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ABOUT COVER

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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

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ORIGINAL ARTICLE

Observational Study

Hepatitis C virus related cirrhosis decreased as indication to liver transplantation since the introduction of direct-acting antivirals: A single-center study

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Abstract

AIM

To evaluate waiting list (WL) registration and liver transplantation (LT) rates in patients with hepatitis C

virus (HCV)-related cirrhosis since the introduction of direct-acting antivirals (DAAs).

METHODS

All adult patients with cirrhosis listed for LT at Padua University Hospital between 2006-2017 were retrospectively collected using a prospectively-updated database; patients with HCV-related cirrhosis were divided by indication for LT [dec-HCV *vs* HCV/hepatocellular carcinoma (HCC)] and into two interval times (2006-2013 and 2014-2017) according to the introduction of DAAs. For each patient, indications to LT, severity of liver dysfunction and the outcome in the WL were assessed and compared between the two different time periods. For patients receiving DAA-based regimens, the achievement of viral eradication and the outcome were also evaluated.

RESULTS

One thousand one hundred and ninty-four [male (M)/female (F): 925/269] patients were included. Considering the whole cohort, HCV-related cirrhosis was the main etiology at the time of WL registration (490/1194 patients, 41%). HCV-related cirrhosis significantly decreased as indication to WL registration after DAA introduction (from 43.3% in 2006-2013 to 37.2% in 2014-2017, $P = 0.05$), especially amongst dec-HCV (from 24.2% in 2006-2013 to 15.9% in 2014-2017, $P = 0.007$). Even HCV remained the most common indication to LT over time (289/666, 43.4%), there was a trend towards a decrease after DAAs introduction (from 46.3% in 2006-2013 to 39% in 2014-2017, $P = 0.06$). HCV patients (M/F: 43/11, mean age: 57.7 ± 8 years) who achieved viral eradication in the WL had better transplant-free survival (log-rank test $P = 0.02$) and delisting rate ($P = 0.002$) than untreated HCV patients.

CONCLUSION

Introduction of DAAs significantly reduced WL registrations for HCV related cirrhosis, especially in the setting of decompensated cirrhosis.

Key words: Liver transplantation; Hepatitis C; Cirrhosis; Sustained virological response

Core tip: All-oral direct-acting antivirals significantly modify the natural history of hepatitis C virus (HCV) infection. According to our study, liver transplantation for HCV decompensated cirrhosis will decrease in the next future.

Ferrarese A, Germani G, Gambato M, Russo FP, Senzolo M, Zanetto A, Shalaby S, Cillo U, Zanus G, Angeli P, Burra P. Hepatitis C virus related cirrhosis decreased as indication to liver transplantation since the introduction of direct-acting antivirals: A single-center study. *World J Gastroenterol* 2018; 24(38): 4403-4411 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i38/4403.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i38.4403

INTRODUCTION

Hepatitis C virus (HCV)-related liver disease has been the most common indication for liver transplantation (LT) in Western Europe for the last 20 years[1]. In Italy, due to the high prevalence of HCV in the general population[2,3], HCV-related decompensated cirrhosis and hepatocellular carcinoma (HCC) have been the main indications for LT to date[4]. The scenario of HCV treatment has evolved rapidly since 2011, due to the approval of oral direct-acting antiviral agents (DAAs). The first oral interferon-free drug available worldwide, sofosbuvir, was registered in Italy in 2014[5]. Since then, several highly-effective and well-tolerated DAA regimens have been approved, with real-life data confirming the high sustained virological response (SVR) rates seen in the registration trials, even in the setting of end-stage liver disease[6-8]. Improvement in liver function, as measured by Child-Turcotte-Pugh (CTP) and MELD scores, are reported in nearly two in three decompensated cirrhotic patients treated with DAAs[9,10]. These safe and effective new antiviral therapies will probably lead to a reduction of waiting list (WL) registrations due to HCV[11,12]. However, the role of DAAs in the Italian scenario has not been explored yet.

Therefore, the aims of our study were to evaluate the changing rates of waiting list (WL) registrations and LT for patients with HCV-related cirrhosis, with or without HCC, after introduction of DAAs.

MATERIALS AND METHODS

All patients registered on the WL for LT at Padua University Hospital between January 2006 and December 2017 were assessed. After WL registration, patients' data were collected prospectively in an electronic database.

