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Patient-reported symptoms during and after direct acting antiviral therapies for chronic hepatitis C: The PROP UP Study

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Abstract

Background & Aims: A comprehensive analysis of changes in symptoms and functioning during and after direct acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) has not been conducted for patients treated in real-world clinical settings. We evaluated patient-reported outcomes (PROs) in a diverse cohort of HCV patients treated with commonly-prescribed DAAs.

Methods: PROP UP is a U.S. multicenter observational study of 1,601 HCV patients treated with DAAs in 2016–2017. PRO data were collected at baseline (T1), early on-treatment (T2), late on-treatment (T3) and 3-months post-treatment (T4). PRO mean change scores were calculated from baseline and a minimally important change (MIC) threshold was set at 5%. Regression analyses investigated patient and treatment characteristics independently associated with PRO changes on-treatment and post-treatment.

Results: Of 1,564 patients, 55% were male, 39% non-white, 47% had cirrhosis. Sofosbuvir/ledipasvir was prescribed to 63%, sofosbuvir/velpatasvir to 21%, grazoprevir/elbasvir to 11%, and paritaprevir/ombitasvir/ritonavir+dasabuvir to 5%. During DAA therapy, mean PRO scores improved slightly in the overall cohort, but did not reach the 5% MIC threshold. Between 21–53% of patients experienced >5% improved PROs while 23–36% experienced >5% worse symptoms. Of 1,410 patients with evaluable sustained virologic response (SVR) data, 95% achieved SVR. Among those with SVR, all mean PRO scores improved, with the 5% MIC threshold met for fatigue, sleep disturbance, and functioning well-being. Regression analyses identified subgroups, defined by age 35–55, baseline mental health issues and a high number of health comorbidities as predictors of PRO improvements.

Conclusions: In real-world clinical practices, we observed heterogeneous patient experiences during and after DAA treatment. Symptom improvements were more pronounced in younger patients, those with baseline mental health issues and multiple comorbidities.

Lay Summary: Patients who received direct-acting antiviral medications for hepatitis C in usual care at several liver centers in the US on the whole did not experience significant changes in baseline symptoms during treatment. We observed a full range of patient experiences with some patients experiencing substantial symptom improvements, yet others experiencing less

improvements and some even worsening of symptoms. The 1346 patients who were cured of hepatitis C experienced improvements in fatigue, sleep disturbance, and functional well-being, and trends for improved pain and depression; whereas the 64 who were not cured experienced minimal improvements.

Keywords

HCV; liver; PRO; patient-reported outcome; quality of life; treatment; sleep; pain; functioning; symptom

Introduction

Patients with chronic hepatitis C virus (HCV) infection often report neuropsychiatric, somatic, and gastrointestinal symptoms including fatigue, sleep disturbance, musculoskeletal pain, depression, and abdominal pain (1–3). Patients may attribute these symptoms to HCV, a chronic viral infection associated with several extrahepatic disorders. Recent studies show that health-related quality of life and other patient-reported outcomes (PROs) improve during all-oral direct-acting antiviral (DAA) therapy and after patients achieve a sustained virological response (SVR) (4–6). These studies were based exclusively on data derived from industry-sponsored registration trials. It remains critical to determine if these findings can be generalized to patients treated in real-world clinical practices given inherent biases of registration trial data (7, 8).

Clinical trials enroll highly selected patients and typically under-represent important subgroups of the HCV population (9–11). Patients with psychosocial vulnerabilities (e.g., active psychiatric, drug use, alcohol abuse) are often excluded, yet these patients make up a sizeable majority of the population in need of treatment. In addition, a majority of these trials are comprised of predominantly White patients (66–97%) and those without advanced fibrosis (<20% cirrhosis) (9–11). Prior studies have also focused heavily on quality of life, work productivity, and fatigue outcomes but have not comprehensively evaluated specific somatic, gastrointestinal and neuropsychiatric symptoms often associated with chronic HCV (2). A more comprehensive description of symptom and function changes would enhance our understanding of the full spectrum of patients' experiences. Finally, PRO studies that allow for comparing patient experiences across different DAA regimens are lacking.

The current study enrolled a diverse cohort of patients initiating DAA therapy at several academic and community-based practices and includes a significant number of previously under-represented subgroups. We evaluated changes in overall symptom burden, specific HCV symptoms, functional well-being and health comorbidities in patients prescribed one of four DAA regimens: sofosbuvir/ledipasvir (SOF/LED); SOF/velpatasvir (SOF/VEL); Grazoprevir/Elbasvir(GRZ/ELB) and ombitasvir/paritaprevir/ritonavir with dasabuvir (PrOD) and provide a comprehensive characterization of real-world patient experiences during and after DAA therapy.

Patients and Methods

Study Design

The PROP UP study is funded by the Patient-Centered Outcomes Research Institute (PCORI) and described in detail in prior publications(12, 13). In brief, it is a multi-center, prospective, observational cohort study that enrolled patients across the U.S. to characterize patients' experiences associated with HCV, DAA treatments, and virologic cure. The current analysis utilized data collected at four time points: (T1) "Baseline" prior to starting DAA; (T2) "Early On-Treatment" week 4±2 weeks; (T3) "Late On-Treatment" last 2–3 weeks of therapy (e.g., weeks 10–12 for 12-week course); and (T4) "Post-Treatment" 12±2 weeks post-treatment.

Participants and Settings

PROP UP enrolled a total of 1,601 patients between January 2016 and October 2017 at 11 U.S. centers (9 academic hepatology centers, 2 private gastroenterology practices). All sites obtained Institutional Review Board approval and all patients provided informed consent prior to data collection.

Baseline characteristics

Sociodemographics.—Patients self-reported the following characteristics at baseline: date of birth, biological sex, race, ethnicity, educational attainment, annual household income, and employment status.

Mental health issues.—Patients who self-reported a history of any past psychiatric hospitalization or were taking psychiatric medications for 'depression, anxiety or nerve problems' at baseline were categorized as having mental health issues.

Drug use.—Patients who self-reported use of non-prescription illicit street drugs or misuse of prescription medications in the year before enrollment using validated items from the Substance Abuse Mental Illness Symptoms Screener (SAMISS) were categorized as having substance use issues (14).

Alcohol abuse.—Patients who scored ≥5 on three alcohol questions at baseline related to current frequency, quantity, and binge drinking using validated items from the Alcohol Use Disorders Identification Test (AUDIT) and the SAMISS were classified as having alcohol abuse (14, 15).

Cirrhosis.—Patients were classified as having cirrhosis (Yes/No) based on review of clinical, laboratory, imaging, histology, and transient elastography data in electronic health records. Aspartate aminotransferase (AST) to platelet ratio index (APRI) >2.0 and the Model for End-Stage Liver Disease (MELD) ≥12 were used to indicate advanced liver disease only in patients classified as having cirrhosis (16, 17). Adjudication of cases with inconsistent data was made by an experienced hepatologist (M.W.F.) or site investigators/ hepatologists.

Additional laboratory and treatment markers.—HCV genotype, HCV RNA level, AST, alanine aminotransferase (ALT), albumin, total bilirubin, platelets, hemoglobin, creatinine, international normalized ratio (INR), HIV, treatment regimen, treatment duration, and treatment experience were also recorded.

Sustained virologic response (SVR).—SVR was defined as an undetectable HCV RNA at 10 or more weeks after treatment completion. In 15 patients, lack of SVR was based on quantifiable HCV RNA around follow-up week 4.

