

Alcoholic Liver Disease Patients Listed for Liver Transplantation: An Overview from 2002-2017

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Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: July 9, 2020

Revised: July 27, 2020

Accepted: July 29, 2020

Published online: October 21, 2020

ABSTRACT

ALD patients comprise a larger proportion of listings for liver transplantation (LT) than in the past, and represent a population undergoing demographic change in the United States. This study examined the OPTN/UNOS transplantation waitlist STAR files from March 2002 - December 2017. All adults listed for LT were included ($n = 135,956$). Yearly demographic trends in ALD-related listings and listing outcomes (transplantation vs. death on waitlist) were reviewed. Alcoholic cirrhosis has increased from 4.3% of the LT candidates in 2002 to 8.3% in 2017. While alcoholic hepatitis accounted for only 0.64% of listings in 2017, its share has doubled since 2004. The proportion of women listed for ALD increased (21.8% in 2002 vs. 28.34% in 2017). Furthermore, proportionally fewer ALD listings are White patients (79.42% in 2002 vs. 75.66% in 2017). While the proportion of Hispanic LT candidates increased (12.87% vs. 15.94%

$p = 0.00$), proportionally, Hispanic ALD patients remained constant (15.68%, 15.84%). Since 2015, the percentage of ALD patients on the waitlist receiving transplants increased (from 41% in 2014 to 45% and 49% in 2015 and 2016). This increase is more than the increase for patients transplanted for non-ALD indications (39% to 40% and 41%). Transplant-to-death ratio increased to 7.6 in 2017 in the ALD group but only to 4.3 in the non-ALD group. This descriptive study provides an update on the relative prevalence of ALD in the LT population, demographic changes, and waitlist outcomes.

Key words: Alcoholic Liver; Liver Transplantation

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Joshi M, Godfrey EL, Goss JA, Rana A. Alcoholic Liver Disease Patients Listed for Liver Transplantation: An Overview from 2002-2017. *Journal of Gastroenterology and Hepatology Research* 2020; 9(5): 3309-3312 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2939>

Abbreviations (in order of appearance):

ALD	Alcoholic liver disease
HCV	Hepatitis C virus
LT	Liver transplantation
DAA	Direct-acting antiviral
CLD	Chronic liver disease
NASH	Non-alcoholic steatohepatitis
OPTN	Organ Procurement and Transplantation Network
UNOS	United Network for Sharing Organs
STAR	Standard Transplant and Analysis Research

INTRODUCTION

Between 1990 and 2017, yearly global adult per-capita consumption of alcohol increased from 5.9 L to 6.5 L and is forecasted to reach 7.6 L by 2030. Researchers have determined that in 2017, 20% of adults were heavy episodic drinkers, up from 1990 when it was estimated at 18.5%. This prevalence is expected to increase to 23% by 2030^[1]. A large portion of the disease burden associated with alcohol use and mortality is due to alcoholic liver disease (ALD), a category that encompasses fatty liver, alcoholic cirrhosis, and alcoholic hepatitis.

In the United States, ALD-associated mortality increased by 8.2% from 2000 to 2013 (9.7 to 10.5 deaths per 100,000)^[2]. While chronic hepatitis C virus (HCV) infection was the leading indication for liver transplantation (LT) from 1995-2015, observable declines in HCV-related waitlist registrations have been attributed to the management of HCV through direct-acting antiviral (DAA) based regimens^[3]. This trend is mirrored globally. While Hepatitis B remains the most common cause of liver disease in China, ALD and NASH are gaining salience even as screening and DAA-based regimens for viral hepatitis prevail^[2,5]. Similarly, ALD prevalence has skyrocketed in India^[5].

The population of ALD patients changes as it grows. In many textbooks, ALD is still described as a disease afflicting middle-aged men. However, this heuristic is losing salience as alcohol use by women worldwide increases and the population of ALD patients becomes progressively younger. Alcohol-associated liver disease and hepatitis are often caused by as little as half as much cumulative alcohol consumption in women compared with men^[6].

