Future Trends in Demand for Liver Transplant: Birth Cohort Effects Among Patients With NASH and HCC

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Background. With increasing US adiposity, nonalcoholic steatohepatitis (NASH) is now a leading liver transplant (LT) indication. Given its association with hepatocellular carcinoma (HCC), the burden of NASH is substantial. We analyzed birth cohort effects among NASH LT registrants, with and without HCC. **Methods.** All new LT registrants in United Network for Organ Sharing (1995-2015) were identified. Birth cohorts were defined as: 1936-1940, 1941-1945, 1946-1950, 1951-1955, 1956-1960, 1961-1965, 1966-1970, 1971-2015. Poisson regression examined trends in LT registration, by disease etiology (NASH, hepatitis C virus [HCV], other liver disease etiologies [OTHER]), and HCC. **Results.** We identified 182368 LT registrants with median age of 52 years (range, 0-86 years). Nine percent (n = 16160) had NASH, 38% (n= 69004) HCV, 53% (n = 97204) OTHER. HCC was present in: 13% (n = 2181), 27% (n = 18 295), and 11% (n = 10902), of NASH, HCV, and OTHER, respectively. Liver transplant registration for HCC increased significantly from 2002 to 2015 across all etiologies (NASH, 6%-18%; HCV, 19%-51%; OTHER, 9%-16%; $P < 0.0001$ for all). NASH LT registrations, with and without HCC, increased sharply in patients born from 1945 to 2015. This upward NASH trend is in stark contrast to HCV LT registrations, which showed a general decline. Notably, a sharp rise in LT registrations is occurring among younger NASH patients (35-55 years), mirroring the increasing adiposity across all age groups in the US population. **Conclusions.** NASH LT registrants, with and without HCC, have increased over time, and are projected to increase unabated in the future, notably among younger birth cohorts ("Adipose Wave Effect"). HCC LT registration patterns demonstrate that, compared with HCV, NASH patients encompass younger birth cohorts. These data illustrate that the full impact of NASH on demand for LT is yet to be realized.

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Obesity and obesity-related diseases, such as insulin resistance and diabetes mellitus (DM), are well-documented public health burdens. As of 2016, the global prevalence of overweight (body mass index [BMI], $\geq$ 25 kg/m^2) was 39%, with a 13% prevalence of obesity (BMI, $\geq$ 30 kg/m^2).[1] Rates of obesity are further endemic in the United States; 39.8% of adults and 18.5% of children are obese.[2,3] The most concerning trend is the rise in the obesity among the pediatric population, with a recently reported sharp increase in obesity prevalence among children aged 2 to 5 years.[4] With regard

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to obesity-related diseases, the prevalence of DM in the United States rose to 9.5% in 2015.[5] Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) most frequently occur in the setting of obesity-related diseases, with estimated US prevalence rates of 45% and more than 3% to 5%, respectively.[6,7] Also, the rate of progression from NASH to NASH-related cirrhosis is estimated to be approximately 15% to 20%. As such, NASH has emerged as a leading indication for liver transplant (LT) waitlist registration in the United States and has been projected in some studies to become the most common indication in the near future.[8,9] Regarding the evolution of NASH cirrhosis and future demand for LT, a concerning population trend is the increasing exposure of individuals, including the vyounger segment of the population, to unhealthy dietary patterns and inactivity that largely contribute to an increasing prevalence of overweight and obesity among younger patients. These individuals are at highest risk for developing NASH-related cirrhosis over their lifetimes. Although NASH prevalence increases with age, it remains unclear whether it is actual chronological age that contributes to the increased risk, or rather the cumulative exposure to environmental and metabolic risk factors over an individual's lifetime.

Nonalcoholic steatohepatitis cirrhosis is known to be associated with increased risk of hepatocellular carcinoma (HCC), with NASH accounting for up to 13% of HCC cases in the United States,[10] NASH is also reported as the fastest growing cause of HCC among LT registrants, with HCC being the most common indication for LT in the United States.[11,12]

Investigations of LT waitlist registration and transplantation rates in the United Network for Organ Sharing (UNOS) database describe a rising prevalence of NASH and HCC among the "Baby Boomer" generation (adults born 1945-1965).[13] However, it remains unclear if age-related trends in the prevalence of obesity and NAFLD/NASH in the United States, correlate with concurrent variation in rates of LT waitlist registration for patients with NASH among younger age groups. Also, the association of NASH with HCC is even less well defined among the younger age groups. These trends have important clinical and health policy relevance with regard to informing the medical community and policy makers of the burden of NASH cirrhosis, with and without HCC, which is anticipated in the coming decades.

In this investigation, we conducted birth cohort and age group analyses to demonstrate observed and projected trends in LT registration among patients with NASH cirrhosis (with and without HCC), and conducted a comparative analysis with cirrhosis due to hepatitis C virus (HCV), and other liver disease etiologies (OTHER).

