Japanese Journal of Gastroenterology and Hepatology

Research Article ISSN 2435-1210 | Volume 5

Predictive Factors of Decompensation and Death in 670 Patients with Hepatitis C Treated with Direct-Acting Antivirals

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Received: 15 Nov 2020
Accepted: 03 Dec 2020
Published: 05 Dec 2020

Citation:

Fassio E. Predictive Factors of Decompensation and Death in 670 Patients with Hepatitis C Treated with Direct-Acting Antivirals. Japanese Journal of Gstroenterology and Hepatology. 2020; V5(5): 1-8.

Keywords

Hepatitis C Treatment with direct-acting antivirals; Decompensation on direct-acting antiviral treatment; Death on direct-acting antiviral treatment

1. Abstract

Sustained virological response 12 weeks after treatment (SVR12) with direct-acting antivirals (DAAs) is excellent in patients with hepatitis C but little has been published regarding decompensation and/or death during therapy.

1.1. Objectives: Objectives of this prospective, observational, multicenter study were to describe SVR12 in real life patients with advanced fibrosis/cirrhosis treated with DAAs and to analyze variables associated with hepatic decompensation and death.

1.2. Methods: we enrolled 670 patients (384 males), median age 57 years; 64% had cirrhosis; genotypes 1, 2, 3 and 4 in 505, 70, 81 and 13 patients, respectively. Main DAA regimens prescribed were sofos-

buvir (SFV) + daclatasvir ± ribavirin in 473 patients; paritaprevir/r + ombitasvir + dasabuvir ± ribavirin in 105; SFV + ribavirin in 24; SFV/ledipasvir ± ribavirin in 39; and elbasvir/grazoprevir in 17.

1.3. Results: SVR12 rate was 95.5%. Decompensation was observed in 39 (5.8%) patients, death in 11 (1.6%). Variables significantly associated with decompensation or deaths were similar: cirrhosis stage, bilirubin, prothrombin activity, MELD or Child-Pugh scores. ROC curve analysis showed that MELD score ≥10 (HR 5.1, 95% CI, 1.9-13.6) and Child-Pugh score ≥7 (HR 4.6, 95% CI, 2.1-10.1) were predictive of decompensation and/or death.

1.4. Conclusion: DAAs were effective and safe in patients with compensated cirrhosis but further studies in decompensated cirrhosis are needed to better delineate the MELD and/or Child-Pugh scores that ensure a good safety profile or being appropriate for indicating liver transplant instead of antiviral therapy.

2. Introduction

The advent of direct-acting antiviral (DAA) drugs has produced a true revolution in the treatment of chronic hepatitis C. The new regimens use a combination of 2 or 3 drugs that act on different steps in the viral replication and significantly increase antiviral efficacy and decrease the incidence of substitutions associated with resistance. In registration trials of various DAA combinations, viral eradication was achieved in more than 90% of patients [1-4]. Compared to previous treatments, based on interferon, the new DAA regimens are not only more effective but also of shorter duration and better tolerated, with a lower rate of adverse effects. In addition, DAA regimens are almost universally applicable, as they do not have the multiple contraindications of interferon.

The antiviral efficacy of the new DAA regimens was also found in populations previously considered "difficult to treat" and predictors of lower response, such as patients with cirrhosis [5-8] or those co-infected with HIV [9,10]. Recently, studies from the United States of America [11] and Europe [12] have confirmed a high percentage of viral eradication in a series of consecutive and unselected "real life" patients, with a high proportion of advanced fibrosis/cirrhosis. In the North American study, the sustained virological response rate at 12 weeks after treatment completion (SVR12) was 90.6% in cirrhotic patients with genotype 1 [11] and 93.4% in Spanish patients with cirrhosis [12].

In a previous study by our group, we described an SVR12 rate of 94.5% in a series of 330 patients with hepatitis C and stage F3 or F4 fibrosis (26% F3, 74% F4), with 54% of them previously treated without achieving viral eradication [13]. The SVR12 percentages for the main treatments analyzed were not significantly different from those described in the registration trials of pharmaceutical companies. Safety profile was acceptable, with generally mild adverse effects and decompensation of cirrhosis in 21 patients (6.4%) and death during treatment or early post therapy follow-up in 7 patients (2.1%) [13]. One of the least studied aspects so far is which variables are different between the majority of patients who achieve viral eradication and the minority who do not, as well as if there are any variables that are capable of predicting which patients are at higher risk of presenting hepatic decompensation and/or death associated with treatment with DAAs.