Patients with acute liver failure, with indications for LT other than cirrhosis, re-LT, or patients younger than 18 years old were excluded from the study. Patients were divided into two main groups according to indication to WL registration: patients with HCC and compensated liver disease (*e.g.* MELD < 15; HCC-group), and patients with decompensated disease, independently from presence of HCC (*e.g.* MELD ⩾ 15 or complications of portal hypertension; dec-group). Patients with a combined diagnosis of HCV and other cause of liver disease (*e.g.*, alcohol, autoimmune liver disease) were classified as HCV. Alcohol-related or HBV-related (or HBV/HDV) liver disease were diagnosed according to current guidelines[13], and they were assessed in separate groups. Similarly, all patients with autoimmune, cholestatic liver diseases or less common indications to LT were grouped together. Patients listed for cryptogenic cirrhosis who had a body mass index (BMI) > 30 were

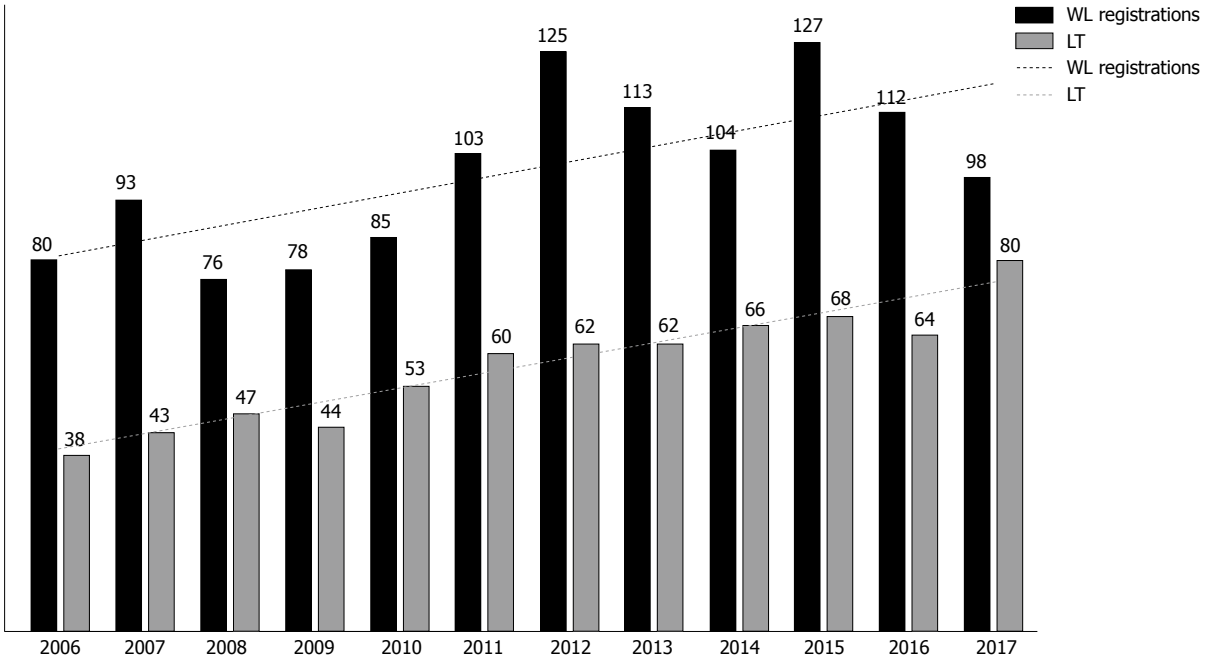

Figure 1 Overall trends in waiting list registrations and liver transplantations at Padua University Hospital in the study period. WL: Waiting list; LT: Liver transplantation.

classified as metabolic liver disease[14,15], and grouped together with patients having a known diagnosis of non-alcoholic steatohepatitis (NASH). Patients with diagnosis of HCC were received WL prioritization according to previously published policy[16], updated in 2016[16,17]. Patients with HCV-related liver disease were treated from 2014 with DAAs, according to the recommendations of the national regulatory agency[5]. Each patient was strictly followed-up during and after treatment with DAA; only patients with durable clinical improvements after SVR achievement were delisted. Patients were also divided into two different time intervals: pre-DAA period (2006-2013) and post-DAA period (2014-2017).