The increased prevalence of ALD can be attributed to increased alcohol consumption across all sub-groups of the population or improved diagnosis and reporting. Due to a likely combination, documented cases of ALD in the LT population are on the rise in new population sub-groups - among women and racial/ethnic minorities in the United States.

We present a demographic update of the population of ALD-related LT listings and a summary of the waitlist outcomes (transplant vs. waitlist death) that these patients experience at large. This information can continue to guide the conversation surrounding screening and management for the rising number and proportion of patients affected by ALD.

MATERIALS AND METHODS

The OPTN/UNOS liver transplantation waitlist STAR files from March 2002 to December 2017 were examined. A total of 135,956 individuals over the age of 18 were included. All adults listed for liver transplantation were included, regardless of exception status or indication for listing.

Descriptive statistics (mean, standard deviation, etc.) were used to evaluate the listing population demographics and calculate numbers of individuals listed for each major indication. Percent of individuals receiving transplants and their average wait time, percent of individuals dying on the list and their average wait time, and the ratio thereof were also assessed. Additionally, geographic factors were assessed. Stata 15 (College Station, TX) was used to perform all data analysis.

RESULTS

Alcoholic Liver Disease is the Leading Indication for LT

As has been observed in previous studies, the most significant declining LT indication is HCV cirrhosis. Furthermore, Hepatitis C positive serostatus has declined in transplant recipients from 50% positive in 2002 to 10% positive in 2017 due to effective antiviral therapies.

Alcoholic liver disease, including fatty liver, alcoholic cirrhosis and alcoholic hepatitis, has surpassed all other indications for LT (Figure 1). Specifically, the annual proportion of LT indications related to alcoholic cirrhosis has increased more than that of alcoholic hepatitis. Alcoholic cirrhosis has increased in prevalence as an LT indication from 4.3% of the LT candidates in 2002 to 8.3% of LT candidates in 2017.

Increase in Listings for Alcoholic Hepatitis

Although alcoholic hepatitis accounts for only 0.64% of listings in 2017, this proportion still represents a doubling of alcoholic hepatitis-related LT indications since 2004 ($p = 0.00$). In 2002 and 2003, no listings reported alcoholic hepatitis as a declared diagnosis. In the 20 years since the 1997 AST/AASLD guidelines, in which alcoholic hepatitis was an absolute contraindication to placement on the waitlist, the number of alcoholic hepatitis patients listed has gradually increased.

Proportion of Women with ALD Listed for LT Increases from 2002-2017

While the population of ALD patients listed for LT is largely comprised of men, the proportion of women is increasing over time (21.8% in 2002 vs. 28.34% in 2017, $p = 0.00$). For comparison, among the overall LT population the proportion of women is higher, but relatively stagnant (41.8% in 2002 vs. 41.4% in 2017, $p = 0.61$). (Figure 2).

LT Candidates with ALD are Younger on Average than the Overall LT Population

While the mean age of LT candidates overall has increased steadily (50.6 in 2002 to 54.6 in 2017, $p = 0.00$), the mean age of ALD patients listed for LT has remained between 51 and 52 since 2002. In 2017, relative to the overall population of LT candidates, ALD patients are younger on average (54.6 vs. 51.7, $p = 0.00$).

Regional Variation in Growth of ALD-Related Listings

The increase in ALD is observed across all 11 OPTN regions in the United States but has been reported at twice the rate in Region 2 (Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia). In this region, ALD was shown to increase by 1.3% annually compared to the average half point reported in other regions. This could be attributed to a true population difference, a change in reporting, or a combination of both.

Racial/Ethnic Makeup of the ALD Population

White LT candidates with ALD decreased (79.42% in 2002 vs. 75.66% in 2017, $p = 0.00$). However, relative to LT candidates at large (72.63% in 2002 vs. 67.11% in 2017 $p = 0.00$), the pool of LT candidates with ALD is consistently comprised of proportionally more White patients. Furthermore, these proportions are high in relation to the United States population—the United States Census Bureau reported that 68.2% of the U.S. population was White, non-Hispanic in 2002, trending downwards towards 60.4% in 2019^[7,8] (Figure 3).

