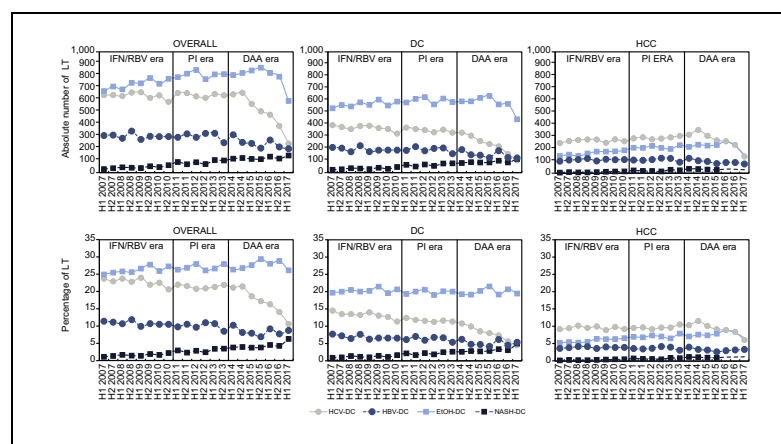


Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry

Graphical abstract



Highlights

- DAAs have dramatically improved the outcome of cirrhotic patients with HCV infection.
- Since the advent of DAAs there has been a 50% decline in the number of liver transplants.
- At least 600 liver grafts every year can currently be allocated to indications other than HCV.
- Survival of LT recipients with HCV or HBV infection is currently comparable, because of DAAs.

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Lay summary

After the advent of direct-acting antivirals in 2014, a dramatic decline was observed in the number of liver transplants performed both in patients with decompensated cirrhosis due to hepatitis C virus (HCV), minus 60%, and in those with hepatocellular carcinoma associated with HCV, minus 41%. Furthermore, this is the first large-scale study demonstrating that the survival of liver transplant recipients with HCV-related liver disease has dramatically improved over the last three years and is now comparable to the survival of recipients with hepatitis B virus infection. The reduction in HCV-related indications for LT means that there is a greater availability of livers, at least 600 every year, which can be allocated to patients with indications other than HCV.

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Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry

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See Editorial, pages 767–768

Background & Aims: Direct-acting antivirals (DAAs) have dramatically improved the outcome of patients with hepatitis C virus (HCV) infection including those with decompensated cirrhosis (DC). We analyzed the evolution of indications and results of liver transplantation (LT) in the past 10 years in Europe, focusing on the changes induced by the advent of DAAs. **Methods:** This is a cohort study based on data from the European Liver Transplant Registry (ELTR). Data of adult LTs performed between January 2007 to June 2017 for HCV, hepatitis B virus (HBV), alcohol (EtOH) and non-alcoholic steatohepatitis (NASH) were analyzed. The period was divided into different eras: interferon (IFN/RBV; 2007–2010), protease inhibitor (PI; 2011–2013) and second generation DAA (DAA; 2014–June 2017). **Results:** Out of a total number of 60,527 LTs, 36,382 were performed in patients with HCV, HBV, EtOH and NASH. The percentage of LTs due to HCV-related liver disease varied significantly over time ($p < 0.0001$), decreasing from 22.8% in the IFN/RBV era to 17.4% in the DAA era, while those performed for NASH increased significantly ($p < 0.0001$). In the DAA era, the percentage of LTs for HCV decreased significantly ($p < 0.0001$) from 21.1% (first semester 2014) to 10.6% (first semester 2017). This decline was more evident in patients with DC (HCV-DC, –58.0%) than in those with hepatocellular carcinoma

(HCC) associated with HCV (HCV-HCC, –41.2%). Conversely, three-year survival of LT recipients with HCV-related liver disease improved from 65.1% in the IFN/RBV era to 76.9% in the DAA era, and is now comparable to the survival of recipients with HBV infection ($p = 0.3807$).

Conclusions: In Europe, the number of LTs due to HCV infection is rapidly declining for both HCV-DC and HCV-HCC indications and post-LT survival has dramatically improved over the last three years. This is the first comprehensive study of the overall impact of DAA treatment for HCV on liver transplantation in Europe.

Lay summary: After the advent of direct-acting antivirals in 2014, a dramatic decline was observed in the number of liver transplants performed both in patients with decompensated cirrhosis due to hepatitis C virus (HCV), minus 60%, and in those with hepatocellular carcinoma associated with HCV, minus 41%. Furthermore, this is the first large-scale study demonstrating that the survival of liver transplant recipients with HCV-related liver disease has dramatically improved over the last three years and is now comparable to the survival of recipients with hepatitis B virus infection. The reduction in HCV-related indications for LT means that there is a greater availability of livers, at least 600 every year, which can be allocated to patients with indications other than HCV.

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Keywords: Liver Transplantation; Waiting list; HCV; HBV; NASH; EtOH.

