

# NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances

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**OBJECTIVES:** Chronic infection with hepatitis C virus (HCV) was previously the leading indication for liver transplant (LT) in the United States. However, since 2014 the use of direct-acting antivirals (DAAs) has decreased the chronic HCV burden, while the prevalence of nonalcoholic steatohepatitis (NASH) has risen substantially through the last decade. Both gender and ethnic disparities in indications for LT have been shown in the past but no data on this have been reported since the implementation of DAAs.

**METHODS:** We assessed changes in etiologies for LT listing and in gender and ethnic differences in those listed for LT. Adult patients registered for LT in the United Network for Organ Sharing/Organ Procurement and Transplantation Network database between January 1, 2004 and December 31, 2016 were included. Multinomial logistic regression modeling was used to test for changes in waitlist or liver transplant rates.

**RESULTS:** The study included 127,164 adult patients registered for LT. By 2016, alcoholic liver disease (ALD) was the leading etiology for waitlisting and LT; NASH was second; hepatocellular carcinoma (HCC) due to chronic HCV and chronic HCV alone were 3rd and 4th. NASH was the leading cause for LT for women and the 2nd leading cause for men (following ALD). NASH increased as the cause in all ethnic subgroups and was the leading cause in 2016 among Asian, Hispanic, and non-Hispanic white females. We also found that although the indication for liver transplant for hepatocellular carcinoma (HCC) due to HCV has increased over the years, this indication decreased for the first time between 2015 and 2016 in both males and females.

**CONCLUSIONS:** NASH is currently the second leading cause for LT waitlist registration/liver transplantation overall, and in females, the leading cause. Given the rate of increase, NASH will likely rise to become the leading indication for LT in males as well.

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## INTRODUCTION

Chronic infection with hepatitis C virus (HCV) was previously the leading etiology of chronic liver disease among patients registered for liver transplant (LT) in the United States (U.S.) [1, 2]. However, since the advent of direct-acting antivirals (DAAs) in 2014, the burden of chronic HCV has decreased [3, 4]. Over the

course of the last decade, nonalcoholic steatohepatitis (NASH) has risen to be the second leading etiology of chronic liver disease among new LT registrants in the U.S. [4–7]. The leading cause of LT in the U.S. in 2013 was chronic HCV followed by NASH, but more recent data from 2015 showed that alcoholic liver disease (ALD) was the leading cause followed by NASH [4, 5].

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It is currently thought that NASH will be the leading cause of LT by 2020 [8]. The previous reports from Wong et al and Goldberg et al. [4, 5] investigated LT etiologies one year prior to and one year post-implementation of DAAs. However, gender and race differences on the LT list have not been assessed since DAAs became the standard treatment for chronic HCV.

When gender disparities in LT were studied in the past, it was shown that compared to men women had increased LT waiting-list mortality and lower transplantation rates, pointing to the need for further research to understand these disparities and close the gap between males and females [9, 10]. Ethnic disparities have also been shown to exist throughout the process of LT, from disease recognition to treatment to registration [11, 12]. African Americans are disproportionately affected by chronic HCV, and have been shown to have more severe liver disease at the time of waitlist registration compared to non-Hispanic whites [13, 14]. Prior to the adoption of the Model for End-Stage Liver Disease (MELD)-based liver allocation system, African Americans were noted to have significantly lower transplant rates which subsequently improved in the MELD era [15–17]. NASH and ALD have been largely associated with minority populations in the U.S. and the incidence of subsequent chronic liver disease and HCC is growing fastest among Hispanics [12, 18, 19]. However, studies have shown significantly lower transplant rates among minorities, particularly Hispanics and Asians, when compared to non-Hispanic whites [12]. Given the shifting demographics of the U.S., the goal of this study was to assess changes in gender and ethnic differences in waitlist registration and LT over time, especially after the implementation of DAAs. We hypothesized that the decrease in chronic HCV due to the use of DAAs and the steadily rising increase in NASH in the U.S. will have led to changes in gender and racial disparities in the LT waitlist registration and indications.

## METHODS

### Study design and participants

The study cohort included adult patients aged 18 years and older registered for LT in the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) database between January 1, 2004 and December 31, 2016. Registered patients with a previous LT were excluded along with those registered for another organ other than kidney; patients listed for both liver and kidney were included. Disease diagnosis coding in the UNOS/OPTN registry determined the etiology of chronic liver disease. Based on methods in previous studies, patients with both HCV and ALD disease diagnosis codes were grouped into a separate category to combine HCV/ALD [5]. Of the patients with HCC, the underlying liver disease was determined based on secondary disease diagnosis codes. Similar to previous studies, a modified NASH category was created to include patients with a diagnosis of NASH or those with cryptogenic cirrhosis in the setting of body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> or diabetes mellitus [5].

### Statistical analysis

Multinomial logistic regression modeling was used to test for changes in the rates of waitlist or liver transplant of each diagnostic category over each year of data within each strata. Post-hoc testing across strata was performed with linear hypothesis testing of regression coefficients. Percent change values over time were computed as the difference in observed counts divided by the prior count. The analysis was performed using SAS v9.4 software.