Black/African American LT candidates with ALD-related listings have increased proportionally (3.40% vs. 4.50% $p = 0.10$). The overall proportion of Black/African American LT candidates in the overall LT population has increased from 2002-2017 as well (8.81% vs. 10.22% $p = 0.07$). These trends still represent a lower proportion than the overall U.S. population, which was comprised of 12.7% Black/African American residents in 2002 and trending towards 13.4% in 2019^[7,8] (Figure 4).

Hispanic LT candidates make up the second largest group of LT candidates listed for non-ALD or ALD etiologies. While the proportion of Hispanic LT candidates has increased from 2002-2017 (12.87% vs. 15.94% $p = 0.00$), the percentage of Hispanic ALD patients has remained nearly constant (15.68%, 15.84% $p = 0.89$). Furthermore, the U.S. population has seen growth in this group

(13.4% in 2002, 18.4% in 2017)^[7,8].

Increasing Proportion of Asian & Native American ALD LT Candidates 2002-2017

The most dramatic changes have taken place in the ethnic groups that make up the smallest proportion of LT candidates. Twice as many Asian LT candidates were listed for LT in 2017 than in 2002 (408 and 203 respectively $p = 0.035$). Among ALD-related LT listings, this population has grown twelve-fold from 5 listings in 2002 to 61 listings in 2017 ($p = 0.00$). The US Population has seen a small increase in proportion of Asian residents (4.0% in 2002 to 5.9% in 2019)^[7,8]. In 2002, Asians made up 0.41% of the ALD-related LT listings and in 2017, 1.82%.

Furthermore, among Native Americans/Alaskan Natives, a consistently high proportion of LT listings are attributed to ALD. In 2002, 9 out of the 15 total listings were due to ALD, and in 2017, 50 out of the 66 listings were attributed to ALD ($p = 0.049$). While these two groups make up a relatively small portion of the United States population—and consequently the overall LT population and ALD population—the disproportionate increase in ALD-related LT listings elicits more questions about the disease burden in these groups.

Alcoholic Liver Disease Patients on the Waitlist

Across ALD and non-ALD groups, the transplantation rate increased at similar rates until 2014. Since 2015, the percentage of ALD patients on the waitlist that received transplants increased (from 41% in 2014 to 45 and 49% in 2015 and 2016). This increase is more than the increase in percentage of patients transplanted for non-ALD indications (39% to 40 and 41%).

Examined as a ratio of patients transplanted to waitlist deaths, transplant to death percentage among patients with ALD has improved in parallel with the non-ALD population. In 2002 this ratio was under 2 (1.8 for ALD, 1.6 for non-ALD) and in 2015, it rose to over 3 (3.6 for ALD, 3.3 for non-ALD). Transplant to death ratio increased to 7.6 in 2017 in the ALD group but only to 4.3 in the non-ALD group, again indicating increased transplantation. This may be related to presentation of ALD at later stages of disease, with higher lab MELD scores at listing (23.6 for ALD vs. 20.22 for non-ALD in 2016).

DISCUSSION

The number of LT candidates listed for ALD-related etiology is increasing rapidly over time as the prevalence of alcohol use disorders increases. As this population grows in size, there are observable changes. In 2017, women comprised a larger proportion of LT candidates with ALD than in any previous year. This population is trending towards greater diversity, though it is still comprised of disproportionately more White patients when compared to the overall LT population and the U.S. population. Compared to other patients, LT candidates listed for ALD had higher MELD scores at listing and were more likely to receive a transplant and less likely to die while waiting.

Limitations

Even among listed LT candidates and transplant recipients, it is argued that the contribution of alcohol use disorders and ALD is underestimated^[9]. Alcohol use disorders after LT have been discovered to be independent of LT indication, meaning that patients with non-ALD etiology are equally likely to have or develop an alcohol use disorder when compared to patients diagnosed with

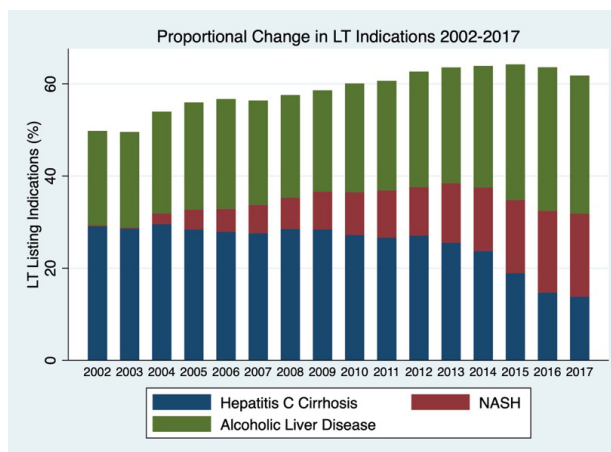


Figure 1 Listing indications for liver transplantation (LT).