The objectives of this prospective, multicenter, observational study were:

1. To describe the percentage of sustained virological response to treatment of chronic hepatitis C with DAAs in unselected "real life" patients.
2. To analyze the baseline variables associated with hepatic decompensation and death.

3. Methods

This was a prospective, observational, multicenter study. Given that one of the objectives of the study was to analyze whether "real life" patients with chronic hepatitis C treated with DAAs would obtain similar SVR12 rates to those described in the registration trials, hepatologists from all over Argentina whose primary care activities were in public hospitals, which are the care centers that usually have the greatest logistical difficulties and serve patients with multiple comorbidities and more heterogeneous adherence, were invited to participate. Hepatologists from 25 different medical centers in 14 cities across the country participated in the study.

Patients aged ≥ 18 years with chronic hepatitis C and serum HCV RNA who received treatment with DAAs and who signed an informed consent form to participate in the study were included. The study was approved by the local ethics committees of all participating hospitals. In each case, the attending physician established whether the patient met the criteria defined for receiving treatment with DAA drugs according to the current Guidelines of the Argentine Association for the Study of Liver Diseases (AAEEH).

Patients were excluded if they received treatment with DAAs in a clinical trial funded by the pharmaceutical industry; if they received interferon as part of the antiviral regimen; if they had a diagnosis of hepatocellular carcinoma before treatment; and if they were pregnant or of reproductive age with the intention of becoming pregnant and/or getting their partner pregnant during treatment or up to 6 months after treatment.

The choice of the specific antiviral treatment regimen and its duration was decided by the attending physician according to the AAEEH Guidelines, the availability of different drugs, and the presence or absence of social or private health system coverage for the evaluated patient. In patients with medical coverage, the attending physician decided the combination of DAAs to be used. In those without coverage, the physician could not decide the regimen because the National Program for AIDS, STD and Viral Hepatitis of the Argentine Republic only had the antivirals sofosbuvir (original

or copies), daclatasvir and ribavirin available during the study period.

All patients were managed during antiviral treatment at the discretion of the attending physician. No additional procedure was required outside of the "standard of care" for this study. In general, all physicians indicated a study of HCV-RNA viral load at the end of treatment and always conducted a viral load study at 12 weeks after treatment completion. Only patients who had week 12 post treatment viral load results were included in this analysis.

Baseline variables were recorded, such as age, gender, presence of co-infection with HIV and/or HBV, history of excessive alcohol intake, genotype and viral subtype, viral load, fibrosis stage by histological examination (METAVIR and/or Ishak classification) or by transient elastography, presence of cirrhosis (in patients with cirrhosis, cirrhosis status, compensated versus decompensated), AST, ALT, AST/ALT ratio, hemoglobin, and APRI, Child-Pugh and MELD scores. In addition, presence of extrahepatic manifestations and history of previous treatment for hepatitis C, the type of treatment received and type of response (relapser versus non responder) were recorded.

During treatment, the type of specific DAA regimen, its duration, adverse events, interruption due to adverse events, episodes of hepatic decompensation, type of decompensation, and deaths (during treatment and in early post treatment follow-up) were recorded.

SVR12 was defined by no detection of serum HCV RNA using a sensitive method (real-time PCR with a detection limit of 10-15 IU/ml) at 12 weeks after treatment completion.

4. Statistical Analysis

To describe the qualitative variables, the distribution of frequencies, percentages and 95% confidence intervals (CIs) were calculated. In the case of quantitative variables, the mean or median, standard deviation or inter quartile range were calculated, as well as the 95% CI for the mean.

To compare quantitative variables between groups, Student's test for independent samples, one-way ANOVA, and in cases of noncompliance with assumptions of normality and homocedasticity, robust ANOVAs (Brown-Forsythe) and nonparametric Mann-Whitney and Kruskal-Wallis tests were applied. To compare the relationship between qualitative variables, an independence test (Chi square) was applied. To compare proportions between groups, a binomial test for independent samples with Bonferroni correction was used, and 95% CIs for the difference in proportions were calculated.