Outcome data were collected at the latest available follow-up for each patient. Informed consent was obtained, and the study was approved by the local Ethical Committee (Comitato Etico per la Sperimentazione Clinica della Provincia di Padova, n. AOP/1405).

Statistical analysis

Categorical and continuous variables were calculated as frequencies and means ± SD, respectively, and were compared using the Fisher's test or Student's *t*-test, as appropriate. *P* values < 0.05 were considered statistically significant. Survival analyses were performed using Kaplan-Meier curves (log-rank test). Analyses were performed using SPSS software version 18 (Chicago, IL, United States).

RESULTS

A total of 1469 patients were listed for LT at Padua University Hospital from January 2006 to December 2017. Two hundred seventy-five patients (18.7%) were excluded from the study for the following reasons: 100 (6.8%) patients were younger than 18 years old at WL registration, 87 (5.9%) patients had undergone previous LT, and 88 (6%) patients did not have cirrhosis as indication for LT, leaving 1194 (81.3%) patients for the current analysis.

Considering this cohort, overall WL registration rates increased from 94/year in 2006-2013 to 110/year in 2014-2017, with a concomitant rise in the number of LT performed overtime, from 51/year in 2006-2013 to 69.5/year in 2014-2017 (Figure 1).

Trajectories of WL registrations for HCV-related disease before and after DAA introduction

Overall, HCV related liver disease (490/1194, 41%), with or without HCC, was the main indication for WL registration over time, followed by alcohol and HBV (24% and 15.5%, respectively). At WL registration, there were no differences between HCV and non-HCV patients in terms of age, gender, BMI, however HCV patients had higher prevalence of HCC (61.8% *vs* 42%; *P* = 0.001), and lower MELD score (15 ± 6 *vs* 16.7 ± 6.8, *P* = 0.01) compared with non-HCV patients (Table 1).

When WL registration rates were compared in the whole cohort between pre-DAA and post-DAA periods, HCV significantly decreased as indication to LT (43.3% in 2006-2013 *vs* 37.2% in 2014-2017, *P* = 0.05). Notably, there was a significant drop in the WL registration rates for dec-HCV (from 24.2% in 2006-2013 to 15.9% in 2014-2017, *P* = 0.007), whereas HCV/HCC remained a stable indication (from 19% in 2006-2013 to 21% in 2014-2017, *P* = 0.4, Figure 2).

Dec-HCV patients had similar characteristics al WL registration between two different interval time

Table 1 Characteristics at waiting list registration between hepatitis C virus and non- hepatitis C virus patients

	HCV *n* = 490 (%)	Non-HCV *n* = 704 (%)	*P* value
Age (yr)	56 ± 7.8	55 ± 10	ns
Gender (male)	393 (80)	532 (75.5)	ns
BMI	25 ± 4	25 ± 4	ns
Blood group			ns
0	206 (42)	311 (44.2)	
A	199 (40.6)	282 (40)	
AB	19 (3.8)	30 (4.3)	
B	66 (13.4)	81 (11.5)	
HCC (yes)	303 (61.8)	295 (42)	0.001
Child-Pugh classes			0.04
A	137 (28)	163 (23)	
B	185 (38)	252 (36)	
C	168 (34)	289 (41)	
MELD at WL registration	15 ± 6	16.7 ± 6.8	0.01

HCV: Hepatitis C virus; BMI: Body mass index; HCC: Hepatocellular carcinoma; MELD: Model of End-Stage Liver Disease; WL: Waiting list.

