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Original Article

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Abstract

Background and Aims: With the availability of direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection and changing liver disease etiology for liver transplantation (LT), data on the changes in LT recipient population in the DAA era are scanty. ***Methods:*** The United Network for Organ Sharing (UNOS) registry (01/2007 to 06/2018) was used to develop a retrospective cohort of LT recipients for HCV, alcohol-associated liver disease (ALD), and non-alcoholic steatohepatitis (NASH). LT recipients in the DAA era (2013-2018) were compared with those in the pre-DAA era (2007-2012) era for recipient characteristics. Chi-square and analysis of variance were the statistical tests used for categorical and continuous variables, respectively. ***Results:*** Of 40,309 LT recipients (21,110 HCV, 7586 NASH, and 11,713 ALD), the 21,790 in the DAA era (9432 HCV, 7240 ALD, and 5118 NASH) were more likely to be older, female, obese, diabetic, have acute-on-chronic liver failure with a higher model for end-stage liver disease score, receive grafts with a lower donor risk index, and have waited on the LT list for a shorter period compared with their pre-DAA era counterparts. Specific to ALD, LT recipients with alcohol hepatitis were more likely to be younger at the time of LT. Of 9895 LT recipients with hepatocellular carcinoma, recipients in the DAA era were observed to have a higher proportion of HCV (43% vs. 32%, $p<0.001$), a lower proportion of ALD (9% vs. 12%, $p<0.001$), and no change for NASH (13% vs. 13%, $p=0.9$) compared with the pre-DAA era. Within the hepatocellular carcinoma population, LT recipients in the DAA era were older, diabetic, and waited on the LT list longer compared with their pre-DAA counterparts. ***Conclusions:*** Along with changing liver disease etiology in the DAA era, the LT recipient population demographics, comorbidities, liver disease severity, and graft quality are changing. These changes are relevant for future studies, immunosuppression, and post-transplant follow-up.

Keywords: DAA; Cirrhosis; OLT.

Abbreviations: ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; AH, alcoholic hepatitis; DAA, direct-acting antiviral; DRI, donor risk index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; UNOS, United Network for Organ Sharing.

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Introduction

Direct-acting antiviral (DAA) therapy has dramatically impacted the landscape of hepatitis C virus (HCV) infection treatment. Unlike interferon-based therapy, DAA treatment has excellent safety and efficacy, with an over 95% HCV cure rate.[1] This change has resulted in a decrease in the requirement of liver transplantation (LT) for HCV. At the same time, LT frequency for alcohol-associated liver disease (ALD) and non-alcoholic steatohepatitis (NASH) cirrhosis has increased, with ALD becoming the top indication for LT followed by NASH cirrhosis.[2–5] In contrast, HCV remains the leading indication of LT among patients with cirrhosis complicated by hepatocellular carcinoma (HCC).[5] However, the data on changes in the DAA era study population is scanty compared to the era prior to the availability of DAA.

Methods

Study population and definitions

The United Network for Organ Sharing (UNOS) database (01/2007 to 06/2018) was stratified for LT recipients in the pre-DAA (2007-2012) and DAA (2013-18) eras. The study population included LT recipients with ALD, NASH, and HCV. Patients who received transplants for HCC and one of these three etiologies were included. In the database, UNOS codes characterized liver disease etiologies and HCC. For each LT recipient, the model for end-stage liver disease (MELD) score and donor risk index (DRI) were calculated using the standard formulae based on specific recipient and donor variables, respectively. Organ failure and acute-on-chronic liver failure (ACLF) were defined using the European Association for the Study of Chronic Liver Failure consortium criteria.[6]

Data analyses

Etiology-specific baseline characteristics of LT recipients were compared for the pre-DAA era versus the DAA era. These characteristics were also compared for recipients with and without HCC. Chi-square and analysis of variance statistical tests were used for comparison of categorical and continuous

variables, respectively. All the analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-tailed *p*-value of <0.05 was considered to be of statistical significance. Since this is a database study using de-identified data, no institutional review board approval was needed. However, a disclosure author agreement was completed with the UNOS, the organization that provided the database for the study.