To determine the MELD and Child-Pugh cut-off values, ROC curves were used contrasting the area under the curve with the Hanley & McNeil approximation method. The cut-offs found were also evaluated through diagnostic tests (sensitivity, specificity and predictive values). To estimate survival in weeks, Kaplan-Meier survival curves and log-rank (Mantel-Cox) comparisons were used. The combination of hepatic decompensation and/or death was established as the endpoint for the MELD and Child-Pugh score variables, dichotomized according to the cut-off values found by the ROC curve analysis. Patients who dropped out due to other causes or a change in therapy were considered censored data.

In all cases, the statistical tests applied were for independent samples. A significance level lower than 5% was used to reject the null hypothesis.

5. Results

(Table 1) shows demographic, clinical, biological, histological and virological parameters of the patients enrolled in the study. A total of 670 patients were included, with a median age of 57 years (inter quartile range 49-66) and a predominance of male participants (n 384; 57.3%). Seventy-nine patients (11.8%) had co-infection with HIV, and only 4 were co-infected with HBV, while 105 (15.7%) patients had a history of excessive alcohol consumption.

Table 1: Clinical, biological and virological data of the 670 patients included in the study

Age (years) ł	57 (49-66)
Gender(male/female) n (%)	384 (57.3)/286 (42.7)
Anti-HIV (negative/positive) n (%)	591 (88.2)/79 (11.8)
Chronic alcoholism (negative/positive) n (%)	565 (84.3)/105 (15.7)
Cirrhosis n (%)	429 (64.02)
Compensated/decompensated cirrhosis (n)	372/57
HCV-RNA viral load (log. IU/ml) ł	6.12 (5.6-6.6)
Genotypes 1/2/3/4/1+4 (n)	505/70/81/13/1
AST (IU/L) ‡	82 ± 55
ALT (IU/L) ‡	90 ± 67
Platelet count (x10^3/µL) ‡	161 ± 70
Total bilirubin (mg/dl) ‡	1.03 ± 0.87
Serum albumin (g/dl) ‡	3.91 ± 0.5
Serum creatinine (mg/dl) ‡	0.9 ± 0.63
Prothrombin activity (%) ‡	84 ± 16
MELD score ‡	8.36 ± 2.88
Child-Pugh score ‡	5.5 ± 0.99
łmedian (quartile 1-quartile 3); ‡ mean ± standard deviation	

Most treated patients had cirrhosis, which was present in 429 cases (64.02%; compensated in 372 and decompensated in 57).

Two hundred and seventy-nine patients (41.6%) had received prior interferon-based treatment for hepatitis C, without achieving viral eradication (non response in 174 cases and virological response and relapse in 105 cases).

The most frequently observed genotype was 1, present in 505 cases (75.4%) (1a in 207, 1b in 271, 1 in 16, 1a/b in 1), followed by genotype 2 (70 cases, 10.4%), genotype 3 (81 cases, 12.1%), genotype 4 (13 cases, 1.9%), and mixed genotype (1 + 4) in 1 case.

The main DAA treatments prescribed were sofosbuvir plus daclatasvir, with or without ribavirin (RBV), during 12-24 weeks, in 473 patients; paritaprevir/r plus ombitasvir plus dasabuvir, with or without RBV, during 12 weeks, in 105 patients; sofosbuvir plus RBV, during 12-20 weeks, in 24 patients; sofosbuvir/ledipasvir, during 12 weeks, in 39 patients; elbasvir/grazoprevir, during 12 weeks, in 17 patients. Another 12 patients were given sofosbuvir plus simeprevir or sofos-

buvir plus elbasvir/grazoprevir.

5.1. Antiviral Efficacy

Treatment of chronic hepatitis C with DAAs obtained SVR12 in 640 of 670 patients (95.5%). Considering the main treatment regimens prescribed, SVR12 was demonstrated in 448 of the 473 (94.7%) patients treated with sofosbuvir plus daclatasvir (with or without RBV); in 103 of 105 (98.1%) patients treated with paritaprevir/r plus ombitasvir plus dasabuvir (with or without RBV); in 26 of the 29 (89.6%) patients treated with sofosbuvir plus ribavirin; in 39 of 39 (100%) patients treated with sofosbuvir/ledipasvir (with or without RBV); and in 17 of 17 (100%) patients treated with elbasvir/grazoprevir.

