference | 0.995 |
|-----|----|--------------|-----------|--------|-----------|-------|
| Yes | 909/913 (99.6) | Reference | <0.001 | Reference | 0.995 |

| Previous Experience | 857/864 (99.2) | Reference | <0.001 | Reference | 0.098 |
|---------------------|----------------|-----------|--------|-----------|-------|
| Naive               | 73/80 (91.3)   | Reference | <0.001 | Reference | 0.098 |

| Viral load | ≥ 800,000 IU mL⁻¹ | 271/281 (96.4) | Reference | 0.002 | Reference | 0.196 |
|------------|-------------------|----------------|-----------|--------|-----------|-------|
|           | <800,000 IU mL⁻¹  | 659/663 (99.4) | Reference | 0.002 | Reference | 0.196 |

| Elevated ALP    | 838/852 (98.4) | 0.997 |
|-----------------|----------------|-------|
| Elevated AST    | 636/646 (98.5) | 0.557 | NA |
| Elevated ALT    | 177/187 (94.7) | <0.001 | 0.010 |

All variables with p-value < 0.25 were included in the multivariate analysis. Abbreviations: OR, odds ratio; CI, confidence interval; HCV, hepatitis C virus; DM, diabetes mellitus; HTN, hypertension; CKD, chronic kidney disease; IHD, ischemic heart disease. HIV, human immunodeficiency viruses; HBV, Hepatitis B virus; Rapid virological response (RVR); End-of-treatment response (ETR); Sustained virological response (SVR); IFN, interferon; ALP, Alkaline phosphatase; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase.

**Table 4. Rates of SVR at 12 weeks after treatment completion among patients with different disease severities and treatment regimens**
| Treatment regimen   | Chronic HCV (no cirrhosis) | Compensated cirrhosis (CC) | Decompensated cirrhosis (DC) | Total (N=993) |
|--------------------|---------------------------|----------------------------|-------------------------------|---------------|
| SOF+DCV            | 895/906(98.8%)            | 30/32(93.8%)               | 5/6(83.3%)                    | 930/944(98.5%)|
| SOF+DCV+RBV        | 37/41(90.2%)              | -                          | -                            | 37/41(90.2%)  |
| SOF+RBV            | 6/8(75%)                  | -                          | -                            | 6/8(75%)      |
| Total              | 938/955(98.2%)            | 30/32(93.8%)               | 5/6(83.3%)                    | 973/993(98%)  |

Abbreviations: SOF, sofosbuvir; DCV, daclatasvir; RBV, ribavirin.

**Table 5. Treatment related adverse events**

| Adverse events   | SOF+DCV (N=944) | SOF+DCV+RBV (N=41) | SOF+RBV (N=8) | Total (N=993) | P value |
|------------------|-----------------|---------------------|---------------|---------------|---------|
| Headache         | 551(58.4%)      | 19(46.3%)           | 7(87.5%)      | 577(58.1%)    | 0.074   |
| Nausea           | 521(55.2%)      | 25(61%)             | 3(37.5%)      | 549(55.3%)    | 0.457   |
| Abdominal pain   | 442(46.8%)      | 19(46.3%)           | 3(37.5%)      | 464(46.7%)    | 0.870   |
| Myalgia          | 698(73.9%)      | 28(68.3%)           | 8(100%)       | 734(73.9%)    | 0.174   |
| Arthralgia       | 566(60%)        | 26(63.4%)           | 5(62.5%)      | 597(60.1%)    | 0.898   |
| Dizziness        | 154(16.3%)      | 9(22%)              | 1(25.5%)      | 164(16.5%)    | 0.607   |
| Insomnia         | 320(33.9%)      | 8(19.5%)            | -             | 328(33%)      | **0.022**|
| Fatigue          | 153(16.2%)      | 12(29.3%)           | -             | 165(16.6%)    | **0.040**|
| Skin rash        | 414(43.9%)      | 21(51.2%)           | -             | 435(43.8%)    | **0.028**|
| Oral ulcers      | 283(30%)        | 17(41.5%)           | -             | 300(30.2%)    | **0.051**|

**Figures**
Flow chart of study population cohort

Figure 1

**Inclusion criteria:**
- Age ≥ 18 years
- Diagnosed as chronic HCV patients
- Treated patients with DAAs

**Exclusion criteria:**
- Patients with age < 18 years
- Patients with pregnancy
- Patients on non-DAA therapy
- Patients with incomplete profile

**Identification of HCV chronic patients taking DAAs from 2015-2019 (1200)**

**Selected patients included in final analysis (993)**

**Sustained virologic response12 rates in patients taking DAAs**

**Comparison**

| SOF+DCV  | SOF+DCV+RBV | SOF+RBV |
|----------|-------------|---------|
| (n = 944) | (n = 41)    | (n = 8) |

**Statistical analysis**

- Assessment of clinically-laboratory characteristics of SVR12 and predictors
- Assessment of therapy combination for SVR12, predictors and adverse effects

**Tabulation of results, interpretations, discussion and conclusive remarks**
