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***Retrospective Cohort Study***

**Direct-acting antivirals for chronic hepatitis C treatment: The experience of two tertiary university centers in Brazil**

Lourenço MS *et al*. Interferon-free therapy for HCV in Brazil

Mariana Sandoval Lourenço, Patricia Momoyo Y Zitelli, Marlone Cunha-Silva, Arthur Ivan N Oliveira, Cláudia P Oliveira, Tiago Sevá-Pereira, Flair José Carrilho, Mario G Pessoa, Daniel F Mazo

**Mariana Sandoval Lourenço, Marlone Cunha-Silva, Tiago Sevá-Pereira, Daniel F Mazo,** Division of Gastroenterology, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Sao Paulo 13083-878, Brazil

**Patricia Momoyo Y Zitelli, Arthur Ivan N Oliveira, Cláudia P Oliveira, Flair José Carrilho, Mario G Pessoa, Daniel F Mazo,** Division of Clinical Gastroenterology and Hepatology, Department of Gastroenterology, University of São Paulo School of Medicine, Sao Paulo 05403-900, Brazil

**Author contributions:** Lourenço MS and Mazo DF conceived the idea, designed the study, took care of patients, collected and assembled the data, contributed to the data analysis and interpretation and wrote the manuscript; Zitelli PMY, Cunha-Silva M and Oliveira AIN took care of patients, collected and assembled the data; Oliveira CP, Sevá-Pereira T, Carrilho FJ and Pessoa MG critically reviewed the manuscript; All authors approved the final version of the manuscript for publication.

**Corresponding author: Daniel F Mazo, MD, PhD, Medical Assistant, Professor,** Division of Gastroenterology, Department of Internal Medicine, School of Medical Sciences, University of Campinas, Rua Carlos Chagas 420, São Paulo 13083-878, Brazil. dmazo@unicamp.br

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**Abstract**

BACKGROUND

Hepatitis C virus (HCV) treatment has undergone major changes in recent years. Previous interferon-based therapies have been replaced by oral direct-acting antivirals (DAA) regimens, with high sustained virologic response (SVR) rates, and a lower incidence of adverse events (AEs).

AIM

To evaluate the efficacy and safety of DAAs for HCV treatment in subjects from two tertiary university centers in Brazil.

METHODS

This is a multicenter retrospective cohort study of 532 patients with chronic hepatitis C (CHC), undergoing treatment with interferon-free regimens from November 2015 to November 2019. The therapeutic regimen was defined by the current Brazilian guidelines for HCV management at the time of treatment. Demographic, anthropometric, clinical, and laboratory variables were evaluated. SVRs were assessed at 12 to 24 wk after therapy by intention-to-treat (ITT), and modified ITT (m-ITT) analysis. AEs and serious adverse events (SAEs) were registered. In the statistical analysis, a *P* value of < 0.05 was considered significant.

RESULTS

The mean age was 56.88 years, with 415 (78.5%) being HCV genotype 1, followed by genotype 3 (20.1%). Moreover, 306 (57.5%) subjects had cirrhosis, and a third of them had decompensated cirrhosis. Sofosbuvir (SOF) plus daclatasvir ± ribavirin was the most frequently used treatment (66.9%), followed by SOF plus simeprevir (21.2%). The overall ITT SVR was 92.6% (493/532), while the m-ITT SVR was 96.8% (493/509). Variables associated with treatment failure *via* ITT evaluation were hepatic encephalopathy (OR: 4.320; 95%CI: 1.920-9.721, *P* = 0.0004), presence of esophageal varices (OR: 2.381; 95%CI: 1.137-4.988, *P* = 0.0215), previous portal hypertensive bleeding (OR: 2.756; 95%CI: 1.173-6.471, *P* = 0.02), higher model for end-stage liver disease scores (OR: 1.143, 95%CI: 1.060–1.233, *P* = 0.0005), lower serum albumin levels (OR: 0.528, 95%CI: 0.322-0.867, *P* = 0.0115), higher serum creatinine (OR: 1.117, 95%CI: 1.056-1.312, *P* = 0.0033), and international normalized ratio (INR) levels (OR: 5.542, 95%CI: 2.023-15.182, *P* = 0.0009). AEs were reported in 41.1% (211/514) of patients, and SAEs in 3.7%. The female gender, higher body mass index, esophageal varices, higher INR values, and longer treatment duration were independently associated with AE occurrence.

CONCLUSION

Treatment with oral DAAs attains a high SVR rate, with fewer SAEs in a real-life cohort of subjects with CHC, from two tertiary university centers in Brazil.

**Key Words:** Chronic hepatitis C; Antiviral agents; Hepatitis C virus; Sustained virologic response; Liver cirrhosis; Safety

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**Core Tip:** Hepatitis C virus treatment has recently undergone major changes. In this multicenter retrospective cohort study of 532 patients with chronic hepatitis C treated with oral direct-acting antiviral regimens, the overall intention-to-treat (ITT) sustained virologic response (SVR) was 92.6% (493/532), and the modified-ITT SVR was 96.8% (493/509). Advanced liver disease was related to treatment failure. Adverse events (AEs) were reported in 41.1% (211/514) of patients, and serious AEs in 3.7%. The female gender, higher body mass index, presence of esophageal varices, higher international normalized ratio values, and longer treatment were independently linked to AE occurrence.

**INTRODUCTION**

Hepatitis C represents a global health problem. It is estimated that there are approximately 71 million people on a global basis who are chronically infected with the hepatitis C virus (HCV), with a prevalence of 1.1%[1]. However, many carriers are unaware of the infection, and do not receive treatment[2]. Despite the rising prevalence of metabolic-dysfunction associated fatty liver disease, HCV is a major cause of cirrhosis, and hepatocellular carcinoma (HCC) worldwide[3]. It is estimated that 0.53% of the total Brazilian population has antibodies against HCV, while in 2019, this virus was the leading cause of death for viral hepatitis in Brazil[4,5].

The main objective of therapy is the eradication of the virus, defined as sustained virologic response (SVR), associated with a reduction of liver inflammation and fibrosis, and the incidence of hepatic decompensation and HCC[6]. In addition, SVR leads to a decrease in mortality from both hepatic and non-hepatic causes[7,8].

HCV treatment has undergone major changes to date[9]. Previous interferon-based therapies with lower SVR rates and several adverse events (AEs)[9] were replaced by oral direct-acting antiviral (DAA) regimens, with SVR rates greater than 90% and a lower incidence of AEs[10-13]. Significant advances in the understanding and management of this disease started over twenty years ago[14]. These early efforts were recognized by the 2020 Nobel Prize in Physiology or Medicine[15].