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Introduction

Viral hepatitis C has long been the most common indication for liver transplantation (LT) in Europe and in the US, with over

20% of all LT candidates on the waiting list having chronic hepatitis C virus (HCV) infection.^{1,2} Until recently, the expected survival rates for HCV infected liver graft recipients were the lowest among all indications, due to severe and rapid HCV recurrence with interferon (IFN)-based therapies giving low cure rates.¹⁻³ The approval of first generation direct-acting antiviral agents (DAAs), telaprevir and boceprevir, in 2011, marked the beginning of a new era. These protease inhibitors (PI) were more effective than the previous IFN-based regimens, but side-effects and frequent drug-drug interactions limited their use for patients with advanced liver disease. In 2014, more potent and better tolerated DAAs became available, and were offered first to patients with compensated and even decompensated cirrhosis. Most patients achieved a sustained virological response (SVR), allowing hepatic function to improve within months of completing treatment in the majority of patients with decompensated cirrhosis (DC) and a model for end-stage liver disease (MELD) score below 20. This resulted in one of four patients being removed from the waiting list.⁴⁻¹² Concurrently, the great majority of patients with compensated cirrhosis treated with DAAs did not progress to DC and avoided LT. To better understand the impact of the new DAAs pre and post-LT, we have interrogated the ELTR registry. The two main objectives of this study were to investigate whether DAAs had influenced indications for LT and improved post-LT outcome of HCV recipients. Only patients with HCV, hepatitis B virus (HBV), alcohol (EtOH) and non-alcoholic steatohepatitis (NASH) etiologies and listed for DC or for hepatocellular carcinoma (HCC) over the last decade were analyzed.

Patients and methods

This is a population-based cohort study of adult patients based on data from the European Liver Transplant Registry database (ELTR) who received a primary liver graft. The methods and approach used to obtain the data have been described previously.^{13,14} An overview of data, approximately 95% of all LTs performed in the European Union were prospectively collected using a standardized questionnaire. The following information is available for each LT: date and indication for LT, donor and recipient characteristics, graft and patient outcomes and location of LT centers, according to a sub-division of Europe: i) Central-North area, ii) Mediterranean area and iii) Eastern area. The list of European countries included in each area is reported in [Table S1](#). The data quality in the ELTR register is guaranteed by an internally developed control quality program and by regular audit monitoring of the contributing centers.¹⁴ This study considers data collected in the ELTR register from January 1st 2007 to June 30th 2017. Patient classification includes five groups based on etiology of liver disease: A) HCV, B) HBV, C) EtOH, D) NASH and E) all others indications (OTHERs). Patients with greater than one etiology were assigned the most relevant one according to this ranking: i) HCV, ii) HBV, iii) EtOH and iv) NASH. For example, a patient with HCV and EtOH was classified as HCV, while a patient with HCV and HBV was classified as HCV. Following the US convention,^{15,16} patients with a diagnosis of cryptogenic cirrhosis and a body mass index (BMI) >30 were classified as NASH.

Evaluating the impact of DAA

Fully understanding the impact of the various HCV treatment options that have entered the European market over the last

decade necessitated the division into periods defined as eras, for specific treatment against HCV infection as follows:

- A) IFN/RBV era – from 2007 to 2010 when only IFN and ribavirin (RBV) were available
- B) PI era – from 2011 to 2013 when PI became available
- C) DAA era – from 2014 to June 2017 when DAAs became available

Statistical analysis

Descriptive statistical analysis was performed using median and interquartile range (IQR) as central tendency and dispersion parameters for continuous data and proportions for categorical data. To assess the difference of baseline characteristics stratified by different etiology, proportional test was used for categorical variables and Kruskal-Wallis test for continuous variables. The same test was used to assess age at LT, DC prevalence, and age of donor within the eras and across different etiologies. Differences in the prevalence of various etiologies over time were compared by Cochran-Armitage test for trend, both in the overall population and in patients with the same indication (DC or HCC) for LT. This analysis was also performed respecting the three different European areas. Survival time was calculated from surgery to death or liver retransplantation (LrT) or to the last follow-up visit with a maximum follow-up of 36 months. Kaplan-Meier analysis was applied to estimate the survival. The nonparametric log-rank test was used to compare survival curves. Cox proportional hazard models were used to assess the hazard ratios (HRs) between different eras within the same liver disease and indication. The Cox models were also used to assess the HRs between different etiologies of liver disease within the same era and indication. The HRs were estimated unadjusted and adjusted for possible confounders: MELD at LT, age at LT and age of donor. Missing data for confounders were considered as follows: single confounders less than 5% were ignored; if greater than 5%, the post-LT outcomes were compared between those with and without missing data. No change indicated a random distribution of missing data with zero impact on results, thus the variable was included, and not included if a significant change was seen. Cumulative incidence curves for death or LrT for disease recurrence, either HCV disease recurrence or HCC recurrence, or for other causes, were constructed considering time to death or LrT as competing risks. Gray's Test for Equality was applied to compare Cumulative Incidence Functions among eras. A *p* value <0.05 was considered to be statistically significant. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

Results

Baseline

A total of 60,527 patients received an LT between January 2007 and June 2017 with 36,382 having one of the following etiological diagnoses: HCV (20.6%), HBV (9.8%), EtOH (26.9%) or NASH (2.8%) ([Table 1](#)). The OTHER group (39.9%) included cholestatic disease (9.5%), autoimmune and cryptogenic cirrhosis (6.2%), acute hepatic failure (4.8%), metabolic diseases (3.2%), benign tumors (1.9%), malignant tumor other than HCC (1.5%), and a variety of miscellaneous indications (12.8%). Median (IQR) age at LT was 55 (47–61) years. Indications for LT were DC in 71.7% and HCC in 28.3% of the cases with HCC indication being more prevalent in patients with HCV and HBV infection, com-

Table 1. Baseline Characteristics of LT recipients in Europe (January 2007-June 2017).