MATERIALS AND METHODS

Study Population

We identified all unique patients (0-86 years) who were registered for primary LT on the waitlist in the United States from 1995 to 2015 using UNOS Standard Transplant Analysis and Research Files (released March 2016). New LT registrants were used to calculate observed annual trends. Patients listed for retransplantation were excluded.

Defining Liver Disease Etiology and HCC

Liver disease etiology in LT registrants was determined based upon UNOS coding. Primary, secondary, and text diagnoses were reviewed and classified into 3 etiologic categories: (i) NASH, including diagnosis code 4214 or text indication of NASH. Patients were also classified as NASH cirrhosis if they met the following criteria: diagnosis of cryptogenic cirrhosis [CC] with any of the following diagnosis codes: 4208 or 4213 or text indication of CC, along with an indication of DM[14]; (ii) HCV, including diagnosis codes 4204, 4206, 4216, or 4593, or text indication of HCV; and (iii) OTHER liver disease etiology, which included all patients without a diagnosis of either NASH or HCV, as defined above. Patients with both HCV and NASH diagnoses (n = 290, 0.2%) were classified to HCV, and classification did not change overtime.

Concomitant HCC was also identified through the UNOS diagnoses data, including diagnosis codes 4400 and 4401 or text indication of HCC, or assignment of an HCC exception.

Thus, using the aforementioned criteria, 6 main categories were created for comparison: (1) NASH without HCC (NASH/NoHCC), (2) NASH with HCC (NASH/HCC), (3) HCV without HCC (HCV/NoHCC), (4) HCV with HCC (HCV/HCC), (5) OTHER without HCC (OTHER/NoHCC), (6) OTHER with HCC (OTHER/HCC).

Defining Birth Cohort and Age Groups

Patients were divided into birth cohorts and categorized into subgroups of 5-year increments beginning from 1936. Patients born after 1970 were combined into a single group due to sample size. Patients born before 1936 were not included in the birth cohort analyses due to very advanced age resulting in limited relevance to the intended analyses regarding LT registration. The birth cohorts included the following: 1936 to 1940, 1941 to 1945, 1946 to 1950, 1951 to1955, 1956 to 1960, 1961 to 1965, 1966 to 1970, 1971 to 2015.

Patients were also divided into age groups, based on date of birth and date of LT waiting list registration. The age groups included the following (age in years): 0 to 17, 18 to 34, 35 to 44, 45 to 54, 55 to 64, and 65 to 86.

Statistical Analysis

The study population was described using counts, proportions, and medians with interquartile ranges (IQR). Patients with and without HCC were compared using the χ^2 test. Rates for new LT registrants by calendar year were calculated for the overall study population and for each of the 6 liver disease etiologic categories. The complete data set was used to generate future projections in new LT registrations. Poisson generalized additive regression models examined associations between LT waitlist registration and birth cohort, by waitlist registration year, for NASH and HCV. These models were used to assess trends in LT waitlist registrations. Interactions assessed differences in registration trends by etiologic category and HCC. *P* values were calculated for overall increase in LT registrations over the study period. Projections of predicted counts of new LT registrants for calendar years outside of the range of the observed data were based on extrapolation of the regression models. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4.3 (R Foundation for Statistical Computing). The generalized additive models were fitted using the R package mgcv.[15]

RESULTS

Overall Population Characteristics

From 1995 to 2015, there were 182368 new LT registrants. The median age was 52 years (IQR, 44-59 years) and 63% (n = 114329) of registrants were male. Nonalcoholic steatohepatitis was the primary liver disease etiology in 9% (n = 16160) of LT registrants, and HCV was the primary liver disease etiology in 38% (n = 69001). HCC was present in 17% (n = 31378) of all LT registrants. Liver transplant surgery was performed in 56% (n = 101193) of the LT registrants during the study period.

Population Characteristics by Liver Disease Etiology and HCC Status

The population characteristics according to liver disease etiology (NASH, HCV, OTHER) stratified by no HCC versus HCC are shown in Table 1. The median (unstratified) age of NASH LT registrants was higher (59 years; IQR, 54-64 years) compared with HCV (53 years; IQR, 48-59 years) and OTHER (51 years; IQR, 37-59 years) ($P < 0.0001$). Patients with NASH/HCC represented the oldest group (63 years; IQR, 58-67) compared with patients with HCV/HCC (57 years; IQR, 53-61) and OTHER/HCC (58 years; IQR, 52-64]; $P < 0.0001$). In every group, patients with HCC were older than patients without HCC ($P < 0.0001$ for all comparisons).

Among individuals with NASH, 49% were women, compared with 28% and 42% of individuals with HCV and OTHER, respectively. The proportion of African American individuals was lowest within NASH (n = 357; 2%) compared with HCV (n = 7087; 10%) and OTHER (n = 9344; 9%).

Within the study population, HCC was most prevalent among HCV LT registrants (n = 18295; 27%); however, HCC was also prevalent among individuals with NASH (n = 2181; 13%), followed by individuals in the OTHER etiology category (n = 10902; 11%). Patients with HCC were more likely to be transplanted compared with those without HCC among all diagnostic etiology categories (NASH/HCC, 75% vs NASH/NoHCC, 49%; HCV/HCC, 75% vs HCV/NoHCC, 50%; and OTHER/HCC, 70% vs OTHER/NoHCC, 54%, $P < 0.0001$, for all).

