Nonalcoholic Steatohepatitis Is the Fastest Growing Cause of Hepatocellular Carcinoma in Liver Transplant Candidates

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BACKGROUND & AIMS: **Although hepatitis B and C have been the main drivers of hepatocellular carcinoma (HCC), nonalcoholic steatohepatitis (NASH) has recently become an important cause of HCC. The aim of this study was to assess the causes of HCC among liver transplant (LT) candidates in the United States.**

METHODS: **The Scientific Registry of Transplant Recipients (2002–2016) was used to estimate the trends in prevalence of HCC in LT candidates with the most common types of chronic liver disease: alcoholic liver disease (ALD), chronic hepatitis B (CHB), chronic hepatitis C, and NASH.**

RESULTS: **158,347 adult LT candidates were included. Of these, 26,121 (16.5%) had HCC; this proportion increased from 6.4% (2002) to 23.0% (2016) (trend $P < .0001$). Over the study period, CHC remained the most common etiology for HCC (65%). The proportions of HCC accounted for by CHC and ALD remained stable (both trend $P > .10$), the proportion of CHB decreased 3.1-fold ($P < .0001$), while the proportion of NASH in HCC increased 7.7-fold (from 2.1% to 16.2%; $P < .0001$). Furthermore, since 2002, the prevalence of HCC in LT candidates with NASH increased 11.8-fold, while this rate increased 6.0-fold in CHB, 3.4-fold in ALD, and 2.3-fold in CHC (all $P < .0001$); the increasing trend in NASH was steeper than that for any other etiology ($P < .0001$ in a trend regression model). The proportion of LT candidates with HCC who ultimately received a transplant or died while waiting did not differ between etiologies ($P > .05$).**

CONCLUSIONS: **Nonalcoholic steatohepatitis is the most rapidly growing cause of HCC among US patients listed for liver transplantation.**

Keywords: Transplant Waitlist; UNOS; OPTN; Mortality; Liver Cancer; NAFLD.

The progressive form of nonalcoholic fatty liver disease (NAFLD), which is represented predominantly by nonalcoholic steatohepatitis (NASH), is rapidly becoming a top indication for liver transplantation in the United States.[1,2] There are a number of reasons for this rapid growth of NAFLD and NASH. First, the epidemic of obesity, type 2 diabetes mellitus (DM), and other components of the metabolic syndrome fuels the burden of this disease.[3] In fact, the global prevalence of NAFLD is estimated to be approximately 25%,[4] and it can be as

Abbreviations used in this paper: **ALD, alcoholic liver disease; CHB, chronic hepatitis B; CHC, chronic hepatitis C; DM, diabetes mellitus; HCC, hepatocellular carcinoma; LT, liver transplant; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SRTR, Scientific Registry of Transplant Recipients.**

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2018.05.057

high as 60% to 70% in patients with DM.[5,6] In addition to high prevalence, NAFLD and NASH also have been linked to increased mortality,[7,8] and, as the number of components of the metabolic syndrome increases, so does the risk for mortality in NAFLD.[9]

Adding further to the increased morbidity and mortality risks, NAFLD and NASH also are fueling the increasing prevalence of hepatocellular carcinoma (HCC).[10,11] In 1 study from Korea, after controlling for demographic variables, NAFLD with and without fibrosis showed a strong association with the incidence of HCC.[12] Another study from the United Kingdom suggested that NAFLD is the leading cause of HCC.[13] Furthermore, a study from France reported that the prevalence of NAFLD in patients with HCC increased from 2.6% (1995) to 19.5% (2014).[14] In a retrospective study of liver transplant (LT) recipients in the United States from 2002 to 2012, NASH was noted to be the second leading etiology of HCC-related liver transplantation,[15] whereas other similarly designed studies also have shown or projected the presence of an increasing trend.[2,16–20]

All this is accompanied by an alarming conundrum in the field of NAFLD and NASH: despite rapid growth in the burden of the disease, there are no validated diagnostic or prognostic noninvasive biomarkers for NASH and related fibrosis, and there are no effective pharmacologic therapies with proven efficacy and safety.[21–23]

In earlier studies, NASH increasingly was shown to contribute to the cohort of patients who receive a liver transplant in the United States, including those who received a transplant because of HCC.[2,15,16,18,20] It is plausible that patients with NASH actually may present late in the course of their disease with more advanced liver disease and a higher stage of HCC, both of which potentially can affect their status on the transplant list and their post-LT outcomes. Therefore, the aim of our study was to use the most recent longitudinal data from a national registry to assess changes in LT listings for HCC according to underlying etiologies of liver disease and to compare their on-the-list and post-LT outcomes.

What You Need to Know

Background

Historically, hepatitis C was the major driver of hepatocellular carcinoma in the United States.

Findings

Although in 2017 hepatitis C remained the most common cause of hepatocellular carcinoma in waitlisted liver transplant candidates, its contribution is decreasing. In turn, nonalcoholic steatohepatitis (NASH) currently accounts for 18% of all hepatocellular carcinoma listings: an 8-fold growth since 2002, and the second most common cause.

Implications for patient care

Because NASH is on a trajectory to become the most common cause of hepatocellular carcinoma in the United States, effective prevention strategies and treatment options are urgently needed for this currently underserved patient population.

Methods

Study Cohort

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network, and has been described elsewhere. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors.