Results

Study population

A total of 40,409 LT (21,790 in the DAA era) were performed between Jan 2007 and June 2018. Of these, 21,110 LT (9432 in the DAA era) were performed for HCV, 11,713 (7240 in the DAA era) for ALD, and 7586 (5118 in the DAA era) for NASH (Table 1). A total of 267 LT (206 in the DAA era) among recipients with ALD were performed because of a primary indication of alcoholic hepatitis (AH), with a higher proportion in the DAA era versus the pre-DAA era (2.9% vs. 1.4%, $p<0.001$). Overall, about 25% of LT ($n=9975$) were performed for liver disease complicated by HCC, with no significant differences between DAA and pre-DAA eras ($p=0.75$). Among the HCC LT recipients, 7786 LT (4008 in the DAA era) were performed for HCV, 1151 (629 in the DAA era) for ALD, and 958 (648 in the DAA era) for NASH (Table 2). Etiology-specific change on concomitant HCC in the DAA era showed a significant increase for HCV (43% vs. 32%, $p<0.001$), decrease for ALD (9% vs. 12%, $p<0.001$), and no change for NASH (13% vs. 13%, $p=0.9$).

Baseline characteristics of LT recipients in the DAA era versus pre-DAA era

Demographics: Overall, in the DAA era, as compared to the pre-DAA era, LT recipients were older (57 vs. 55 years, $p<0.001$). This was more apparent for HCV (58 vs. 55 years, $p<0.001$) and NASH (60 vs. 59 years, $p<0.001$) cases. However, LT recipients with ALD were younger in the DAA era (53 vs. 55 years, $p<0.001$). Similarly, more females received LT in the DAA era (30% vs. 27%, $p<0.001$). These female LTs were mainly contributed by ALD (25% vs. 22%, $p=0.002$), with no gender differences for HCV- and NASH-related transplants. There were no racial differences between the two eras. However, in the DAA era, more minorities (Blacks, Hispanics, and other races) received LT because of NASH (25% vs. 22%, $p<0.001$) and ALD (31% vs. 29%, $p=0.004$) indications.

Among HCC transplants: Within the HCC transplant subgroup, recipients were older (61 vs. 58 years, $p<0.001$). There were no gender differences for any of the etiologies. Although there was no overall racial difference, in the DAA era, HCV-related LTs were more often performed for minorities (41% vs. 40%, $p<0.001$).

Comorbidities: Patients in the DAA era were more often obese (41% vs. 39%, $p<0.001$), diabetic (31% vs. 28%, $p<0.001$), and in need of dialysis (18% vs. 13%, $p<0.001$) versus the pre-DAA era. In the DAA era, the proportion of obese recipients decreased for NASH (60% vs. 65%, $p<0.001$), without any change for the other two indicators. In contrast, in the DAA era, diabetes was a more frequent comorbidity for HCV (25% vs. 24%, $p<0.02$), less frequent comorbidity for ALD (20% vs. 24%, $p<0.001$), and, although there appeared to be an increasing trend, there was no statistical difference in NASH (59% vs. 57%, $p=0.22$). The use of dialysis was more frequent in the DAA era for all etiologies (14% vs. 11% for HCV, 19% vs. 14% in NASH, and 23% vs. 17% in ALD, $p<0.001$).

Among HCC transplants: The frequency of obesity was similar for all etiologies. However, diabetes (34% vs. 29%, $p<0.001$) and use of dialysis (3.4% vs. 2.5%, $p=0.012$) were more frequent in the DAA era versus the pre-DAA era, especially among LT for HCV that were HCC-related.

Transplant characteristics: The mean MELD score at LT was higher in the DAA era (21.2 vs. 21, $p<0.001$). This change was mainly contributed by ALD (25 vs. 23, $p<0.001$). There was no statistical difference in NASH (22 vs. 22, $p=0.87$) and a decrease in MELD among HCV-related (18 vs. 20, $p<0.001$) LT. Similarly, LT was more often performed for ACLF in the DAA era (40% vs. 36%, $p<0.001$). The etiology-specific proportion of ACLF showed an increase for ALD (51% vs 43%, $p<0.001$) and NASH (41% vs. 38%, $p=0.003$) without there being a significant difference for HCV (31% vs. 32%, $p=0.1$). Within ALD etiology, as compared to the pre-DAA era, the proportion of LT for ACLF 2 and 3 (severe ACLF) and for AH was more frequent in the DAA era (36% vs. 26% and 2.9% vs. 1.4%, respectively, $p<0.001$). Overall, the mean wait time on the LT list was 2 weeks shorter in the DAA era (252 vs. 266 days, $p=0.002$). The wait time was primarily contributed by ALD etiology (157 vs. 200 days, $p<0.001$). In the DAA era, LT recipients with NASH (342 vs. 306 days, $p<0.001$) and HCV (218 vs. 199 days, $p<0.03$) waited longer. Overall, a better quality graft was used in the DAA era with a DRI mean lower than in the pre-DAA era (1.56 vs. 1.57, $p<0.001$). This was observed for all the etiologies (1.53 vs. 1.55 for HCV, 1.59 vs. 1.61 for NASH, and 1.57 vs. 1.61 for ALD, $p<0.02$).