Patient-Reported Outcomes

Additional details about these PROs are provided in the published protocol and baseline cohort analysis (12, 18).

Individual symptom clusters.—The National Institutes of Health's Patient-Reported Outcomes Measurement Information System® (PROMIS®) instruments were used to assess 10 specific symptoms that fall into three symptom clusters: *Neuropsychiatric Cluster* (depression, anxiety, anger, cognitive concerns); *Somatic Cluster* (pain interference, fatigue, sleep disturbance); and *Gastrointestinal Cluster* (abdominal pain, diarrhea, nausea/vomiting) (19–21). There is no PROMIS instrument to measure headache, therefore the Headache Impact Test (HIT-6) was used to capture headaches that may be associated with DAA therapy (22, 23). The HIT-6 has a 5-point Likert response scale ranging from "Never" to "Always." We previously evaluated the psychometric properties of the PROMIS and HIT-6 instruments in patients with HCV and have found satisfactory reliability and validity (18, 24). Higher PROMIS and HIT-6 scores reflect worse symptom experiences.

Overall symptom burden.—A comprehensive list of 32 symptoms common to many health conditions were assessed using the Memorial Symptom Assessment Scale (MSAS) (25, 26). Participants reported the presence or absence of symptoms (yes=1/no=0), and if present, its severity (0–4), frequency (0–4) and level of distress (0–4). The total score (TMSAS) could range from 0–4 and was multiplied by 10 for ease of interpretation with other PROs.

Functional well-being.—The HCV-PRO is a newly developed HCV-specific survey designed to evaluate the functioning and psychological well-being of patients with HCV (27, 28). The scale includes 16 items that measure various aspects of physical and emotional functioning, productivity, intimacy, and perceived quality of life related to having HCV. The 16 items are summed to produce a total score transformed on a scale of 0 (worst) to 100 (best). Unlike the other PROs, higher scores on the HCV-PRO are associated with *better* functional well-being. To display change in the HCV-PRO score in the same figures (below), the HCV-PRO change score was reverse coded.

Statistical Analysis Strategy

Primary Analysis.—The mean changes in each PRO score from T1 to T2, T3 and T4 Post-Treatment were estimated along with corresponding 95% confidence intervals (95% CIs). For the investigation of change from baseline to on-treatment in the primary analyses,

we used the average of the T2 and T3 PRO scores because these scores were moderately to highly correlated (r = 0.52 – 0.79). The estimates of mean changes were computed without adjustment for other covariates or confounders. The primary analysis focused on symptom-specific estimates of the magnitude of mean change from T1 to T2/T3 and T4 in the combined cohort, each of four DAA cohorts, those who achieved SVR and other subgroups of interest.

Descriptives.—Tabular and graphical methods were used to visualize the data (means, standard deviations (SD), range), change in PROs, or percent change from baseline.

Minimally Important Change (MIC).—To aid our clinical interpretation of the unadjusted PRO change scores, we defined a 5% change from baseline as the "minimally important change (MIC)" threshold based on the published literature and feedback from our patient engagement group about what amount of change would be meaningful to them related to treatment decision-making (5, 29). For the PROMIS symptom measures in which T-scores are standardized to a mean of 50 and a standard deviation of 10, previous studies have suggested 2.0–5.0 points as the MIC threshold in other populations (21, 30, 31). Evaluation of the PROMIS baseline data revealed that 5% change in baseline scores would range from 1.9–2.8 points for each of the 10 PROMIS measures. Thus, we set the MIC for all PROMIS measures at *2.5* points. For the HIT-6, a 5% change from baseline was estimated at 2.3 points, while the HIT-6 MIC in the literature is estimated at 1.5–2.5 (32). Therefore, we set the MIC for the HIT-6 at *2.5* points. A 5% change from baseline for the HCV-PRO was 3.6 points, thus we set the MIC for the HCV-PRO at 4 points. A 5% MIC change in the TMSASx10 score was 3.0 points. These MIC thresholds are conservative estimates to mitigate the risk of committing Type I error (i.e., false positives). A PRO change score that increased >5% is suggestive of clinically significant worse symptoms, whereas a PRO change score that decreased >5% is suggestive of clinically significant improvements.

Multivariable regression models using data-splitting strategies.—Generalized linear regression models were used for both exploratory and confirmatory evaluation of predictors of PRO change from baseline to on-treatment and baseline to post-treatment. Absolute mean PRO change scores (continuous) were used as the dependent variables. We used a two-stage modeling strategy based on data splitting. Participants were randomly assigned to two groups: Sample 1 or Sample 2.

Sample 1 was used for exploratory model building efforts to generate a set of candidate predictor variables that might be associated with change in each PRO. Model building with Sample 1 relied on unsupervised use of least absolute shrinkage and selection operator (LASSO) methods and model averaging algorithms. Sample 2 was used for confirmation. In Sample 2, the variables in the hypothesized model were considered validated if their regression coefficients were statistically significant at $p<0.01$. Candidate predictor variables available for inclusion in the exploratory models in Sample 1 included the following baseline covariates: age, sex, race, education, income, employment, cirrhosis status, alcohol abuse, substance use, and mental health issues, ethnicity, MELD score in cirrhosis patients, HIV, DAA treatment cohort, ribavirin (RBV) use, treatment duration, treatment experience, and number of health comorbidities.

Multiple imputation.—For use in multivariable regression models, missing values of baseline covariates (not PROs) were assumed to satisfy the missing-at-random criterion and were addressed via multiple imputations. A multivariate multiple imputation algorithm (SAS procedure MI) was used to generate 20 completed copies of the dataset. Each statistical regression model of interest was fitted to all 20 datasets. The 20 sets of results were combined (SAS procedure MIANALYZE) to produce the final results for each multivariable regression model.

Sensitivity Analyses.—To guide our level of trust in the main results, sensitivity analyses were performed in which the methods and assumptions used were perturbed using variations on multiple age (years) versus using age-groups), use of alternative methods for addressing confounding, and imputation variable-selection methods (with and without supervision), definitions of variables (e.g., exploring the two on-treatment assessment windows (T2/T3) separately to compare with our main results.

Statistical Computations.—Statistical computations were performed using SAS System software version 9.4 (SAS Institute, Cary, NC). PROMIS T-scores were computed using R software, version 3.1.2 (2014 The R Foundation for Statistical Computing), and RStudio software, version 1.0.136 (RStudio Inc.).

Results

Study Flowchart

The study flowchart is provided in Figure 1. Of the 1601 patients enrolled, 1564 patients (98%) completed PROs early on-treatment (T2), late on-treatment (T3), or at 12-weeks post-treatment (T4) and were included in the analyses of the total cohort. The cohort of patients prescribed daclatasvir/sofusbuvir were excluded due to low sample size (n=22). Of those with baseline and post-treatment PROs, 1410 patients (90%) had post-treatment HCV RNA available to determine SVR status. Of these, 1346 (95%) achieved SVR. A total of 154 patients had missing HCV RNA data: 10 died, 4 withdrew before T4 and 140 did not return for post-treatment follow-up labs.