In this study, we included all waitlisted candidates and transplant recipients at least 18 years of age who were listed or underwent liver transplantation for HCC (recorded as a primary or secondary diagnosis) in the United States between 2002 and 2017. Patients' outcomes (receiving a transplant, waitlist drop-out resulting from either on-list mortality or removal from the list because of deterioration, post-transplant HCC recurrence, mortality, and graft loss) were recorded as of March 1, 2018.

Statistical Analysis

By using candidates' listing diagnoses, patients with HCC were grouped based on the etiology of their liver disease into 5 groups: chronic hepatitis B (CHB), chronic hepatitis C (CHC; without CHB or alcoholic liver disease [ALD]), ALD (without CHC), ALD + CHC, and NASH (including cryptogenic cirrhosis because, despite some controversy,[24] it conventionally is believed that in the US population the vast majority of patients with cryptogenic cirrhosis have a NASH etiology of liver disease[25–28]); patients with CHB + CHC were excluded owing to limited sample size of that group. Clinicodemographic parameters were compared across the 5 groups using the chi-square or Kruskal–Wallis nonparametric tests. The trends in HCC prevalence over time were assessed statistically using Kendall's correlation coefficients and were compared between liver disease etiologies using a linear trend regression model. Independent predictors of post-transplant outcomes were studied using logistic and Cox proportional hazard regression models; only predictors with a P value less than .05 were included in the models.

All analyses were run in SAS 9.4 (SAS Institute, Cary, NC). The study concept was initiated by the Global NASH Council members who reviewed the study concept, the

data, and the manuscript draft. The study was granted a nonhuman subject research status by our Institutional Review Board.

Results

There were 170,540 patients (≥18 years old at listing) on the liver transplant wait list from 2002 to 2017. Among these patients, 28,935 (17.0%) had a listing diagnosis of HCC, of whom 24,431 had another listing diagnosis that we considered as the etiology of HCC. These included 1698 (7.0%) patients with CHB, 13,663 (55.9%) patients with CHC, 2690 (11.0%) patients with NASH, 2520 (10.3%) patients with ALD alone, and 1936 patients with ALD + CHC. Averaged across all study years, waitlisted candidates with NASH-related HCC were older, more likely to be female and white, and had the highest rates of obesity, type 2 diabetes, and hypertension in comparison with other HCC patients (Table 1).

Prevalence of Hepatocellular Carcinoma in Waitlisted Candidates With Different Etiologies of Liver Disease

The prevalence of HCC among the waitlisted candidates increased from 6.4% in 2002 to 22.0% in 2017 (tau = 0.883; $P < .0001$). A significantly increasing trend was observed in all 5 studied etiologies (tau from 0.80 to 1.0; all $P < .0001$). The relative increase in HCC prevalence with reference to the first year of our study period (2002), however, varied between the etiologies. In particular, from 2002 to 2016, the prevalence of HCC increased 2.4-fold in CHB, 6.2-fold in CHC, 3.1-fold in ALD alone, 6.4-fold in ALD + CHC, and 11.5-fold in NASH (Figure 1). In a regression model that was used to compare the slopes of those relative increases, the most rapidly growing HCC prevalence that occurred in listed patients with NASH had a significantly steeper slope in comparison with that of the next most rapidly growing prevalence of HCC, which was in CHC ($\beta = 0.80 \pm 0.06$ in NASH, 0.36 ± 0.01 in CHC; $P < .0001$ for the year-etiology

Table 1. Demographic and Clinical Parameters of Waitlisted Candidates With HCC of Different Etiologies