	Entire cohort	HCV	HBV	EtOH	NASH	Others	p value
N (%)	60,527 (100.0%)	12,452 (20.6%)	5,918 (9.8%)	16,287 (26.9%)	1,725 (2.8%)	24,145 (39.9%)	
Indication (%)							
DC	71.69	53.6	62.9	74.5	75.3	81.0	<0.0001
HCC	28.31	46.4	37.1	25.5	24.7	19.0	
Age, yr	55 (47.2–61.3)	55.1 (49.6–60.8)	53.4 (45.5–59.6)	57.6 (52–62.5)	59.8 (54–64.4)	51.8 (39.3–60.5)	<0.0001
Male sex, %	69.3	76.2	79.5	82.7	67.8	54.2	<0.0001
BMI, kg/m ²	25.5 (22.8–28.9)	25.5 (23.2–28.4)	25.6 (23.1–28.4)	26.7 (23.9–30.1)	31.5 (29.3–34.3)	24.5 (21.9–27.7)	<0.0001
Donor age, yr	52.9 (38.8–65.6)	54.8 (41.8–66.5)	48 (31.1–63.7)	57.4 (44.2–69.7)	52 (38–63.5)	50 (35.7–62.2)	<0.0001
MELD score							
DC	17 (12–25)	17 (12–23)	17 (12–24)	18 (13–25)	19 (13–23)	17 (11–26)	<0.0001
HCC	11 (8–17)	11 (8–18)	11 (8–17)	13 (9–18)	12 (8–17)	10 (8–15)	<0.0001

*Kruskal-Wallis test or proportion test. Data are show as median (IQR). BMI, body mass index; DC, decompensated cirrhosis; EtOH, alcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplant; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.

pared to EtOH, NASH or OTHERS (Table 1). Patients with EtOH or NASH were older and had a higher BMI and MELD score at LT.

Characteristics of LT within the different eras

Median recipient age and median donor age increased across the three eras in HCV, HBV, EtOH but not in patients with NASH ($p < 0.0001$). DC as a main indication for LT significantly decreased only in HCV and EtOH patients ($p < 0.0001$). MELD score at LT increased by 1 to 2 points only in recipients with HCV and HBV (Table 2).

Evolution of liver disease etiologies and indications for LT in Europe

The total number of LT performed in Europe remained stable across the years (Fig. S1). The 20% decline observed in the first semester of 2017 is attributed to the delay in receiving the relevant data, attributed to a minority of centers sending their updated files to the registry every 12 months and not every

6 months, as required. Percentage and absolute numbers of LTs according to main indication for LT (overall, DC and HCC) and etiology (HCV, HBV, EtOH, NASH) are shown divided by era (Fig. 1) and divided by semesters (Fig. 2). The percentage of LTs for HCV in each era varied from 22.8% in IFN/RBV to 17.4% in the DAA era ($p < 0.0001$) (Fig. 1A), with a decline from 13.2% to 8.0% ($p < 0.0001$) in HCV-DC patients (Fig. 1B) and from 9.5% to 9.4% ($p = 0.2718$) in HCV-HCC (Fig. 1C). Overall, the most significant change of HCV as an indication for LT was found within the DAA era, declining from 21.1%, (first semester 2014) to 10.6% (first semester 2017) ($p < 0.0001$) (Fig. 2A). When separating HCV-DC from HCV-HCC, the percentage of HCV-DC as an indication for LT went from 11.4% (first semester 2014) to 4.5% (first semester 2017) ($p < 0.0001$) (Fig. 2B), while that of HCV-HCC went from 10.6% to 6.1% ($p < 0.0001$) (Fig. 2C). Whereas the percentage of HBV-HCC as indication for LT remained constant overtime (around 3.5%), patients undergoing LT for HBV-DC significantly decreased ($p < 0.0001$) overtime,

Table 2. Trends in the Demographic and clinical Characteristics of LT patients based on aetiology of Liver Disease.

	HCV	HBV	EtOH	NASH
Median age at LT, yr				
IFN era	54.2 (48.3–60.7)	52.7 (44.8–58.7)	56.7 (51.1–61.2)	59.1 (53.4–63.3)
PI era	55.0 (49.7–60.6)	53.6 (45.7–59.5)	57.7 (51.9–62.5)	60.2 (55.0–64.6)
DAA era	56.1 (51.4–61.3)	54.3 (46.3–60.8)	58.8 (53.3–63.5)	59.9 (53.9–65.0)
p value	<0.0001	<0.0001	<0.0001	0.0106
DC, %				
IFN era	58.1	63.69	77.42	77.71
PI era	54.64	63.29	73.61	75.58
DAA era	46.05	61.32	72.14	74.15
p value	<0.0001	0.2771	<0.0001	0.4223
Median age of donor, yr				
IFN era	53.4 (40.1–65.1)	47.6 (30.7–62.6)	54.5 (41.6–66.8)	50.4 (37.8–62.6)
PI era	54.8 (42.0–66.1)	46.8 (29.7–64.6)	58.9 (45.7–70.9)	51.9 (36.3–63.6)
DAA era	57.5 (44.9–69.9)	50.2 (33.7–64.3)	59.3 (45.9–71.7)	52.7 (39.8–63.9)
p value	<0.0001	0.0008	<0.0001	0.1887
MELD score at LT – DC				
IFN era	16 (12–22)	17 (12–25)	18 (13–25)	17 (14–24)
PI era	17 (12–23)	17 (12–24)	19 (14–26)	17 (13–23)
DAA era	17 (13–23)	19 (14–25)	18 (13–25)	17 (13–22)
p value	0.0017	<0.0001	0.0024	0.6237
MELD score at LT – HCC				
IFN era	12 (8–18)	11 (8–16)	13 (9–19)	12 (8–18)
PI era	11 (8–19)	10 (7–16)	13 (9–18)	12 (8–16)
DAA era	11 (8–18)	11 (8–17)	12 (8–17)	11 (9–16)
p value	0.1156	0.1883	0.0013	0.8963

*Kruskal-Wallis test or proportion test. Data are show as median (IQR); DAA, direct-acting antiviral; DC, decompensated cirrhosis; EtOH, alcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor.