Patient characteristics

Table 1 describes the baseline characteristics of the total cohort and the four DAA subgroups. The majority of patients were prescribed SOF/LED (63%) and 5% were prescribed PrOD. In the overall cohort 55% were male, 33% were Black (61% White), and mean age 58 years (SD=11; range 23–86). The majority were from lower socioeconomic status groups with 54% ≤ high school degree, 74% < $40,000 per year income, and 45% receiving or applying for disability benefits. Over half of patients had 4+ health comorbidities, with an average of 4 (range: 0–17). The majority were infected with HCV genotype 1, 4, or 6 (83%), 82% received 12 weeks of therapy and 13% were prescribed RBV. Of the 47% classified as having cirrhosis, 14% had a MELD ≥12. Notably, several other patient subgroups often under-represented in registration trials were well-represented in this cohort: 39% non-white, 37% with mental health issues, 15% with alcohol abuse, and 23% with substance use.

Patient characteristics across the four DAA subgroups were similar except for the cohort prescribed GRZ/ELB, which included a higher proportion of patients who were black, on disability, with lower income, with a higher number of comorbidities, and higher mean creatinine scores, likely contributing to elevated MELD scores. As expected, more patients on PrOD were prescribed RBV.

Change in PRO scores from baseline to on- and post-treatment

Figure 2 shows the mean change and MIC threshold value for 13 PROs from baseline to T2, T3 and T4 in the total cohort (n=1,564). During treatment, the majority of PRO scores reduced slightly from baseline (- sign suggests symptom reduction); however, diarrhea, nausea, and headache increased slightly early in treatment (+ sign suggest symptom worsens). The magnitude of PRO mean changes during DAA therapy was small and none of the mean changes reached the 5% clinically significant MIC thresholds. All PRO means improved from baseline to post-treatment (-signs suggest improvements) with fatigue, sleep disturbance and functional well-being reaching the MIC thresholds for >5% clinically significant improvements.

We also evaluated PRO mean change scores stratified by four DAA subgroups (Supplemental Materials Figs. 1a–1c). Overall, the magnitude of PRO mean changes was very small and the *vast majority* of changes did *not* reach the 5% clinical thresholds. However, some trends are worth noting. Whereas the majority of PRO mean change scores reduced slightly during treatment for patients prescribed SOF/LED, SOF/VEL and GRZ/ELB, patients prescribed PrOD consistently showed worse PRO change scores during treatment, with diarrhea and nausea mean change scores reaching the MIC for clinically worse symptoms. Finally, the only clinically significant improvement in PRO on-treatment was a 6.5 point improvement in HCV-PRO functional well-being in the GRZ/ELB cohort.

Proportion of change in PROs and pre-existing conditions from baseline to on-treatment

While the *mean* score changes in the overall cohort from baseline to on-treatment were small in magnitude, we observed wide variability in individual patient's change scores. Figure 3 shows the proportion of patients deemed to have little or no change (<5% change from baseline in either direction), those with clinically significant *improvements*, and those with clinically significant *worsening*. For example, over 40% reported substantial improvements in fatigue, sleep disturbance, overall symptom burden and functional well-being, approximately 30% experienced worsening of these symptoms.

PRO changes stratified by SVR status

As previously noted, of 1,410 patients with evaluable SVR data, 1,346 (95%) achieved SVR and 64 (5%) did not, with 140 (10%) patients lost to follow-up with missing post-treatment HCV RNA data. As shown in Figure 4, all PRO mean scores improved from baseline to early post-treatment in patients who achieved SVR, with clinically significant improvements in fatigue (−4.1), sleep disturbance (−3.0) and functional well-being (−6.4), and a trend for depression and pain to improve (−2.3). Among the 64 patients who did not achieve SVR, five mean PRO scores worsened during early post-treatment and no PROs showed clinically significant improvements (>5% MIC), with the exception of fatigue (−2.8). Similarly, Figure

5 shows the percent change in PRO mean scores from baseline to early post-treatment. Patients who achieved SVR exhibited the most clinically significant improvements in functional well-being (20%), overall symptom burden (13%), and somatic symptoms. In contrast, the 64 patients who did not achieve SVR had worsening or negligible changes for most PROs except a few. It is essential to note that 91% of all patients who completed their T4 post-treatment surveys were unaware of their SVR status at the time of survey completion.

Compared to patients who achieved SVR, the 64 patients who did not achieve SVR were more likely to be male (62% vs.55%), had cirrhosis (56% vs. 47%), treatment experience (33% vs. 18%), longer duration of therapy (13% vs. 8%), RBV use (19% vs. 13%) and APRI >2.0 (20% vs. 14%) (Table 2).

Compared to patients who achieved SVR, those who did not have a follow-up HCV RNA test (n=140) tended to be younger (15% vs. 5%), have lower income (89% vs. 73%), higher rates of unemployment (17% vs. 6%), mental health issues (54% vs. 35%), and treatment inexperience (91% vs. 82%) but they *did not* have a higher rate of alcohol abuse (16% vs. 15%) or drug use (24% vs. 22%) (Table 2).

Multivariable models for symptom changes on- and post-treatment

Using data-splitting strategies and data from all patients (n=1564), multivariable analyses showed that ages 35 to 55 (for anger and overall symptom burden) and baseline mental health issues (for depression, fatigue, functional well-being) were the most consistent independent predictors of symptom improvements during DAA therapy (Suppl Table 1). We also found that patients prescribed PrOD had worse of overall symptom burden (1.8 [0.4, 3.2, $p<0.01$]) and a trend towards worse fatigue (3.3 [−0.1,6.8]; $p=0.06$) during therapy relative to patients prescribed SOF/LED. Other patient characteristics predictive of greater symptom improvements included other race, being disabled, having a higher number of comorbidities, and being treatment naive.

Similarly, multivariable analyses of patients who achieved SVR (n=1,346) showed that ages 35 to 55 was the most consistent independent predictor of post-treatment symptom improvements including anger, anxiety, fatigue, abdominal pain, and overall symptom burden (Suppl Table 2). Other patient characteristics associated with greater symptom improvements after viral cure included age 20–34, white race, a higher number of health comorbidities, mental health disturbance, and substance use at baseline. Patients prescribed PRoD experienced less improvements in anxiety after treatment compared to patients treated with SOF/LED. The majority (71%) of the PrOD cohort also received RBV compared to 12% in other DAA cohorts.

It is important to note that the following patient- and treatment-level characteristics were not selected as predictors in any of the final multivariable models: sex, ethnicity, cirrhosis status, MELD, HIV, income, education, alcohol use, or treatment duration.

Sensitivity Analysis

Several sensitivity analyses were performed in which the methods and assumptions used were perturbed using variations on multiple imputation, variable-selection methods, definitions of variables, and alternative methods for addressing confounding. We also explored the two on-treatment assessment windows (T2/T3) separately to compare with our main results. These and all analyses produced results similar to the main analysis described above, increasing trust in the main results.

Discussion

Many patients with chronic HCV experience symptoms that may be attributed to their disease (2, 3). These patients look forward to viral eradication that may ameliorate those troublesome symptoms. Although interferon-free DAA regimens have been shown to be well tolerated in clinical trials, these reports require confirmation from a broader and more heterogeneous cohort of patients treated in real world clinical settings. The current study represents the largest, most comprehensive investigation of patients' experiences during and after treatment with several interferon-free DAA regimens prescribed in clinical practice. This real-world clinical cohort was geographically heterogeneous and diverse with regard to race, cirrhosis status, and a wide range of comorbidities, including psychiatric, alcohol and substance use issues (12, 13). To our knowledge, this is the first study to provide comparative PRO data collected from patients prescribed DAA regimens developed by different pharmaceutical companies and to include PRO data from patients who did and did not achieve viral cure. Finally, we determined whether these PRO changes were clinically meaningful using a conservative threshold. It is important to note that the vast majority (91%) of patients had no knowledge of SVR status before completing their post-treatment PRO surveys, providing strong evidence that improvements in PROs post-treatment are likely the result of viral eradication on biological processes, and not mere psychological placebo effect.