There were no significant differences between patients with or without SVR12 in the following qualitative variables: gender, coinfection with HIV, co-infection with HBV, history of alcoholism, genotype, presence of extrahepatic manifestations, treatment-experienced versus naïve patients, or current type of treatment (data not shown). In contrast, a significant difference was observed for the presence of cirrhosis: 63.1% (95% CI, 59.2-66.7) among patients with SVR12 and 83.3% (95% CI, 67.3-93.3) among patients without SVR12 (p 0.024).

As for the quantitative variables, there were no significant differences between patients with and without SVR12 regarding age or baseline HCV-RNA viral load, AST, ALT, hemoglobin, serum albumin, creatinine or APRI index (data not shown). Table 2 shows the variables that were significantly different between patients with and without SVR12: platelet count, bilirubin, prothrombin activity, MELD score and Child-Pugh score.

Table 2: Baseline quantitative variables that were significantly different between patients with chronic hepatitis C, treated with direct-acting antivirals, with SVR12 (n = 640) and without SVR12 (n = 30).

Variable	SVR12 (n = 640)	No SVR12 (n = 30)	p
	Mean ± SD	Mean ± SD	
Platelet count (x10³/µL)	162.5± 70.3	131.8 ± 77.9	0.025
Serum bilirubin (mg/dl)	1.0 ± 0.9	1.5 ± 1.1	0.010
Prothrombin activity (%)	84.6 ± 15.9	77.7 ± 20.6	0.027
MELD score	8.3 ± 2.8	9.7 ± 4.3	0.007
Child-Pugh score	5.4 ± 0.9	6.3 ± 1.9	0.000
SVR12, sustained virological response at 12 weeks after treatment completion. SD, standard deviation.			

5.2. Variables Related to Hepatic Decompensation or Death

During treatment with DAAs, 39 of 670 (5.8%) patients had one or more complications of cirrhosis (ascites in 13, bacterial infection in 13, hepatic encephalopathy in 7, acute kidney injury in 3, and upper gastrointestinal bleeding in 3). Qualitative variables such as gender, co-55infection with HIV, co-infection with HBV, history of alcoholism, genotype, presence of extrahepatic manifestations, treatment-experienced versus naïve patients, or current type of treatment were not significantly different between patients with and without hepatic decompensation. In contrast, the categorical variable of cirrhosis was present in 62.1% (95% CI, 58.3-65.8) of patients who did not have hepatic decompensation and in 97.1% (95% CI, 87.4-99.7) of those who had hepatic decompensation (p 0.001). Among the quantitative variables, several were significantly different between patients who presented and those who did not present hepatic decompensation: AST, AST/ALT ratio, hemoglobin, platelets, bilirubin, albumin, prothrombin activity, MELD score, Child-Pugh score and APRI (Table 3).

Table 3: Baseline quantitative variables that were significantly different between patients with chronic hepatitis C, treated with direct-acting antivirals, with decompensation (n = 39) and without decompensation (n = 631) of liver disease during treatment.

Variable	Decompensation Mean ± SD	No decompensation Mean ± SD	p
AST (IU/L)	100 ± 49	81 ± 55	0.030
AST/ALT	1.4 ± 0.4	1.0 ± 0.4	0.000
Hemoglobin (g/dL)	13.2 ± 2.0	14.5 ± 2.7	0.006
Platelets (x10³/µL)	103.1 ± 56.5	164.4 ± 70.1	0.000
Bilirubin (mg/dl)	2.1 ± 1.3	1.0 ± 0.9	0.000
Albumin (g/dL)	3.5 ± 0.6	4.0 ± 1.6	0.000
Prothrombin activity (%)	67.2 ± 20.5	85.3 ± 15.4	0.000
MELD score	12.6 ± 3.7	8.1 ± 2.6	0.000
Child-Pugh score	7.3 ± 1.8	5.4 ± 0.8	0.000
APRI	2.8 ± 2.5	1.8 ± 2.0	0.008
SD, standard deviation			