## RESULTS

### Liver transplant registration between 2004 and 2016

The study included 127,164 adult patients registered for LT. The characteristics of the study population are shown in supplementary Table 1. Overall, the average age was  $54.3 \pm 10.2$  years, 64.5% were male, 70.6% were Caucasians, and the average BMI and MELD score were  $28.7 \pm 5.8$  kg/m<sup>2</sup> and  $21.1 \pm 11.3$ , respectively. Between 2004 and 2016, ALD rose to become the leading cause of waitlist registration by adults for LT followed by NASH, while HCV with HCC and HCV alone were the 3<sup>rd</sup> and 4<sup>th</sup> leading causes (Supp. Figure 1). Since 2004, there was a 68% decrease in the number of waitlist registrants diagnosed with HCV as the primary etiology ( $p < 0.0001$ ) (Supp. Table 2) and a 97% increase in NASH ( $p < 0.0001$ ) as etiology for waitlist registrants. Between 2015 and 2016 alone, there was an 11% increase in NASH ( $p = 0.0385$ ) with a 24% decrease in HCV ( $p < 0.0001$ ) (Supp. Table 2). Between 2004 and 2016, there was a 1413% increase ( $p < 0.0001$ ) in the rate of waitlist registrants with HCC and NASH, the largest change observed across all disease categories. During the entire period there was also an overall increase in the rate of waitlist registrations with HCC due to HCV; however, between 2015 and 2016, there was a decrease in this rate of 12% ( $p = 0.003$ ) (Supp. Table 2), a change that was statistically significant in males but not in females (Table 1).

### Gender and ethnic differences in liver transplant registration

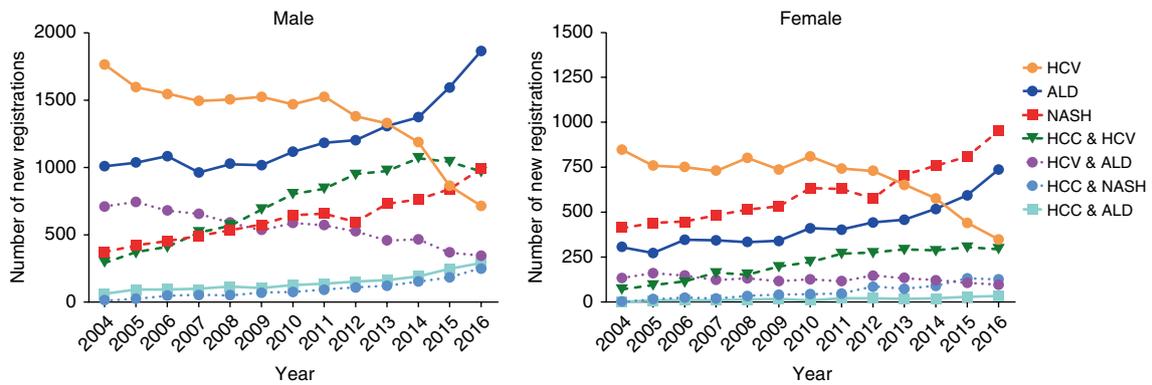
Among both males and females between 2004 and 2016 there was a significant rate increase in waitlist registration due to NASH (114% change in males and 80% change in females,  $p < 0.0001$ ) (Table 1). There was a 2383% increase in NASH with HCC in the female cohort in this time period among waitlist registrants ( $p < 0.0001$ ) (Table 1), a change approximately twice the change in males (1172%) over this period. By 2016, NASH had become the leading cause of LT waitlist registration for women while in men the leading cause continued to be ALD (Fig. 1). ALD as the etiology for waitlist registration continued to increase between 2004 and 2016 in both males and females, although the change in females was larger than that in men (87 vs 49%,  $p = 0.0008$ ) (Table 1).

There were also ethnic differences in waitlist registration for LT. Between 2004 and 2016, NASH continued to rise as a cause of waitlist registration across all ethnic groups (Fig. 2). Among Asian, Hispanic, and non-Hispanic white females, NASH was the leading cause of waitlist registration in 2016, whereas HCV remained the leading cause in African American females (Fig. 2). Asian females had an 854% change in NASH waitlist registration while

**Table 1** Change in rates of liver transplant waitlist registration over time by gender

Etiology	Males 2016 v 2004		Males 2016 v 2015		Females 2016 v 2004		Females 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-67%	<0.0001	-22%	<0.0001	-68%	<0.0001	-27%	<0.0001
ALD	49%	<0.0001	10%	0.0957	87%	<0.0001	15%	0.0564
NASH	114%	<0.0001	12%	0.0991	80%	<0.0001	9%	0.2061
HCC & HCV	171%	<0.0001	-12%	0.0139	233%	<0.0001	-11%	0.1576
HCV & ALD	-61%	<0.0001	-12%	0.0932	-43%	0.0103	-15%	0.2266
HCC & NASH	1172%	<0.0001	29%	0.0203	2383%	<0.0001	-11%	0.3322
HCC & ALD	273%	<0.0001	11%	0.3195	n/a	<0.0001	5%	0.8819

Percent change computed from observed counts over time and p-values computed from multinomial regression analysis within each sex; n/a indicates percent change not computed due to zero observations in divisor  
HCV Hepatitis C virus, ALD Alcoholic liver disease, NASH Non-alcoholic steatohepatitis, HCC Hepatocellular carcinoma



**Fig. 1** Number of new waitlist registrants by disease category and gender. Left side shows number of new waitlist registrants by disease category in males while the right side shows this number in females. HCV hepatitis C virus, ALD alcoholic liver disease, NASH nonalcoholic steatohepatitis, HCC hepatocellular carcinoma

Asian males had a 552% change (Table 2). The African American population had less increase in the rate of waitlist registration for NASH compared to the other ethnic groups. Strikingly, between 2004 and 2016 Hispanic females had a 3010% change in the rate of waitlist registration for NASH with HCC while non-Hispanic white females had a 1992% change (Table 2).