In Brazil, acquiring and dispensing of all oral DAA regimens for patients with chronic hepatitis C (CHC) was provided through the Sistema Unico de Saude, the national public healthcare system[16]. There are few studies in large centers showing experience with DAAs in patients with chronic HCV infection. So, the aim of this study was to evaluate the efficacy and safety of DAAs for treatment of HCV-infected patients from two tertiary university centers in the southeastern region of the country.

**MATERIALS AND METHODS**

***Study design and patient selection***

This is a multicenter retrospective cohort study, carried out at the liver outpatient clinics of the Division of Gastroenterology at the University of Campinas (UNICAMP), and the Department of Gastroenterology at the University of São Paulo School of Medicine (FMUSP) for patients with CHC, who underwent treatment with interferon-free regimens from November 2015 to November 2019.

Inclusion criteria were: (1) age ≥ 18 years and the presence of CHC, defined by HCV RNA positivity through a polymerase chain reaction (PCR) for at least 6 mo, regardless of the HCV genotype; and (2) those treated with oral DAAs. Exclusion criteria were: diagnosis of any other liver disease, human immunodeficiency virus, or hepatitis B virus coinfection, active HCC, liver transplant recipients, previous treatment for HCV with interferon-free regimens, and lack of information on the current HCV treatment.

***HCV treatment regimen***

The therapeutic regimen was defined by the current Brazilian guidelines for HCV management at the time of treatment[16-18]. HCV therapy was composed of the DAAs: sofosbuvir (SOF), daclatasvir (DCV), simeprevir (SMV), ledipasvir, and the combined regimen ombitasvir plus veruprevir/ritonavir plus dasabuvir. Ribavirin (RBV) was also used. Relevant drug-drug interactions were checked prior to use of DAAs.

***Variables evaluated***

Demographic and anthropometric variables [age, gender, body mass index (BMI)], presence of comorbidities (arterial hypertension, diabetes mellitus, dyslipidemia, hypothyroidism, psychiatric disorders, previous alcohol use), and laboratory variables were evaluated through computerized medical records. Serum biochemical assessment was conducted before treatment, and 12 to 24 wk after the end of treatment, as per routine clinical practice. Serum HCV-RNA levels were assessed with real-time PCR and the Amplicor HCV Monitor 2.0 test (Abbott Molecular, Des Plaines, IL, United States, detection limit: 12 IU/mL). Viral genotyping was performed with Versant® HCV Genotype 2.0 LiPA test (Imunogenetics, Ghent, Belgium).

The staging of hepatic fibrosis was assessed prior to treatment with histology, according to the Metavir classification, or use of non-invasive methods (transient elastography, APRI, and FIB-4). In patients with cirrhosis, Child-Pugh and model for end-stage liver disease (MELD) scores were also assessed.

***HCV treatment efficacy analysis***

SVR was defined as undetectable HCV-RNA at 12 or 24 wk following treatment. An intention-to-treat (ITT) analysis was performed, considering patients who abandoned treatment, were lost to follow-up, or did not have complete information about their medical records, seen as virologic failures. A modified intention-to-treat (m-ITT) analysis was carried out, excluding efficacy for patients lost to follow-up, or who discontinued therapy, or any deaths unrelated to treatment or its adverse events.

***Safety assessment***

The analysis of AE was classified according to the Common Terminology Criteria for Adverse Events[19]. Management of anemia was considered with a drop in hemoglobin (Hb) greater than 3 points or associated symptoms if Hb > 10 g/dL. Anemia was classified into grade 1 (Hb 10-8 g/dL), grade 2 (Hb < 8 g/dL or need for a blood transfusion), grade 3 (risk of death), and grade 4 (death). Serious adverse events (SAEs) were considered: (1) hepatic decompensation; (2) need for hospitalization; (3) need to discontinue treatment; and (4) events resulting in death[20].

***Ethical aspects***

This study was approved by the Ethics Committee of UNICAMP and Clinics Hospital of FMUSP (Approval No. 2042967 and 2670862, respectively). The protocol was conducted in accord with the ethical guidelines of the 2013 World Medical Association Declaration of Helsinki[21]. Informed consent was waived for participants.

***Statistical analysis***

To describe the sample according to the variables under study, frequency tables of categorical variables with absolute frequency (*n*) and percentage (%) values, as well as descriptive statistics of numerical variables, with mean and standard deviation were used. To assess the relationship between categorical variables, the Chi-square test and, when necessary, Fisher's exact test were used. For numerical variables, the Mann-Whitney test was utilized. To assess factors related to treatment failure and AEs, univariate and multivariate logistic regression was performed whenever methodologically feasible. The selection of variables in the multivariate logistic regression analysis was done in a stepwise manner. Odds ratio (OR) and 95%CI were calculated. A *P* value of < 0.05 was considered significant. The Statistical Analysis System (SAS) for Windows software package, version 9.4 (SAS Institute Inc, 2002-2008, Cary, NC, United) was used for statistical analyses by biomedical statisticians from the Statistics Service at the School of Medical Sciences of the University of Campinas.

**RESULTS**

***Baseline characteristics***

A total of 532 patients treated with DAAs were included in the study. There was a slight predominance of males, with the mean age of 56.88 years. The mean BMI was 27.01, with most patients having comorbidities, mainly arterial hypertension and diabetes mellitus. There was a predominance of patients with HCV genotype 1 (78.5%), followed by genotype 3 (20.1%). Over 50% of patients were treatment-experienced. Three hundred six (57.5%) patients had cirrhosis, and a third had decompensated liver disease. The main baseline for demographic, clinical, and laboratory characteristics of the study population are shown in Table 1.

***HCV therapeutic regimens and efficacy analysis***

The combination of SOF plus DCV, associated with RBV, was the most frequently used treatment (66.9%), followed by SOF plus SMV (21.2%). Table 2 shows HCV treatment regimens in the study population. The overall ITT SVR rate was 92.6% (493/532), and the m-ITT SVR rate was 96.8% (493/509). Twenty-three patients were lost to follow-up, with no conclusive SVR data at the end of treatment (Table 3). In the ITT analysis, pretreatment variables related to treatment failure were a higher MELD score (*P* = 0.001), higher serum levels of aspartate aminotransferase (AST) and international normalized ratio (INR) (*P* = 0.043 and *P* = 0.023, respectively), lower serum albumin levels (*P* = 0.032), and a higher frequency of liver-related complications [hepatic encephalopathy (*P* = 0.001), esophageal varices (*P* = 0.018), and previous portal hypertensive bleeding (*P* = 0.039)], as shown in Table 4.