During treatment with DAAs or subsequent early follow-up, 11 of 670 (1.6%) patients died. Death was secondary to complications of cirrhosis in 9 patients (bacterial infection plus sepsis, progression of hepatic insufficiency or hepatocellular carcinoma) and non-hepatic causes in 2 patients (acute lymphoid leukemia and acute myocardial infarction). Once again, among the categorical variables, the presence of cirrhosis was significantly different, being present in 63.4% (95% CI, 59.6-67.0) of patients who did not die and in 100% of those who died (p 0.012). In addition, cirrhosis status (compensated versus decompensated) was also significantly different: among patients who did not die, 87.6% (95% CI, 84.3-90.5) had compensated cirrhosis, and 12.4% (95% CI, 9.5-15.7) had decompensated cirrhosis. Among those who died, 54.5% (95% CI, 27.0-80.0) had compensated cirrhosis, and 45.5% (95% CI, 20.0-73.0) had baseline decompensated cirrhosis (p 0.001). Among the baseline quantitative variables, platelet count, bilirubin, prothrombin activity, MELD score and Child-Pugh score were significantly different between patients who died and those who did not (Table 4).

Table 4: Baseline quantitative variables that were significantly different between patients with chronic hepatitis C, treated with direct-acting antivirals who died (n = 11) and those who did not die (n = 659) during treatment/immediate follow-up.

Variable	Death	No death	p
	Mean ± SD	Mean ± SD	
Platelets (x10³/µL)	94.1 ± 23.4	162.2 ± 70.8	0.002
Bilirubin (mg/dl)	2.4 ± 1.3	1.0 ± 0.9	0.000
Prothrombin activity (%)	68.9 ± 16.6	84.6 ± 16.1	0.001
MELD score	12.7 ± 4.5	8.3 ± 2.8	0.000
Child-Pugh score	7.1 ± 1.3	5.4 ± 1.0	0.000
SD, standard deviation			

Given that the end points hepatic decompensation and death were scarce in relation to the sample size and that all deaths were observed in patients with decompensated cirrhosis, it was decided, for the rest of the analysis, to group these 2 end points together. A ROC curve was constructed (Figure 1), which determined that the best cut-off values to separate patients who presented decompensation and/or death from those who did not were Child-Pugh score > 6 points and MELD score > 9 points. Tables 5 and 6 show the sensitivity, specificity, positive and negative predictive values, and positive and negative odds ratio of said Child-Pugh and MELD cut-off scores, respectively, for identifying patients with higher risk of presenting hepatic decompensation and/or death.

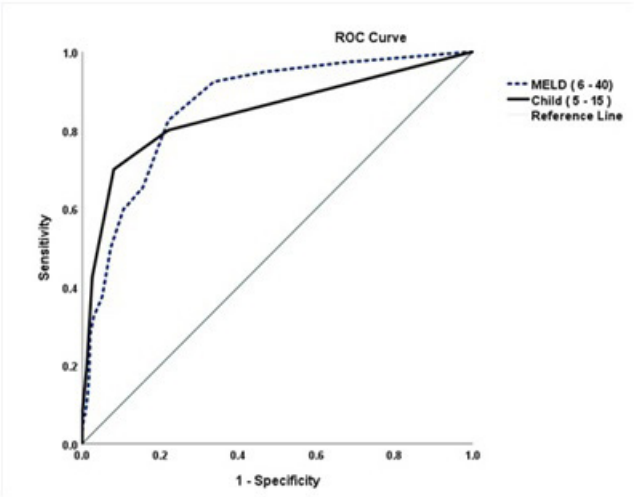

Figure 1: ROC curve analyzing the MELD and Child-Pugh scores in their ability to differentiate patients with chronic hepatitis C treated with direct-acting antivirals who exhibited hepatic decompensation and/or death.