An important observation in this study is that while the average change in PRO scores of the total cohort was small, one-quarter to one-third reported *worsening* of symptoms during DAA therapy. Previous PRO studies focused on reporting overall mean change scores, but neglected to describe the full distribution of patients' experiences. Our findings have implications for how clinicians might help set expectations with patients initiating DAA therapy, for example providing a balanced perspective that some patients experience no changes, others experience improvements, but a third may experience worsening of baseline symptoms. In accordance with other studies, PRO scores improved from baseline to post-treatment, with clinically meaningful improvements specifically in fatigue, sleep disturbance and functional well-being. These improvements were more pronounced in patients who achieved SVR. While other studies have reported improvement in quality of life in patients who achieved SVR (5), our study uniquely demonstrates that sleep and pain issues improve after viral eradication. This is particularly meaningful since the prevalence of sleep and pain disorders are high among patients with chronic HCV (2, 33–36).

We observed that younger patients (ages 35 to 55), and those with mental health issues or more health comorbidities reported the greatest symptom improvements during and after

therapy. These patients represent vulnerable subgroups with psychosocial and medical challenges who may benefit the most from being given the opportunity to rid themselves of a stigmatizing infectious disease and engage in healthcare. These patients tended to have the worst symptoms at baseline with more room for improvement (data not shown), suggesting the possibility of regression towards the mean. We found that cirrhosis was not independently associated with PRO changes during therapy or after viral cure indicating that patients with and without cirrhosis tend to experience similar symptom benefits. It should be clarified that most patients with cirrhosis in this cohort had compensated liver disease.

Overall, PRO changes in the cohorts of patients prescribed SOF/LED, SOF/VEL or GRZ/ELB were similar across the DAA cohorts while on-treatment with overall improvement in symptoms after treatment completion, 33% of which were clinically substantial improvements. Therefore, patients can be counseled regarding the overall stability of symptoms during HCV therapy and improvements post-SVR regardless of which of these regimens are prescribed. Patients prescribed PrOD had less improvement in PROs during treatment, including clinically significant diarrhea and nausea, and experienced the least improvements after completing treatment. It should be noted that the number of patients who received PrOD was small and a higher proportion received ribavirin, which likely contributed to worsening symptoms during treatment. Nevertheless, PrOD is no longer used in the U.S. and many other countries, having been superseded by simpler, better tolerated DAA regimens.

In this real-world cohort, 9% of patients did not return for follow-up HCV RNA testing to determine SVR status. This was an unexpected finding since one would assume that most patients understood that DAAs are expensive and many had to wait a long time for insurance approval in order to receive treatment. Patients who never came back for follow-up HCV RNA testing were disproportionately younger, had lower incomes, higher rates of unemployment, disability, mental health issues, and were more likely to be treatment naïve. Contrary to speculation, these patients who were non-compliant with follow-up did *not* have higher rates of baseline drug or alcohol abuse. These data indicate the importance of educating all patients about the importance of post-treatment laboratory tests, in particular younger patients and those at greater risk for being lost to clinical follow-up.

A few limitations are worth noting. The observational study design precludes any definitive head-to-head statistical comparisons of DAA regimens. Amongst DAA regimens, SOF/LED was the most commonly prescribed while the other three DAA regimens were prescribed less often. This study also included a relatively small number of patients with advanced liver disease or liver transplantation. Aside from laboratory tests, minimal clinical data were extracted from electronic health records. The scope of this study did not include clinical data on fibrosis staging, decompensation events, medications or comorbid liver diseases or chronic illnesses. Thus, by design, we have not compared patient-reported information with clinical health data or to classify cirrhosis according to Child-Pugh scores. Our findings may not generalize to other subpopulations or clinical settings, including younger people who are actively injecting drugs or persons receiving medication-assisted treatment for opioid use disorders.

The strengths of this study are worth noting. This study is the largest comprehensive real-world PRO study during and after treatment with different DAA regimens. We provided comparative data on four commonly prescribed DAA regimens. The study population included many subpopulations under-represented in registration trials. Unlike prior studies, we provided the full spectrum of patients' experiences including those who experienced worsening of symptoms. Although the non-SVR subgroup was small (n=64), our study suggests that there may be differences in changes in PROs post-treatment between patients who do and do not achieve SVR. These data are consistent with the positive effects of viral eradication on patients' functioning and specific symptoms. Finally, PROP UP has been a highly patient-centered study since its inception with patients engaged throughout all phases of study development to ensure that our findings are meaningful and relevant to people affected by the disease (12, 39).

CONCLUSION

This comprehensive assessment of changes in neuropsychiatric, somatic and gastrointestinal symptoms, and functional well-being during and after therapy with all-oral DAA therapies provides new insights relevant to patients, clinicians and other stakeholders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Selected abbreviations

ALT	alanine aminotransferase test

AST	aspartate aminotransferase test
APRI	AST to platelet ratio index
AUDIT	Alcohol Use Disorders Identification Test
CI	Confidence interval
DAA	Direct acting antiviral
FIB-4	Fibrosis-4 Index for Liver Fibrosis
GI	Gastrointestinal
HCV	hepatitis C virus
MSAS	Memorial Symptom Assessment Scale
PCORI	Patient-Centered Outcomes Research Institute
PRO	patient-reported outcome
PROMIS®	Patient-Reported Outcome Measurement Information System®
PROP UP	The Patient-Reported Outcomes Project of HCV-TARGET
RBV	Ribavirin
SD	standard deviation
TMSAS	Total Memorial Symptom Assessment Scale

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Highlights

- Overall change in symptoms and functioning on DAAs was not clinically meaningful
- Patients' experiences are very heterogeneous
- Patients prescribed one DAA regimen experienced the worst symptoms
- Patients cured have clinical improvement in fatigue, sleep, and functioning
- Patients not cured have minimal improvements