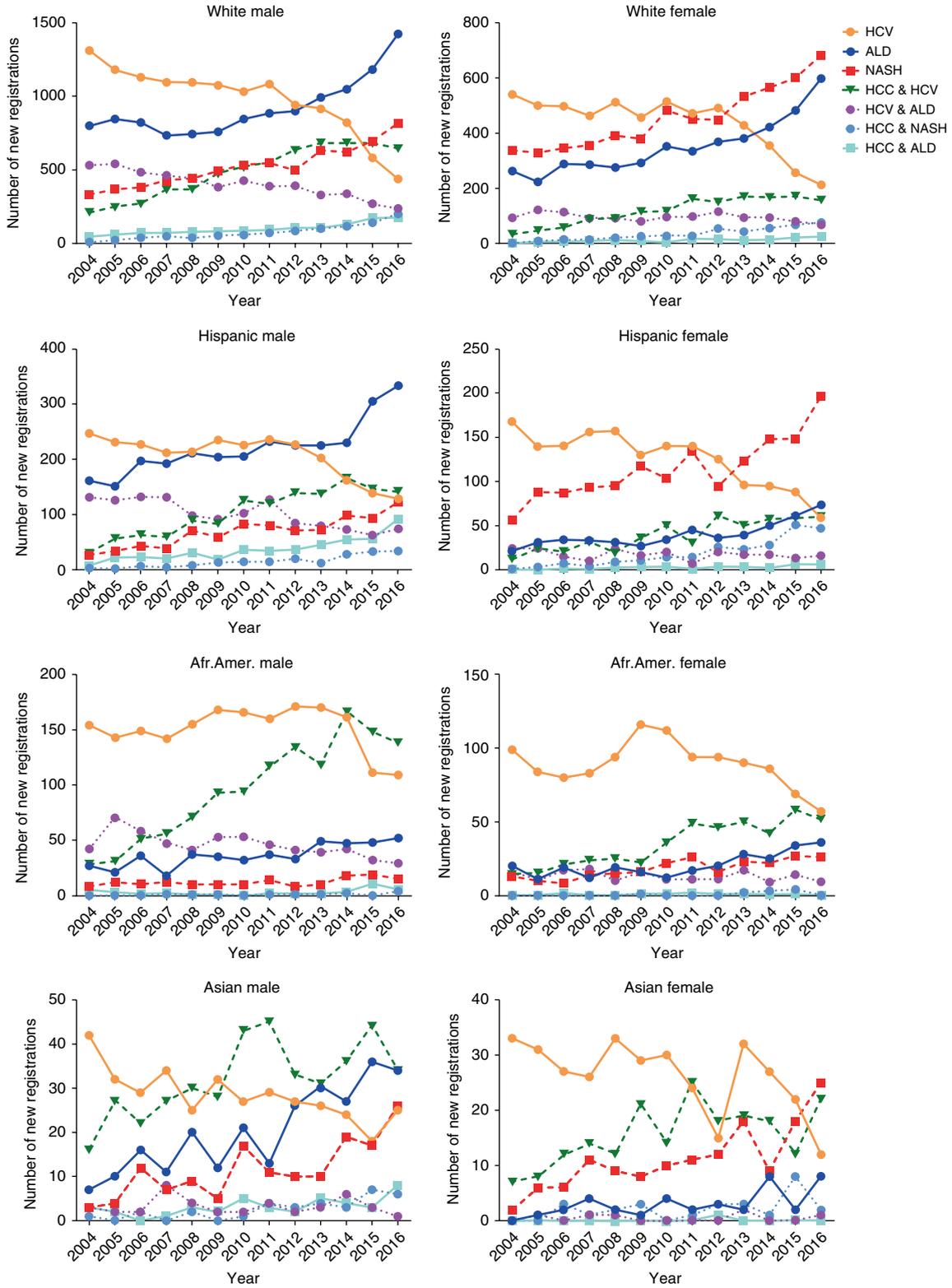
**Liver transplant indications by 2016**

By 2016 ALD had become the leading cause of LT overall, increasing by 42% from 2004, while HCV as the cause had decreased by 55% (Supp. Table 3). NASH rose to be the second leading cause of transplant, increasing by 109% between 2004 and 2016 (Supp. Figure 2); ( $p < 0.001$ ) (Supp. Table 3). Between 2004 and 2016, there was a 940% increase ( $p < 0.0001$ ) of HCC due to NASH as an indication for LT. Although there was also an overall increased rate of HCC due to HCV during this period, we found that there was a decrease of 27% in the rate of waitlist registrants with HCC due to HCV between 2015 and 2016 ( $p < 0.0001$ ) (Supp. Table 2). This change was statistically significant in both males and females (Table 1).