In (Figures 2 and 3), Kaplan-Meir curves show the estimation of survival over time in weeks and the probability of presenting decompensation and/or death in relation to the Child-Pugh score (cut-off value 6) and the MELD score (cut-off value 9), respectively. Risk of presenting decompensation and/or death was significantly higher in patients treated with DAAs with a baseline Child-Pugh score ≥ 7 points than in those with a score up to 6 points (log-rank test, p <0.001) (Figure 2). Similarly, risk of presenting decompensation and/or death was significantly higher in patients treated with DAAs with a baseline MELD score ≥ 10 points than in those with a score up to 9 points (log-rank test, p <0.001) (Figure 3). In the Cox correlation (table 7), the hazard ratios for Child-Pugh score ≥ 7 points was 4.65 (95% CI, 2.13-10.16) and for MELD score ≥ 10 points was 5.12 (95% CI, 1.91-13.67).

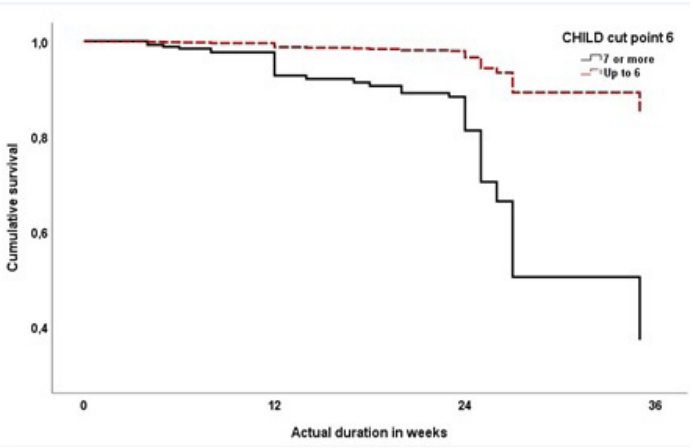

Figure 2: Kaplan-Meier curve showing that probability of presenting hepatic decompensation and/or death is significantly different in patients with chronic hepatitis C treated with DAAs and a baseline Child-Pugh score ≥ 7 points in respect to those with a baseline score up to 6 points (log rank test, p <0.001).

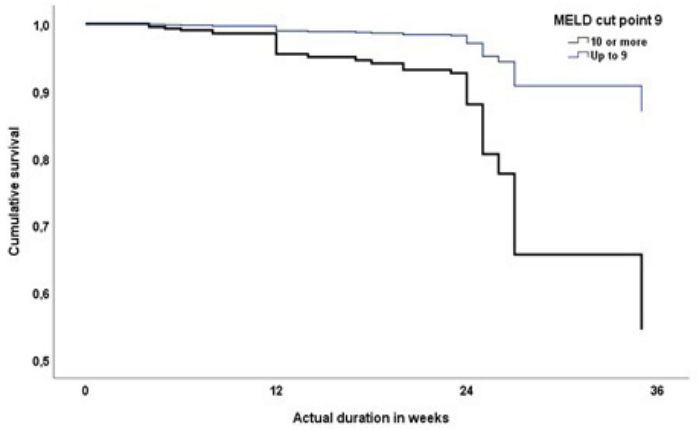

Figure 3: Kaplan-Meier curve showing that probability of presenting hepatic decompensation and/or death is significantly different in patients with chronic hepatitis C treated with DAAs and a baseline MELD score ≥ 10 points in respect to those with a baseline score up to 9 points (log rank test, p <0.001).

6. Discussion

The results of this prospective, observational, multicenter study confirm that the new treatment regimens with DAAs achieve similar percentages of viral eradication in "real life" chronic hepatitis C patients to those observed in the registration trials conducted by the pharmaceutical industry. To our knowledge, this is the largest series of unselected "real life" patients reported in Argentina. It was a difficult-to-treat population exhibiting some of the characteristics that were predictors of poor response in the era of interferon-based treatments: cirrhosis in 429 of the 670 (64%) patients (compensated

in 372, decompensated in 57); non response to previous treatments in 278 patients (41.5%); and anti-HIV positive in 79 patients (12%). Despite these negative traits, chronic HCV infection was cured in 640 of 670 patients (95.5%). The percentage of SVR12 was greater than 90% with all combinations of antivirals, except for sofosbuvir plus ribavirin, which was used by physicians only at the beginning of the study in patients with genotype 2. This regimen is not a real combination of DAAs and was no longer prescribed in the second part of this observational study.

