Nonalcoholic steatohepatitis is the most common indication for liver transplantation among the elderly: Data from the United States Scientific Registry of Transplant Recipients

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Abstract
As the US population ages, more elderly patients may need liver transplantation. Our aim was to assess recent trends among elderly individuals requiring liver transplant in the United States. Scientific Registry of Transplant Recipients data (2002–2020) were used to select elderly (≥65 years) liver transplant candidates and assess on-list and posttransplant outcomes. During the study period, 31,209 liver transplant candidates ≥65 years were wait listed. Common etiologies included nonalcoholic steatohepatitis (NASH; 31%), hepatitis C (23%), and alcoholic liver disease (18%); 30% also had hepatocellular carcinoma (HCC). Over time, the proportion of patients ≥65 years among all adult liver transplant candidates increased from 9% (2002–2005) to 23% (2018–2020) (trend, p < 0.0001). The proportion of NASH among elderly candidates increased from 13% (2002–2005) to 39% (2018–2020). Of the elderly candidates, 54% eventually received transplants. In multivariate analysis, independent predictors of a higher chance of receiving a transplant for the elderly included more recent years of listing, male sex, higher Model for End-Stage Liver Disease (MELD) score, and HCC (all p < 0.01). Posttransplant mortality in elderly transplant recipients was higher than in younger patients but continued to decrease over time. In multivariate analysis, independent predictors of higher posttransplant mortality for elderly transplant recipients were earlier years of transplantation, older age, male sex, higher MELD score, history of diabetes, retransplantation, and having HCC (all p < 0.01). The proportion of elderly patients in need of liver transplantation in the United States is sharply increasing. NASH is the most common indication for liver transplantation among the elderly. The outcomes of these patients have been improving in the past 2 decades.
INTRODUCTION

Since the beginning of the era of human liver transplantation in the 1960s, the liver transplantation procedure has evolved to become well standardized and is currently considered the only curative option for patients with end-stage liver disease and hepatocellular carcinoma (HCC). Given the shortage of available organs, numerous attempts have been made to optimize selection of recipients who would benefit the most from liver transplantation. In earlier years, it was believed that elderly patients would be substantially less likely to survive transplant surgery or the necessary posttransplant management, so arbitrary age limits were applied to potential liver transplant candidates. However, by the early 1990s, growing evidence suggested that patients older than 60 years can have reasonably high short-term survival outcomes that were not profoundly inferior, if at all, to those of younger patients and that these outcomes were accompanied by a clear survival benefit for the patients.

Over the last 2 decades, the demand for liver transplantation among the elderly has been increasing owing to aging of the US population, improved management of chronic liver diseases so that end-stage disease develops later in life, and also tectonic shifts in the distribution of chronic liver disease etiologies. The latter were driven primarily by the rapidly growing prevalence of nonalcoholic steatohepatitis (NASH) in the general population and accompanied by a substantial reduction in the burden of chronic hepatitis C (CHC), which has been mitigated by highly effective direct-acting antivirals. The increase in the prevalence of HCC, which is most commonly found among older patients, has also contributed to the changing profile of a patient in the United States with end-stage liver disease.

The aim of this study was to assess recent trends in the demand for and outcomes of liver transplantation among elderly patients by using a national registry of solid organ transplants.

MATERIALS AND 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 (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight on the activities of the OPTN and SRTR contractors.

In this study, we included all wait-listed candidates and liver transplant recipients ≥65 years of age who were listed or underwent liver transplantation in the United States between the years 2002 and 2020. Multiorgan transplantations (e.g., liver–kidney) were also included. Patient outcomes (receiving a transplant, on-list mortality, or removal from the list due to deterioration, posttransplant mortality, or graft loss) were censored as of December 2, 2020. Patients 18–64 years of age were used as controls.

Statistical analysis

For assessment of time trends, the study period was split into the following five roughly equal subperiods: 2002–2005, 2006–2009, 2010–2013, 2014–2017, and 2018–2020 (not including the month of December 2020). Chi-squared and Kruskal-Wallis tests were used to compare patients’ demographic and clinical characteristics and wait-list outcomes across the subperiods. Factors independently associated with time to receiving a transplant were assessed using a Cox proportional hazard model while adjusting for the year of listing, organ procurement organization region, as well as clinical and demographic confounders, with wait-list dropout (removal due to death or deterioration) as a competing risk. In addition, time to posttransplant mortality was assessed using a Cox proportional hazard model using the same predictors. Two-sided \( p \leq 0.05 \) was considered statistically significant.

All analyses were run in SAS, version 9.4 (SAS Institute, Cary, NC). The study was granted a non-human subject research status by the Inova Health Systems Institutional Review Board that waived the need for informed consent.