**Gender and ethnic differences in liver transplant indications by 2016**

By 2016 NASH had become the leading indication for LT in females, followed by ALD and then HCV (Fig. 3). In males, by 2016 ALD had become the leading cause of transplant followed by NASH (Fig. 3). The female population displayed a 91% increase in NASH as the indication for transplant between 2004 and 2016 ( $p < 0.0001$ ), while males had a 120% increase in the same time period ( $p < 0.0001$ ) (Table 3). There was a 32% increase in the rate of NASH as the cause of LT in males and a 19% increase in females from 2015 to 2016 ( $p < 0.0001$ ). There was a decrease in HCV with HCC as a cause for transplant by 27% in both males ( $p < 0.0001$ ) and females ( $p = 0.0025$ ) while HCV alone as a cause for transplant decreased by 15% in males ( $p = 0.0437$ ) and 23% in females between 2015 and 2016 ( $p = 0.0042$ ) (Table 3).

In the analysis of ethnic differences, it was shown that NASH continued to increase as a cause of transplant over time (Fig. 4) between 2004 and 2016. Among non-Hispanic white, Hispanic, and Asian females, NASH was the leading indication for LT in 2016 (Fig. 4, Table 4). Increases in NASH as the cause of

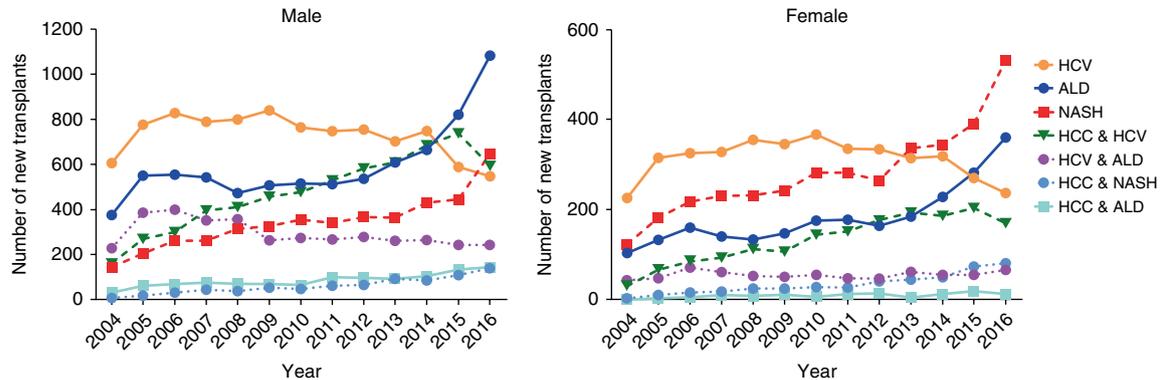


**Fig. 2** Number of new waitlist registrants by disease category and ethnicity by gender over time. Left side shows number of new waitlist registrants by disease category and ethnicity in males while the right side shows new waitlist registrants by disease category and ethnicity in females. HCV hepatitis C virus, ALD alcoholic liver disease, NASH nonalcoholic steatohepatitis, HCC hepatocellular carcinoma

**Table 2** Change in rates of liver transplant waitlist registration over time by ethnicity and gender

Etiology	White Male 2016 v 2004		White Male 2016 v 2015		White Female 2016 v 2004		White Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-71%	<0.0001	-29%	<0.0001	-68%	<0.0001	-25%	0.0022
ALD	50%	<0.0001	12%	0.2546	85%	<0.0001	13%	0.2957
NASH	106%	<0.0001	9%	0.5069	65%	<0.0001	3%	0.9557
HCC & HCV	154%	<0.0001	-12%	0.0147	276%	<0.0001	-17%	0.0625
HCV & ALD	-62%	<0.0001	-17%	0.0181	-39%	0.1441	-21%	0.1177
HCC & NASH	1645%	<0.0001	36%	0.0259	1992%	<0.0001	3%	0.9568
HCC & ALD	223%	<0.0001	0%	0.6733	n/a	0.8713	-1%	0.8637
Etiology	Hispanic Male 2016 v 2004		Hispanic Male 2016 v 2015		Hispanic Female 2016 v 2004		Hispanic Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-65%	<0.0001	-14%	0.7761	-77%	<0.0001	-39%	0.0052
ALD	41%	0.0004	1%	0.3817	130%	0.0003	9%	0.8631
NASH	210%	<0.0001	21%	0.0869	129%	<0.0001	21%	0.3374
HCC & HCV	230%	<0.0001	-10%	0.9974	231%	<0.0001	-8%	0.5374
HCV & ALD	-62%	<0.0001	8%	0.3483	-56%	0.0415	12%	0.8715
HCC & NASH	670%	0.0003	-5%	0.8268	3010%	0.0004	-16%	0.3132
HCC & ALD	793%	<0.0001	51%	0.0088	n/a	0.9489	-9%	0.8042
Etiology	AA Male 2016 v 2004		AA Male 2016 v 2015		AA Female 2016 v 2004		AA Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-45%	0.0015	5%	0.5807	-52%	<0.0001	-8%	0.5651
ALD	48%	0.0892	16%	0.3948	51%	0.2355	18%	0.6140
NASH	44%	0.3496	-15%	0.7361	68%	0.1967	7%	0.9029
HCC & HCV	280%	<0.0001	0%	0.7838	212%	0.0007	0%	0.8678
HCV & ALD	-47%	0.0328	-3%	0.9548	-50%	0.0872	-29%	0.4008
HCC & NASH	n/a	0.9778	n/a	0.9742	n/a	0.9999	-100%	0.9765
HCC & ALD	-23%	0.7510	-51%	0.2206	n/a	0.9999	-100%	0.9789
Etiology	Asian Male 2016 v 2004		Asian Male 2016 v 2015		Asian Female 2016 v 2004		Asian Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-55%	0.0179	29%	0.4815	-72%	0.0028	-45%	0.2076
ALD	265%	0.0007	-13%	0.5475	n/a	0.9781	305%	0.0622
NASH	552%	0.0010	42%	0.3213	854%	0.0013	41%	0.1978
HCC & HCV	60%	0.0504	-28%	0.1535	140%	0.0242	86%	0.0642
HCV & ALD	-75%	0.2904	-69%	0.3014	n/a	0.9915	n/a	0.9902
HCC & NASH	351%	0.1250	-21%	0.6541	n/a	0.9832	-75%	0.1143
HCC & ALD	101%	0.2125	147%	0.1979	n/a	0.9999	n/a	0.9999