When assessing m-ITT SVR, the presence of cirrhosis (*P* = 0.049), higher serum values of AST (*P* = 0.030), higher MELD scores (*P* = 0.004), presence of hepatic encephalopathy (*P* = 0.006), and male gender (*P* = 0.049) negatively impacted SVR achievement. Genotype 3 HCV patients had numerically lower SVR rates than non-genotype 3 subjects (93% *vs* 97.7%-100%), almost reaching statistical significance (*P* = 0.055). In the univariate logistic regression analysis, baseline variables associated with treatment failure by ITT evaluation were: hepatic encephalopathy (OR: 4.320; 95%CI: 1.920-9.721, *P* = 0.0004), presence of esophageal varices (OR: 2.381; 95%CI: 1.137-4.988, *P* = 0.0215), previous portal hypertensive bleeding (OR: 2.756; 95%CI: 1.173-6.471, *P* = 0.02), higher MELD scores (OR: 1.143, 95%CI: 1.060–1.233, *P* = 0.0005), lower serum albumin levels (OR: 0.528, 95%CI: 0.322-0.867, *P* = 0.0115), higher serum creatinine (OR: 1.117, 95%CI: 1.056-1.312, *P* = 0.0033), and INR levels (OR: 5.542, 95%CI: 2.023-15.182, *P* = 0.0009), shown in Table 5. It was not possible to perform multivariate logistic regression analysis, due to the low occurrence of non-responders and missing data.

***Safety analysis***

AEs were reported in 41.1% (211/514) of patients. The most frequent AE was fatigue, present in 140 patients (27.7%), followed by anemia in 87 patients (17.2%) and headache in 47 patients (9.3%). Anemia or a fall in hemoglobin ≥ 2 g/dL points occurred in 87 patients (17.2%). Of these, only one patient did not use RBV, and already had a hemoglobin of 11.2 g/dL before treatment. Of 312 patients who used RBV, 86 (27.5%) had a drop in hemoglobin during treatment, 61 required a dose reduction, and 15 had RBV suspended. Five patients required treatment with erythropoietin, and 4 required blood transfusion. SAE occurred in 20 patients (3.7%), as 14 had decompensation of their liver disease, with 7 hospitalized. Three patients died during the study evaluation.

In the univariate logistic regression analysis, baseline factors associated with the occurrence of AE were female gender (OR: 1.718, 95%CI: 1.205-2.450, *P* = 0.0028), higher BMI (OR: 1.060, 95%CI: 1.019-1.102, *P* = 0.0040), presence of cirrhosis (OR: 2.127, 95%CI: 1.476-3.065, *P* < 0.0001), liver-related complications [ascites (OR: 2.187, 95%CI: 1.352-3.536, *P* = 0.0014), hepatic encephalopathy (OR: 3.524, 95%CI: 1.762-7.044, *P* = 0.0004), and the presence of esophageal varices (OR: 2.795, 95%CI: 1.874-4.169, *P* ≤ 0.0001)], higher MELD (OR: 1.071, 95%CI: 1.019-1.126, *P* = 0.0073) and Child-Pugh scores (OR: 1.196, 95%CI: 1.014-1.410, *P* = 0.0332), lower serum albumin (OR: 0.432, 95%CI: 0.314-0.595, *P* < 0.0001), higher bilirubin (OR: 1.283, 95%CI: 1.052-1.564, *P* = 0.0138) and INR values (OR: 3.835, 95%CI: 1.539-9.560, *P* = 0.0039), higher RBV daily dose (OR: 1.249, 95%CI: 1.132-1.379, *P* < 0.0001), and longer treatment duration (OR: 1.071, 95%CI: 1.034-1.109, *P* = 0.0001), as shown in Table 6. Factors independently associated with AE occurrence were female gender (OR: 2.191, 95%CI: 1.145-1.192, *P* = 0.0178), higher BMI (OR: 1.107, 95%CI: 1.038-1.180, *P* = 0.0020), presence of esophageal varices (OR: 3.463, 95%CI: 1.688-7.105, *P* = 0.0007), higher INR values (OR: 3.748, 95%CI: 1.060-13.251, *P* = 0.0403), and longer treatment duration (OR: 1.062, 95%CI: 1.003-1.125, *P* = 0.0406).

**DISCUSSION**

This study evaluated the efficacy and safety of all oral DAAs for CHC treatment in a cohort of 532 patients, followed at two Brazilian tertiary university centers. Most patients were HCV genotype 1, with a slight predominance of males, similar to that found in other studies carried out in our country[22-24].

Our results show the high effectiveness of DAAs in this real-life cohort, reaching global SVR rates of 92.6% in the ITT analysis, and 96.8% in the m-ITT evaluation. However, lower rates of m-ITT SVR were observed in patients with cirrhosis. Advanced liver disease negatively impacts response to treatment, especially in those with decompensated disease, who are considered a more difficult group to treat[25-27]. Although SOF plus DCV was the most common regimen in the present study, it is interesting to cite that other effective treatments have been made available, such as SOF plus velpatasvir, elbasvir plus grazoprevir and glecaprevir plus pibrentasvir, for both naïve and DAA experienced patients[6]. SOF plus velpatasvir plus RBV was effective in patients with decompensated cirrhosis[6]. Treatments with drug combinations might be important to ultimately control the emergence of resistance-associated substitutions, and as rescue therapy for non-responders[6,28].

In the m-ITT SVR analysis, HCV genotype 3 individuals had an almost significant lower SVR rate in comparison to non-genotype 3 patients. Published data show that HCV genotype 3, previously considered an “easy to treat” genotype in the interferon era, with cure rates of up to 70%, turned out to be more challenging in the DAA era, with lower SVR rates compared to other HCV genotypes[26,27]. HCV genotype 3 interferes with the metabolism of lipids and glucose, and is associated with an increased risk of progressing to cirrhosis and HCC, which may negatively impact SVR rates[29,30]. SOF plus pegylated-interferon and RBV for 12 wk is also a treatment option in HCV genotype 3 patients[31-33].

In the m-ITT SVR analysis, we observed that HCV therapeutic failure was linked to male gender, higher MELD scores and AST values, presence of cirrhosis and hepatic encephalopathy. In the ITT analysis, lower serum albumin, higher creatinine and INR levels, history of hepatic encephalopathy, esophageal varices, and upper gastrointestinal bleeding were related to lower SVR rates. Several of these factors reflect advanced liver disease. Less severe disease, with lower Child-Pugh scores and serum bilirubin values and higher albumin levels, were associated with a greater chance of achieving SVR[34,35]. A large Spanish cohort of over 3000 patients showed that high values of transient elastography, cirrhosis, serum levels of bilirubin, and albumin values < 3.5 g/dL were significantly associated with therapeutic failure[36]. In Brazil, a 2018 study of 527 patients showed that in those with cirrhosis, the factors associated with SVR were lower MELD scores, higher albumin values, and glomerular filtration rates[37].