Within the OTHER group, 30% of patients carried a diagnosis of alcohol liver disease (alcoholic cirrhosis or acute alcoholic hepatitis). When compared with the remainder of the patients in the OTHER group, those with alcohol liver disease were older with median age of 53 years (vs 47 years) and more often carried a diagnosis of diabetes (19% vs 10%) (**Table S1, SDC,** http://links.lww.com/TP/B647).

Age Group Analysis of Observed LT Registration Rates Among All Patients With NASH Versus HCV Versus OTHER

We first compared LT registration rates among patients by age group among the different etiologies (NASH vs HCV vs OTHER (Figure 1, and **Figures S1 and S2, SDC,** http://links.lww.com/TP/B647). Overall, NASH LT registrants showed a steady and marked increase in LT registration, rising from 117 LT registrations in 1995 to 687 in 2005 (487% increase) and to 1856 in 2015 (1486% increase) ($P < 0.0001$; Figure 1). The comparison between 1995 and years subsequent to 2004 may be confounded by there being no formal diagnosis code in UNOS for NASH before 2004; however, a comparison between the 687 NASH LT registrations in 2005 and the 1856 NASH LT registrations in 2015 continues to reveal a marked increase (170%) ($P < 0.0001$). This striking upward trend in NASH LT registrations is in stark contrast to HCV and OTHER where LT registrants showed plateauing with decline, or only mild increase, in registration rates over the same

TABLE 1.

Patient Characteristics

	NASH		HCV		OTHER	
	No HCC (n = 13979)	HCC (n = 2181)	No HCC (n = 50709)	HCC (n = 18295)	No HCC (n = 86302)	HCC (n = 10902)
Sex, n (%)						
Females	7161 (51)	782 (36)	15306 (30)	3823 (21)	38465 (45)	2502 (23)
Age: median (IQR), y	58 (53-63)	62 (58-66)	52 (47-57)	57 (52-61)	48 (33-57)	58 (52-63)
Race/ethnicity, n (%)						
White	11232 (80)	1643 (75)	36290 (72)	11935 (65)	60976 (71)	6514 (60)
Black	339 (3)	18 (1)	4845 (9)	2242 (12)	8634 (10)	810 (7)
Latino	2004 (14)	423 (20)	7972 (16)	2938 (16)	11660 (13)	1576 (15)
Asian	1043 (2)	66 (3)	233 (2)	928 (5)	3743 (4)	1864 (17)
Other	171 (1)	31 (1)	559 (1)	252 (2)	1389 (2)	138 (1)
Birth cohort, n (%)						
1936-1940	1215 (9)	187 (9)	2395 (5)	748 (4)	5754 (7)	939 (9)
1941-1945	2459 (18)	504 (23)	4093 (8)	1623 (9)	9441 (11)	1757 (16)
1946-1950	3691 (26)	717 (33)	9841 (19)	4250 (23)	12554 (14)	2526 (23)
1951-1955	2827 (20)	419 (19)	16254 (32)	6483 (35)	12162 (14)	2503 (23)
1956-1960	1779 (13)	217 (10)	11163 (22)	3715 (20)	10076 (12)	1560 (14)
1961-1965	1006 (7)	91 (4)	4573 (9)	1118 (6)	7603 (9)	742 (7)
1966-1970	511 (4)	31 (1)	1401 (3)	249 (1)	5012 (6)	311 (3)
1971-2015	491 (3)	15 (1)	989 (2)	109 (1)	23700 (28)	564 (5)
Transplanted, n (%)	6789 (49)	1630 (74)	25266 (50)	13709 (75)	46180 (54)	7619 (70)