Among HCC transplants: The mean MELD score was lower in the DAA era (11 vs. 12, $p<0.001$), mainly for LT recipients with HCV-related HCC (10.7 vs. 11.5, $p<0.001$). There were not mean differences for the other two indicators. In the DAA era, LT recipients with HCC waited a month longer (423 vs. 390 days, $p<0.008$), mainly for HCV (426 vs. 386 days, $p<0.004$) and NASH (371 vs. 292 days, $p<0.01$) cases. There were no differences for ALD cases (459 vs. 484 days, $p=0.53$). In the DAA era, although graft quality was better, with a mean DRI lower for all etiologies, the results were not significant (1.55 vs. 1.56, $p=0.19$), probably due to a small sample size compared to when analyses were performed for all LT.

Discussion

The main findings of this UNOS database analysis are that the recipients of LT in the DAA era, as compared to the pre-DAA era, are more likely to be older females, have obesity and diabetes as comorbidities, have higher MELD with more frequent transplants for ACLF and organ failure, and receive better grafts with a shorter wait time on the LT list. Although ACLF and multiple organ failure are associated with high mortality and poor prognosis without LT, the disease severity may not be fully reflected in the MELD-Na score. With the advancement of intensive care and organ failure supportive care, many studies recommend early recognition and transplant evaluation for patients with ACLF and advocate for additional priority on the waitlist.[7–9] Specific to HCV, the LT for HCC increased in the DAA era, while a decreased rate for

Table 1. Baseline characteristics of all liver transplant recipients: DAA (2013-18) versus pre-DAA (2007-2012) eras

	HCV (n=21,110)			NASH (n=7586)			ALD (n=11,713)			Total (n=40,409)		
	Pre-DAA (11,678, 55%)	DAA (9432, 45%)	*p*	Pre-DAA (2468, 33%)	DAA (5118, 67%)	*p*	Pre-DAA (4473, 38%)	DAA (7240, 62%)	*p*	Pre-DAA (18,619, 46%)	DAA (21,790, 54%)	*p*
Age in years (mean, SD)	55, 7	58, 7	<0.001	59, 8	60, 8	<0.001	55, 9	53, 10	<0.001	55, 8	57, 9	<0.001
% Female	26	26	0.88	44	46	0.23	22	25	0.002	27	30	<0.001
% C, B, H	62,11, 24	61, 12, 24	<0.001	78, 2, 18	75, 2, 20	<0.001	71, 3, 24	69, 3, 25	0.004	66, 8, 24	67, 7, 23	0.95
% Obese	36	35	0.47	65	60	<0.001	35	35	0.34	39	41	<0.001
% Diabetic	24	25	<0.02	57	59	0.22	24	20	<0.001	28	31	<0.001
% On dialysis	11	14	<0.001	14	19	<0.001	17	23	<0.001	13	18	<0.001
% ACLF	32	31	<0.1	38	41	0.003	43	51	<0.001	36	40	<0.001
MELD score (mean, SD)	20, 11	18, 11	<0.001	22, 9	22, 10	0.87	23, 10	25, 10	<0.001	21, 10.5	21.2, 11	<0.001
Wait time in days (mean, SD)	306, 544	342, 565	<0.001	199, 337	218, 360	<0.03	200, 443	157, 343	<0.001	266, 501	252, 453	0.002
DRI (mean, SD)	1.55, 0.34	1.53, 0.35	<0.001	1.61, 0.39	1.59, 0.37	<0.02	1.61, 0.39	1.57, 0.36	<0.001	1.57, 0.36	1.56, 0.36	<0.001

Abbreviations: ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; B, Blacks; DAA, direct-acting antiviral; C, caucasians; DRI, donor risk index; H, Hispanics; HCV, hepatitis C virus; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis.