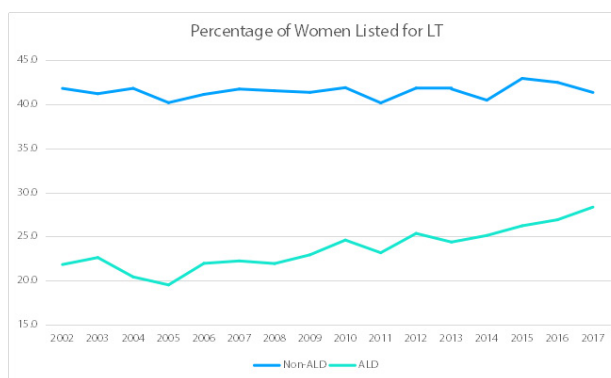


Figure 2 Percentage of women listed for liver transplantation (LT).

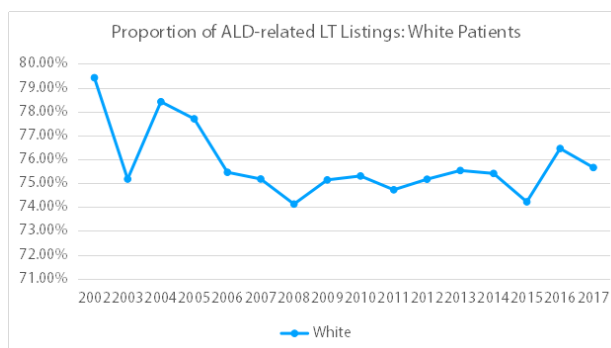


Figure 3 Proportion of alcoholic liver disease (ALD) related liver transplantation listings for White patients.

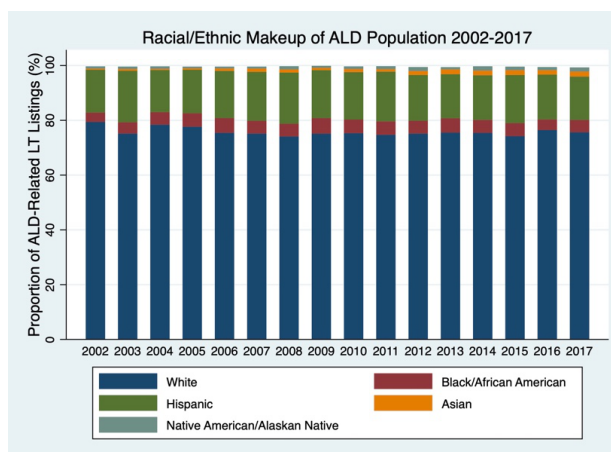


Figure 4 Racial/Ethnic makeup of ALD (alcoholic liver disease) population, 2002-2017.

ALD^{9,10]}. In other words, alcohol use disorders “hide in plain sight” among LT recipients. As a result, the line of demarcation between the ALD and non-ALD groups defined in this study is diminished. Overlapping diagnoses and misclassification can contribute to potential error in this analysis.

CONCLUSIONS

Alcoholic liver disease prevalence is increasing, presents at a later disease stage, and accounts for a greater relative proportion of transplants than other LT indications. It is affecting an increasingly diverse population compared to the past: more women and more non-White patients are listed for LT caused by ALD each year. It remains a challenge to implement screenings and preventative measures to address alcohol use disorders that remain unrecognized in the LT population. This study provides an update on the relative prevalence of ALD in the LT population and a description of shifting demographics.

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Figure 1: Listing indications for liver transplantation (LT)