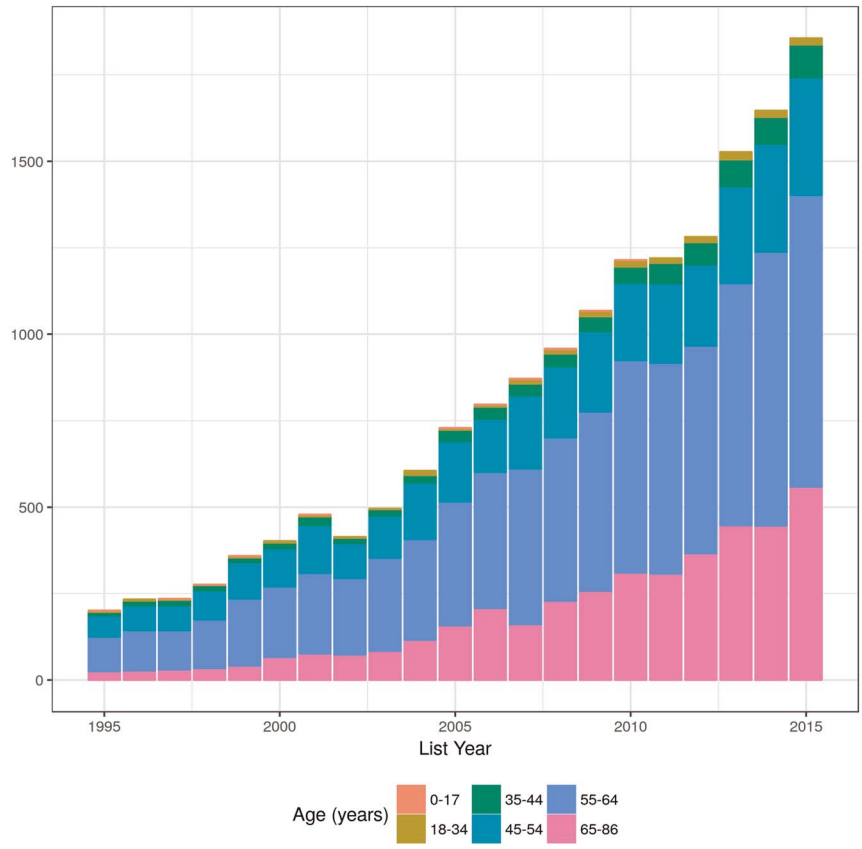

FIGURE 1. Observed liver transplant registration rates among patients with NASH, by age group.

period, respectively (HCV: n = 1596 in 1995, n = 3599 in 2005, and n = 3075 in 2015, representing 125% increase from 1995 to 2005, but a 14% decrease from 2005 to 2015, $P < 0.0001$ for overall 1995 to 2015 change; and OTHER: n = 3417 in 1995, n = 4705 in 2005, and n = 5658 in 2015, representing a 37% increase from 1995 to 2005, and a 20% increase from 2005 to 2015, $P < 0.0001$) (**Figures S1 and S2, SDC,** http://links.lww.com/TP/B647).

Age Group Analysis of Observed LT Registration Rates Among Patients With NASH Versus HCV Versus OTHER, by HCC Status

Trends in HCC LT registration rates differed from non-HCC groups, with the NASH/HCC and HCV/HCC categories demonstrating an increase among all age groups over the 20-year study period (**Figures S3 and S4, SDC,** http://links.lww.com/TP/B647; OTHER etiology diagnostic category data not shown for ease of demonstration). Notably, NASH/HCC showed the largest and steepest increase (n = 1 in 1995, n = 65 in 2005, n = 340 in 2015, representing a 6400% increase from 1995 to 2005 and a 423% increase from 2005 to 2015), compared with HCV/HCC (n = 50 in 1995, n = 904 in 2005, n = 1555 in 2015, representing a 1708% increase from 1995 to 2005 and a 72% increase from 2005 to 2015), and compared with OTHER/HCC (n = 74 in 1995, n = 567 in 2005, n = 892 in 2015, representing a 666% increase from 1995 to 2005 and a 57% increase from 2005 to 2015; $P < 0.0001$, for all). In the NASH/HCC category, comparison between 1995 and years subsequent to 2004 may be confounded by there being no formal diagnosis code in the UNOS database for NASH before 2004; however, a comparison between the 65 NASH/HCC LT registrations in 2005 and the 340 NASH/HCC LT registrations in 2015 continues to reveal a marked 423% increase ($P < 0.0001$). Trends in LT registration increased among both NASH/NoHCC and NASH/HCC categories, but the NASH/HCC patients demonstrate a sharper increase in registrations over time (**Figures S3 and S5, SDC,** http://links.lww.com/TP/B647). LT registrations increased among HCV/HCC patients with signs of plateauing in 2012, whereas registrations among HCV/NoHCC patients started plateauing in the early 2000s and have shown a steady decline since 2010 (**Figures S4 and S6, SDC,** http://links.lww.com/TP/B647).

Particularly striking was the sustained increase in NASH/HCC LT registrants among younger persons (for example, 35-54 years old), most notably from 2005 onward, which was not observed among HCV/HCC or OTHER/HCC registrants. This mirrored the similar yearly sustained increase in LT registration rates among all younger patients with NASH (with and without HCC). These data reveal a persistent increase in LT registrations for NASH (with and without HCC) among patients who were exposed to the obesity epidemic at a younger age, a phenomenon that we call the "Adipose Wave Effect."

Birth Cohort Analysis of Observed and Projected Trends in LT Registration Rates: Overall Comparison of NASH and HCV

We evaluated birth cohort effects by examining LT registration rates for NASH versus HCV over the study period from 1995 to 2015, with registrants divided into 5-year subgroups

by birth year (Figure 2 and **Figure S7, SDC,** http://links.lww.com/TP/B647).