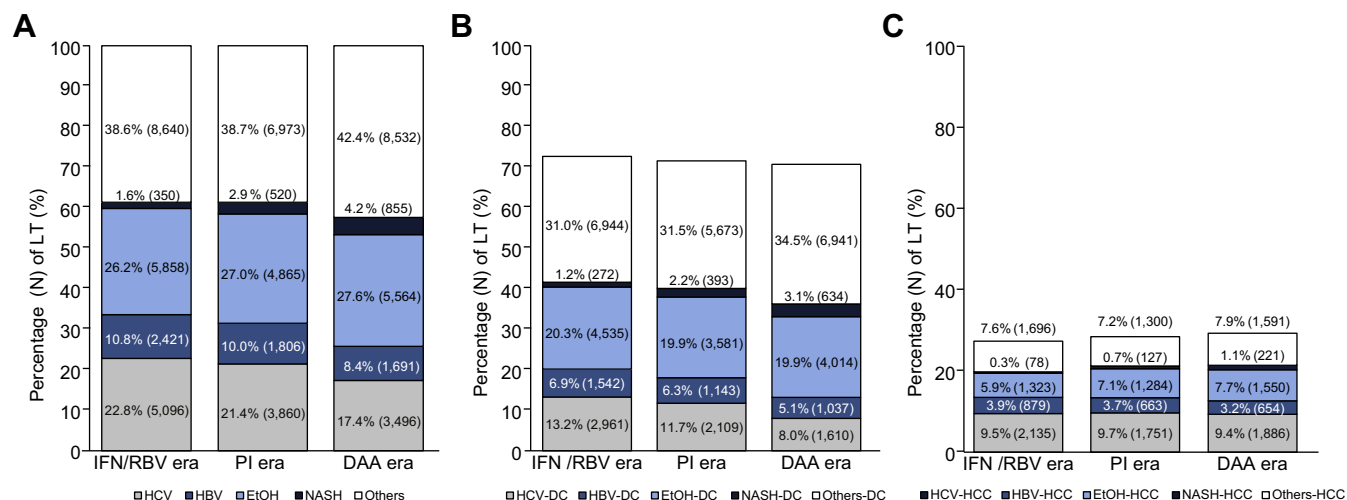


Fig. 1. Percentage and number of LTs in the three eras stratified by etiology of liver disease. DAA, direct-acting antiviral; DC, decompensated cirrhosis; EtOH, alcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor; RBV, ribavirin.