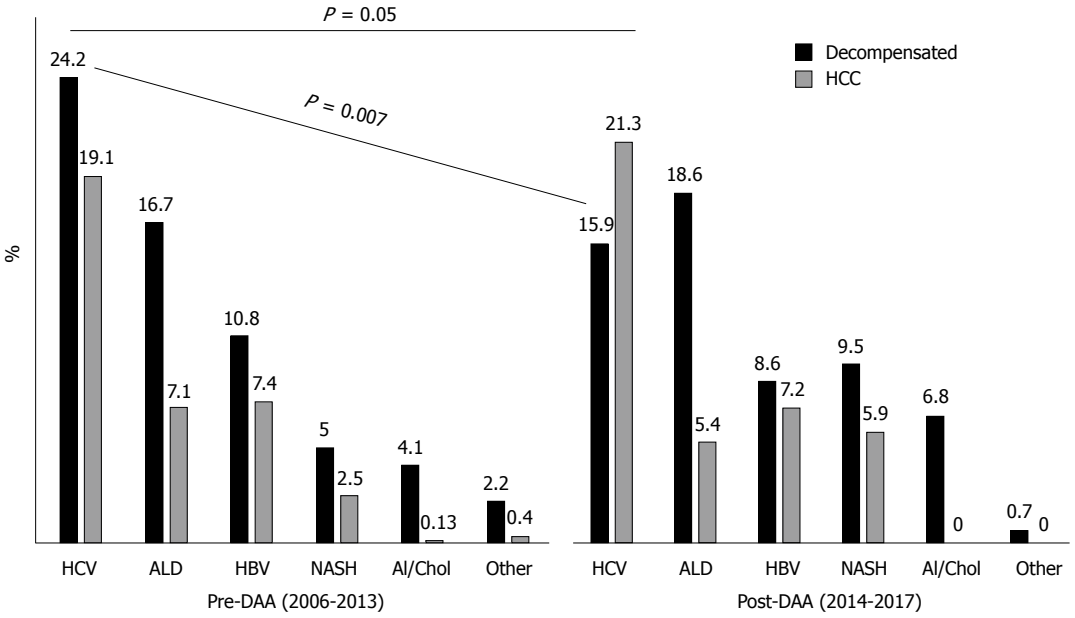

Figure 2 Trends in waiting list registration before and after direct-acting antiviral introduction. ALD: Alcoholic liver disease; DAA: Direct-acting antivirals; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; NASH: Non-alcoholic steatohepatitis.

periods, whereas HCV/HCC patients in the last period were older (57 ± 7 years *vs* 59 ± 6 years, *P* = 0.03) and had lower CTP score (*P* = 0.01). The number of patients registered in the WL after achievement of SVR was higher in the post-DAA period, both amongst dec-HCV (7.3% in 2006-2013 *vs* 24.2% in 2014-2017, *P* = 0.004) and HCV/HCC (from 7% in 2006-2013 to 25.5% in 2014-2017, *P* = 0.001). Similarly, there was a significant increase in treatments while on the WL after DAA introduction, both amongst dec-HCV (from 4.9% in 2006-2013 to 20% in 2014-2017, *P* = 0.009) and HCV/HCC patients (from 4% in 2006-2013 to 26.5% in 2014-2017, *P* = 0.001) (Table 2).

Trajectories of LT for HCV-related disease before and after DAA introduction

Overall, HCV related disease remained the first indication to LT over time (43.4%), followed by alcohol and HBV (22.6% and 16%, respectively). At the time of LT, HCV patients were older than non-HCV patients (57 ± 7.5 *vs* 55 ± 10, *P* = 0.02), and had lower CTP score (*P* = 0.03) and MELD score (17 ± 8 *vs* 18 ± 8, *P* = 0.01) (Table 3).

Overall, there a was a trend towards a decrease in LTs for HCV related disease after DAA introduction (from 46.3% in 2006-2013 to 39% of overall LT in 2014-2017, *P* = 0.06). When HCV patients were stratified according to the main indication to transplantation, LT rates for decompensated disease (from 23.4% in 2006-2013 to 18.3% in 2014-2017, *P* = 0.1) and for HCC (from 22.9% in 2006-2013 to 20.8% in 2014-2017, *P* = 0.5) did not significantly change (Figure 3).

Characteristics of dec-HCV patients at time of LT did not differ across the two periods, except for a higher prevalence of HCC at the time of transplant in

Table 2 Characteristics of hepatitis C virus patients at waiting list registration before and after direct-acting antiviral introduction, according to indication to waiting list registration (decompensated liver disease or hepatocellular carcinoma)