Overall, NASH LT registrants increased in all birth cohorts over time, except among individuals born between 1936 and 1945, with the patients who were born from 1936 to 1945 representing individuals aged 70 to 79 years in the year 2015, making this particular birth cohort less physiologically conducive to being registered for LT ($P < 0.0001$, for comparison of birth cohorts rising vs not rising within NASH). The steepest increase in NASH LT registrations occurred not only within the baby boomer cohort (1951-1960), but also occurred very notably among younger birth cohorts (1961-2015). It is worthwhile explicitly stating that individuals born after 1970 were only 45 years or younger in 2015. These persistent upward trends in NASH LT registrations among the younger birth cohorts are projected to continue into the future and are further demonstration of the *Adipose Wave Effect* (Figure 2).

The observed and projected trends in LT registrations by birth cohort in NASH patients are in striking contrast to the observed and projected trends among HCV patients, where patients in the younger birth cohorts (born after 1960) show only a mild increase in registration rates, whereas all other HCV birth cohorts are projected to decrease ($P < 0.0001$, for comparison of birth cohorts with HCV) (**Figure S7, SDC,** http://links.lww.com/TP/B647).

Birth Cohort Analysis of Observed and Projected Trends in LT Registration Rates: Comparison of NASH and HCV by HCC Status

We demonstrate the observed and projected trends in HCC-positive and HCC-negative LT registrants among patients with NASH (Figures 3 and 4)] and HCV (***S8 and S9, SDC,*** http://links.lww.com/TP/B647) by birth cohorts. The NASH/HCC LT registrants began to rise beginning in the early to mid 2000s in all except the older birth cohorts (1936-1950), which demonstrated a rise a decade earlier (Figure 3). A sharper increase in HCC-positive LT registrants is observed within the NASH baby boomer cohort, particularly in more recent years, as compared with the HCV baby boomer cohort that showed a steady decline in LT registrations among patients born between 1946 and 1960 ($P < 0.0001$) (**Figure 3 and Figure S8, SDC,** http://links.lww.com/TP/B647). In projected trends, NASH/HCC and NASH/NoHCC patients born after 1950 demonstrate sustained increases in LT registration rates (Figures 3 and 4), as contrasted with HCV/HCC and HCV/NoHCC that show a steady decline in LT registrations over time (**Figures S8 and S9, SDC,** http://links.lww.com/TP/B647) ($P < 0.0001$; the exception being the 1961-1965 HCV/HCC birth cohort that has yet to reach its peak). NASH/HCC and NASH/NoHCC are also projected to have a very steep rise in LT registrants in the future among the youngest birth cohorts (1971-2015), even when these NASH patients, with and without HCC, will still be younger than 50 years.

NASH Diagnosis Sensitivity Analyses

In an effort to address potential concerns for misclassification of patients with CC as NASH cirrhosis,[16] we evaluated the robustness of our analyses by performing 2 additional comparisons using the following NASH diagnosis criteria: (i) NASH diagnosis code only (no inclusion of CC); and (ii)

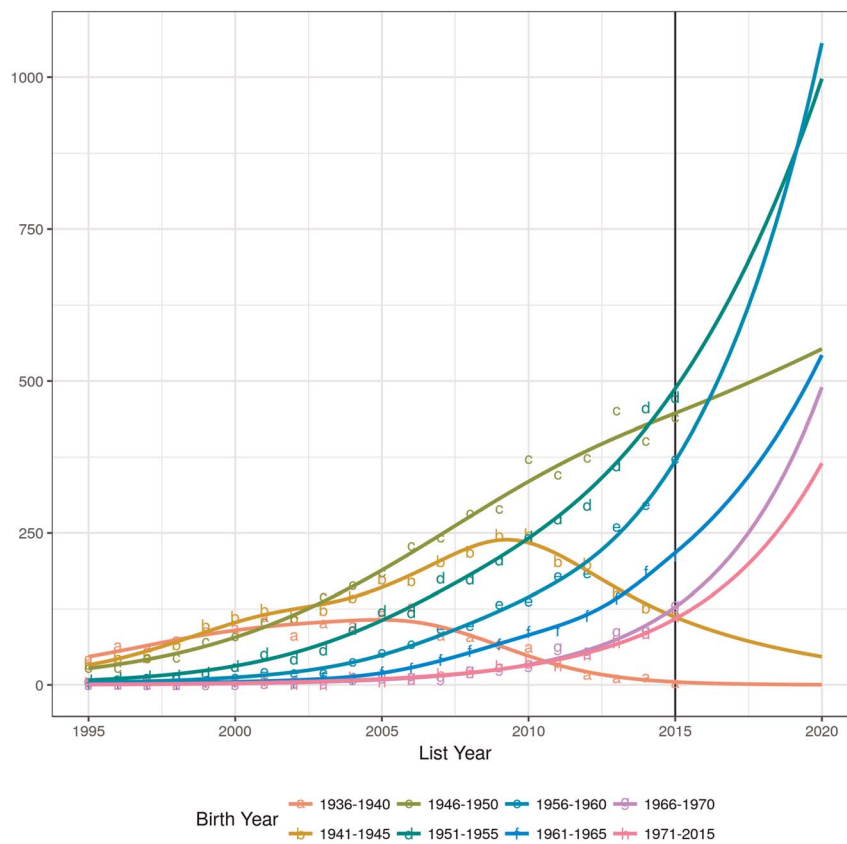

FIGURE 2. Observed and projected trends in liver transplant registration among patients with NASH, by birth cohort.