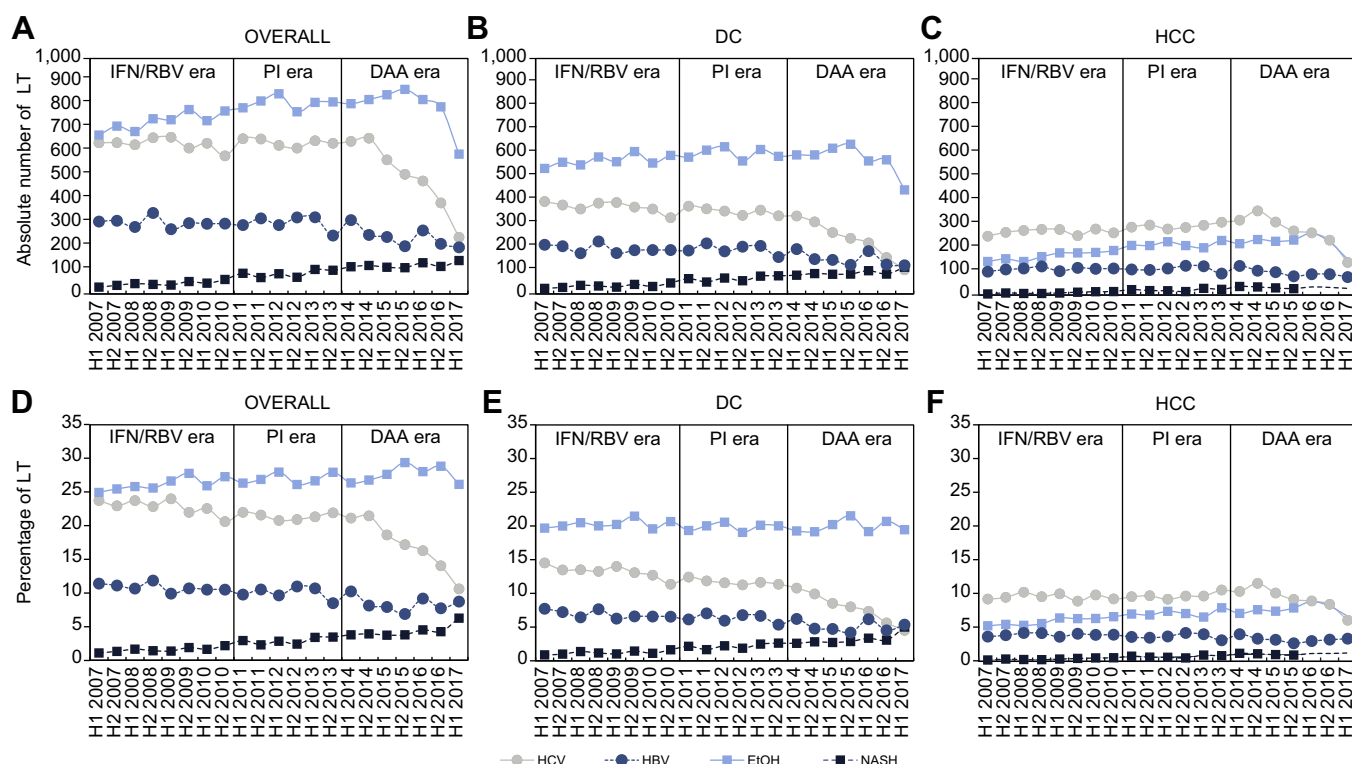


Fig. 2. Absolute number and percentage of LT by etiology of liver disease and indication for LT. X-axis is the semester of LT registration. *The decline in the total number of LTs in the first semester 2017 is because 20% of centers send their data to the ELTR registry every 12 months and not every 6 months. DAA, direct-acting antiviral; DC, decompensated cirrhosis; ELTR, European Liver Transplant Registry; EtOH, alcohol; H2, second semester; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor; RBV, ribavirin.

from 7.7% (first semester 2014) to 5.4% (first semester 2017) (Fig. 2). In patients with NASH, the rate of LT increased in the same period from 0.9% to 5.0% ($p < 0.0001$) when the indication was DC, and from 0.2% to 1.2% ($p < 0.0001$) when HCC was the main indication (Fig. 2). Twenty-five percent of liver transplants performed in Europe are due to EtOH, representing the most common indication for LT, a figure which remained quite stable over the study period (Figs. 1 and 2).

Evolution of liver disease etiologies and indications for LT in European areas

Significant differences emerged from the comparison of the three European areas. The Mediterranean countries had the highest percentage of LT in HCV recipients, while Eastern European countries had the highest percentage of LTs performed in patients with HBV infection and the lowest in those with alcohol-related disease (Fig. S2). In all three European areas, a

remarkable reduction in prevalence of HCV LT over time was observed, the main reduction occurring within the DAA era. The overall effect was an increase in LTs performed for etiologies other than HCV. In Northern Europe, the incidence of NASH as an indication for LT arrived at 10.0% in the first semester of 2017, being the highest of all three European areas.

Impact of DAAs on survival after LT

Three-year patient survival for the different indications (DC or HCC) and etiologies (HCV, HBV, EtOH or NASH) are reported (Figs. 3 and 4). Three-year survival of patients with HCV-DC improved from 65.1% in the IFN era to 76.9% in the DAA era ($p < 0.0001$) with HCV recurrence as cause of death or LrT decreasing from 6.37% in IFN/RBV era to 1.27% in DAA era ($p < 0.0001$) (Table 3). A similar trend was observed in patients with HCC associated with HCV (Fig. 4), with HCV recurrence as cause of death or LrT decreasing from 5.89% in the IFN era to 0.60% in DAA era ($p < 0.0001$) and HCC recurrence as a cause of death remaining stable ($p = 0.71$) (Table 3). Patients with HBV and NASH with or without HCC showed similar survival across the three eras (Figs. 3 and 4). Overall, the historical survival gap between patients with HCV infection and those with HBV and EtOH observed in the IFN/RBV era has disappeared in the DAA era (Fig. 5). All Cox proportional hazard models were also performed adjusting for possible confounders such as MELD score at LT, age of the recipient and age of the donor. The results in terms of three-year patient survival of the adjusted and unadjusted models were similar (Tables S2 and S3).

Discussion

Although an impact of new DAAs on liver transplantation was anticipated, no large-scale data relative to Europe have been available to date. This ELTR/ELITA study based on more than 60,000 patients provides two novel and important pieces of information.

Firstly, while the number of LTs performed in Europe over the last decade has remained stable, the percentage of LTs in patients with HCV infection has almost halved since 2014, the decrease being more evident in HCV-DC (−58.8%) than in HCV-HCC (−41%). In absolute terms, this means that approximately 315 fewer transplants were performed in HCV patients across Europe in the first semester of 2017 when compared to the first semester of 2014. Concurrently, the percentage of patients receiving an LT for NASH has progressively increased from 1% to 6%, while the number of livers transplanted into patients with alcohol-related liver disease or with hepatitis B infection has not changed significantly.

Secondly and most relevant, survival of LT recipients with HCV-related liver disease has dramatically improved over the last three years, and is now comparable to the survival of recipients with HBV infection. These results are most likely the direct consequence of the availability of the new DAAs.