RESULTS

There were 31,209 elderly liver transplant candidates in the SRTR between 2002 and 2020. Their characteristics (mean ± SD or percentage) were age 68 ± 3 years, 80% were 65–69 years of age, and 98.5% were younger than 75 years; 61% were male, 73% were non-Hispanic white, 30% were college educated, 14% were employed, 66% were primarily covered by Medicare, 33% had type 2 diabetes, body mass index (BMI) was 29 ± 5 kg/m², functional status (scale, 0–100) was 65 ± 22, Model for End-Stage Liver Disease (MELD) score was 19 ± 10, and 3% were liver retransplant recipients (Table 1). The primary etiologies of chronic liver disease in patients ≥65 years included NASH (31%), CHC (23%), alcoholic liver disease (ALD; 18%),
primary biliary cholangitis (PBC; 5%), chronic hepatitis B (CHB; 3%), autoimmune hepatitis (3%), and primary sclerosing cholangitis (PSC; 3%); 30% also had HCC (Table 1).

In comparison to younger liver transplant candidates, patients ≥65 years were less commonly male, black, or Hispanic; more commonly college educated; had a lower employment rate; and were predominantly covered by Medicare (all p < 0.01) (Table 1). Elderly patients also had lower MELD scores and overall less severe liver disease (as indicated by lower rates of life support use, ascites, bacterial peritonitis, and hepatic encephalopathy), but they had more type 2 diabetes and cancer (all p < 0.01) (Table 1). In addition, older patients had a different distribution of primary listing etiologies of liver disease, with the most common etiology for the cohort being NASH (31% vs. 13%) in patients 18–64 years across all study years; these rates were 36% versus 19%, respectively, in 2014–2020 (p < 0.0001). Furthermore, the rate of HCC was also 2 times higher in older patients (30% in ≥65 vs. 15% in 18–64 year olds across all study years, 35% vs. 18% in 2014–2020, respectively; p < 0.0001) (Table 1).

Over time, the proportion of patients ≥65 years among all adult liver transplant candidates increased from 9% (2002–2005) to 23% (2018–2020) (trend, p < 0.0001) (Table 2; Fig. 1). During this period, the proportion of NASH among liver transplant candidates ≥65 years increased from 13% (2002–2005) to 39% (2018–2020) while the proportion of CHC decreased from 27% to 18%, respectively (p < 0.0001) (Table 2). The rate of HCC also increased from 14% to 34% (p < 0.0001) (Table 2). Among other notable trends, the proportion of male patients among elderly liver transplant candidates increased from 57% in 2002–2005 to 63% in 2014–2017, and the proportion with Medicare coverage increased from 64% to 69%, respectively, along with an increase in employment and the proportion with college education (p < 0.01) (Table 2). There was no steady trend in MELD scores, while the use of life support decreased along with the rates of ascites, hepatic encephalopathy, and retransplantations (p < 0.01) (Table 2). At the same time, there was a notable increase in the rate of bacterial peritonitis, portal vein thrombosis, as well as type 2 diabetes and cancer (p < 0.0001) (Table 2).

Of included elderly liver transplant candidates, 54% eventually received a transplant, 12% died while waiting, 14% were removed from the list due to deterioration, 2% refused a transplant, 4% improved, 7% were removed for other reasons, and 8% were still on the list as of the censoring date (Table 3). The crude rate of transplantation over time followed a nonmonotonous trend (55% in 2002–2005 vs. 52% in 2010–2013 vs. 58% in 2014–2017) (Table 3). Although the rate of on-list mortality decreased substantially (from 20% in 2002–2005 to 10% in 2014–2017), it was accompanied by a similar increase in the removal from the list due to deterioration (from 8.5% in 2002–2005 to 16%–18% in 2010–2017) (Table 3). In comparison to younger candidates, the elderly liver transplant candidates had a lower crude transplant rate (54% vs. 59%, p < 0.0001) and a higher rate of removal due to deterioration (14% vs. 9%, p < 0.0001) but similar on-list mortality (p > 0.05) (Table 4).

In multivariate analysis, independent predictors of a higher chance of receiving a transplant in patients ≥65 years were a more recent year of listing, older age, male sex, higher MELD score, and HCC (all p < 0.01) (Table 5). In contrast, being Hispanic, having pretransplant type 2 diabetes, and listing diagnoses of PBC and PSC were associated with a lower chance of receiving a transplant in ≥65 year olds (all p < 0.01) (Table 5).

In this study, data were available for 18,855 elderly liver transplant recipients. Of those, 91% were single-organ liver transplants and the remainder were kidney–liver transplants. Posttransplant mortality was significantly higher in ≥65 year olds versus younger liver transplant recipients at all time points (all p < 0.0001) (Table 4). Despite this, there was a steady decrease in posttransplant mortality among elderly patients who received a liver transplant so that 5-year mortality decreased from 37% in 2002–2005 to 23% in 2014–2015 while 1-year mortality went from 19% in 2002–2005 to 8% in 2018–2019 (all p < 0.0001) (Table 3; Fig. 2).