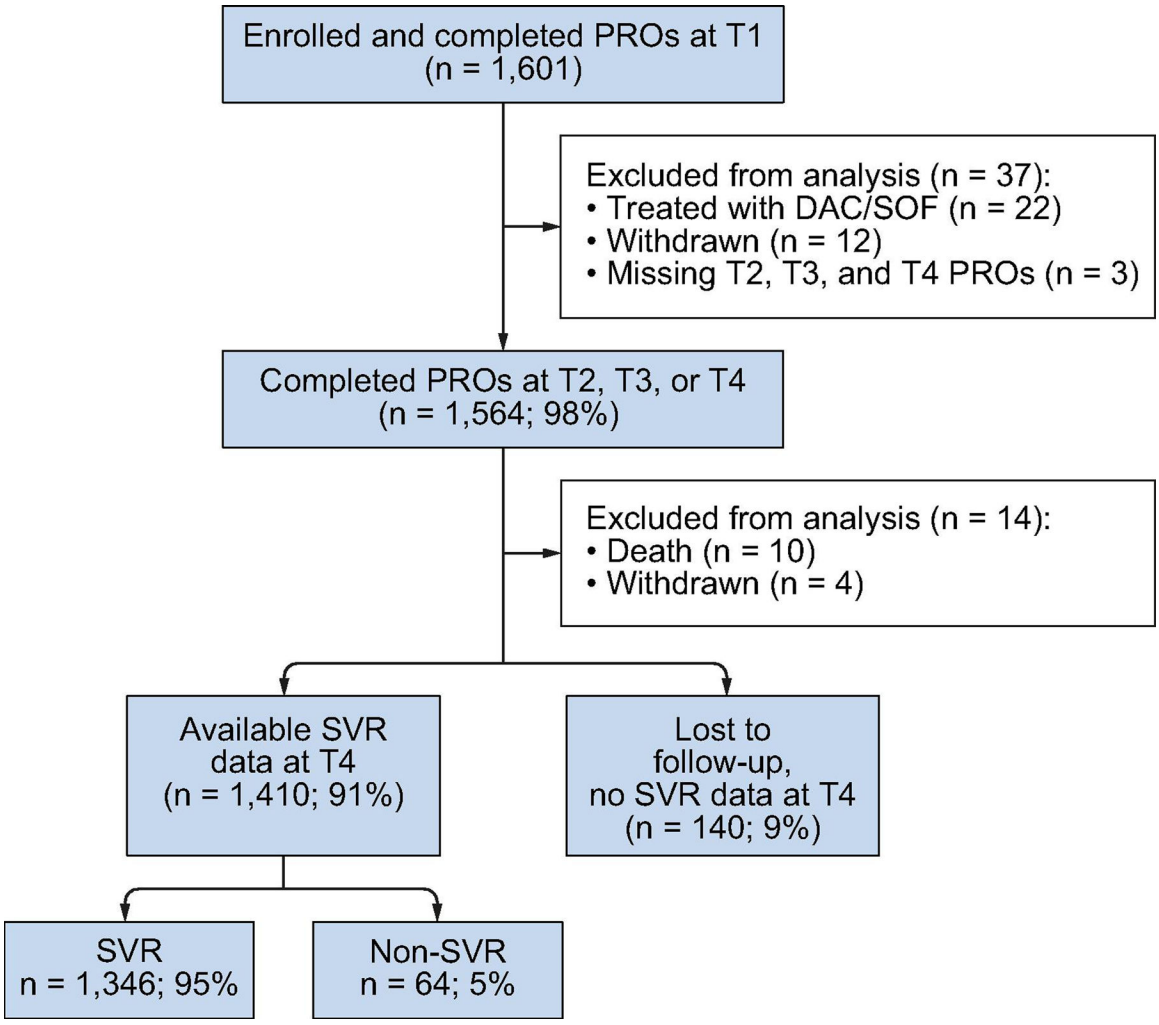
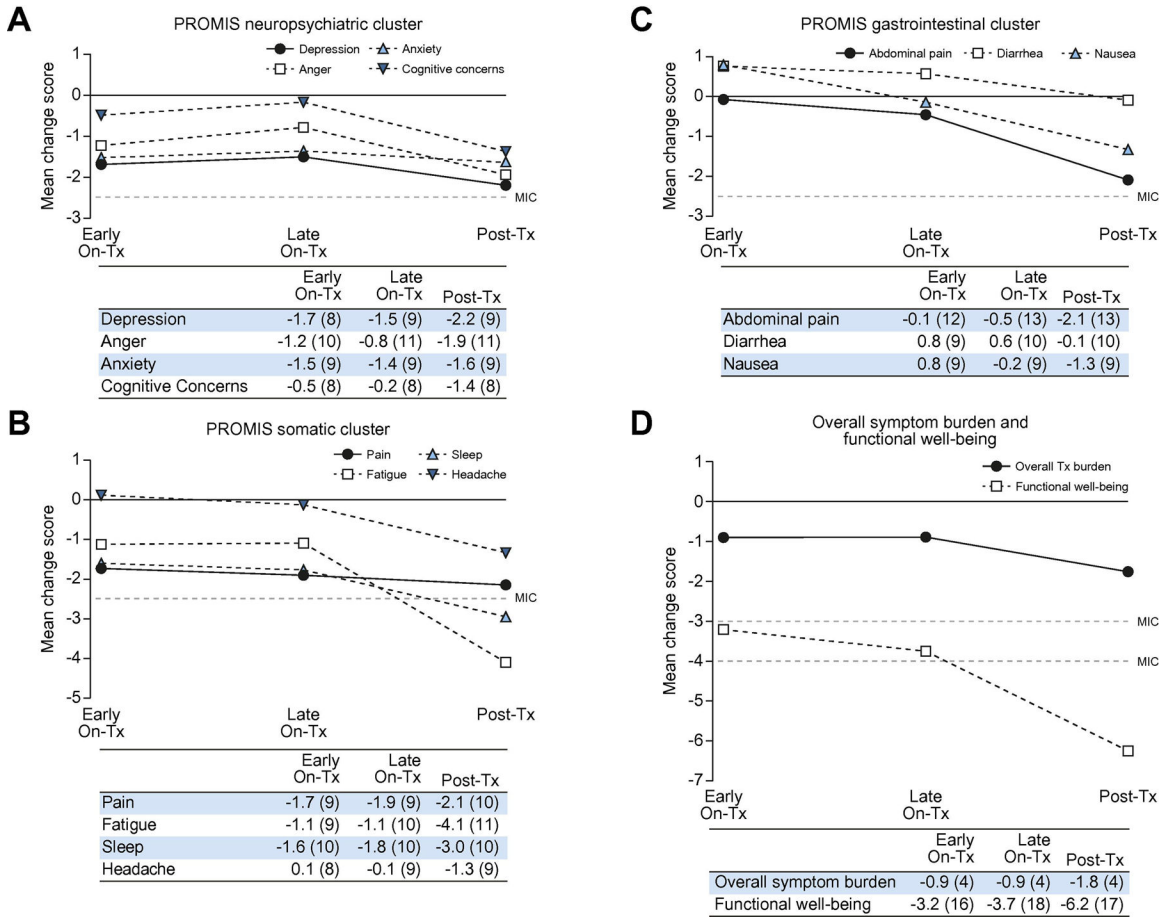


Fig. 1. Study flowchart

NOTE: DAC/SOF: daclatasvir/sofosbuvir, T1: baseline, T2: early on-treatment, T3: late on-treatment, T4: early post-treatment.



	Early On-Tx	Late On-Tx	Post-Tx
Depression	-1.7 (8)	-1.5 (9)	-2.2 (9)
Anger	-1.2 (10)	-0.8 (11)	-1.9 (11)
Anxiety	-1.5 (9)	-1.4 (9)	-1.6 (9)
Cognitive Concerns	-0.5 (8)	-0.2 (8)	-1.4 (8)

	Early On-Tx	Late On-Tx	Post-Tx
Pain	-1.7 (9)	-1.9 (9)	-2.1 (10)
Fatigue	-1.1 (9)	-1.1 (10)	-4.1 (11)
Sleep	-1.6 (10)	-1.8 (10)	-3.0 (10)
Headache	0.1 (8)	-0.1 (9)	-1.3 (9)

	Early On-Tx	Late On-Tx	Post-Tx
Abdominal pain	-0.1 (12)	-0.5 (13)	-2.1 (13)
Diarrhea	0.8 (9)	0.6 (10)	-0.1 (10)
Nausea	0.8 (9)	-0.2 (9)	-1.3 (9)

	Early On-Tx	Late On-Tx	Post-Tx
Overall symptom burden	-0.9 (4)	-0.9 (4)	-1.8 (4)
Functional well-being	-3.2 (16)	-3.7 (18)	-6.2 (17)

Fig. 2. Mean PRO change scores at on-treatment and post-treatment in overall sample (n=1564)

NOTE: Unadjusted PRO change scores at the following time points are shown: Early On-Tx: Early Treatment Phase; Late On-Tx: Late Treatment Phase; Post-Tx: Early Post-Treatment. DAA: Direct-Acting Antiviral. MIC: Minimally Important Change defined as > 5% change in PRO score suggests clinically significant change. The 5% MIC threshold for the PROMIS and Headache measures is ±*2.5* points; the MIC for Functional Well-Being is ±4 points; the MIC for Overall Symptom Burden is ±3.0. Negative change scores=PRO score improved; Positive change scores=PRO score worsened. Missing values for all PROs were 4%−8% (functional well-being missing 14%−16%).