Regarding HCV infected patients with DC before LT, data from clinical trials indicate that the new DAAs are not only highly effective in curing HCV infection, but can favor the reversal of decompensation in one in three patients, provided the MELD score is below 20. This may explain part of the decline in the number of LTs for HCV observed in more recent years. As

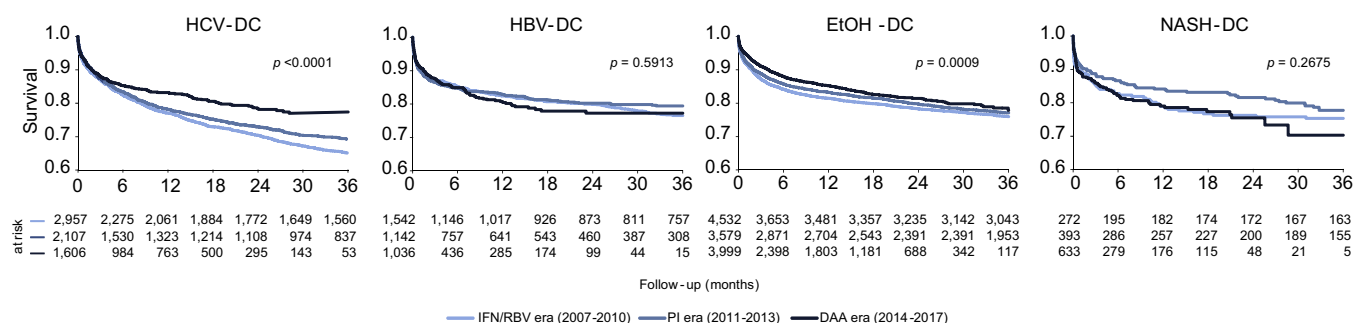


Fig. 3. Survival after LT in patients with DC. Kaplan-Meier analyses comparing IFN era, PI era and DAA era, within the same etiology of liver disease. The nonparametric log-rank test was used to compare survival curves. DAA, direct-acting antiviral; DC, decompensated cirrhosis; EtOH, alcohol; HBV, hepatitis B virus; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor; RBV, ribavirin.

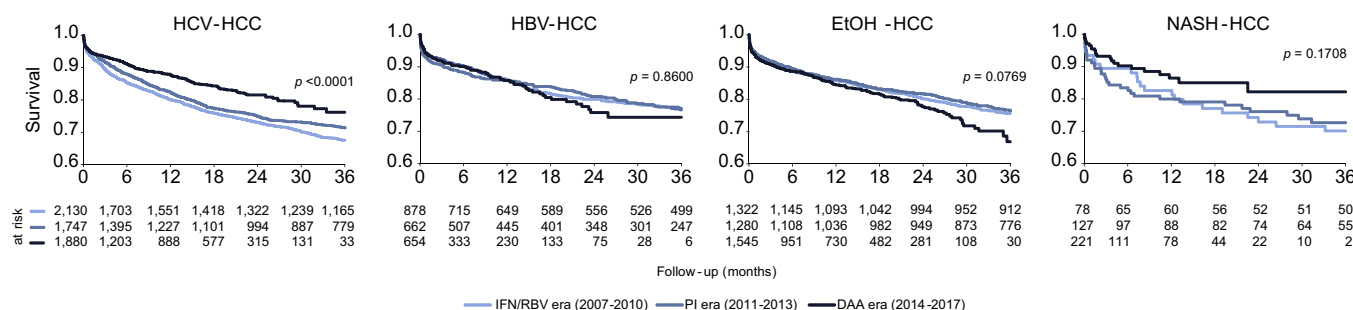


Fig. 4. Survival after LT in patients with HCC. Kaplan-Meier analyses comparing IFN era, PI era and DAA era, within the same etiology of liver disease. The nonparametric log-rank test was used to compare survival curves. DAA, direct-acting antiviral; EtOH, alcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor; RBV, ribavirin.

Table 3. DC and HCC patients – death or LrT cumulative incidence (%) in the three eras, stratified by etiology of liver disease and cause of death.

Cause of death or LrT	IFN era (2007–2010)			PI era (2011–2013)			DAA era (2014–2017)		
	Cumulative incidence (%)			Cumulative incidence (%)			Cumulative incidence (%)		
	1 yr	2 yr	3 yr	1 yr	2 yr	3 yr	1 yr	2 yr	3 yr
HCV-DC (N)		2,957			2,107			1,606	
HCV recurrence*	2.51	4.79	6.37	3.31	4.85	5.51	0.91	0.91	1.27
Other cause*	17.36	20.93	23.89	14.53	17.33	19.32	13.17	17.17	18.25
Not indicated	3.06	3.87	4.60	4.01	4.88	5.60	2.74	3.50	3.50
HBV-DC (N)		1,542			1,142			1,036	
HBV recurrence	0.22	0.31	0.50	0.00	0.00	0.00	0.00	0.00	0.00
Other cause	14.38	14.38	16.18	12.97	14.66	15.07	15.21	17.09	17.09
Not indicated	3.00	3.61	4.19	4.18	5.09	5.50	4.32	5.63	5.63
EtOH-DC (N)		4,532			3,579			3,999	
EtOH recurrence	0.09	0.11	0.19	0.03	0.16	0.19	0.03	0.16	0.16
Other cause*	15.23	17.68	19.58	13.54	16.13	18.33	11.30	14.03	16.19
Not indicated	3.25	3.92	4.28	3.20	4.01	4.40	3.47	4.40	5.78
NASH-DC (N)		272			393			633	
NASH recurrence	2.67	3.11	3.11	0.82	0.82	1.27	1.31	2.24	2.24
Other cause	12.75	14.50	15.40	13.32	14.77	16.87	13.78	15.17	18.22
Not indicated*	5.68	6.11	6.11	1.71	2.80	4.11	5.86	7.11	9.27
HCV-HCC (N)		2,130			1,747			1,880	
HCV recurrence*	2.50	4.31	5.89	2.39	3.79	4.42	0.37	0.60	0.60
HCC recurrence	6.47	8.81	10.40	5.85	8.42	9.63	5.60	8.48	10.50
Other cause*	9.22	11.73	13.82	7.89	10.37	11.78	5.37	8.11	11.48
Not indicated	1.75	2.02	2.42	1.53	2.43	2.87	0.85	1.25	2.35
HBV-HCC (N)		878			662			654	
HBV recurrence	0.00	0.14	0.14	0.00	0.00	0.00	0.00	0.00	1.46
HCC recurrence	6.10	6.10	11.15	4.71	7.68	9.47	4.98	8.37	8.37
Other cause	5.87	7.66	9.01	6.82	8.07	9.61	8.19	13.92	13.92
Not indicated	2.22	2.76	3.06	2.59	3.44	3.70	1.09	1.90	1.90
EtOH-HCC (N)		1,322			1,280			1,545	
EtOH recurrence	0.00	0.16	0.32	0.08	0.08	0.45	0.11	0.11	0.11
HCC recurrence	4.92	6.83	7.97	4.84	6.11	7.19	5.92	7.19	10.06
Other cause	8.46	11.88	15.06	8.24	11.03	14.65	8.28	13.89	19.37
Not indicated	0.77	0.93	1.09	0.64	1.06	1.33	1.24	1.44	3.58
NASH-HCC (N)		78			127			221	
NASH recurrence	1.32	2.69	2.69	0.00	0.00	0.00	0.00	0.00	0.00
HCC recurrence	4.07	9.60	11.00	4.10	5.11	7.40	3.25	7.50	7.50
Other cause	9.38	12.18	13.58	12.50	14.43	15.55	8.21	8.21	8.21
Not indicated	2.67	2.67	2.67	3.43	4.41	4.41	2.10	2.10	2.10