In multivariate analysis, independent predictors of higher posttransplant mortality in the elderly liver transplant recipients were earlier years of undergoing transplantation, older age, male sex, higher MELD score, history of type 2 diabetes, liver retransplantation, presence of HCC at baseline, and HCC recurrence in follow-up (all p < 0.01) (Table 6).

Liver transplantation in subgroups of elderly patients

Because male sex was found to be associated with outcomes of elderly liver transplant candidates and recipients in multivariate models, we compared parameters and outcomes of elderly male and female patients (Table S1). Elderly male patients were more commonly white, college educated, employed, and covered by private insurance than elderly female patients (p < 0.01) despite similar age (p > 0.05). Male patients also had lower mean MELD scores, less ascites and hepatic encephalopathy, and a different distribution of liver disease etiologies (more viral hepatitis and ALD, less NASH and autoimmune liver diseases), including a significantly higher rate of HCC (36% in men vs. 21% in women) (all p < 0.01). Accordingly, male patients had a higher crude transplant rate (56% vs. 51%) while experiencing lower on-list death and deterioration rates (p ≤ 0.01) (Table S1). In this context, improvement of the transplantation rate over
time was observed in elderly patients of both sexes (adjusted hazard ratio [aHR], 1.022; 95% confidence interval [CI], 1.016–1.027) per year for men and aHR, 1.044; 95% CI, 1.036–1.051) per year for women. Both were $p < 0.0001$ in a multivariate competing risk model adjusted for confounders.

| Table 1: Comparison of clinicodemographic characteristics of liver transplant candidates ≥65 versus 18–64 years of age at listing |
|-----------------------------------------------|
| **Number** | 31,209 | 175,977 | 207,186 |

### Sociodemographic parameters

| **Age ≥65** | **Age 18–64** | **$p$** | **All Candidates 18+** |
|-----------------|-----------------|---------|------------------------|
| **Age, years** | 68.1 ± 2.5 | 52.1 ± 9.7 | <0.0001 | 54.5 ± 10.7 |
| **Male sex** | 19,072 (61.1%) | 113,641 (64.6%) | <0.0001 | 132,713 (64.1%) |
| **Non-Hispanic white** | 22,756 (72.9%) | 123,779 (70.3%) | <0.0001 | 146,535 (70.7%) |
| **Non-Hispanic black** | 1896 (6.1%) | 15,757 (9.0%) | <0.0001 | 17,653 (8.5%) |
| **Asian** | 1774 (5.7%) | 7334 (4.2%) | <0.0001 | 9108 (4.4%) |
| **Hispanic** | 4488 (14.4%) | 26,598 (15.1%) | 0.0008 | 31,086 (15.0%) |
| **Other race/ethnicity** | 295 (0.9%) | 2509 (1.4%) | <0.0001 | 2804 (1.4%) |
| **US citizen** | 29,758 (95.8%) | 16,7571 (95.5%) | 0.0194 | 197,329 (95.5%) |
| **College degree** | 8356 (29.8%) | 37,048 (24.3%) | <0.0001 | 45,404 (25.2%) |
| **Employed** | 3948 (13.9%) | 37,608 (25.2%) | <0.0001 | 41,556 (23.4%) |
| **Private insurance** | 8146 (26.3%) | 10,8671 (62.5%) | <0.0001 | 116,817 (57.1%) |
| **Medicare** | 20,495 (66.3%) | 25,928 (14.9%) | <0.0001 | 46,423 (22.7%) |
| **Medicaid** | 1244 (4.0%) | 31,631 (18.2%) | <0.0001 | 32,875 (16.1%) |
| **Other insurance** | 933 (3.0%) | 6189 (3.6%) | <0.0001 | 7122 (3.5%) |
| **Uninsured** | 99 (0.3%) | 1327 (0.8%) | <0.0001 | 1426 (0.7%) |