AEs were present in 41.1% of the study population, the main ones being fatigue, anemia, and headache; while only 3.7% subjects had SAEs. Our results reinforce the safety of DAAs for the treatment of hepatitis C in the Brazilian population. However, our AE rates were lower than the rates reported in other studies in our country, in which AEs are described in up to 90% of treated patients[38], and SAEs in up to 8.5% of cases[39]. The retrospective study design and possible underreport of AEs on medical charts, could justify the lower AE rate in the present cohort. In addition, more than half of our study population included patients without cirrhosis or with compensated liver disease, in which treatment is safer[39,40]. In our study, the main factors associated with the occurrence of AEs in the univariate logistic regression analysis were female gender, higher BMI, higher Child-Pugh and MELD scores, presence of cirrhosis and its complications, lower values of albumin, higher values of bilirubin and INR, use of ribavirin, and longer treatment. Patients with decompensated cirrhosis, in addition to having lower SVR rates, were also more likely to experience treatment-related AEs, which leads to earlier discontinuation of therapy and, in part, justifies its lower efficacy[41]. In Brazil, a study with 214 patients showed that the factors of HCV treatment discontinuation were advanced age, multiple comorbidities, higher MELD score, higher fibrosis index, and lower hemoglobin[39].

This study has some limitations. Despite the large number of patients, it is a retrospective study, relying on data from medical records. In addition, it was carried out in two public reference centers for hepatology and liver transplantation, which may incur a selection bias for more severe patients. Yet, this study evaluated a large Brazilian cohort of patients with decompensated cirrhosis.

**CONCLUSION**

In conclusion, in this cohort of patients with CHC followed at two public healthcare facilities in the southeastern region of Brazil, treatment with DAAs proved to be effective, with global SVR rates above 92%, and safe, with a low occurrence of SAEs.

**ARTICLE HIGHLIGHTS**

***Research background***

Hepatitis C represents a global health problem and a major cause of cirrhosis, and hepatocellular carcinoma. Hepatitis C virus (HCV) treatment has undergone major changes in recent years with the advent of direct-acting antivirals (DAA) regimens.

***Research motivation***

In Brazil, acquiring and dispensing of all oral DAA regimens for patients with chronic hepatitis C (CHC) is provided through the national public healthcare system. However, there are few studies in large centers showing experience with DAAs in patients with chronic HCV infection.

***Research objectives***

We aimed to evaluate the efficacy and safety of DAAs for HCV treatment in subjects from two tertiary public university centers in the southeastern region of Brazil.

***Research methods***

We evaluated 532 adult patients with CHC who underwent treatment with interferon-free regimens from November 2015 to November 2019. Demographic, anthropometric, clinical, and laboratory variables were evaluated. Sustained virologic response (SVR) rates were assessed at 12 to 24 wk after therapy by intention-to-treat (ITT), and modified ITT (m-ITT) analysis. Adverse events (AEs) and serious adverse events (SAEs) were registered.

***Research results***

Sofosbuvir (SOF) plus daclatasvir ± ribavirin was the most frequently used treatment (66.9%), followed by SOF plus simeprevir (21.2%). The overall ITT SVR was 92.6% (493/532), while the m-ITT SVR was 96.8% (493/509). Variables associated with treatment failure *via* ITT evaluation were hepatic encephalopathy, presence of esophageal varices, previous portal hypertensive bleeding, higher model for end-stage liver disease scores, lower serum albumin levels, and higher serum creatinine and international normalized ratio (INR) levels. AEs were reported in 41.1% (211/514) of patients, and SAEs in 3.7%. The female gender, higher body mass index, esophageal varices, higher INR values, and longer treatment duration were independently associated with AE occurrence.

***Research conclusions***

Treatment with oral DAAs attains a high SVR rate, with fewer SAEs in a real-life cohort of subjects with CHC, from two tertiary university centers in Brazil.

***Research perspectives***

Long-term follow-up studies of patients after successful HCV eradication are important.

**REFERENCES**

1 **World Health Organization**. Global hepatitis report, 2017 [cited 2021 Mar 24]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

2 **World Health Organization**. Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva: World Health Organization 2018 [cited 2021 Mar 24]. Available from: http://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf

3 **Polaris Observatory HCV Collaborators.** Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2**: 161-176 [PMID: 28404132 DOI: 10.1016/S2468-1253(16)30181-9]

4 **Benzaken AS**, Girade R, Catapan E, Pereira GFM, Almeida EC, Vivaldini S, Fernandes N, Razavi H, Schmelzer J, Ferraz ML, Ferreira PRA, Pessoa MG, Martinelli A, Souto FJD, Walsh N, Mendes-Correa MC. Hepatitis C disease burden and strategies for elimination by 2030 in Brazil. A mathematical modeling approach. *Braz J Infect Dis* 2019; **23**: 182-190 [PMID: 31145876 DOI: 10.1016/j.bjid.2019.04.010]

5 **Ministério da Saúde do Brasil.** Secretaria de Vigilância em Saúde. Boletim Epidemiológico de Hepatites Virais-2020. Brasilia, Brazil, 2020 [cited 2021 Mar 24]. Available from: http://www.aids.gov.br/pt-br/pub/2020/boletim-epidemiologicohepatites-virais-2020

6 **European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu.**; Clinical Practice Guidelines Panel: Chair:; EASL Governing Board representative:; Panel members:. EASL recommendations on treatment of hepatitis C: Final update of the series☆. *J Hepatol* 2020; **73**: 1170-1218 [PMID: 32956768 DOI: 10.1016/j.jhep.2020.08.018]

7 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]

8 **Tada T**, Kumada T, Toyoda H, Kiriyama S, Tanikawa M, Hisanaga Y, Kanamori A, Kitabatake S, Yama T, Tanaka J. Viral eradication reduces all-cause mortality, including non-liver-related disease, in patients with progressive hepatitis C virus-related fibrosis. *J Gastroenterol Hepatol* 2017; **32**: 687-694 [PMID: 27577675 DOI: 10.1111/jgh.13589]

9 **Martinello M**, Bajis S, Dore GJ. Progress Toward Hepatitis C Virus Elimination: Therapy and Implementation. *Gastroenterol Clin North Am* 2020; **49**: 253-277 [PMID: 32389362 DOI: 10.1016/j.gtc.2020.01.005]

10 **Nelson DR**, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, Thuluvath PJ, Ortiz-Lasanta G, Rabinovitz M, Bernstein D, Bennett M, Hawkins T, Ravendhran N, Sheikh AM, Varunok P, Kowdley KV, Hennicken D, McPhee F, Rana K, Hughes EA; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; **61**: 1127-1135 [PMID: 25614962 DOI: 10.1002/hep.27726]

11 **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM; AI444040 Study Group. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

12 **Lawitz E**, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, Godofsky E, Herring RW, Poleynard G, Sheikh A, Tobias H, Kugelmas M, Kalmeijer R, Peeters M, Lenz O, Fevery B, De La Rosa G, Scott J, Sinha R, Witek J. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2). *Hepatology* 2016; **64**: 360-369 [PMID: 26704148 DOI: 10.1002/hep.28422]