	dec-HCV			HCV/HCC		
	Pre-DAA *n* = 181 (%)	Post-DAA *n* = 70 (%)	*P* value	Pre-DAA *n* = 144 (%)	Post-DAA *n* = 94 (%)	*P* value
Gender (male)	139 (77)	53 (75.7)	ns	118 (82)	82 (87)	ns
Age (yr)	55 ± 8	55 ± 9	ns	57 ± 7	59 ± 6	0.03
BMI	25 ± 3	25 ± 4	ns	24.7 ± 3	25 ± 3.6	ns
Refractory ascites (yes)	74 (40)	32 (45.7)	ns	-	-	
Blood group			ns			ns
0	86 (47.8)	32 (45.7)		62 (43)	35 (39)	
A	70 (38.4)	25 (35.7)		52 (36)	42 (44)	
AB	4 (2.2)	4 (5.7)		6 (4)	5 (5)	
B	21 (11.5)	9 (12.8)		24 (17)	12 (12)	
HCC (yes)	41 (22.5)	24 (34.2)	ns	-	-	
Comorbidities			ns			ns
None	134 (74.1)	44 (62.8)		104 (72.2)	76 (80)	
HBV	7 (3.8)	2 (2.8)		8 (5.5)	3 (3.2)	
Alcohol	34 (18.6)	19 (27.1)		26 (18)	10 (10.6)	
Metabolic	6 (3.2)	5 (7.3)		6 (4.3)	5 (5.3)	
Child-Pugh classes			ns			0.01
A	6 (3.3)	3 (4.2)		64 (44.5)	64 (68)	
B	67 (37)	25 (35.7)		67 (46.5)	26 (27)	
C	108 (59.6)	42 (60)		13 (9)	4 (4)	
MELD score	18.7 ± 6	19.3 ± 6	ns	11 ± 3.5	11 ± 3.4	ns
HCV Genotype[1]			ns			ns
1a	18 (15.1)	14 (23)		11 (10.2)	16 (18.8)	
1b	68 (57.1)	34 (55.7)		67 (62)	39 (45.8)	
2	12 (10)	3 (4.9)		10 (9.3)	4 (4.7)	
3	16 (13.4)	6 (9.8)		15 (13.9)	22 (25.8)	
4	5 (3.3)	4 (6.5)		5 (4.6)	4 (4.7)	
SVR achievement						
None	159 (87.8)	39 (55.7)		128 (89)	45 (47.8)	
Before WL registration	13 (7.1)	17 (24.2)	0.004	10 (7)	24 (25.5)	0.001
IFN based	13 (7.1)	2 (2.8)		10 (7)	6 (6.3)	
During WL registration	9 (4.9)	14 (20)	0.009	6 (4)	25 (26.5)	0.001

[1]HCV genotype was available in 373 patients at the time of WL registration. HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; DAA: Direct-acting antivirals; BMI: Body mass index; HBV: Hepatitis B virus; MELD: Model of End-Stage Liver Disease; SVR: Sustained virological response; WL: Waiting list.

Table 3 Characteristics at the time of liver transplantation between hepatitis C virus and non-hepatitis C virus patients *n* (%)

	HCV *n* = 289	Non-HCV *n* = 377	*P* value
Age (yr)	57 ± 7.5	55 ± 10	0.02
Gender (male)	240 (83)	288 (76)	0.04
Blood group			ns
0	118 (40.8)	167 (44.2)	
A	124 (43)	147 (39)	
AB	12 (4.1)	19 (5)	
B	35 (12.1)	44 (11.8)	
Child-Pugh classes			
A	82 (25)	84 (22.2)	
B	99 (36.7)	116 (30.7)	0.03
C	108 (38.2)	177 (47)	
MELD score	17 ± 8	19 ± 8	0.01
Waiting time (mo)	9.6 ± 12	10 ± 14	ns

HCV: Hepatitis C virus; MELD: Model of End-Stage Liver Disease.

the post-DAA period (20.8% in 2006-2013 *vs* 37.3% in 2014-2017, *P* = 0.04). Similarly, no significant differences were found on characteristics of HCV/HCC patients at time of LT between the two periods. Prevalence of patients transplanted after achievement of SVR was significantly higher in the post-DAA period, both amongst dec-HCV (from 8.8% in 2006-2013 to 29.4% in 2014-2017, *P* = 0.01) and HCV/HCC (from 11% in 2006-2013 to 41% in 2014-2017, *P* = 0.0001) (Table 4).