Percent change computed from observed counts over time and p-values computed from multinomial regression analysis within each ethnicity and sex; n/a indicates percent change not computed due to zero observations in divisor  
 AA African Americans, HCV Hepatitis C virus, ALD Alcoholic liver disease, NASH Non-alcoholic steatohepatitis, HCC Hepatocellular carcinoma



**Fig. 3** Number of liver transplants by indication and gender. Left side shows number of liver transplants by disease category in males while the right side shows this number in females. HCV hepatitis C virus, ALD alcoholic liver disease, NASH nonalcoholic steatohepatitis, HCC hepatocellular carcinoma

**Table 3** Change in rates of liver transplant indication over time by gender

Etiology	Males 2016 v 2004		Males 2016 v 2015		Females 2016 v 2004		Females 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-56%	<0.0001	-15%	0.0437	-54%	<0.0001	-23%	0.0042
ALD	41%	<0.0001	20%	0.0017	53%	<0.0001	11%	0.3989
NASH	120%	<0.0001	32%	<0.0001	91%	<0.0001	19%	0.0896
HCC & HCV	84%	<0.0001	-27%	<0.0001	129%	<0.0001	-27%	0.0025
HCV & ALD	-48%	<0.0001	-9%	0.4470	-32%	0.5055	5%	0.9280
HCC & NASH	876%	<0.0001	17%	0.1947	1080%	<0.0001	-6%	0.6049
HCC & ALD	118%	<0.0001	0%	0.8961	n/a	0.8754	-45%	0.0931

Percent change computed from observed rates over time and *p*-values computed from multinomial regression analysis within each sex; n/a indicates percent change not computed due to zero observations in divisor  
HCV Hepatitis C virus, ALD Alcoholic liver disease, NASH Non-alcoholic steatohepatitis, HCC Hepatocellular carcinoma

transplant were seen in the male ethnic subgroups as well. Most notably this was evident in Asian males with a 597% increase from 2004 to 2016, followed by Hispanic males with a 240% increase and then non-Hispanic white males with a 115% increase (Table 4).

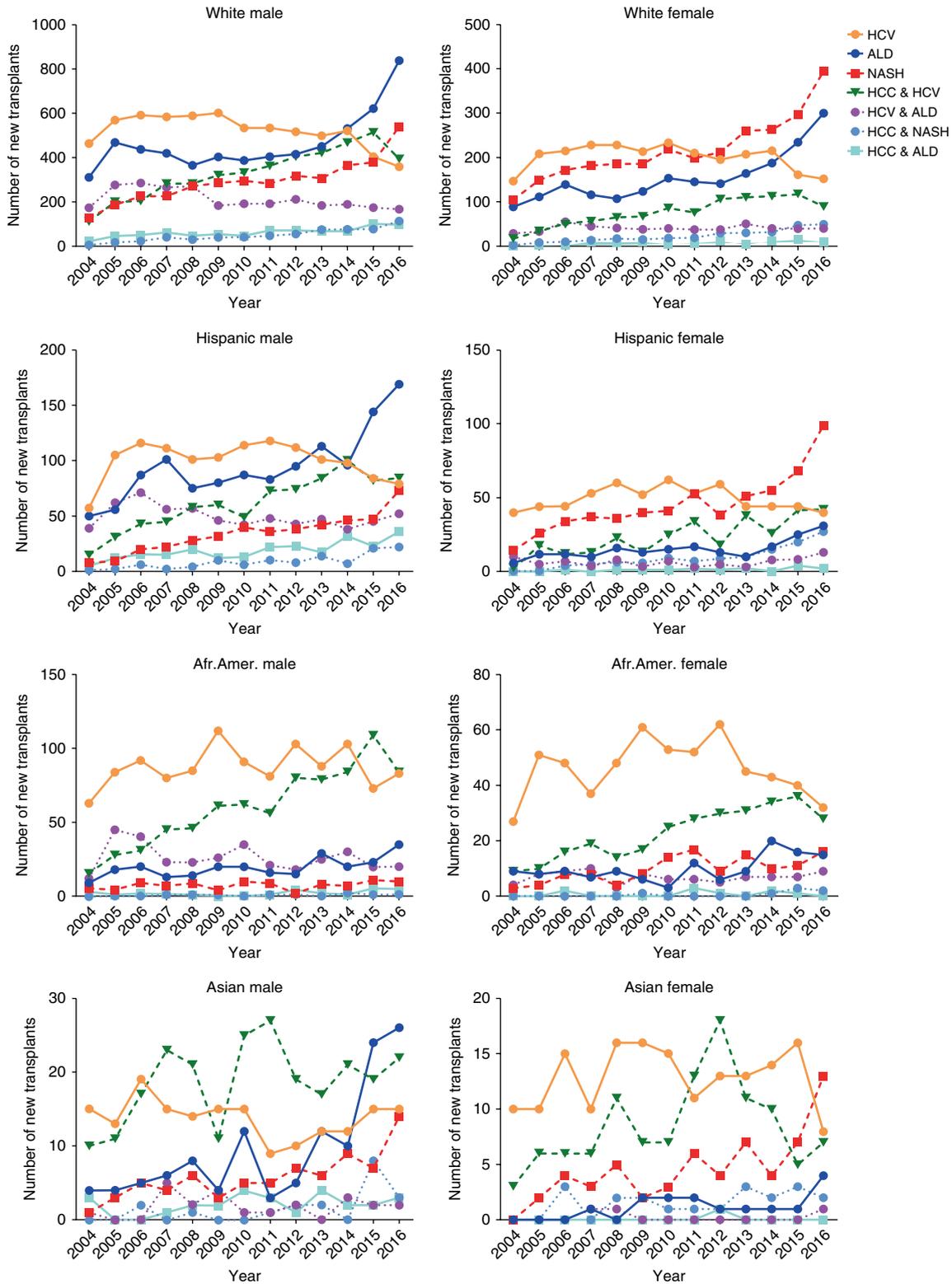
#### Cryptogenic cirrhosis vs NASH-only coding for liver transplant registration and indication