	CHB	CHC	NASH	ALD	ALD + CHC	*P*
N	1698	13,663	2690	2520	1936	
Age at listing, *y*	57.2 ± 9.1	59.2 ± 6.3	62.9 ± 6.8	60.6 ± 7.3	57.4 ± 6.0	<.0001
Male sex	1418 (83.5%)	10,628 (77.8%)	1728 (64.2%)	2259 (89.6%)	1708 (88.2%)	<.0001
Caucasian	366 (21.6%)	8801 (64.4%)	1935 (71.9%)	1761 (69.9%)	1296 (66.9%)	<.0001
African American	143 (8.4%)	1863 (13.6%)	37 (1.4%)	70 (2.8%)	178 (9.2%)	<.0001
Asian	1103 (65.0%)	712 (5.2%)	102 (3.8%)	48 (1.9%)	17 (0.9%)	<.0001
Hispanic	63 (3.7%)	2103 (15.4%)	581 (21.6%)	603 (23.9%)	409 (21.1%)	<.0001
Other race/ethnicity	23 (1.4%)	184 (1.3%)	35 (1.3%)	38 (1.5%)	36 (1.9%)	.4542
US citizen	1379 (81.2%)	13,054 (95.5%)	2530 (94.1%)	2358 (93.6%)	1885 (97.4%)	<.0001
College degree	573 (37.8%)	2529 (20.2%)	746 (30.1%)	530 (23.0%)	180 (10.2%)	<.0001
Private insurance	1035 (62.0%)	7622 (56.2%)	1421 (53.3%)	1295 (51.6%)	933 (48.3%)	<.0001
Public insurance	606 (36.3%)	5888 (43.4%)	1236 (46.4%)	1209 (48.2%)	994 (51.4%)	<.0001
Self-pay	29 (1.7%)	64 (0.5%)	8 (0.3%)	6 (0.2%)	5 (0.3%)	<.0001
Employed	619 (41.3%)	4137 (32.9%)	730 (28.3%)	566 (24.2%)	431 (24.3%)	<.0001
BMI, kg/m^2	25.7 ± 4.4	28.5 ± 5.0	31.9 ± 5.7	29.2 ± 5.0	28.4 ± 5.1	<.0001
Obese (BMI, ≥30)	244 (14.4%)	4481 (32.9%)	1624 (60.5%)	1008 (40.0%)	633 (32.8%)	<.0001
Type 2 diabetes	316 (19.3%)	2991 (22.5%)	1566 (60.3%)	796 (32.7%)	374 (19.8%)	<.0001
Coronary artery disease	12 (1.5%)	149 (2.5%)	51 (5.6%)	31 (3.3%)	20 (2.5%)	<.0001
Stroke	6 (0.7%)	58 (0.9%)	16 (1.7%)	8 (0.8%)	7 (0.9%)	.2044
COPD	4 (0.5%)	156 (2.5%)	26 (2.8%)	23 (2.4%)	30 (3.7%)	.0010
Functional status, 0–100	76.9 ± 18.3	73.6 ± 17.1	71.0 ± 17.4	70.6 ± 17.7	69.0 ± 18.0	<.0001
MELD score	11.9 ± 7.4	13.7 ± 7.9	15.4 ± 8.5	15.6 ± 8.0	15.4 ± 8.6	<.0001
Drug-treated hypertension	322 (28.0%)	2816 (32.7%)	634 (47.3%)	497 (35.4%)	350 (29.1%)	<.0001
Re-transplant	20 (1.2%)	146 (1.1%)	14 (0.5%)	11 (0.4%)	25 (1.3%)	.0015
On life support[a]	12 (0.7%)	69 (0.5%)	14 (0.5%)	16 (0.6%)	15 (0.8%)	.5038
In ICU	19 (1.5%)	97 (1.1%)	16 (1.1%)	16 (1.1%)	26 (2.0%)	.0397
Ascites	606 (35.7%)	6924 (50.7%)	1583 (58.8%)	1632 (64.8%)	1177 (60.8%)	<.0001
Hepatic encephalopathy	390 (23.0%)	5271 (38.6%)	1210 (45.0%)	1250 (49.6%)	969 (50.1%)	<.0001
Variceal bleeding	14 (1.2%)	159 (1.8%)	35 (2.6%)	36 (2.6%)	34 (2.9%)	.0062
Spontaneous bacterial peritonitis	29 (1.7%)	346 (2.6%)	58 (2.2%)	118 (4.7%)	99 (5.2%)	<.0001
Had TIPSS	31 (1.9%)	403 (3.0%)	130 (4.9%)	204 (8.2%)	109 (5.7%)	<.0001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; MELD, model for end-stage liver disease; TIPSS, transjugular intrahepatic portosystemic shunt.

[a]Ventilator, ventricular assist device or total artificial heart, artificial liver, extracorporeal membrane oxygenation, intra-aortic balloon pump, intravenous inotropes, prostaglandin E.

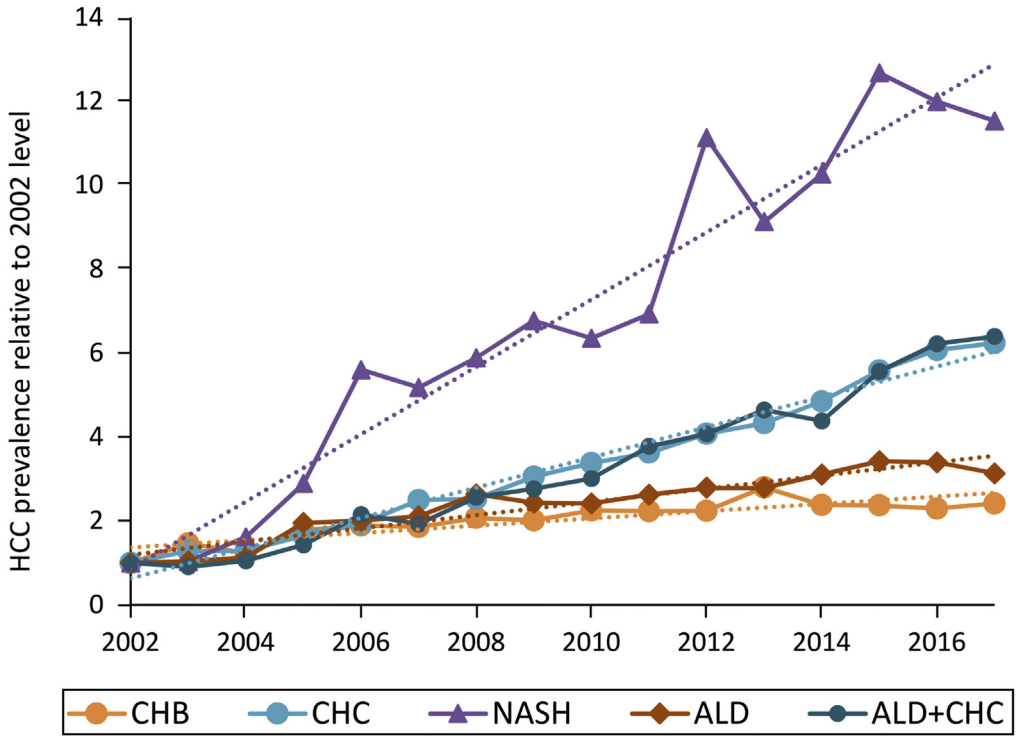

Figure 1. Prevalence of HCC in waitlisted candidates by etiology relative to that in 2002. *Dotted lines* represent linear trends.

interaction term). Although the prevalence of HCC in NASH varied between clinical populations, the presence of a significantly increasing trend was universal across gender and age groups, as well as in patients with and without type 2 diabetes (all tau > 0.65, all $P < .0005$) (Supplementary Figure 1).