Outcome of HCV patients treated with DAA in the setting of LT

Since 2014, 88 out of 164 (53.5%) patients with HCV

Table 4 Characteristics of hepatitis C virus patients at liver transplantation before and after direct-acting antiviral introduction, according to indication to waiting list registration (decompensated liver disease or hepatocellular carcinoma) *n* (%)

	dec-HCV			HCV/HCC		
	Pre-DAA *n* = 91	Post-DAA *n* = 51	*P* value	Pre-DAA *n* = 89	Post-DAA *n* = 58	*P* value
Gender (male)	74 (81)	40 (78.4)	ns	77 (86.5)	49 (84.5)	ns
Age (yr)	54.8 ± 8	56 ± 8	ns	57 ± 7	58 ± 7	ns
Refractory ascites (yes)	37 (40.6)	27 (53)	ns	-	-	
Blood group			ns			ns
0	41 (45)	21 (41.7)		37 (41.5)	19 (32.7)	
A	35 (38)	22 (43.3)		39 (43.8)	28 (54.9)	
AB	3 (3.3)	3 (5.8)		4 (4.5)	2 (3.4)	
B	12 (13)	5 (9.8)		9 (10.2)	9 (15.5)	
HCC (yes)	19 (20.8)	19 (37.3)	0.04	-	-	
Child-Pugh classes			ns			0.001
A	3 (3.2)	1 (1.9)		38 (42.6)	42 (72.4)	
B	27 (29.6)	17 (33.3)		42 (47.2)	12 (20.6)	
C	61 (67.1)	33 (64.7)		9 (10)	4 (6.8)	
MELD at LT	24 ± 6.5	23 ± 7.5	ns	11.7 ± 4	11.2 ± 3	ns
SVR at time of LT (yes)	8 (8.8)	15 (29.4)	0.002	10 (11)	24 (41)	0.0001
SVR after IFN-based regimens	7 (7.6)	2 (3.9)		9 (10.1)	1 (1.7)	
Waiting time (mo)	8.3 ± 12	10.6 ± 12	ns	9 ± 7.7	10 ± 11	ns

HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; DAA: Direct-acting antivirals; BMI: Body mass index; MELD: Model of End-Stage Liver Disease; LT: Liver transplantation; SVR: Sustained virological response.

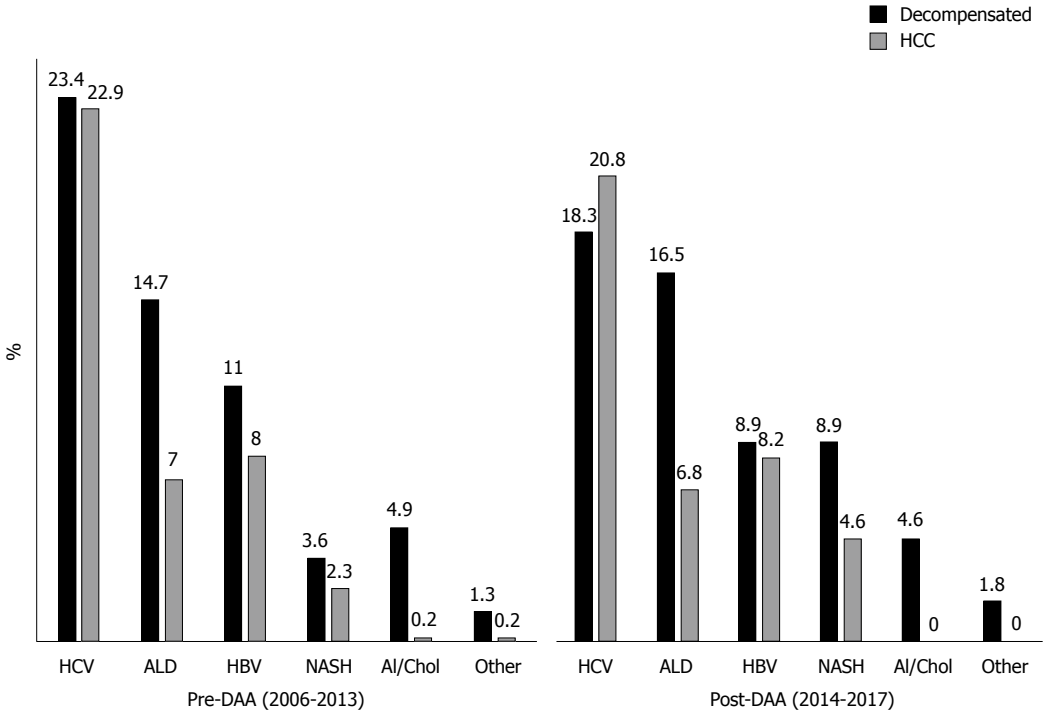

Figure 3 Trends in liver transplantation before and after direct-acting antiviral introduction. ALD: Alcoholic liver disease; DAA: Direct-acting antivirals; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma; NASH: Non-alcoholic steatohepatitis.