In our study, we followed the methods used in multiple recent studies by including cryptogenic cirrhosis with BMI  $\geq 30$  kg/m<sup>2</sup> or diabetes mellitus as an indication for NASH in the UNOS transplant list [4, 5]. This is plausible and well-accepted as NASH has been inferred as the most likely cause of liver disease in patients with a diagnosis of cryptogenic cirrhosis and metabolic syndrome, given the disappearance of NASH-defining histological findings once cirrhosis develops [20, 21]. However, we sought to investigate if our findings would change if we excluded cryptogenic cirrhosis with BMI  $\geq 30$  kg/m<sup>2</sup> or diabetes mellitus as an indication for NASH. Although this might exclude a large population of patients and underrepresent subjects with NASH as the indication for LT, with our analysis we found no change in the general findings. Overall, NASH was still the 2nd leading cause of

liver transplant registration and indication following ALD (data not shown). NASH remained the leading cause of liver transplant registration and indication in women. NASH was also the 2nd leading cause of liver transplant indication following ALD in men, and the 3rd leading cause of liver transplant registration with no significant difference from the 2nd leading cause, HCC due to HCV, although the latter is now on the decline.

#### DISCUSSION

In this study, the etiologies of waitlist registration and LT were evaluated in a population of 127,164 patients from the UNOS database to compare differences in males and females and in ethnic subgroups for the first time since implementation of DAAs for treatment of chronic HCV. We report for the first time that in 2016 NASH was the leading cause of waitlist registration and liver transplant in females. In males, there was also an increased incidence of NASH as the etiology of LT waitlist registration but ALD continued to prevail as the leading etiology. In all ethnic subgroups, the incidence of NASH continued to rise over the 14 years assessed. Most notably, there was a significant rise in NASH



**Fig. 4** Number of liver transplants by indication and ethnicity by gender over time. Left side shows number of liver transplants by disease category and ethnicity in males while the right side shows the number of liver transplants by disease category and ethnicity in females. HCV hepatitis C virus, ALD alcoholic liver disease, NASH nonalcoholic steatohepatitis, HCC hepatocellular carcinoma