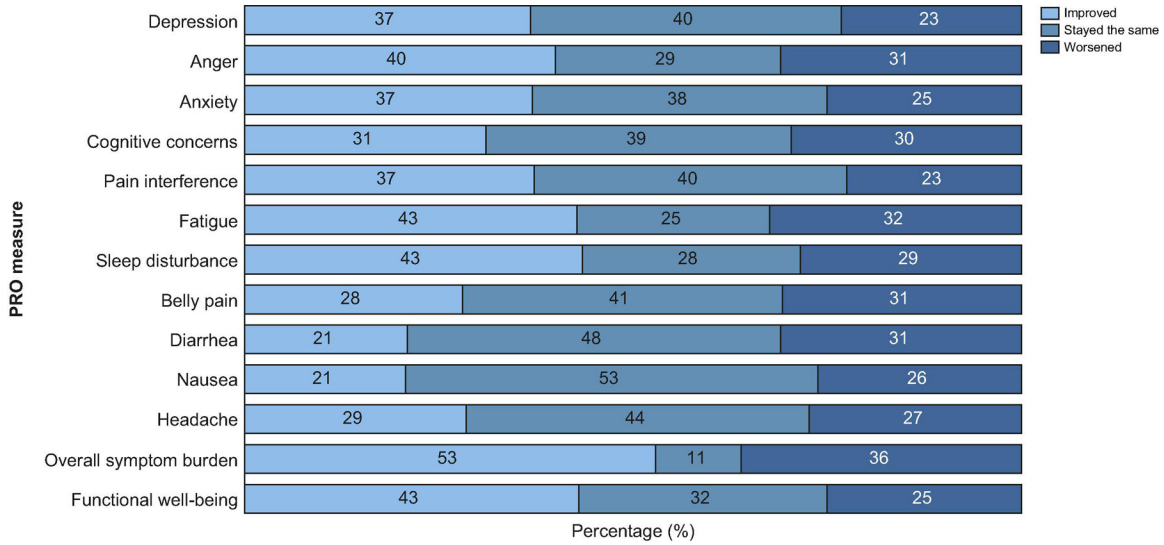


Fig. 3. Proportion of patients whose symptoms stayed the same, improved or worsened during DAA therapy

NOTE: DAA: Direct-Acting Antiviral. Missing values for all PROs were 1%−3%, except Functional well-being was missing for 9% of patients. Improved ≥ 5% improvement from baseline; Worsened ≥ 5% worse from baseline score.

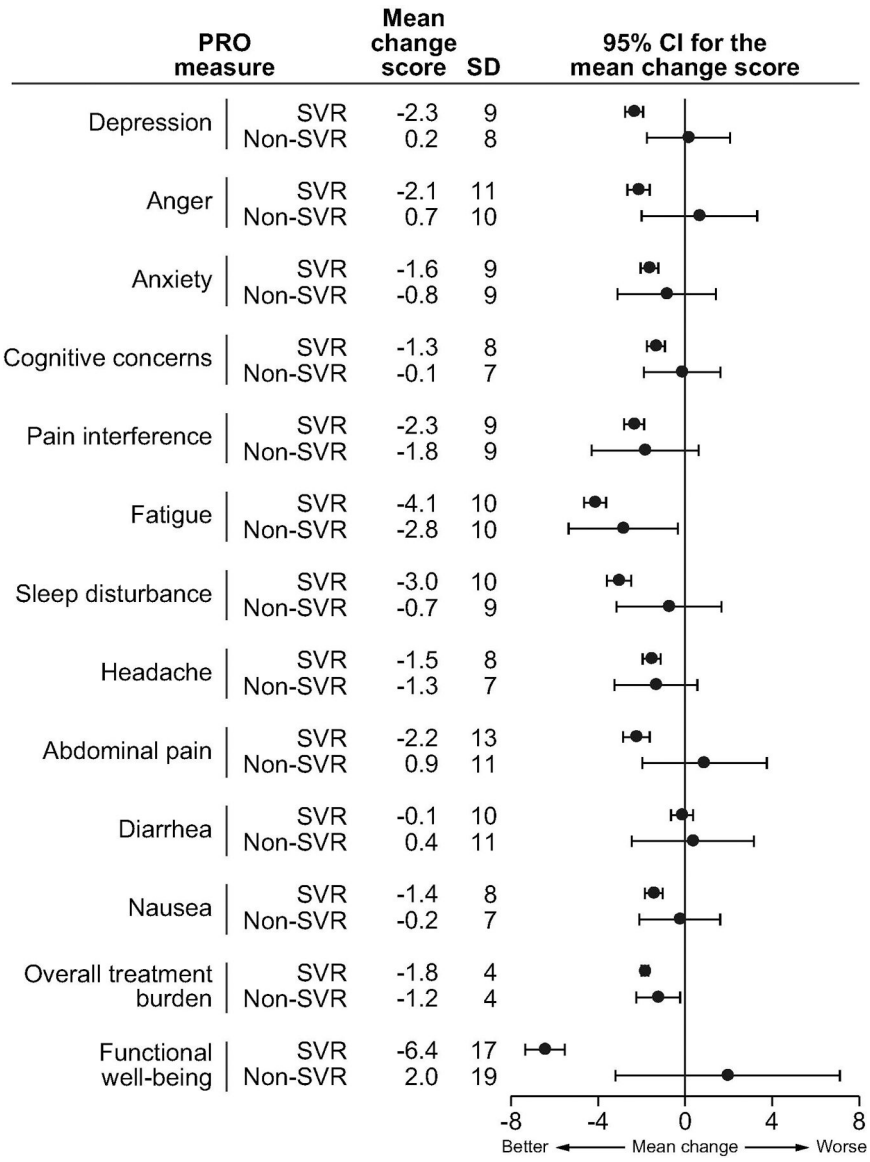


Fig. 4. PRO mean change scores from baseline to early post-treatment by SVR status

NOTE: PRO mean change scores from Baseline to Early Post-Treatment (Early Post-Tx). CI: confidence interval; SVR: Sustained Virologic Response. For patients who achieved SVR, functional well-being change scores were missing for 13%−22% of patients; for the ten PRO measures, change scores were missing for 0% - 6% of patients. Among non-SVR patients, for all PRO measures, change scores were missing for 0% - 17% of patients.