Prevalence of Different Liver Disease Etiologies in Liver Transplant Waitlisted Patients With Hepatocellular Carcinoma

The contribution of each etiology to HCC in patients listed for LT also changed over time (Figure 2). Although CHC remained the most common etiology of HCC in waitlisted candidates (47.9%–60.3%; trend $P = .89$), and the proportions accounted for by ALD and ALD + CHC also remained stable (8.3%–14.2%, $P = .39$; and 5.8%–9.9%, $P = .30$, respectively), the proportion of NASH in HCC increased 8.5-fold (from 2.1% in 2002 to 17.9% in 2017: tau = 0.83; $P < .0001$), whereas the proportion of CHB in HCC in patients listed for LT decreased 2.9-fold, from 14.3% in 2002 to 4.9% in 2017 (tau = -0.92; $P < .0001$) (Figure 3). In a round of sensitivity analysis, we have found that after 2008 the growth of the NASH category was affected only minimally by the impact of cryptogenic cirrhosis listings included in it (Supplementary Figure 2).

Outcomes of Candidates With Hepatocellular Carcinoma Listed for Liver Transplantation

Of all waitlisted candidates with HCC and ALD, ALD + CHC, CHB, CHC, or NASH, 66.7% eventually were transplanted, and 16.8% dropped out from the list (died or were removed owing to deterioration). There were no consistent differences between the transplantation rates observed in HCC patients according to underlying etiologies (Supplementary Figure 3*A*). Similarly, there was no difference in the waitlist dropout rates (all $P > .05$) (Supplementary Figure 3*B*), although patients with HCC and CHB occasionally experienced a longer waiting period until receiving a transplant (Supplementary Figure 3*C*). In addition, there was no consistent difference in waitlist outcomes between patients with specifically identified listing diagnoses of NASH and cryptogenic cirrhosis (all but 2012 $P > .05$) (Supplementary Table 1). The data on staging of HCC was available for 18,374 (81.6%) included patients with HCC. Of these, 95.4% were listed within Milan criteria, and no difference between etiologies was found ($P = .29$).

Post-Transplant Outcomes of Patients With Hepatocellular Carcinoma

Post-transplant data were available for 18,446 LT recipients with HCC, including 1078 with CHB, 8958 with CHC with or without ALD, 1631 with NASH, 1510 with ALD alone, and 1227 with ALD + CHC. Clinicodemographic data were similar to that reported earlier for waitlisted candidates (data not shown).

The rate of post-transplant HCC recurrence was the lowest in patients with NASH and the highest in patients with CHB ($P = .014$), whereas time to recurrence of 2.3 to 2.8 years was similar across all etiologies ($P = .19$). In multivariate analysis, the only factors associated

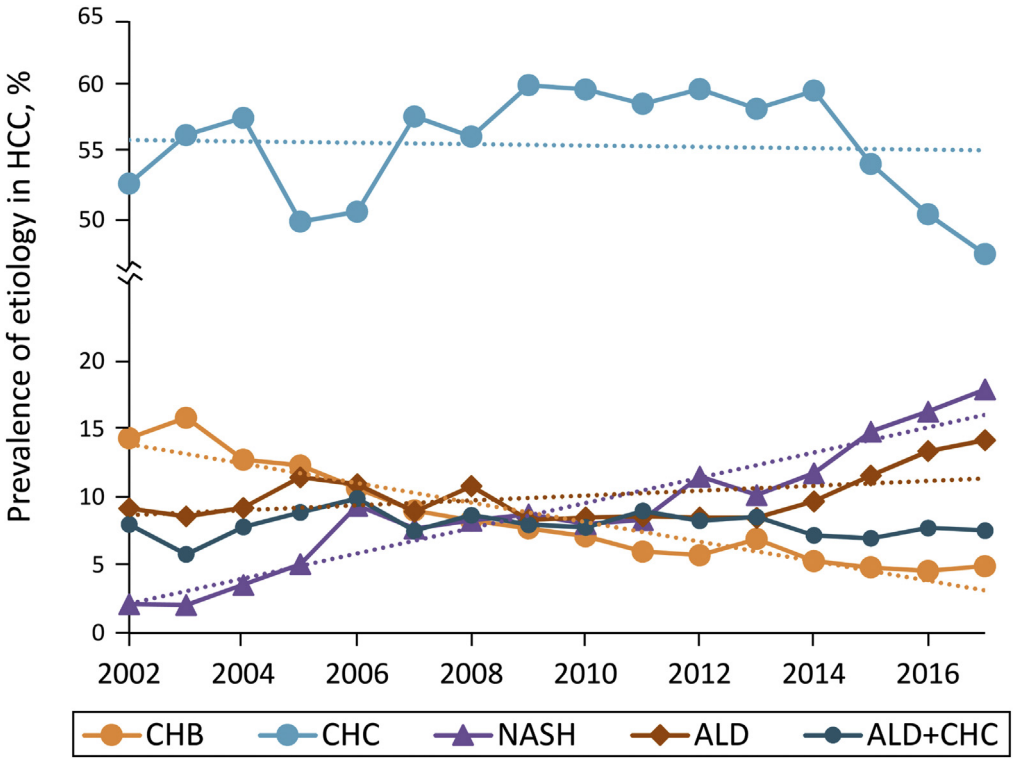

Figure 2. Prevalence of liver disease etiologies in patients with HCC and available etiology. *Dotted lines* represent linear trends.