**Table 4** Change in rates of liver transplant indication over time by ethnicity and gender

Etiology	White Male 2016 v 2004		White Male 2016 v 2015		White Female 2016 v 2004		White Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-60%	<0.0001	-19%	0.0325	-51%	0.0023	-18%	0.0754
ALD	40%	<0.0001	23%	0.0031	59%	<0.0001	11%	0.4761
NASH	115%	<0.0001	30%	0.0011	75%	<0.0001	15%	0.2499
HCC & HCV	76%	<0.0001	-30%	<0.0001	147%	<0.0001	-34%	0.0032
HCV & ALD	-50%	<0.0001	-13%	0.3364	-33%	0.7150	-11%	0.5297
HCC & NASH	877%	<0.0001	32%	0.0594	1042%	0.0001	-10%	0.5413
HCC & ALD	121%	<0.0001	-12%	0.4873	n/a	0.8867	-38%	0.2245
Etiology	Hispanic Male 2016 v 2004		Hispanic Male 2016 v 2015		Hispanic Female 2016 v 2004		Hispanic Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-48%	0.1939	-17%	0.6369	-69%	0.0003	-26%	0.9582
ALD	26%	0.0099	4%	0.4803	62%	0.1808	1%	0.2915
NASH	240%	<0.0001	37%	0.0791	122%	0.0041	19%	0.3648
HCC & HCV	109%	0.0007	-9%	0.9536	560%	0.0060	-18%	0.8301
HCV & ALD	-50%	0.1930	2%	0.6563	-59%	0.1017	33%	0.2008
HCC & NASH	720%	0.0175	-7%	0.9749	749%	0.0264	10%	0.5864
HCC & ALD	235%	0.0045	38%	0.1680	n/a	0.9834	-59%	0.4801
Etiology	AA Male 2016 v 2004		AA Male 2016 v 2015		AA Female 2016 v 2004		AA Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-36%	0.1625	14%	0.6539	-43%	0.0449	-26%	0.0858
ALD	88%	0.0594	53%	0.1986	-20%	0.5601	-13%	0.4280
NASH	-3%	0.8627	-9%	0.7752	157%	0.1622	34%	0.7373
HCC & HCV	171%	0.0004	-23%	0.1325	50%	0.3749	-28%	0.0823
HCV & ALD	-19%	0.8326	0%	0.9185	8%	0.9484	19%	0.9778
HCC & NASH	n/a	0.9850	0%	0.9803	n/a	0.9906	-38%	0.4857
HCC & ALD	-19%	0.9106	-16%	0.7258	n/a	0.9999	-100%	0.9854
Etiology	Asian Male 2016 v 2004		Asian Male 2016 v 2015		Asian Female 2016 v 2004		Asian Female 2016 v 2015	
	Change	p-value	Change	p-value	Change	p-value	Change	p-value
HCV	-50%	0.1456	-12%	0.7087	-55%	0.3071	-47%	0.2713
ALD	223%	0.0198	-5%	0.8352	n/a	0.9924	321%	0.1741
NASH	597%	0.0482	76%	0.2544	n/a	0.9850	96%	0.1303
HCC & HCV	9%	0.5996	2%	0.9961	31%	0.4726	47%	0.4249
HCV & ALD	0%	0.9228	-12%	0.8857	n/a	0.9965	n/a	0.9952
HCC & NASH	n/a	0.9762	-67%	0.1025	n/a	0.9918	-30%	0.7946
HCC & ALD	-50%	0.4894	32%	0.7776	n/a	0.9999	n/a	0.9999

Percent change computed from observed counts over time and p-values computed from multinomial regression analysis within each ethnicity and gender; n/a indicates percent change not computed due to zero observations in divisor

AA African Americans, HCV Hepatitis C virus, ALD Alcoholic liver disease, NASH Non-alcoholic steatohepatitis, HCC Hepatocellular carcinoma

in the Hispanic population overall. There was a very substantial increase in waitlist registration and indication for LT for HCC due to NASH in Hispanic females over this 14-year period. We also report for the first time a decrease in LT and waitlist registration for HCC due to HCV between 2015 and 2016.

The increasing prevalence of NASH has been attributed to rising obesity, diabetes mellitus type 2, and dyslipidemia [22, 23]. Wong et al reported that in 2013 NASH became the second leading etiology of liver disease among new adult LT waitlist registrants [5]; Goldberg et al. reported that NASH was the 3rd leading cause of LT waitlist registration in adults in 2015 [4]. Using the most recent UNOS/OPTN data our study shows that NASH is now the second leading cause of LT waitlist registration overall, but demonstrates for the first time that NASH is the primary cause in females. Several prior studies have noted that men are more predisposed to NAFLD than females taking into account visceral adiposity based on waist-to-hip circumference ratio [24–29]. However, a study by the NASH Clinical Research Network found that females have more severe stages of NAFLD [30] and our finding may be in part attributable to this [30]. In addition, it is possible that our finding results from a difference in women's behavior in seeking medical care [30]. In addition, it has been consistently shown that men regularly consume more alcohol than women and are more likely to drink excessively [31], and that the likelihood of developing ALD is based on both the duration and amount of heavy drinking [32] which may have been an important factor in keeping ALD in the higher position as a cause of LT in men.

The fact that a high prevalence of NASH in the Hispanic population has led to increasing rates of LT waitlist registration is not surprising but poses a substantial healthcare challenge given that between 2000 and 2010 Hispanics accounted for approximately 50% of U.S. population growth [33]. Prior studies have reported an increased prevalence of NAFLD in the Hispanic population and noted some gender differences as well [18, 34, 35]. NAFLD is more common in Hispanics than in other ethnic groups, probably due to the high prevalence of the associated metabolic abnormalities in this population, as well as possible genetic differences such as PNPLA3 [36, 37]. While metabolic syndrome is often higher in the African American population, our study highlighted a lower frequency of NASH as an indication for transplant when compared to other ethnic groups. The paradoxical lower frequency of NASH in the African American population despite rates of obesity and insulin resistance similar to or greater than those in Hispanic patients has been noted in prior studies, with this ethnic difference attributed to genetic or environmental factors [18, 35, 37, 38]. However, NASH is increasing as a cause of waitlist registration and LT in African American females. This is not surprising since our recent epidemiological study showed that although African Americans have a lower overall risk of NAFLD compared to other ethnic groups, it is a significant cause of chronic liver disease and cirrhosis in this ethnic group [34].

The increase in HCC due to NASH has been previously reported [39, 40], supporting our finding that this is significantly on the rise

as a cause for waitlist registration for LT. Previous reports projected that HCC due to HCV would not peak until 2025 to 2030 [41, 42]. One of these studies took into consideration the implementation of the DAAs [41]. Recent UNOS data showed that HCC due to HCV as a cause of LT had not decreased in the post-DAA era as of 2015 [3]. In contradiction, we report for the first time a decline in HCC due to HCV as a cause for waitlist registration and LT indication from 2015 to 2016. This could be due to the fact that DAAs decreased the incidence of HCC [43]. It is also plausible that DAAs reduced the rate of hepatic decompensation allowing HCC due to HCV to be managed through other treatments such as resection. Further studies are needed to explore this important finding.