Table 2. Baseline characteristics of recipients for hepatocellular carcinoma: DAA (2013-18) versus pre-DAA (2007-2012) eras

	HCV (n=7786)			NASH (n=958)			ALD (n=1151)			Total (n=9975)		
	Pre-DAA (3778, 49%)	DAA (4008, 51%)	*p*	Pre-DAA (310, 32%)	DAA (648, 68%)	*p*	Pre-DAA (522, 45%)	DAA (629, 55%)	*p*	Pre-DAA (4610, 46%)	DAA (5365, 54%)	*p*
Age in years (mean, SD)	57, 6	61, 6	<0.001	62, 6	64, 6	<0.001	59, 8	61, 8	<0.001	58, 6	61, 6	<0.001
% Female	22	21	0.45	37	35	0.56	12	10	0.4	22	21	0.87
% C, B, H	60, 10, 26	59, 12, 24	<0.001	75, 1, 20	70, 1, 25	0.35	63, 2, 30	64, 4, 30	<0.03	62,8,26	61,5,13	0.43
% Obese	35	35	0.87	66	61	0.13	38	40	0.61	38	38	0.25
% Diabetic	25	27	0.04	68	73	0.14	37	35	0.59	29	34	<0.001
% On dialysis	2.5	3.2	0.049	2.9	4.5	0.25	2.5	3.2	0.49	2.5	3.4	0.012
MELD score (mean, SD)	11.5, 7.5	10.7, 7.8	<0.001	12.4, 6.5	12.8, 8.1	0.39	13, 7	12.4, 8	0.21	12, 7	11, 8	<0.001
Wait time in days (mean, SD)	386, 618	426, 587	<0.004	292, 445	371, 436	<0.01	484, 729	459, 623	0.53	390, 622	423, 578	<0.008
DRI (mean, SD)	1.55, 0.35	1.54, 0.35	0.15	1.65, 0.4	1.60, 0.39	<0.08	1.61, 0.38	1.61, 0.37	0.93	1.56, 0.36	1.55, 0.36	0.19

Abbreviations: ALD, alcohol-related liver disease; B, Blacks; C, Caucasians; DAA, direct-acting antiviral; DRI, donor risk index; H, hispanics; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, model for end-stage liver disease; NASH: non-alcoholic steatohepatitis.

HCC-related LT was observed for ALD and NASH. Within the HCC population, LT recipients in the DAA era were more likely to be older, diabetic, require dialysis, and wait longer on the LT list. This is consistent with a recent publication that indicated DAA treatment prior to LT was associated with a longer waitlist time. However, DAA improved the outcome and mitigated LT need in low MELD recipients.[10] Meanwhile, graft survival outcomes also improved among HCV-positive recipients in the DAA era.[11]

The increasing age of LT recipients may be due to increasing longevity and better management of patients delaying the need for LT.[12] However, LT recipients for ALD were younger in the DAA era, likely due to the increased frequency of high-risk drinking in this age group, with the development of ACLF and organ failure.[13] A significant proportion of this change in the ALD population is due to increasing LT for AH, as observed in this study and in alignment with earlier reports.[13,14] These changes, along with increasing hospitalizations observed in other studies on ACLF related to NASH, accounted for increased frequency of LT for ACLF and organ failure with a higher MELD score.[3] Despite the LT population in the DAA era becoming more obese and diabetic due to an increasing prevalence of these comorbidities in the population, a more rigorous evaluation of LT candidates for NASH cirrhosis probably explains lower rates of obesity in this etiology in the DAA era. Observation of increasing LT for HCC related to HCV cirrhosis in the DAA era is similar to the earlier observation of HCV still being the leading indication for HCC-related LT in the USA.[5] Better quality grafts are used in the DAA era compared to the pre-DAA era, to optimize post-transplant outcomes given that the recipient age and disease severity have increased in the DAA era, and these factors are negatively associated with post-transplant survival.[15]

In conclusion, the changes in the LT recipient population in the DAA era, as a result of changing liver disease etiology for LT, are relevant for designing future studies for this population, for developing post-transplant immunosuppression, and follow-up protocols.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Writing of the manuscript (CX), provision of statistical expertise and analysis of data (YFK), conceptualization of the study, interpretation of the data, and provision of intellectual input (AKS). All the authors approved the final version of the manuscript.

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