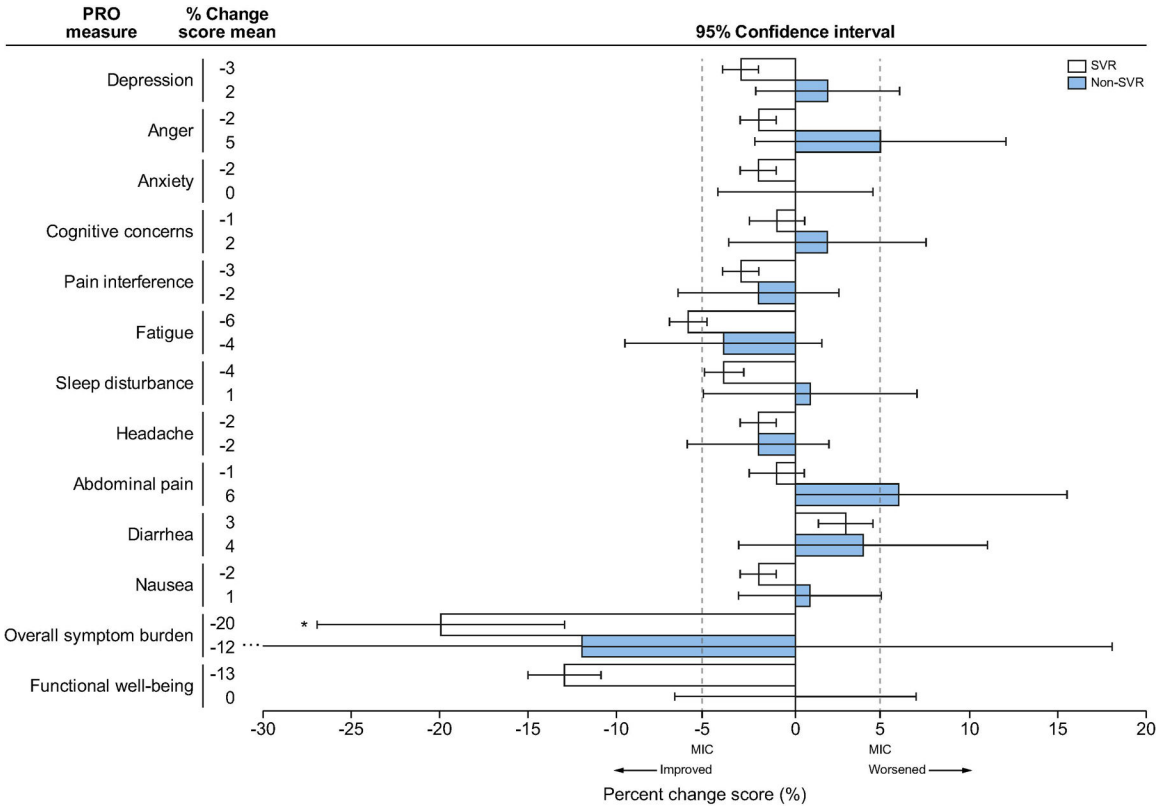


Fig. 5. Percent change in PRO scores from baseline to post-treatment by SVR status

NOTE: Percent change in PRO mean scores from Baseline to Early Post-Treatment (Early Post-Tx). Horizontal bars denotes 95% confidence intervals. *The lower limit of the 95% CI = −42 for Overall Symptom Burden in the Non-SVR group. Dotted vertical lines represent 5% MIC thresholds. SVR: Sustained Virologic Response. For patients who achieved SVR (n=1346), functional well-being change scores were missing for 15% of patients; for the ten PRO measures, change scores were missing for 0% - 5% of patients. For patients who did not achieve SVR (n=64), headache and functional well-being change scores were missing for 17% and 20% of patients, respectively; for the eight other PRO measures, change scores were missing for 0% - 13% of patients.

Table 1.

Patient characteristics by DAA therapy cohort

Characteristics	DAA cohort therapy				
	A	**S**	**S**	**G**	**P**
		OF/LED	**OF/VEL**	**RZ/EL**	
	II			**B**	**rOD**
	(n=1564)	**(n=989)**	**(n=335)**	**(n=170)**	**(n=70)**
			n (%)		
Sociodemographic features					
Age, years (mean, SD)	58 (11)	58 (10)	57 (11)	59 (10)	54 (12)
<35	86 (5)	52 (5)	18 (5)	74 (4)	9 (13)
35–55	372 (24)	252 (23)	89 (27)	40 (24)	18 (26)
>55	1106 (71)	712 (72)	228 (68)	123 (72)	43 (61)
Sex					
Male	867 (55)	545 (55)	193 (58)	92 (54)	37 (53)
Female	697 (45)	444 (45)	142 (42)	78 (46)	33 (47)
Race					
Black	512 (33)	361 (37)	49 (15)	84 (50)	18 (26)
White	953 (61)	577 (59)	249 (75)	78 (46)	49 (70)
Other	94 (6)	48 (5)	36 (11)	74 (4)	34 (4)
Ethnicity					
Hispanic/Latino	63 (4)	31 (3)	23 (7)	85 (5)	11 (1)
Non-Hispanic/other	1427 (96)	911 (97)	292 (93)	157 (95)	67 (99)
Education					
≤ High school diploma or equivalent	840 (54)	539 (55)	169 (51)	95 (56)	37 (53)
> High school	709 (46)	442 (45)	160 (49)	74 (44)	33 (47)
Annual household income					
< $40K	1134 (74)	709 (73)	232 (72)	139 (83)	52 (74)

Characteristics	DAA cohort therapy				
	A	**S**	**S**	**G**	**P**
		OF/LE	**OF/VE**	**RZ/EL**	
	II	**D**	**L**	**B**	**rOD**
	(n=1564)	**(n=989)**	**(n=335)**	**(n=170)**	**(n=70)**
			n (%)		
Sociodemographic features					
≥ $40K	3	2	9	2	1
	95 (26)	58 (27)	0 (28)	9 (17)	8 (26)
Employment					
Working full or part time	5	3	1	3	3
	40 (36)	40 (36)	37 (42)	1 (19)	2 (46)
Receiving/applying for disability	6	4	1	1	2
	76 (45)	37 (45)	15 (35)	05 (63)	9 (42)
Unemployed	1	6	3	1	4
	08 (7)	0 (6)	4 (10)	0 (6)	(6)
Retired/homemaker/student	1	1	3	2	4
	89 (12)	27 (13)	8 (12)	0 (12)	(6)
Liver Clinical, Laboratory and Treatment Markers					
Genotype					
Genotype 1, 4 or 6	1	9	7	1	7
	287 (83)	70 (99)	9 (23)	68 (100)	0 (100)
Genotype 2	1	3	1	0	0
	35 (9)	(0)	32 (40)	(0)	(0)
Genotype 3	1	2	1	0	0
	25 (8)	(0)	23 (37)	(0)	(0)
Cirrhosis status					
Cirrhotic	7	4	1	7	3
	38 (47)	58 (46)	68 (51)	7 (46)	5 (50)
Noncirrhotic	8	5	1	9	3
	18 (53)	28 (54)	64 (49)	1 (54)	5 (50)
MELD status in cirrhotic patients					
MELD 6–11	5	3	1	4	2
	27 (86)	43 (89)	17 (83)	4 (68)	3 (92)
MELD ≥ 12	8	4	2	2	2
	9 (14)	2 (11)	4 (17)	1 (32)	(8)
AST to Platelet Ratio Index (APRI)					
APRI ≤ 2.0	1	8	2	1	6
	293 (86)	21 (87)	52 (79)	58 (93)	2 (91)
APRI > 2.0	2	1	6	1	6
	08 (14)	22 (13)	9 (21)	1 (7)	(9)
ALT, U/L (mean (SD))	7	7	8	5	7