Our study highlights the burden of ALD, NASH and HCV as etiologies of LT. This is not surprising as these etiologies are of significance in the general U.S. population. The Centers for Disease Control and Prevention (CDC) estimates chronic hepatitis C to affect 2.7–3.9 million people in the U.S. In 2015, the CDC estimated that there were 21,028 alcoholic liver disease deaths, accounting for a rate of 6.5 per 100,000 population [44]. It is estimated that 10–15% of alcoholics will develop cirrhosis. Based on a recent meta-analysis by Younossi and colleagues, the prevalence of NAFLD in North America is estimated as 24.13%. We have shown that NAFLD is the most common cause of cirrhosis in the multiethnic cohort from California and Hawaii [7, 45].

There are several limitations to our study. First, given that the data was obtained from the UNOS registry, errors in miscoding or entering diagnoses may have occurred since the classification of NASH or any other etiology as the indication for waitlist registration/transplant does not require confirmation [5]. The observed increase in frequency of NASH as an indication for LT was possibly influenced by ascertainment bias in the setting of increased awareness of NASH as well as the ability to accurately document NASH in the UNOS database starting in 2001 [5, 46, 47]. Although our inclusion of cryptogenic cirrhosis patients with a BMI > 30 kg/m<sup>2</sup> in the NASH category is consistent with previously published studies, a potential limitation of our analysis is that several of these patients likely had ascites in the setting of chronic liver disease and their dry weight after paracentesis or diuresis was not accounted for [5, 46, 47]. However, our overall findings did not change when we performed a separate analysis excluding cryptogenic cirrhosis patients with a BMI ≥ 30 kg/m<sup>2</sup> from the NASH category. Another limitation is that fatty liver may occur concomitantly with other liver diseases such as HCV in those with obesity and/or metabolic syndrome [48]. Since NAFLD/NASH are currently diagnoses of exclusion, neither the UNOS database nor our current study account for this important phenomenon. Despite these limitations, our study highlights key trends that reflect the dynamic epidemiology of waitlisted and transplanted patients in the U.S. Awareness of the gender and ethnic differences could allow us to tailor diagnostic and interventional measures that target specific populations susceptible to particular liver diseases. Our study is the most recent to assess these differences and the most detailed analysis since DAAs for treatment of chronic hepatitis C were implemented.

Most importantly, this is the first study to show that NASH is the leading cause of LT in women. It also shows the significant risk of HCC due to NASH, especially in women, and the decline in HCC due to HCV.

## CONCLUSION

In summary, with the advent of DAAs, the burden of chronic HCV has decreased [3, 4], while over the course of the last decade, NASH has risen to be the second leading etiology of chronic liver disease among new LT registrants in the U.S [4–7]. This combination of events has resulted in substantial changes in the etiologies underlying LT waitlisting and transplant. Importantly, we report here that HCC due to HCV decreased as an etiology for LT for the first time between 2015 and 2016. NASH is currently the second leading indication overall and, in females, the leading indication for waitlist registration/liver transplantation in the U.S. Hispanic, white and Asian females are more likely to have NASH as the leading indication of waitlist registration and LT. Current studies have displayed that NASH patients are less likely to receive LT compared to other disease indications [5]. Based on our study, given the rate of increase in NASH as the primary indication for LT, NASH will likely rise to become the leading indication for LT in males as well. Further studies are needed to develop new therapeutic approaches for the prevention and treatment of NASH as it continues to rise across all subpopulations.

## CONFLICT OF INTERESTS

**Guarantor of the article:** Mazen Nouredin, MD.

**Specific author contributions:** MN, AV: Concept and design of the work; acquisition and interpretation of data for the work; Contributed to drafting the work or revising it critically for important intellectual content; gave final approval of the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CB and TT: Analysis or acquisition and interpretation of data for the work; contributed to drafting the work or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. IKK, NK, VWS, TT, WA, SCL, ASK, VS, and NNN: Interpretation of data for the work; contributed to drafting the work or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Potential competing interests:** MN: Scientific advisory board for OWL Metabolomics, Abbott, Gilead, Intercept and Echosens, and speaker for Abbott's and Echosens. Research support: Gilead, Galmed, Galectin, Genfit, Tobira, Conatus, Zydus and Shire. Minor shareholder of Anaetos. VS: speaker's bureau: Gilead, AbbVie, Intercept, Salix, Advisory board: Gilead, AbbVie.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- Nonalcoholic steatohepatitis followed hepatitis C and alcoholic liver disease as liver transplant causes in 2015.
- With the use of direct-acting antivirals hepatitis C has decreased as a liver transplant indication.
- Hepatocellular carcinoma due to HCV had not decreased as a liver transplant cause by 2015.

### WHAT IS NEW HERE

- NASH is now the leading cause of liver transplant in women across various ethnic groups.
- Hepatocellular carcinoma due to NASH has increased dramatically, especially in Hispanic women.
- Hepatocellular carcinoma due to HCV decreased as a liver transplant indication between 2015 and 2016.

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