independently with having a post-transplant HCC recurrence were the year of transplantation (odds ratio, 0.89; 95% CI, 0.88–0.91 per year) and male sex (odds ratio, 1.52; 95% CI, 1.28–1.82).

Although 1-year outcomes were similar between different HCC-related liver diseases ($P > .05$), the rates of both post-transplant mortality and graft loss became higher in patients with CHC and lower in patients with CHB with longer follow-up evaluation (Table 2). In multivariate analysis, independent predictors of increased post-LT mortality in patients with HCC were older age, black race, having comorbidities, and higher model for end-stage liver disease scores. However, the strongest predictor of post-transplant mortality in patients with HCC was recurrence of HCC (adjusted hazard ratio, 4.17; 95% CI, 3.81–4.56) (Table 3). Patients with cryptogenic cirrhosis had post-transplant outcomes similar to those of patients with a specifically identified listing diagnosis of NASH (all except cause of death due to renal failure $P \geq .05$) (Supplementary Table 1).

Discussion

In this study, we report the prevalence of HCC in patients with different etiologies of chronic liver disease who were listed for liver transplantation in the United States between 2002 and 2017. Our study used the most recent data and clearly showed that both the total number and the proportion of listings for liver transplantation with HCC is increasing across all important etiologies of liver disease and all clinical subgroups. Nevertheless, the slopes of these increasing trends may vary according to the underlying etiology. In this context, the prevalence of HCC seems to be growing at a significantly higher pace for the waitlisted patients with NASH

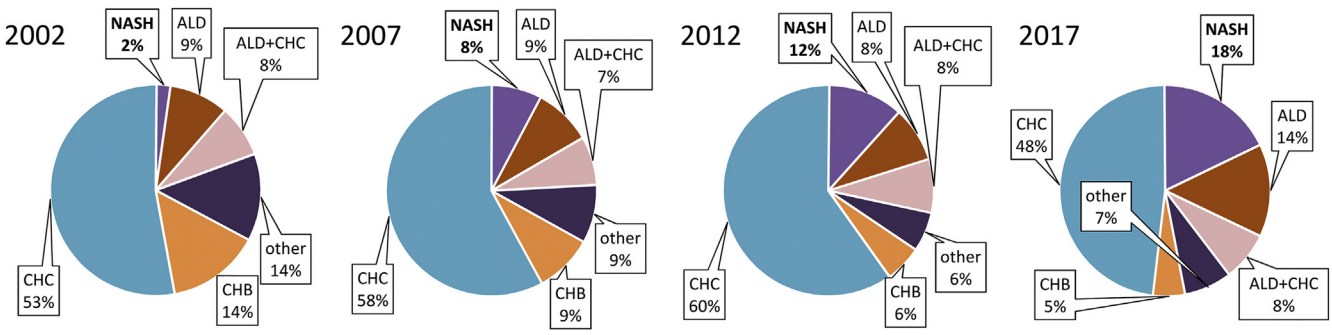

Figure 3. Etiologies of HCC in waitlisted candidates (with available HCC etiology).

Table 2. Post-transplant Outcomes of Transplant Recipients With HCC

	CHB	CHC	NASH	ALD	ALD + CHC	*P*
N	1078	8958	1631	1510	1227	
Discharged alive	1028 (96.8%)	8619 (97.5%)	1523 (95.3%)	1441 (96.6%)	1187 (97.6%)	.0001
Recorded HCC recurrence in follow-up period	102 (10.3%)	708 (8.6%)	90 (6.3%)	91 (6.8%)	93 (8.2%)	.0014
Time to recurrence, *y*	2.3 ± 1.9	2.4 ± 2.2	2.7 ± 2.1	2.4 ± 2.0	2.8 ± 2.5	.19
1-year mortality	66 (8.1%)	631 (10.6%)	93 (10.6%)	79 (8.6%)	82 (10.0%)	.11
3-year mortality	112 (16.7%)	1076 (24.4%)	115 (19.7%)	143 (19.9%)	127 (20.5%)	<.0001
5-year mortality	113 (21.5%)	1087 (34.9%)	111 (28.2%)	158 (31.1%)	138 (30.5%)	<.0001
Cause of death						
Cardiovascular	25 (10.8%)	270 (10.8%)	55 (15.4%)	40 (10.0%)	36 (10.2%)	.11
Graft failure	26 (11.3%)	304 (12.2%)	23 (6.4%)	30 (7.5%)	40 (11.3%)	.0026
Renal failure	1 (0.4%)	35 (1.4%)	9 (2.5%)	4 (1.0%)	6 (1.7%)	.26
Infection	13 (5.6%)	245 (9.8%)	37 (10.3%)	46 (11.5%)	23 (6.5%)	.0379
Malignancy	94 (40.7%)	723 (29.0%)	98 (27.4%)	128 (32.0%)	92 (26.1%)	.0012
Respiratory failure	5 (2.2%)	94 (3.8%)	16 (4.5%)	18 (4.5%)	13 (3.7%)	.61
Multiple organ system failure	12 (5.2%)	199 (8.0%)	27 (7.5%)	28 (7.0%)	30 (8.5%)	.57
1-year graft loss	37 (4.7%)	277 (4.9%)	37 (4.6%)	37 (4.3%)	35 (4.5%)	.91
3-year graft loss	40 (6.7%)	359 (9.8%)	34 (6.8%)	44 (7.2%)	44 (8.2%)	.0164
5-year graft loss	33 (7.4%)	320 (13.8%)	27 (9.0%)	37 (9.7%)	46 (13.0%)	.0005