13 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]

14 **Feinstone SM**, Kapikian AZ, Purcell RH, Alter HJ, Holland PV. Transfusion-associated hepatitis not due to viral hepatitis type A or B. *N Engl J Med* 1975; **292**: 767-770 [PMID: 163436 DOI: 10.1056/NEJM197504102921502]

15 **Burki T**. Nobel Prize for hepatitis C virus discoverers. *Lancet* 2020; **396:** 1058. [PMID: 33038954 DOI: 10.1016/S0140-6736(20)32111-5]

16 **Ministério da Saúde**. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite C e Coinfecções/ Ministério da Saúde. Brasília: Ministério da Saúde, 2015 [cited 2021 Mar 24]. Available from: http://www.aids.gov.br/

17 **Ministério da Saúde**. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite C e Coinfecções/ Ministério da Saúde. Brasília: Ministério da Saúde, 2018 [cited 2021 Mar 24]. Available from: http://www.aids.gov.br/

18 **Ministério da Saúde**. Secretaria de Vigilância em Saúde, Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite C e Coinfecções/ Ministério da Saúde. Brasilia: Ministério da Saúde, 2019 [cited 2021 Mar 24]. Available from: http://www.aids.gov.br/

19 **National Institutes of Health National Cancer Institute**. CTCAE 4.03 Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. May 28, 2009. US Department of Health and Human Services [cited 2021 Mar 24]. Available from: https://www.eortc.be/services/doc/ctc/

20 **Maan R**, van Tilborg M, Deterding K, Ramji A, van der Meer AJ, Wong F, Fung S, Sherman M, Manns MP, Cornberg M, Hansen BE, Wedemeyer H, Janssen HL, de Knegt RJ, Feld JJ. Safety and Effectiveness of Direct-Acting Antiviral Agents for Treatment of Patients With Chronic Hepatitis C Virus Infection and Cirrhosis. *Clin Gastroenterol Hepatol* 2016; **14**: 1821-1830.e6 [PMID: 27404965 DOI: 10.1016/j.cgh.2016.07.001]

21 **World Medical Association.** World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**: 2191-2194 [PMID: 24141714 DOI: 10.1001/jama.2013.281053]

22 **Cheinquer H**, Sette H Jr, Wolff FH, de Araujo A, Coelho-Borges S, Soares SRP, Barros MFA. Treatment of Chronic HCV Infection with the New Direct Acting Antivirals (DAA): First Report of a Real World Experience in Southern Brazil. *Ann Hepatol* 2017; **16**: 727-733 [PMID: 28809742 DOI: 10.5604/01.3001.0010.2717]

23 **Holzmann I**, Tovo CV, Minmé R, Leal MP, Kliemann MP, Ubirajara C, Aquino AA, Araujo B, Almeida PRL. Effectiveness of chronic hepatitis C treatment with direct-acting antivirals in the Public Health System in Brazil. *Braz J Infect Dis* 2018; **22**: 317-322 [PMID: 30036490 DOI: 10.1016/j.bjid.2018.06.004]

24 **Lobato CMO**, Codes L, Silva GF, Souza AFM, Coelho HSM, Pedroso MLA, Parise ER, Lima LMSTB, Borba LA, Evangelista AS, Rezende REF, Cheinquer H, Kuniyoshi ASO, Aires RS, Quintela EHD, Mendes LSC, Nascimento FCV, Medeiros Filho JEM, Ferraz MLCG, Abdala E, Bittencourt PL; Members of the Brazilian Real-Life Study about HCV treatment; Members of the Brazilian Real-Life Study about HCV treatment. Direct antiviral therapy for treatment of hepatitis C: A real-world study from Brazil. *Ann Hepatol* 2019; **18**: 849-854 [PMID: 31537509 DOI: 10.1016/j.aohep.2019.08.001]

25 **Falade-Nwulia O**, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Ann Intern Med* 2017; **166**: 637-648 [PMID: 28319996 DOI: 10.7326/M16-2575]

26 **Macken L**, Gelson W, Priest M, Abouda G, Barclay S, Fraser A, Healy B, Irving W, Verma S. Efficacy of direct-acting antivirals: UK real-world data from a well-characterised predominantly cirrhotic HCV cohort. *J Med Virol* 2019; **91**: 1979-1988 [PMID: 31329295 DOI: 10.1002/jmv.25552]

27 **Daniel KE**, Saeian K, Rizvi S. Real-world experiences with direct-acting antiviral agents for chronic hepatitis C treatment. *J Viral Hepat* 2020; **27**: 195-204 [PMID: 31602715 DOI: 10.1111/jvh.13218]

28 **Sarrazin C**. Treatment failure with DAA therapy: Importance of resistance. *J Hepatol* 2021; **74**: 1472-1482 [PMID: 33716089 DOI: 10.1016/j.jhep.2021.03.004]

29 **Ampuero J**, Romero-Gómez M, Reddy KR. Review article: HCV genotype 3 – the new treatment challenge. *Aliment Pharmacol Ther* 2014; **39**: 686-698 [PMID: 24612116 DOI: 10.1111/apt.12646]

30 **Gondeau C**, Pageaux GP, Larrey D. Hepatitis C virus infection: Are there still specific problems with genotype 3? *World J Gastroenterol* 2015; **21**: 12101-12113 [PMID: 26576095 DOI: 10.3748/wjg.v21.i42.12101]

31 **Lawitz E**, Poordad F, Brainard DM, Hyland RH, An D, Dvory-Sobol H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir with peginterferon-ribavirin for 12 weeks in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology* 2015; **61**: 769-775 [PMID: 25322962 DOI: 10.1002/hep.27567]

32 **Grando AV**, Ferreira PRA, Pessôa MG, Mazo DFC, Brandão-Mello CE, Reuter T, Martinelli ALC, Gonzalez MP, Nastri ACS, Campos AF, Lopes MIBF, Brito JDU, Mendes-Corrêa MC. Peginterferon still has a place in the treatment of hepatitis C caused by genotype 3 virus. *Rev Inst Med Trop Sao Paulo* 2017; **59**: e67 [PMID: 29116287 DOI: 10.1590/S1678-9946201759067]

33 **Garioud A**, Heng R, Amiot X, Rémy AJ, Ollivier-Hourmand I, Mokhtari C, Medmoun M, Renou C, Zougmoré H, Pulwermacher P, Lucidarme D, Rosa-Hézode I, Causse X, Arotcarena R, Zanditenas D, Halfon P, Pariente A, Cadranel JF; Association Nationale des Hépato-gastroentérologues des Hôpitaux Généraux (ANGH), France. Efficacy and safety of treatment of chronic hepatitis C with sofosbuvir and ribavirin with or without peginterferon: a French prospective real-life cohort study of unselected 211 patients. *Eur J Gastroenterol Hepatol* 2019; **31**: 1270-1274 [PMID: 31219848 DOI: 10.1097/MEG.0000000000001450]