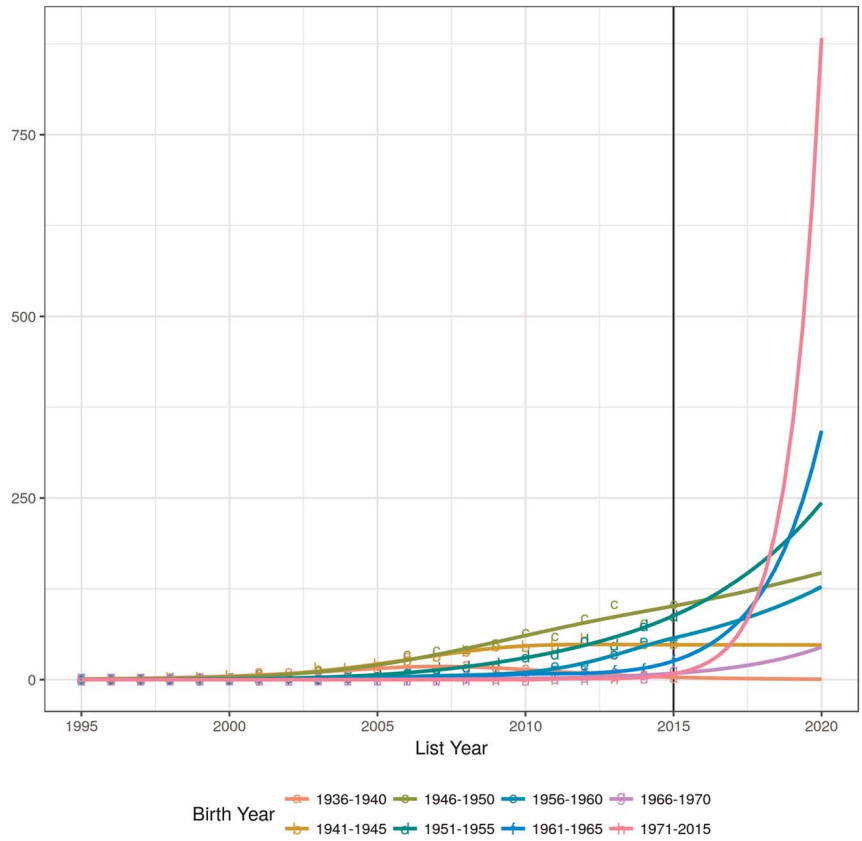

FIGURE 3. Observed and projected trends in liver transplant registration among patients with NASH and HCC, by birth cohort.

NASH and 50% of the CC + DM group. We found that the trends described in our age- and birth cohort-based analyses did not change significantly with these adjusted NASH diagnosis criteria, suggesting that our analyses using NASH and CC + DM are likely accurate representations of NASH LT registrations trends. We further tested for possible misclassification bias by evaluating data only from the years 2005 to 2010 (encompassing a period subsequent to 2004 when UNOS incorporated a formal diagnosis code for NASH) and found that the trends in the age and birth cohort analyses were unchanged from our original analyses using the definition of NASH as NASH and CC + DM (data not shown).

DISCUSSION

Our data demonstrate that a relentless, rising tide of patients who have NASH, with and without HCC, are being registered for LT. These trends are projected to increase unabated in the future, most notably among the younger birth cohorts, which we term as "adipose wave effect". Nonalcoholic steatohepatitis is one of the leading causes of chronic liver disease among patients registered for LT in the United States, and HCC is a very common complication of cirrhosis necessitating LT. Data from the National Health and Nutrition Examination Survey demonstrate that obesity has been increasing in the United States over the past 3 decades and that the rise in prevalence is occurring in all age groups, even among children as young as 2 years, and this rising prevalence has not shown signs of plateauing. The increase in NASH-related LT registrations parallels the increasing rates of obesity and DM in the United States (Figure 5). A recent study demonstrated a 9-year lag time between the increase in obesity prevalence and LT registrations for NASH, suggesting that there may be an obesity-related exposure time effect on the development of NASH cirrhosis.[17] Thus, in the future, patients born after 1970 (which represents our youngest birth cohort) will have suffered the longest lifetime exposure to the obesity epidemic, which we term as "adipose wave effect," putting them at highest risk of developing NASH cirrhosis and need for LT.