Treatment with DAAs showed a good safety profile in this series of patients with a high proportion of advanced fibrosis or cirrhosis, with infrequent and generally ordinary adverse events, which usually did not require interruption of therapy. Hepatic decompensation was observed in only 39 patients (5.8%) and death during treatment or immediate follow-up in 11 patients (1.6%) (9 had a hepatic cause of death). The variables significantly associated with treatment failure or hepatic decompensation and/or death were practically the same: presence of cirrhosis and liver function tests, such as total bilirubin, prothrombin activity or MELD and Child-Pugh scores; other variables such as age, gender, co-infections with HIV or HBV, history of alcoholism or previous antiviral treatments did not show statistical significance. A very provocative result is that the ROC curve identified Child-Pugh and MELD scores cut-off values for better ability to identify an increased risk of decompensation and/or death that are quite low: 6 points and 9 points, respectively. (Figures 2 and 3) show that the Kaplan-Meir survival curves are significantly different for patients with Child-Pugh score ≥ 7 points and for those with MELD score ≥ 10 points (log rank test, p <0.001 in both analysis); and Cox regression confirmed the increased risk of decompensation and/or death in this subgroup of patients (Table 7).

Table 5: Child-Pugh score (cut-off = 6 points) as a variable capable of identifying patients with chronic hepatitis C treated with direct-acting antivirals who are at risk of hepatic decompensation and/or death.

Child-Pugh score cut-off = 6.0	Value	95% CI	
		Lower limit	Upper limit
Prevalence of decompensation or death	7.29%	5.11%	9.46%
Correctly diagnosed patients	90.35%	87.88%	92.82%
Sensitivity	70.00%	55.80%	84.20%
Specificity	91.94%	89.58%	94.31%
Positive predictive value	40.58%	28.99%	52.17%
Negative predictive value	97.50%	96.10%	98.90%
Positive odds ratio	8.69	6.082	12.416
Negative odds ratio	0.326	0.203	0.524

At present, it is controversial whether patients with hepatitis C and decompensated cirrhosis and who are candidates to receive a liver transplant should be treated first with DAAs or with liver transplantation (and later with DAAs in the post transplant period). In the international literature, results similar to ours have been described when treating decompensated cirrhosis patients with DAAs in compassionate use programs. Foster et al., in England, observed further decompensation of cirrhosis in 17% of 467 patients with cirrhosis and Child-Pugh classes B or C; and death during treatment or immediate follow-up after therapy in 1.5% and 2%, respectively [14], emphasizing the difficulties encountered in the management of this population. Another recently published study analyzed the results of a compassionate use program in Germany that included 485 patients treated with sofosbuvir plus daclatasvir, with or without RBV. In this series, the prevalence of cirrhosis was 80% (Child-Pugh classes B + C in 42% of patients with cirrhosis and in 30% of the total studied population) [15]. The percentage of SVR12 observed was 89% ("intention-to-treat"), while 94 patients (19%) experienced serious adverse events during treatment, generally related to advanced liver disease (hepatic encephalopathy in 12, HCC in 8, hepatic insufficiency in 6, etc.) [15]. During treatment or early follow-up, 28 patients died (5.8%), mainly from a hepatic cause of death [15]. In another study, the results of an Australian treatment program (TOSCAR) were reported for a population of 108 patients with hepatitis C and decompensated cirrhosis with MELD score ≥ 15 who received treatment with sofosbuvir plus daclatasvir, with or without RBV [16]. In this series of patients with more advanced liver disease, treatment efficacy was lower, with an SVR12 rate of 70% (intention-to-treat), while 30 of 108 patients could not complete the planned 24-week treatment. Among the 30 patients who did not complete treatment, 16 (14.8% of the total) received a transplant (due to hepatic insufficiency or HCC) and 11 (10.2% of the total) died during treatment (10 due to hepatic insufficiency and 1 due to a cerebrovascular accident) [16]. Finally, in a non interventional, national study from the Spanish Hepa-C registry that investigated the effectiveness and safety of DAA therapy in 843 patients with cirrhosis, there were significant differences in results between those with compensated versus decompensated liver disease [17]. The SVR12 rate was significantly lower in Child-Pugh classes B + C patients than in Child-Pugh class an ones (78 versus 94%, respectively, p < 0,001). In contrast, incident decompensation and death were observed in 16% and 6.4%, respectively, of Child B + C patients versus 4% and 0.9% of Child A patients (both, p < 0.001) [17]. This brief review seems to demonstrate that there is a growing risk of hepatic decompensation and death as the proportion of patients with Child-Pugh classes B + C increases within treatment series. In fact, the incidence of death was 1.6% in our population (with 8.5% of patients with decompensated cirrhosis at baseline), 5.8% in the German study (30% of their patients with decompensated cirrhosis) [15] and 10.2% in the Australian program (100% of the patients with decompensated cirrhosis) [16].