as compared with the other common causes of chronic liver disease. On the other hand, increasing proportions of HCC in patients with CHC and CHB seem to be explained by decreasing numbers of listings for CHC and CHB without HCC: from 2495 patients in 2002 to 1053 in 2017 with non-HCC CHC, from 506 patients in 2002 to 264 in 2017 with non-HCC CHC + ALD, and from 269 patients in 2002 to 144 in 2017 with non-HCC CHB; all this likely is owing to treatment availability for HBV and HCV, which potentially could prevent adverse outcomes, delay disease progression, and, therefore, reduce listing for LT in treated patients with CHB and CHC without HCC. Moreover, although CHC remains the most common cause of HCC in patients listed for liver transplantation, the proportion of HCC accounted for by NASH is the only one that has been increasing steadily and significantly in the past 2 decades. As a result, in 2017, NASH-related HCC represented 18% of all HCC listings, which was an 8.5-fold increase from 2002, and the trend still is growing steadily at approximately 1.9 percentage points per year over the past 4 years.

Table 3. Independent Predictors of Post-transplant Mortality in Patients With HCC ($P < .05$ Only)

Predictor	Adjusted hazard ratio (95% CI)	*P*
Year of transplantation, per year	1.07 (1.05–1.08)	<.0001
Etiology: CHB[a]	0.67 (0.55–0.81)	<.0001
Etiology: NASH[a]	0.76 (0.65–0.89)	.0005
Age, per year	1.015 (1.009–1.022)	<.0001
Race: black	1.39 (1.23–1.57)	<.0001
Race: Asian	0.75 (0.62–0.90)	.0019
Private insurance	0.90 (0.83–0.97)	.0105
History of coronary artery disease	1.26 (1.01–1.57)	.0371
History of stroke	1.47 (1.01–2.13)	.0455
History of COPD	1.54 (1.22–1.95)	.0003
History of DM	1.21 (1.10–1.33)	<.0001
Last MELD score, per 1 point	1.010 (1.004–1.015)	.0007
Recurrence of HCC	4.17 (3.81–4.56)	<.0001

COPD, chronic obstructive pulmonary disease; MELD, model for end-stage liver disease.
[a]Reference etiology group: CHC.

These data provide evidence supporting a number of important issues related to HCC and NASH. First, the rate of HCC in the United States is increasing in patients who qualify and are listed for liver transplantation. This is consistent with other studies that looked at nontransplant cohorts or population-based data.[29] The second important issue is that, although CHC remains the most common etiology of HCC in patients listed for LT, NASH is growing rapidly and now is the second most common in that population. These increasing rates may be related not only to the epidemic of NASH fueled by that of obesity and type 2 DM, but also be influenced by an increased risk of HCC driven by DM itself.[30] Furthermore, although the contribution of CHC to HCC may be decreasing owing to the availability of highly effective antiviral treatment regimens, there is no similar option for patients with NASH. Given that, we believe that NASH-related HCC and its associated burden likely would grow substantially in the future.

Despite the reported differences in the trends, the rates of receiving a liver transplant or dropping off the LT list were similar for different etiologies of HCC. The proportion of candidates being removed from the list as a result of improvement was between 0.7% (NASH) and 2.0% (CHB) in patients with HCC ($P = .0003$). It is important to note that the same proportions in patients without HCC were substantially higher (between 3.6% in NASH and 6.6% in CHB; $P < .0001$), which is expected given the availability of highly effective antiviral

regimens for hepatitis B and the lack of any similar treatment options for patients with NASH. On the other hand, we did not find any evidence of any recent increase in that recompensation rate in non-HCC patients with CHC or CHB, which potentially could contribute to increasing proportions of HCC in patients remaining on the list (Supplementary Figure 4).

Post-transplant adverse outcomes (mortality and graft loss) of transplant recipients with HCC were higher for CHC and lower for CHB compared with NASH. However, it is important to note that more than 95% of HCC patients included in this analysis were listed within Milan criteria regardless of the etiology of liver disease. In this context, the NASH HCC patients who were listed for LT in the United States may represent a biased subpopulation, and although NASH patients who meet the criteria for transplantation may do just as well as their non-NASH counterparts, a large proportion of NASH patients may not meet transplant candidacy criteria at initial presentation owing to more advanced HCC or cardiovascular comorbidities. In addition, although the diagnostic accuracy of ultrasound-based screening generally is poor, which results in under-surveillance for HCC across all etiology sets,[31] more advanced HCC in NASH also may occur owing to lower awareness of the risk of HCC in that population[32] or increased risk of failure of screening secondary to body habitus (visceral obesity). Thus, the population reported here actually may underestimate the true proportion of HCC cases related to NAFLD and NASH in the United States.