34 **Ohya K**, Imamura M, Teraoka Y, Morio K, Fujino H, Nakahara T, Ono A, Murakami E, Kawaoka T, Miki D, Tsuge M, Hiramatsu A, Aikata H, Hayes CN, Mori N, Takaki S, Tsuji K, Aisaka Y, Ishitobi T, Katamura Y, Kodama H, Nabeshima Y, Masaki K, Honda Y, Moriya T, Kohno H, Kohno H, Chayama K. Real-world efficacy of sofosbuvir plus velpatasvir therapy for patients with hepatitis C virus-related decompensated cirrhosis. *Hepatol Res* 2020; **50**: 1234-1243 [PMID: 32914512 DOI: 10.1111/hepr.13555]

35 **Gheorghe LS**, Preda C, Iliescu L, Istratescu D, Chifulescu AE, Pop CS, Trifan A, Stanciu C, Diculescu M, Voiosu T, Baicus C, Tugui L, Iacob S, Tieranu C, Meianu C, Manuc M. Efficacy and Safety of Ledispavir/Sofosbuvir with or without Ribavirin in patients with Decompensated Liver Cirrhosis and Hepatitis C Infection: a Cohort Study. *J Gastrointestin Liver Dis* 2020; **29**: 385-390 [PMID: 32919421 DOI: 10.15403/jgld-2448]

36 **Calleja JL**, Crespo J, Rincón D, Ruiz-Antorán B, Fernandez I, Perelló C, Gea F, Lens S, García-Samaniego J, Sacristán B, García-Eliz M, Llerena S, Pascasio JM, Turnes J, Torras X, Morillas RM, Llaneras J, Serra MA, Diago M, Rodriguez CF, Ampuero J, Jorquera F, Simon MA, Arenas J, Navascues CA, Bañares R, Muñoz R, Albillos A, Mariño Z; Spanish Group for the Study of the Use of Direct-acting Drugs Hepatitis C Collaborating Group. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. *J Hepatol* 2017; **66**: 1138-1148 [PMID: 28189751 DOI: 10.1016/j.jhep.2017.01.028]

37 **Miotto N**, Mendes LC, Zanaga LP, Lazarini MSK, Goncales ESL, Pedro MN, Goncales FL Jr, Stucchi RSB, Vigani AG. All-oral direct antiviral treatment for hepatitis C chronic infection in a real-life cohort: The role of cirrhosis and comorbidities in treatment response. *PLoS One* 2018; **13**: e0199941 [PMID: 29990371 DOI: 10.1371/journal.pone.0199941]

38 **Medeiros T**, Salviato CM, do Rosário NF, Saraiva GDN, Esberard EBC, Almeida JR, Xavier AR, da Silva AA. Adverse effects of direct acting antiviral-based regimens in chronic hepatitis C patients: a Brazilian experience. *Int J Clin Pharm* 2017; **39**: 1304-1311 [PMID: 29079938 DOI: 10.1007/s11096-017-0552-1]

39 **Miotto N**, Mendes LC, Zanaga LP, Goncales ESL, Lazarini MSK, Pedro MN, Gonçales FL Jr, Stucchi RSB, Vigani AG. Predictors of early discontinuation of interferon-free direct antiviral agents in patients with hepatitis C virus and advanced liver fibrosis: results of a real-life cohort. *Eur J Gastroenterol Hepatol* 2017; **29**: 1149-1154 [PMID: 28800033 DOI: 10.1097/MEG.0000000000000944]

40 **de Ávila Machado MA**, de Moura CS, Klein M, Winthrop K, Carleton B, Abrahamowicz M, Feld J, Curtis JR, Beauchamp ME, Bernatsky S. Direct-Acting Antivirals for Hepatitis C: Predictors of Early Discontinuation in the Real World. *J Manag Care Spec Pharm* 2019; **25**: 697-704 [PMID: 31134863 DOI: 10.18553/jmcp.2019.25.6.697]

41 **Mücke MM**, Mücke VT, Lange CM, Zeuzem S. Managing hepatitis C in patients with the complications of cirrhosis. *Liver Int* 2018; **38 Suppl 1**: 14-20 [PMID: 29427491 DOI: 10.1111/liv.13636]

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**Table 1 Characteristics of patients with hepatitis C virus (*n* = 532)**

|  |  |
| --- | --- |
|  | **HCV patients (*n* = 532), % (*n*) or mean ± SD** |
| Age (yr) | 56.88 ± 11.08 |
| Men/women | 51.1% (272)/48.9% (260) |
| High-blood pressure | 44.1% (231/524) |
| Type 2 diabetes | 29.7% (156/526) |
| BMI (*n* = 442) | 27.01 ± 4.99 |
| Dyslipidemia | 20.8% (109/524) |
| Hypothyroidism | 16.2% (85/524) |
| Psychiatric disorder | 10.2% (53/521) |
| Previous alcohol use | 19.2% (102/523) |
| HCV genotype |  |
| 1A | 37.0% (197) |
| 1B | 38.0% (202) |
| 1 non-classified | 3.5% (19) |
| 2 | 0.8% (4) |
| 3 | 20.1% (107) |
| 4 | 0.4% (2) |
| 5 | 0.2% (1) |
| HCV viral load (log IU/mL) | 5.78 ± 0.75 |
| Previous HCV treatment (n=525) |  |
| None | 46.3% (243) |
| Peg-IFN + RBV | 46.1% (242) |
| Peg-IFN + PI | 7.6% (40) |
| Liver fibrosis (Metavir classification) |  |
| F0/F1 | 8.8% (47) |
| F2 | 13.0% (69) |
| F3 | 20.7% (110) |
| F4 | 57.5% (306) |
| Liver-related complications (*n* = 306) |  |
| Ascites | 30.3% (93) |
| Esophageal varices | 72.0% (221) |
| Portal hypertensive bleeding | 15.6% (48) |
| Hepatic encephalopathy | 14.7% (45) |
| AST (U/L) | 61.41 ± 45.06 |
| ALT (U/L) | 61.87 ± 58.29 |
| Total bilirubin (mg/dL) | 1.13 ± 1.08 |
| Albumin (g/dL) | 4.15 ± 2.64 |
| Platelets (/mm3) | 141.82 ± 77.21 |
| INR | 1.18 ± 0.23 |
| Creatinine (mg/dL) | 1.31 ± 1.96 |
| Hemoglobin (g/dL) | 13.73 ± 1.90 |
| Alpha-fetoprotein (ng/mL) | 23.59 ± 103.61 |
| Child-Pugh classification (*n* = 306) |  |
| A | 66.6% (204) |
| B or C | 27.7% (85) |
| Non-classified | 5.7% (17) |
| Child-Pugh Score (*n* = 289) | 5.94 ± 1.54 |
| MELD Score | 10.17 ± 3.95 |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HCV: Hepatitis C virus; INR: International normalized ratio; MELD: Model for end-stage liver disease; Peg-IFN: Pegylated-interferon; PI: Protease inhibitor (boceprevir or telaprevir); RBV: Ribavirin.