In the present study, we initially identified age-related trends in LT registration among patients with NASH, in comparison to patients with HCV or OTHER etiologies of chronic liver disease. After further investigating the observed and projected LT registration rates using birth cohorts, we have discovered 2 main trends. The first trend is that NASH/NoHCC and NASH/HCC LT registrants have been steadily increasing over time, and are projected to continue to increase at a much steeper rate compared with HCV/NoHCC and HCV/HCC, as well as compared with OTHER/NoHCC and OTHER/HCC (data for OTHER category not shown). This finding is in agreement with previous UNOS analyses. Cholankeril et al[8] conducted a UNOS analysis of LT surgeries performed from 2003 to 2014 and found a 162% increase in LT for NASH compared with a 33% increase in LT for HCV and a 55% increase in LT for alcoholic liver disease. Our study examined LT registrants as opposed to LT recipients, because an assessment of LT registrations provides a more comprehensive representation of

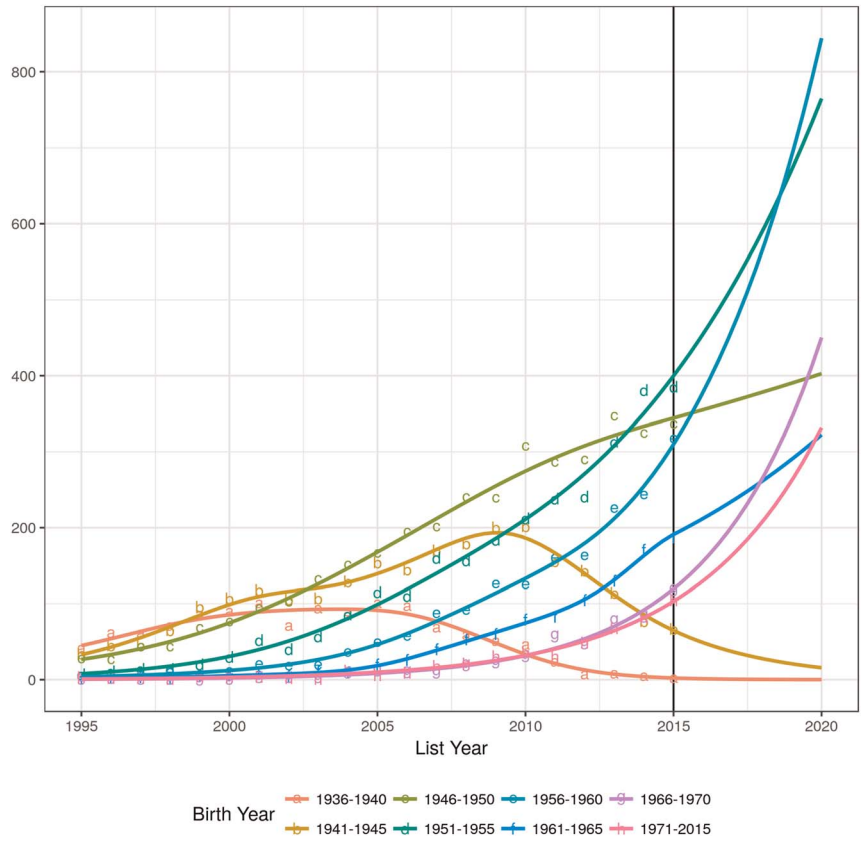

FIGURE 4. Observed and projected trends in liver transplant registration among patients with NASH and No HCC, by birth cohort.

NASH disease burden on the LT community. Specifically, there are many patients who register for LT, but who ultimately do not receive a donor liver for a variety of reasons. In addition, our study spans 2 decades and includes not only patients coded as "NASH" in the UNOS database (NASH did not have an official diagnostic code in the UNOS database until 2004), but we also sought to capture patients whose NASH diagnosis may have been missed by identifying patients with "cryptogenic cirrhosis" who also had a diagnosis of DM. Although a recently published study by Thuluvath et al[16] suggested that cryptogenic cirrhosis is a different entity from NASH, as evidenced by different clinical characteristics that persist between the 2 groups despite adjusting for BMI and DM status, a previously published analysis by Caldwell et al[14] suggests otherwise. We conducted sensitivity analyses investigating trends in LT registration by age group and birth cohort using 2 additional definitions of NASH: (i) NASH diagnosis alone and (ii) NASH plus 50% of CC + DM diagnoses. The results of our original analyses (based on NASH and CC + DM) were not altered by using these more conservative definitions of NASH. Considering limitations of the retrospective review of the UNOS database by Thuluvath et al, which does not account for a previous history of obesity, duration of DM, and other metabolic factors in individual's life,

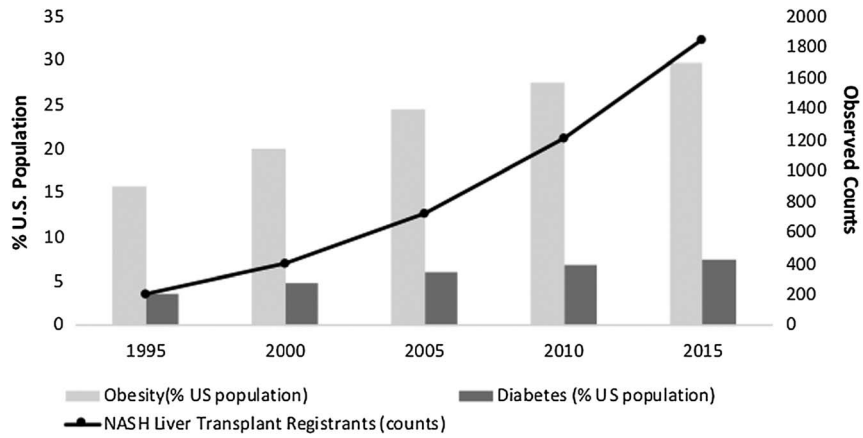

FIGURE 5. Composite illustration of observed US trends in obesity*, diabetes mellitus*, and NASH liver transplant registrations (*cdc.gov).