Limitations of this study included the presence of missing or incomplete data in the data set, inconsistencies in data recording across different transplant centers, or changes in diagnostic criteria and coding practices with time including the presumably interchangeable use of NASH and cryptogenic cirrhosis diagnostic categories. Furthermore, because there were only 2 listing diagnoses included for each patient, 1 of which was required to be HCC, we were unable to study temporal trends extensively in populations of patients with more than 1 cause of chronic liver disease and, most importantly, with NASH being superimposed on another etiology. Finally, the SRTR database did not allow for analysis of potential differences in the proportions of cirrhotic vs noncirrhotic patients with HCC according to underlying etiology, an important issue in light of recent studies suggesting that a higher proportion of NAFLD HCC may occur in noncirrhotic patients compared with other etiologies.[33]

In summary, our data clearly show that the number of patients listed for LT with HCC is increasing, and that the highest rate of that increase in HCC is seen in waitlisted patients with NASH. Although CHC currently remains the most common etiology for HCC in transplant candidates and recipients, because more CHC patients are being cured with new highly effective antiviral regimens, NASH may become the top etiology not only for cirrhotic patients but also for HCC in patients listed for liver transplantation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.05.057.

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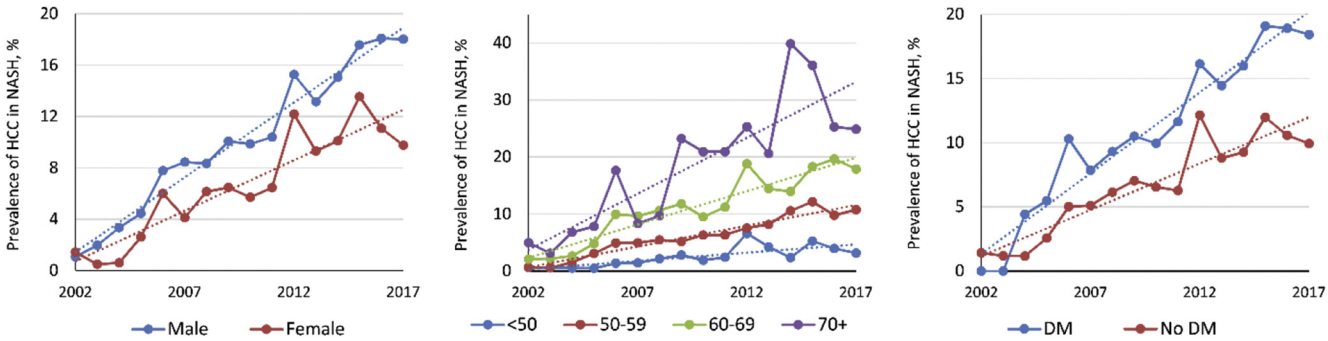
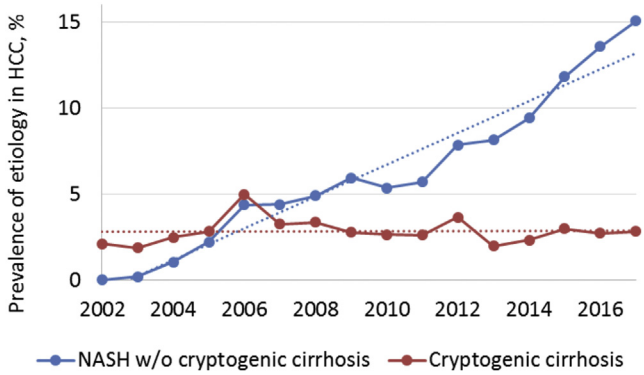
Acknowledgments
The data reported here were supplied by the Minneapolis Medical Research Foundation as the contractor for the Scientific Registry of Transplant Recipients. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the Scientific Registry of Transplant Recipients or the US Government.

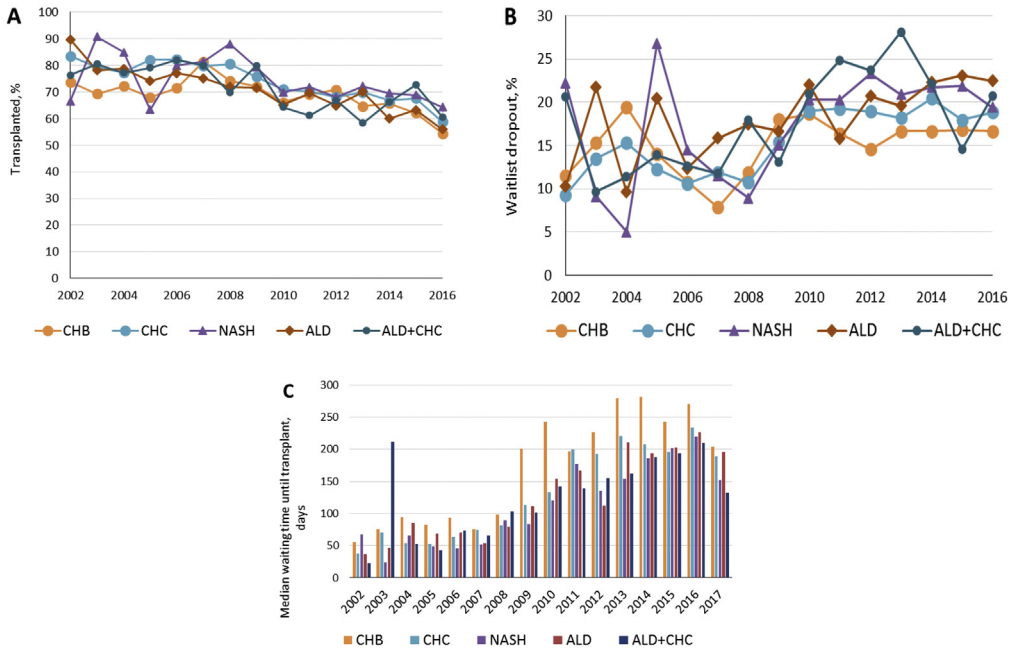
Conflicts of interest
These authors disclose the following: Zobair Younossi is a consultant to BMS, Gilead Sciences, NovoNordisk, Intercept Pharmaceuticals, and GSK; Ira M. Jacobson, Elisabetta Bugianesi, Vincent W. Wong, Manuel Romero-Gomez, and Aijaz Ahmed have received research funds and/or consultant fees from Gilead Sciences and Intercept Pharmaceuticals. The remaining authors disclose no conflicts.