**Table 2 Hepatitis C virus therapeutic regimens (*n* = 532)**

|  |  |
| --- | --- |
| **Features of treatment** | **% (*n*)** |
| Regimens |  |
| SOF + DCV + RBV | 49.2% (262) |
| SOF + SMV | 21.2% (113) |
| SOF + DCV | 17.7% (94) |
| SOF + SMV + RBV | 8.1% (43) |
| 3D | 2.3% (12) |
| 3D + RBV | 0.6% (3) |
| SOF + RBV | 0.6% (3) |
| SOF + LED | 0.2% (1) |
| SOF + LED + RBV | 0.2% (1) |
| Duration |  |
| 12 wk | 77.2% (411) |
| 24 wk | 22.8% (121) |
| Use of RBV | 58.6% (312) |
| Dose of RBV (mg/kg/day) mean ± SD | 12.11 ± 3.01 |

3D: Veruprevir/ritonavir, ombitasvir and dasabuvir; HCV: Hepatitis C virus; LED: Ledipasvir; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; DCV: Daclatasvir.

**Table 3** **Sustained virologic response rates according to therapeutic regimens, hepatitis C virus genotypes and cirrhosis**

|  |  |  |
| --- | --- | --- |
| **SVR** | **ITT (*n* = 532), % (*n*)** | **m-ITT (*n* = 509), % (*n*)** |
| Global | 92.6% (493/532) | 96.8% (493/509) |
| Genotype |  |  |
| 1 | 93.7% (392/418) | 97.7% (392/401) |
| 2 | 100% (4/4) | 100% (4/4) |
| 3 | 87.8% (94/107) | 93.0% (94/101) |
| 4 | 100% (2/2) | 100% (2/2) |
| 5 | 100% (1/1) | 100% (1/1) |
| Treatment regimen |  |  |
| 3D ± RBV | 100% (15/15) | 100% (15/15) |
| SOF + DCV | 86.1% (81/94) | 95.2% (81/85) |
| SOF + DCV + RBV | 94.2% (247/262) | 97.2% (247/254) |
| SOF + RBV | 100% (3/3) | 100% (3/3) |
| SOF + SMV | 92% (104/113) | 96.3% (104/108) |
| SOF + SMV + RBV | 95.3% (41/43) | 97.6% (41/42) |
| SOF + LED ± RBV | 100% (2/2) | 100% (2/2) |
| Presence of cirrhosis |  |  |
| No | 94.6% (214/226) | 98.6% (214/217) |
| Yes | 91.1% (279/306) | 95.5% (279/292) |

3D: Veruprevir/ritonavir, ombitasvir and dasabuvir; DCV: Daclatasvir; HCV: Hepatitis C virus; ITT: Intention-to-treat; m-ITT: Modified intention-to-treat; LED: Ledipasvir; RBV: Ribavirin; SMV: Simeprevir; SOF: Sofosbuvir; SVR: Sustained virologic response.

**Table 4 Variables associated with sustained virologic response by intention-to-treat analysis (*n* = 532)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **SVR (*n* = 493), % (n) or mean ± SD** | **Non-SVR (*n* = 39), % (n) or mean ± SD** | ***P* value** |
| Age (yr) | 56.85 ± 10.96 | 57.23 ± 12.61 | 0.811 |
| Men/women | 50.1% (247)/49.9% (246) | 64.1% (25)/35.9% (14) | 0.092 |
| High-blood pressure | 44.0% (214/486) | 44.7% (17/38) | 0.932 |
| Type 2 diabetes | 29.9% (146/488) | 26.3% (10/38) | 0.639 |
| BMI (*n* = 442) | 26.97 ± 5.01 | 27.59 ± 4.65 | 0.459 |
| Dyslipidemia | 20.0% (97/486) | 31.6% (12/28) | 0.089 |
| Hypothyroidism | 15.8% (77/486) | 21.1% (8/38) | 0.401 |
| Psychiatric disorder | 10.1% (49/484) | 10.8% (4/37) | 0.781 |
| Previous alcohol use | 18.6% (90/485) | 31.6% (12/38) | 0.051 |
| HCV genotype |  |  |  |
| 1 | 79.5% (392) | 66.7% (26) | 0.083 |
| 3 | 19.1% (94) | 33.3% (13) |  |
| Other | 1.4% (7) | 0% (0) |  |
| Previous HCV treatment |  |  |  |
| None | 45.5% (222) | 56.8% (21) | 0.409 |
| Peg-IFN + RBV | 46.7% (228) | 37.8% (14) |  |
| Peg-IFN + PI | 7.8% (38) | 5.4% (2) |  |
| Liver fibrosis (Metavir classification) |  |  |  |
| F0 / F1 | 8.6% (42) | 7.7% (3) | 0.218 |
| F2 | 13.6% (67) | 10.3% (4) |  |
| F3 | 22.2% (109) | 10.3% (4) |  |
| F4 | 55.6% (273) | 71.8% (28) |  |
| Presence of cirrhosis |  |  |  |
| No | 43.4% (214) | 30.8% (12) | 0.124 |
| Yes | 56.6% (279) | 69.2% (27) |  |
| Liver-related complications |  |  |  |
| Ascites | 20.3% (84/413) | 25.7% (9/35) | 0.451a |
| Esophageal varices | 47.8% (197/412) | 68.6% (24/35) | 0.018a |
| Portal hypertensive bleeding | 9.7% (40/412) | 22.9% (8/35) | 0.039a |
| Hepatic encephalopathy | 8.5% (35/413) | 28.6% (10/35) | 0.001a |
| AST (U/L) | 60.41 ± 44.53 | 74.51 ± 50.36 | 0.043a |
| ALT (U/L) | 60.78 ± 55.75 | 76.19 ± 84.74 | 0.434 |
| Total bilirubin (mg/dL) | 1.12 ± 1.09 | 1.24 ± 0.95 | 0.384 |
| Albumin (g/dL) | 4.18 ± 2.73 | 3.70 ± 0.77 | 0.032a |
| Platelets (/mm3) | 142.64 ± 78.05 | 131.10 ± 65.19 | 0.532 |
| INR | 1.17 ± 0.21 | 1.32 ± 0.40 | 0.023a |
| Creatinine (mg/dL) | 1.23 ± 1.74 | 2.32 ± 3.77 | 0.694 |
| Hemoglobin (g/dL) | 13.74 ± 1.86 | 13.65 ± 2.34 | 0.798 |
| Alpha-fetoprotein (ng/mL) | 24.3 ± 107.22 | 13.20 ± 16.37 | 0.412 |
| Child-Pugh classification (%) |  |  |  |
| A | 72.0% (190) | 56.0% (14) | 0.124 |
| B | 25.8% (68) | 44.0% (11) |  |
| C | 2.3% (6) | 0% (0) |  |
| Child-Pugh Score | 5.91 ± 1.49 | 6.28 ± 2.01 | 0.109 |
| MELD Score | 9.98 ± 3.82 | 12.70 ± 4.81 | 0.001a |
| Dose of ribavirin (mg/kg/day) | 12.11 ± 3.01 | 12.07 ± 2.98 | 0.946 |

Chi-square test, Fisher's exact test, and Mann-Whitney test.ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HCV: Hepatitis C virus; INR: International normalized ratio; ITT: Intention-to-treat; Peg-IFN: Pegylated-interferon; PI: Protease inhibitor (boceprevir or telaprevir); RBV: Ribavirin; SVR: Sustained virologic response.a*P* value < 0.05.