related cirrhosis were treated with DAA in the setting of LT (Table 5). Thirty-four (20%) were listed after achievement of SVR, whereas 54 (32.9%) were treated while on the WL. The SVR rate after first treatment with DAA was 88%. Ten patients relapsed after treatment with DAA and achieved SVR after a second treatment while they were on the WL. Sofosbuvir-based regimens were mostly used, whereas ribavirin was used in 43% of patients.

Considering only patients treated while in the WL, 28 (51%) patients underwent LT, whereas 10 (18%) were delisted due to improvement of liver disease, 8 (14.8%) died, and 2 (3.7%) dropped-out due to HCC progression. DAA-treated patients had a higher delisting rate due to improvement of liver disease than untreated HCV patients over time (18% *vs* 2.5%, $P = 0.002$), and

Table 5 Characteristics of hepatitis C virus patients who achieved sustained virological response after treatment with direct-acting antivirals while in the waiting list *n* (%)

	SVR after DAA before the WL *n* = 34	SVR after DAA in the WL *n* = 54
Age (yr)	58 ± 8	57.7 ± 8
Gender (male)	25 (73.5)	43 (79.6)
dec-HCV (yes)	15 (44)	44 (44.4)
MELD score before treament	-	13 ± 5
HCV genotype		
1a	6 (17.6)	6 (11)
1b	17 (50)	34 (63)
2	2 (5.8)	2 (3.7)
3	7 (20.5)	7 (13)
4	2 (5.8)	5 (9.3)
Treatment regimens		
Sofosbuvir	4 (11.7)	27 (50)
Sofosbuvir/Ledipasvir	23 (67.6)	18 (33.3)
Sofosbuvir/Daclatasvir	3 (8.8)	3 (5.5)
Sofosbuvir/Simeprevir	1 (2.9)	4 (7.4)
Other	5 (14.7)	2 (3.7)
Ribavirin use (yes)	1 (2.9)	37 (68.5)
MELD score after treament	12.3 ± 4	13 ± 6
Outcome		
Waiting for LT	16 (47)	6 (11)
Delisted	1 (2.9)	10 (18.5)
LT	10 (29.4)	28 (51.8)
Drop out	5 (14.7)	2 (3.7)
Dead	2 (5.8)	8 (14.8)

SVR: Sustained virological response; DAA: Direct-acting antivirals; HCV: Hepatitis C virus; MELD: Model of End-Stage Liver Disease; LT: Liver transplantation.

a better transplant free survival (log-rank $P = 0.02$).

DISCUSSION

In recent decades, HCV-related cirrhosis has been considered the most prevalent indication for LT in the Western Countries, for both decompensated liver disease and HCC. The introduction of DAAs has significantly modified the natural history of HCV infection, and viral eradication (especially in patients with compensated cirrhosis) has been associated with an improvement of liver function. We consequently explored dynamics of long-term changes in WL registrations and LTs in Our Centre.

Spanning more than a decade, we found that HCV remained the main indication for WL registration not only before, but also after DAA introduction. This might be because the first-generation protease inhibitors were approved in Italy since January 2013[18], but their use was initially limited by side effects and low rates of SVR achievement (less than 50% in cirrhotic patients)[19]. Extended approval of DAA therapies was granted in Italy in 2014, producing a significant drop in the WL registrations for HCV related cirrhosis, moving from 43.3% in the pre-DAA period to 37.2% in 2014-2017. These results are consistent with data recently published by another tertiary center in Italy[20], where the proportion of dec-HCV patients decreased from 49% to 36% in the last years. Two possible explanations may be hypothesized; first, a significant change in HCV epidemiology in Italy in recent years, as shown by several studies[3,21,22], with the highest prevalence of HCV in patients over 70 years old (who are not eligible for LT anymore); second, the achievement of SVR after DAA therapies[23-25], leading to improvement in liver function and reduction of portal-hypertensive complications[26]. Thus, previously decompensated patients, potentially suitable for LT, would therefore not be placed on the WL.