* $p < 0.05$ estimated with the Gray's test for equality of cumulative incidence functions (among era). DAA, direct-acting antiviral; EtOH, alcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LrT, liver retransplantation; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor.

reported in two recent European studies, almost 30% of the patients with DC on the waiting list and with a low priority for LT could be delisted due to clinical improvement following DAA therapy.^{10,11} But the main reason of the decline in the number of LTs is likely the reduced need of listing for LT of new patients with HCV and DC. In fact, when DAAs are administered to patients with compensated cirrhosis, the progression of their liver disease can be generally halted and hepatic decompensation prevented.¹² Two recent papers from the US foresaw the changing scenario we are observing in Europe. Flemming *et al.* observed a 32% decline in the adjusted incidence of waitlisting for LT while Goldberg *et al.* reported a 37% decline in the number of patients receiving a LT for DC while the number of those with HCC are still increasing after 2014.^{15,16} Noticeably, the decline in the percentage of LT for patients with HCV and DC observed in the ELTR register was almost twofold greater than the decline observed in the US, most likely because of our patient inclusion period being extended to June 2017, whereas the two aforementioned studies did not extend their observation beyond 2015. This longer period of time better captures the relevance to the DAA use in the European cohort. The decline in the number of

LTs for HCC in our study is particularly relevant because it is a novel finding which indicates that the evolution of the indications for LT is occurring more rapidly than expected. While we believe that the wide DAA use is the principal reason for the reduced waiting list and reduced transplants performed in patients with HCV, we cannot exclude that the changing epidemiology of HCV infection has also played a role.¹⁷ For example, the majority of patients treated with DAAs are in fact 'baby boomers', being born between 1945 and 1975, and thus their eligibility for LT is progressively decreasing due to aging. However, the rapid drop in the number of LT after 2014 strongly suggests an important effect of DAA on the need for LT. In contrast, the number of patients with NASH requiring LT has increased. This trend has also been demonstrated by other studies, mainly from the US showing a sharp increase in NASH in recent years with further increases expected in the future.^{15,16,18} NASH is now the second most prevalent indication for LT in the US, concurrent with an increasing prevalence of obesity and metabolic syndrome in the US population. These conditions are much less prevalent in most of the European regions and this explains why NASH is still a marginal indication for LT when compared with the US.