Characteristics	DAA cohort therapy				
	A	**S**	**S**	**G**	**P**
		OF/LED	**OF/VEL**	**RZ/EL**	
	II			**B**	**rOD**
	(n=1564)	**(n=989)**	**(n=335)**	**(n=170)**	**(n=70)**
			n (%)		
Sociodemographic features					
Creatinine, mg/dL (mean (SD))	8 (69) 1 (1)	8 (69) 1 (0)	9 (78) 1 (0)	7 (48) 2 (3)	8 (63) 1 (1)
Health comorbidities					
0–1	3 16 (20)	1 99 (20)	8 1 (24)	1 9 (11)	1 7 (24)
2–3	3 94 (25)	2 47 (25)	9 4 (28)	3 2 (19)	2 1 (30)
≥4	8 52 (55)	5 41 (55)	1 60 (48)	1 19 (70)	3 2 (46)
Current kidney disease					
No	1 464 (94)	9 54 (97)	3 16 (96)	1 26 (75)	6 8 (99)
Yes	8 8 (6)	3 2 (3)	1 3 (4)	4 3 (25)	1 (1)
Prescribed treatment duration					
8 weeks	1 54 (10)	1 53 (16)	3 (1)	1 (1)	0 (0)
12 weeks	1 286 (82)	7 52 (76)	3 15 (93)	1 58 (92)	6 1 (87)
16 or 24 weeks	1 24 (8)	8 4 (8)	2 0 (6)	1 1 (7)	9 (13)
Ribavirin					
Without Ribavirin	1 363 (87)	8 71 (88)	3 17 (95)	1 55 (91)	2 0 (29)
With Ribavirin	2 01 (13)	1 18 (12)	1 8 (5)	1 5 (9)	5 0 (71)
Treatment experience					
Treatment naive	1 252 (82)	7 90 (82)	2 66 (81)	1 33 (81)	6 3 (93)
Treatment experienced	2 78 (18)	1 78 (18)	6 3 (19)	3 2 (19)	5 (7)
SVR Achieved					
No	6 4 (5)	3 2 (4)	1 9 (6)	9 (6)	4 (7)
Yes	1	8	2	1	5

Characteristics	DAA cohort therapy				
	All	**SOF/LED**	**SOF/VEL**	**GRZ/ELB**	**PrOD**
	(n=1564)	**(n=989)**	**(n=335)**	**(n=170)**	**(n=70)**
			n (%)		
Sociodemographic features					
	346 (95)	66 (96)	79 (94)	44 (94)	7 (93)
Mental Health and Substance Use Features					
Mental health disturbance					
No	9 82 (63)	6 22 (63)	2 08 (62)	1 16 (69)	3 6 (51)
Yes	5 76 (37)	3 64 (37)	1 25 (38)	5 3 (31)	3 4 (49)
Alcohol abuse					
No	1 327 (85)	8 45 (86)	2 79 (84)	1 47 (87)	5 6 (80)
Yes	2 29 (15)	1 38 (14)	5 5 (16)	2 2 (13)	1 4 (20)
Substance use					
No	1 205 (77)	7 70 (78)	2 44 (73)	1 33 (78)	5 8 (83)
Yes	3 52 (23)	2 15 (22)	8 8 (27)	3 7 (22)	1 2 (17)

NOTE: DAA: Direct-Acting Antiviral, SOF/LED: sofosbuvir/ledipasvir, SOF/VEL: sofosbuvir/velpatasvir, GRZ/ELB: grazoprevir/elbasvir, PrOD: paritaprevir/ombitasvir/ritonavir + dasabuvir, MELD: Model for End-Stage Liver Disease, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, SVR: Sustained Virologic Response. Missing values for all characteristics were ≤4%, except MELD and SVR were missing for 16%−29% and 10%−13% of patients, respectively.

Table 2.

Patient characteristics stratified by SVR status

Characteristics	SVR(n=1346)	Non-SVR(n=64)	Lost to Follow-Up(n=140)
		n (%)	
Sociodemographic features			
Age, years (mean (SD))	59 (10)	60 (8)	50 (12)
<35	63 (5)	1 (2)	21 (15)
35–55	293 (22)	15 (23)	62 (44)
>55	990 (73)	48 (75)	57 (41)
Sex			
Male	739 (55)	40 (62)	77 (55)
Female	607 (45)	24 (38)	63 (45)
Race			
Black	443 (33)	25 (39)	40 (29)
White	814 (61)	37 (58)	94 (67)
Other	84 (6)	2 (3)	6 (4)
Education			
≤ High school diploma or equivalent	721 (54)	32 (52)	79 (57)
> High school	613 (46)	30 (48)	60 (43)
Annual household income			
< $40K	956 (73)	42 (69)	123 (89)
≥ $40K	358 (27)	19 (31)	15 (11)
Employment			
Working full or part time	480 (37)	23 (38)	35 (25)
Receiving/applying for disability	567 (44)	30 (49)	69 (51)
Unemployed	84 (6)	1 (2)	23 (17)
Retired/homemaker/student	171 (13)	7 (11)	9 (7)
Liver Clinical, Treatment and Laboratory Markers			
Genotype			
Genotype 1, 4 or 6	1110 (83)	54 (84)	111 (79)
Genotype 2	114 (9)	5 (8)	16 (12)
Genotype 3	106 (8)	5 (8)	13 (9)
Cirrhosis status			
Cirrhotic	626 (47)	36 (56)	67 (49)
Noncirrhotic	716 (53)	28 (44)	69 (51)
MELD status in cirrhotic patients			
MELD 6–11	451 (87)	29 (88)	45 (85)
MELD ≥ 12	70 (13)	4 (12)	8 (15)
AST to Platelet Ratio Index (APRI)			
APRI ≤ 2.0	1118 (86)	47 (80)	117 (87)
APRI > 2.0	175 (14)	12 (20)	18 (13)
ALT, U/L (mean (SD))	77 (68)	85 (68)	87 (82)

Characteristics	SVR(n=1346)	Non-SVR(n=64)	Lost to Follow-Up(n=140)
		n (%)	
Sociodemographic features			
Creatinine, mg/dL (mean(SD))	1 (1)	1 (0)	1 (1)
Health comorbidities			
0–1	270 (20)	8 (13)	36 (26)
2–3	326 (24)	22 (34)	46 (33)
≥4	748 (56)	34 (53)	58 (41)
Current kidney disease			
No	1256 (94)	60 (95)	137 (98)
Yes	80 (6)	3 (5)	3 (2)
Treatment experience			
Treatment naive	1099 (82)	43 (67)	110 (91)
Treatment experienced	246 (18)	21 (33)	11 (9)
Prescribed treatment duration			
8 weeks	139 (10)	5 (8)	9 (6)
12 weeks	1101 (82)	51 (80)	123 (88)
16 or 24 weeks	106 (8)	8 (13)	8 (6)
Ribavirin			
Without Ribavirin	1171 (87)	52 (81)	127 (91)
With Ribavirin	175 (13)	12 (19)	13 (9)
Mental Health and Substance Use Features			
Mental health disturbance			
No	867 (65)	41 (64)	65 (46)
Yes	473 (35)	23 (36)	75 (54)
Alcohol abuse			
No	1144 (85)	52 (81)	117 (84)
Yes	195 (15)	12 (19)	22 (16)
Substance use			
No	1039 (78)	47 (73)	107 (76)
Yes	300 (22)	17 (27)	33 (24)

NOTE: DAA: Direct-Acting Antiviral, SVR: Sustained Virologic Response, MELD: Model for End-Stage Liver Disease, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase. Missing values for all characteristics were ≤5%, except MELD was missing for 8%−21% of patients, and Treatment Experience was missing for 14% of the lost to follow-up patients.