On the other hand, treating patients with decompensated cirrhosis before transplantation is supported by some publications. Belli et al. observed, in a European multicenter study, that after treatment of 103 patients on a waiting list for liver transplantation (without HCC) with DAAs, significant clinical improvement could be achieved with viral eradication, which allowed removal of approximately 20% of

cases from the transplant list after 60 weeks of follow-up (patients with lower baseline MELD scores had a greater chance of being removed from the list) [18]. Another retrospective, multicenter, Spanish study showed similar results: among 122 patients with decompensated cirrhosis without HCC receiving DAAs, 29 (24%) were removed from the transplant list due to clinical improvement [19].

Table 6: MELD score (cut-off = 9 points) as a variable capable of identifying patients with chronic hepatitis C treated with direct-acting antivirals who are at risk of hepatic decompensation and/or death.

MELD score cut-off = 9	Value	95% CI	
		Lower limit	Upper limit
Prevalence of decompensation or death	6.31%	4.44%	8.18%
Correctly diagnosed patients	80.62%	77.58%	83.65%
Sensitivity	82.93%	71.41%	94.44%
Specificity	80.46%	77.31%	83.61%
Positive predictive value	22.22%	15.63%	28.81%
Negative predictive value	98.59%	97.56%	99.63%
Positive odds ratio	4.244	3.431	5.250
Negative odds ratio	0.212	0.108	0.417

Table 7: Cox regression results: MELD score (cut-off = 9 points) and Child-Pugh score (cut-off = 6 points). Hazard ratio and 95% CI comparing chronic hepatitis C patients treated with direct-acting antivirals who exhibited hepatic decompensation and/or death.

Variables	Hazard Ratio	95% CI	
		Lower	Upper
MELD cut-off =9	5.118	1.916	13.673
Child-Pugh cut-off = 6	4.656	2.132	10.166

Some reviews claim that patients with decompensated cirrhosis should be treated in the post transplant setting given that, when they are treated on the wait listing, there is a decreased SVR12 rate, the clinical improvement is not enough to remove many patients from the transplant list and there are serious safety concerns, including rapid deterioration and death [20].

At the other end, treatment of patients with compensated cirrhosis with DAAs is associated with significant clinical benefits in a relatively short follow-up period. Among 15,059 patients with hepatitis C and advanced liver disease (defined by a FIB-4 index> 3.25) treated at Veterans Affairs hospitals in the USA, those who achieved SVR12 had a 79% reduction in mortality compared to those who did not achieve viral eradication (2.6 deaths per 100 patients/year versus 12.3 deaths per 100 patients/year, respectively, in a mean follow-up of only 1.6 years) ($p < 0.001$), in addition to an incident HCC reduction of 83% [21]. Since the advent of treatment with DAAs, the progression from compensated to decompensated cirrhosis has decreased significantly; consequently, so has the number of patients who need to be listed for liver transplant due to hepatitis C, without HCC, both in the USA [22], and in Europe [23], with reductions of 48-60% with respect to pre-DAAs era.

Although the population analyzed was large and well representative of the "real life" scenario in Argentina, the proportion of patients with decompensated cirrhosis (8.5% of the total) was low, and a greater number should be studied to better delineate the MELD and/or Child-Pugh scores most appropriate for indicating transplantation instead of DAA treatment. In conclusion, the results of this study confirmed the high antiviral efficacy and safety of treatments with DAAs in patients with hepatitis C and compensated cirrhosis, Child-Pugh class A, in our environment. In patients with decompensated cirrhosis (given that the number of patients with these characteristics was limited in the present study), more prospective studies are needed to continue investigating the best MELD and Child-Pugh cut-off scores to ensure a good safety profile.

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