**Table 5** **Factors associated with failure to achieve sustained virologic response by intention-to-treat analysis**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Univariate analysis** | | |
| **OR** | **95%CI** | ***P* value** |
| Age | 1.003 | 0.974-1.033 | 0.8349 |
| Men | 1.811 | 0.814-4.030 | 0.1458 |
| High-blood pressure | 1.029 | 0.530-1.999 | 0.9328 |
| Type 2 diabetes | 0.837 | 0.396-1.767 | 0.6400 |
| BMI | 1.024 | 0.954-1.099 | 0.5120 |
| Dyslipidemia | 1.851 | 0.902-3.800 | 0.0934 |
| Hypothyroidism | 1.416 | 0.626-3.206 | 0.4036 |
| Psychiatric disorder | 1.076 | 0.366-3.165 | 0.8940 |
| Previous alcohol use | 2.026 | 0.985-4.167 | 0.0551 |
| Presence of cirrhosis | 1.726 | 0.854-3.486 | 0.1281 |
| Liver-related complications |  |  |  |
| Ascites | 1.356 | 0.612-3.003 | 0.4526 |
| Esophageal varices | 2.381 | 1.137-4.988 | 0.0215a |
| Portal hypertensive bleeding | 2.756 | 1.173-6.471 | 0.0200a |
| Hepatic encephalopathy | 4.320 | 1.920-9.721 | 0.0004a |
| AST | 1.006 | 1.000-1.012 | 0.0707 |
| ALT | 1.003 | 0.999-1.007 | 0.1402 |
| Total bilirubin | 1.085 | 0.846-1.392 | 0.5198 |
| Albumin | 0.528 | 0.322-0.867 | 0.0115a |
| Platelets | 1.000 | 1.000-1.000 | 0.3813 |
| INR | 5.542 | 2.023-15.182 | 0.0009a |
| Creatinine | 1.117 | 1.056-1.312 | 0.0033a |
| Hemoglobin | 0.975 | 0.818-1.161 | 0.7741 |
| Alpha-fetoprotein | 0.995 | 0.980-1.010 | 0.5055 |
| Child-Pugh score | 1.166 | 0.901-1.511 | 0.2431 |
| MELD score | 1.143 | 1.060-1.233 | 0.0005a |
| Ribavirin dose | 0.996 | 0.832-1.192 | 0.9614 |
| Treatment duration | 1.024 | 0.962-1.090 | 0.4563 |

Univariate logistic regression.ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HCV: Hepatitis C virus; INR: International normalized ratio; MELD: Model for end-stage liver disease; OR: Odds ratio; SVR: Sustained virologic response.a*P* value < 0.05.

**Table 6** **Factors associated with the occurrence of adverse events during treatment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Variable** | **Univariate analysis** | | | **Multivariate analysis** | | |
| **OR** | **95%CI** | ***P* value** | **OR** | **95%CI** | ***P* value** |
| Age | 1.011 | 0.994-1.027 | 0.2086 |  |  |  |
| Women | 1.718 | 1.205-2.450 | 0.0028a | 2.191 | 1.145-1.192 | 0.0178a |
| High-blood pressure | 0.838 | 0.587-1.197 | 0.3315 |  |  |  |
| Type 2 diabetes | 0.994 | 0.675-1.461 | 0.9736 |  |  |  |
| BMI | 1.060 | 1.019-1.102 | 0.0040a | 1.107 | 1.038-1.180 | 0.0020a |
| Dyslipidemia | 0.714 | 0.458-1.114 | 0.1377 |  |  |  |
| Hypothyroidism | 0.971 | 0.603-1.565 | 0.9053 |  |  |  |
| Psychiatric disorder | 1.309 | 0.732-2.340 | 0.3633 |  |  |  |
| Previous alcohol use | 0.953 | 0.610-1.488 | 0.8307 |  |  |  |
| Presence of cirrhosis | 2.127 | 1.476-3.065 | < 0.0001a |  |  |  |
| Liver-related complications |  |  |  |  |  |  |
| Ascites | 2.187 | 1.352-3.536 | 0.0014a |  |  |  |
| Esophageal varices | 2.795 | 1.874-4.169 | < 0.0001a | 3.463 | 1.688-7.105 | 0.0007a |
| Portal hypertensive bleeding | 1.747 | 0.946-3.228 | 0.0749 |  |  |  |
| Hepatic encephalopathy | 3.524 | 1.762-7.044 | 0.0004a |  |  |  |
| AST | 1.000 | 0.997-1.004 | 0.8303 |  |  |  |
| ALT | 0.999 | 0.996-1.002 | 0.4848 |  |  |  |
| Total bilirubin | 1.283 | 1.052-1.564 | 0.0138a |  |  |  |
| Albumin | 0.432 | 0.314-0.595 | < 0.0001a |  |  |  |
| INR | 3.835 | 1.539-9.560 | 0.0039a | 3.748 | 1.060-13.251 | 0.0403a |
| Creatinine | 0.934 | 0.845-1.032 | 0.1818 |  |  |  |
| Hemoglobin | 0.951 | 0.866-1.044 | 0.2910 |  |  |  |
| Alpha-fetoprotein | 0.998 | 0.993-1.003 | 0.3656 |  |  |  |
| Child-Pugh score | 1.196 | 1.014-1.410 | 0.0332a |  |  |  |
| MELD score | 1.071 | 1.019-1.126 | 0.0073a |  |  |  |
| Ribavirin dose | 1.249 | 1.132-1.379 | < 0.0001a |  |  |  |
| Treatment duration | 1.071 | 1.034-1.109 | 0.0001a | 1.062 | 1.003-1.125 | 0.0406a |

Logistic regression.ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HCV: Hepatitis C virus; INR: International normalized ratio; MELD: Model for end-stage liver disease; OR: Odds ratio.a*P* value < 0.05.