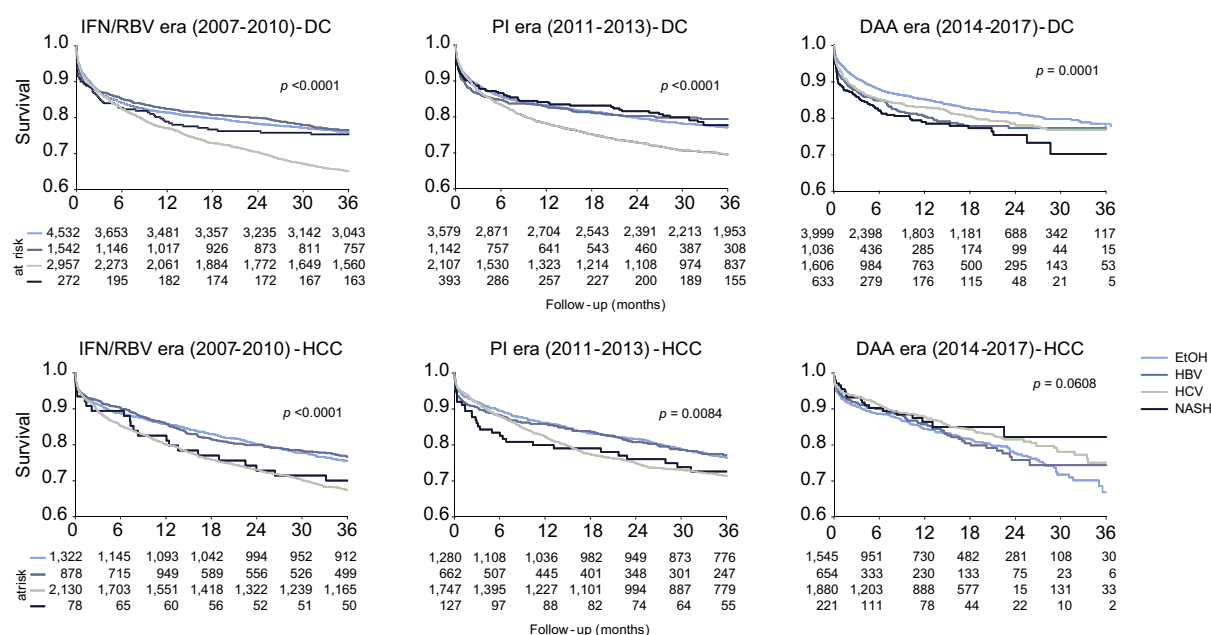


Fig. 5. Survival after LT within the same era. Kaplan-Meier analyses comparing different etiology of liver (HCV, HBV, EtOH and NASH) and transplant indications. The nonparametric log-rank test was used to compare survival curves. DAA, direct-acting antiviral; EtOH, alcohol; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; PI, protease inhibitor; RBV, ribavirin.

Significant differences emerged comparing the three European regions. The Mediterranean countries had the highest percentage of LT in HCV recipients, while Eastern European countries had the highest percentage of LT in HBV recipients in alignment with the different epidemiology of the virus in the population. In addition, a much lower percentage of LT performed in patients with alcohol-related disease in Eastern countries possibly reflects a regional policy that limits the access of these patients to LT programs.

One of the most notable findings of this study is the improved survival rate observed in HCV liver transplant recipients concurrently with the availability of DAAs, beginning in the early post-transplant period and reaching a delta of 12% three years out. The improved survival was observed despite a concomitant increase in both recipient age and pre-LT MELD score and even despite a concomitant increase in donor age, a factor which has been largely reported as one of the major negative factors impacting post-LT outcome in HCV recipients. In addition, adjusted analysis confirmed that the improvement in post-LT survival was independent of donor and recipient age and of MELD score. The extent of the gain in survival and its occurrence early after LT were not fully expected and most likely depend on the combined effect of treating patients with DAAs while listed, thus preventing HCV recurrence, or curing HCV infection early after LT.¹² The HCV recipient survival rate almost reaches that of HBV patients, the candidates with the most positive expected outcomes after LT. This improved survival rate is probably due to different factors, since DAAs are crucial not only for preventing severe HCV recurrence, but also for limiting other complications including early graft dysfunction and immunological or infective complications where HCV may act as a cofactor.^{19–21} This observation will likely encourage a more widespread use of extended criteria grafts also in HCV recipients. A recent study from Spain reported similar trends, although the population size is not comparable to that of the ELTR registry.²²

A positive result of the decreased need of LT for HCV-related indication is greater availability of donor livers, at least 600 every year in Europe, which may be allocated to indications other than HCV. How to best allocate this relatively “increased availability of grafts” is a question that needs to be urgently addressed. It is not unreasonable to anticipate a new scenario where patients once excluded from many LT programs such as those with HCC beyond Milan criteria or those with alcoholic hepatitis are likely to be considered as candidates for LT in the near future.

There are some limitations to our study. Firstly, the ELTR register does not contain information regarding the use of any drugs, including DAAs. Thus, this may indicate an indirect link between improved survival and the use of DAAs. To account for this, the study period was divided in three eras marked by a specific treatment against HCV infection having entered the European market. Secondly, the ELTR database only provides data of liver transplants but not of those on the waiting list. Thirdly, despite the fact that steps have been taken to minimize the risk of bias when evaluating the impact of DAA on post-LT survival analyses, the effect of residual confounders cannot be excluded.

In conclusion, this study based on the data from the ELTR registry, evidences a rapid decrease in the number of LTs in patients with HCV-related decompensated cirrhosis, and to a lesser degree, in those with HCC associated with HCV. This trend is expected to continue provided that current policies aiming to eradicate HCV infection in the population are maintained. In contrast, the demand for LT for patients with NASH is rapidly increasing, although at a slower pace than in the US. Notably, this study shows for the first time on a large scale that DAAs have led to a major improvement in HCV recipient survival.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

Authors' contributions

Luca Saverio Belli: data interpretation, writing. Giovanni Perricone: data interpretation and revision of the manuscript. Rene Adam: custodian of ELTR. Paolo A Cortesi: data analysis. Mario Strazzabosco: data interpretation, writing. Rita Facchetti: data analysis. Vincent Karam; ELTR data analysis. Mauro Salizzoni, Rafael Lopez Andujar, Costantino Fondevila, Paolo De Simone, Antonio Pinna, Joan Fabregat-Prous, Didier Samuel, John O Grady, Enrique Moreno Gonzales, Ramon Charco, Krzysztof Zieniewicz, Luciano De Carlis: data collection and revision of the manuscript. Christophe Duvoux: data interpretation, writing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.jhep.2018.06.010>.

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