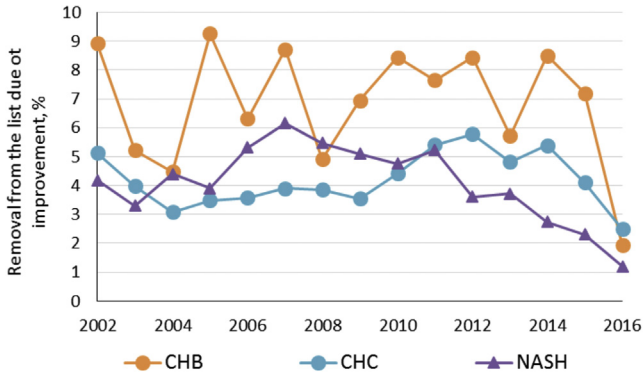
Supplementary Figure 1. Prevalence of HCC in patients with NASH by sex, age group, and DM status.



Supplementary Figure 2. Prevalence of specifically identified listing diagnoses of NASH and cryptogenic cirrhosis in patients with HCC. *Dotted lines* represent linear trends.



Supplementary Figure 3. Waitlist outcomes in waitlisted candidates with HCC. (*A*) Received a transplant; (*B*) waitlist dropout; (*C*) time to receiving a transplant in transplanted patients. *Waitlist dropout includes on-list mortality and removal from the list owing to deterioration.



Supplementary Figure 4. Liver transplant candidates with viral hepatitis and NASH without HCC who were removed from the waitlist because of improvement.

Supplementary Table 1. Outcomes of Liver Transplant Candidates and Transplant Recipients With Specifically Identified Listing Diagnoses of NASH and Cryptogenic Cirrhosis

	Transplanted, %			Waitlist dropout, %		
Year	NASH	Cryptogenic	*P*	NASH	Cryptogenic	*P*
Waitlist outcomes						
2002	-	66.7	NA	-	22.2	NA
2003	100.0	90.0	.74	0.0	10.0	.74
2004	100.0	78.6	.22	0.0	7.1	.5
2005	55.6	69.6	.36	33.3	21.7	.41
2006	81.0	79.2	.83	11.9	16.7	.52
2007	88.0	73.0	.07	6.0	18.9	.06
2008	88.3	87.8	.94	8.3	9.8	.81
2009	79.1	80.0	.90	15.1	15.0	.99
2010	71.9	65.9	.48	21.3	18.2	.67
2011	71.4	72.9	.85	21.0	18.8	.75
2012	72.1	60.0	.06	18.0	34.7	.0048
2013	74.0	65.1	.24	19.8	25.6	.4
2014	71.5	62.3	.19	21.0	24.5	.58
2015	67.5	74.3	.25	21.9	21.6	.96
2016	63.4	69.1	.37	20.1	16.2	.46
2017	31.5	28.4	.61	9.6	11.9	.55

	NASH without cryptogenic cirrhosis	Cryptogenic cirrhosis	
Post-transplant outcomes			
N	1196	435	
Discharged alive	1118 (95.2%)	405 (95.5%)	.81
Recorded HCC recurrence in follow-up evaluation	61 (5.9%)	29 (7.5%)	.26
Time to recurrence, *y*			
1-year mortality	57 (9.8%)	36 (12.2%)	.28
3-year mortality	61 (17.3%)	54 (23.4%)	.07
5-year mortality	60 (27.8%)	51 (28.8%)	.82
Cause of death			
Cardiovascular	34 (15.0%)	21 (15.9%)	.83
Graft failure	12 (5.3%)	11 (8.3%)	.26
Renal failure	2 (0.9%)	7 (5.3%)	.0100
Infection	28 (12.4%)	9 (6.8%)	.09
Malignancy	70 (31.0%)	28 (21.2%)	.05
Respiratory failure	7 (3.1%)	9 (6.8%)	.10
Multiple organ system failure	14 (6.2%)	13 (9.8%)	.21
3-year graft loss	16 (5.3%)	18 (9.3%)	.08
5-year graft loss	10 (6.3%)	17 (12.1%)	.08