as well as an inability to adjust for ascites or edema in BMI calculations, we believe that NASH still likely accounts for a sizable proportion of cryptogenic cirrhosis and thus, we propose that this diagnostic approach to the UNOS database provides a more comprehensive means of identification of NASH patients in UNOS.[18]

The second trend that we have demonstrated is a disturbing pattern of an increasing number of NASH LT registrants in younger age groups and birth cohorts; a pattern that was not observed in the HCV and OTHER diagnosis categories. Cholankeril et al studied the baby boomer cohort effect (born 1945-1965) in LT recipients who had HCC in the setting of HCV, alcohol, or NASH cirrhosis.[13] They observed a 905% increase in NASH-related HCC versus 268% and 208% increases in HCV- and alcohol-related HCC, respectively. This is in general agreement with our findings for LT registrants across a similar period (2005-2015), but including all birth cohorts rather than just baby boomers, where we calculate a 423% increase in NASH/HCC and 72% increase in HCV/HCC LT registrants. Although the lack of increase of LT registrants in older NASH cohorts may be partially attributed to the accumulation of comorbidities with age precluding surgical candidacy, we continue to observe an increase in LT registrations in the 1951 to 1955 birth cohort, which in 2010 to 2015 comprised patients aged 55 to 65 years, which is an average age at transplant in many US LT programs.

Presently, we are seeing only the beginning of the rising wave of younger NASH patients who will require LT in the coming years. This evolving wave of NASH is attributable to both: (i) an actual increase in NASH among younger patients who will have been exposed to environmental factors (such as unhealthy dietary patterns and inactivity) resulting in increasing adiposity, the "adipose wave effect", from a very young age; and (ii) the lower likelihood that these younger patients will suffer from the age-related comorbidities that preclude many older patients with NASH cirrhosis from transplantation. Our data represent the first demonstration of this "adipose wave effect" that may be expected to change the landscape of LT in the coming years.

The strengths of our study include: the use of a large, nationally representative database of all patients registered for LT in the United States from 1995 to 2015 encompassing a very wide age range and a wide range of birth cohorts, along with a comprehensive approach to identifying NASH patients in the UNOS database. With the large sample size afforded by the UNOS data, we were able to calculate estimates of future burden of NASH with regard to LT registrations. However, our study is not without limitations. Our data were obtained through retrospective review of the UNOS database, limited to the variables available in the UNOS data set. As with all studies attempting to retrospectively analyze LT trends in NASH, limitations exist with regard to the fact that NASH was not included as a diagnostic category in the UNOS database until 2004. However, unlike many other published UNOS-based NASH studies, we used a method for identifying cryptogenic cirrhosis patients with DM, in an effort to enrich the NASH population. There may exist an overlap in patients with alcohol liver disease and NASH, resulting in the inclusion of such patients in the NASH category (for example, individuals with a remote history of excessive drinking, or individuals who were hesitant to fully disclose their alcohol use history to the transplant team). This represents an inherent challenge in making a diagnosis of NASH for any investigation into NASH and in identifying patients with NASH using large databases, such as the UNOS database. It is also important to note that there may be an interaction between metabolic risk factors and alcohol use in the development of severe liver disease, further blurring the line between NASH and alcohol liver disease diagnoses.[19] Alcohol may serve as a potentiator of NASH liver disease, and, perhaps, vice versa. Despite our efforts to identify all cases of NASH, it is possible that our data may underestimate the overall burden of NASH in LT registrants, which may only strengthen our conclusions. The early upward trends in the number of NASH LT registrants using data before 2004 are undoubtedly subject to ascertainment bias as NASH became better understood and was correctly coded for in the UNOS database beginning in 2004. Despite this, our data span >10 years beyond 2004, resulting in robust and reliable calculations and graphical representations of time trends in NASH LT registrations.

In conclusion, our study clearly demonstrates the growing impact of NASH on the LT community, using registration for LT as a marker of disease burden. Our data reveal a persistent increase in LT registrations for NASH (with and without HCC) across all age groups. Notably, this rising trend is also seen in younger patients, which is alarming. These younger patients may be experiencing the deleterious metabolic consequences of longer-term exposure to the obesity epidemic at a younger age, a phenomenon that we term, the "Adipose Wave Effect." Unfortunately, being young in the United States may no longer be equated to being healthy, as the United States evolves toward becoming an "adipo-nation." As the prevalence of cirrhosis attributable to NASH continues to rise, understanding trends in the demographics of registrants with studies such as this will afford the transplant community and policy makers opportunities to identify patient characteristics and allocate resources that optimize LT outcomes.

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