On the contrary, in the setting of HCV related cirrhosis, proportion of WL registration for HCC remained stable after DAA introduction (from 19% in 2006-2013 to 21% in 2014-2017; P = ns). Notably, in the post-DAA period, HCC became the first indication to LT amongst HCV patients. This trend was confirmed also in patients with decompensated disease (*e.g.* MELD $\geqslant$ 15), in whom the prevalence of HCC at the time of transplant rose from 20.8% in 2006-2013 to 37.3% in 2014-2017. Development of HCC in patients previously treated with DAA is debated. Several studies[6,27-29] recently showed that HCC may still occur or recur in patients with SVR achievement after DAA therapy (probably due to changes in the immunological microenvironment after viral clearance), and these patients would probably still need for LT.

In our experience, nearly 18% of HCV patients were delisted after achieving SVR, in a significantly higher proportion than in the pre-DAA period. This reinforces the concept that SVR achievement could significantly improve liver function and increase delisting rate in the next future, even if we'll expect that HCV patients will be cured before decompensation, without requiring WL registration. Furthermore, our data were consistent with those reported by Belli *et al*[30], who reported a delisting rate of 20% (though they only considered HCV-related decompensated cirrhosis patients without HCC).

Our study retrospectively collected all data regarding cirrhotic patients from WL registration to final outcome, using a prospectively updated electronic database. There were no significant changes in WL and LT policies during the study period, and the antiviral treatments were administered under the supervision of a tertiary center, in accordance with the changing criteria recommended by the Italian Regulatory Agency. This study has some limitations that need to be acknowledged, however. It was based on a single-center cohort and covered a lengthy period of time. These data, coming from a single-center cohort, might not be extended to the whole Italian scenario, due to its heterogenous epidemiology in terms of etiologies of liver disease. However, recently published data from Northern Italy seemed to be in accordance with our results[20]. Furthermore, criteria for NASH diagnosis significantly changed over, so we included patients with cryptogenic cirrhosis and a BMI > 30, as other Authors had done[15]. Lastly, we were assessing trends of the WL for LT, and some misdiagnosed comorbidities may have interfered

with the natural history of several patients.

In conclusion, our study showed the significant changes occurring in the LT scenario. Even if DAA therapies have significantly contributed to a decrease in the WL registration for dec-HCV, it will take more time for HCV to disappear as an indication for liver transplantation, especially in the setting of LT for HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV)-related cirrhosis has been the first indication for liver transplantation in Western Countries in the last decades. Introduction of all-oral direct-acting antivirals (DAAs) significantly modified the natural history of HCV related liver disease.

Research motivation

Our study aimed at evaluating the change in waiting list registrations and in liver transplantation for HCV related cirrhosis after DAAs introduction.

Research objectives

To evaluate the outcome of patients with HCV related cirrhosis, listed for liver transplantation at Padua University Hospital between 2006 and 2017. Patients were further divided according to two different time periods (2006-2013 *vs* 2014-2017) and according to indication to liver transplantation (decompensated disease *vs* hepatocellular carcinoma).

Research methods

The outcome of patients listed for liver transplantation (LT) for HCV related cirrhosis was retrospectively analysed using a prospectively updated database.

Research results

After DAAs introduction, HCV-related cirrhosis significantly decreased as indication to waiting list registration, especially among patients with decompensated disease. Considering liver transplantation, even HCV remained the most common indication to LT over time (289/666, 43.4%), there was a trend towards a decrease in the last time period (2013-2017). Furthermore, HCV patients who achieved viral eradication had better transplant-free survival than untreated HCV patients.

Research conclusions

The study demonstrated that HCV related cirrhosis might be a decreasing indication to liver transplantation, especially for decompensated liver disease. Viral eradication achieved with DAA-based regimens should reduce decompensation rates and need to LT. This study confirmed what already known in literature about the beneficial role provided by DAAs in patients with HCV related cirrhosis. Viral eradication obtained after DAAs- based regimens should reduce decompensation rates amongst patients with HCV related cirrhosis. Future studies are needed to confirm the changing scenario regarding indications to LT in Western countries.

Research perspectives

Viral eradication obtained after DAA therapy should reduce decompensation rates amongst patients with HCV related cirrhosis. To further investigate trends in waiting list registrations and liver transplantations for HCV related cirrhosis, especially in the setting of hepatocellular carcinoma. Larger, multicentre, prospective studies are the best methods for the future research.

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