### Clinical parameters

| **BMI, kg/m²** | 28.5 ± 5.4 | 28.7 ± 6.0 | 0.07 | 28.7 ± 5.9 |
| **Functional status (0–100)** | 64.7 ± 21.6 | 63.9 ± 23.5 | 0.83 | 64.0 ± 23.2 |
| **Most recent MELD score (laboratory value)** | 19.2 ± 10.0 | 21.0 ± 10.4 | <0.0001 | 20.7 ± 10.3 |
| **On life support** | 833 (2.7%) | 7834 (4.5%) | <0.0001 | 8667 (4.2%) |
| **Ascites** | 22,259 (71.3%) | 131,474 (74.7%) | <0.0001 | 153,733 (74.2%) |
| **Bacterial peritonitis** | 1708 (5.6%) | 11,959 (7.0%) | <0.0001 | 13,667 (6.8%) |
| **Hepatic encephalopathy** | 18,891 (60.5%) | 113,466 (64.5%) | <0.0001 | 132,357 (63.9%) |
| **Portal vein thrombosis** | 2097 (6.9%) | 8750 (5.2%) | <0.0001 | 10,847 (5.4%) |
| **TIPS** | 2263 (7.5%) | 13,195 (7.8%) | 0.08 | 15,458 (7.7%) |
| **History of type 2 diabetes** | 9794 (33.0%) | 32,783 (19.7%) | <0.0001 | 42,577 (21.7%) |
| **History of any cancer** | 7771 (25.5%) | 21,008 (12.4%) | <0.0001 | 28,779 (14.4%) |
| **Prior transplant (non-liver)** | 162 (0.5%) | 1593 (0.9%) | <0.0001 | 1755 (0.8%) |
| **Liver retransplant** | 986 (3.2%) | 10,659 (6.1%) | <0.0001 | 11,645 (5.6%) |

### Primary listing diagnosis

| **CHB** | 830 (2.9%) | 4546 (2.8%) | 0.41 | 5376 (2.8%) |
| **CHC** | 6544 (22.9%) | 47,731 (29.5%) | <0.0001 | 54,275 (28.5%) |
| **NASH** | 8742 (30.6%) | 21,393 (13.2%) | <0.0001 | 30,135 (15.8%) |
| **Autoimmune hepatitis** | 774 (2.7%) | 5155 (3.2%) | <0.0001 | 5929 (3.1%) |
| **ALD** | 5207 (18.2%) | 35,536 (22.0%) | <0.0001 | 40,743 (21.4%) |
| **ALD + CHC** | 697 (2.4%) | 10,379 (6.4%) | <0.0001 | 11,076 (5.8%) |
| **PBC** | 1344 (4.7%) | 4747 (2.9%) | <0.0001 | 6091 (3.2%) |
| **PSC** | 923 (3.2%) | 7931 (4.9%) | <0.0001 | 8854 (4.7%) |
| **HCC** | 9322 (29.9%) | 26,897 (15.3%) | <0.0001 | 36,219 (17.5%) |

Note: Data show percentage or mean ± SD. Abbreviation: TIPS, transjugular intrahepatic portosystemic shunt.
### TABLE 2: Comparison of elderly liver transplant candidates by the period of listing

|                          | 2002–2005 | 2006–2009 | 2010–2013 | 2014–2017 | 2018–2020 | p       | All     |
|--------------------------|-----------|-----------|-----------|-----------|-----------|---------|---------|
| Number (% of all 18+ listings) | 3366 (8.9%) | 4318 (10.5%) | 6122 (13.7%) | 8929 (19.1%) | 8474 (23.1%) | 31,209 (15.1%) |         |
| **Sociodemographic parameters** |           |           |           |           |           |         |         |
| Age, years               | 68.2 ± 2.6 | 68.1 ± 2.6 | 68.0 ± 2.5 | 68.0 ± 2.4 | 68.3 ± 2.5 | <0.0001 | 68.1 ± 2.5 |
| Male sex                 | 1903 (56.5%) | 2535 (58.7%) | 3710 (60.6%) | 5634 (63.1%) | 5290 (62.4%) | <0.0001 | 19,072 (61.1%) |
| Non-Hispanic white       | 3153 (73.0%) | 4431 (72.4%) | 6489 (72.7%) | 6157 (72.7%) | 482 (5.7%) | 0.06 | 22,756 (72.9%) |
| Non-Hispanic black       | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| Asian                    | 385 (6.3%) | 440 (4.9%) | 379 (4.5%) | <0.0001 | 1774 (5.7%) |
| Hispanic                 | 6122 (13.7%) | 866 (14.1%) | 1248 (14.0%) | 1357 (16.0%) | <0.0001 | 4488 (14.4%) |
| Other race/ethnicity     | 28 (0.8%) | 35 (0.8%) | 81 (0.9%) | 99 (0.1%) | <0.0001 | 295 (0.9%) |
| US citizen               | 3320 (96.0%) | 4139 (95.9%) | 5884 (96.1%) | 8522 (95.5%) | 7983 (95.7%) | 0.29 | 29,758 (95.8%) |
| College degree           | 1903 (56.5%) | 2535 (58.7%) | 3710 (60.6%) | 5634 (63.1%) | 5290 (62.4%) | <0.0001 | 19,072 (61.1%) |
| Employed                 | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| Private insurance        | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| Medicare                 | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| Medicaid                 | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| Other insurance          | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| Uninsured                | 129 (3.8%) | 388 (6.3%) | 671 (7.5%) | 482 (5.7%) | <0.0001 | 1896 (6.1%) |
| **Clinical parameters**  |           |           |           |           |           |         |         |
| BMI, kg/m²               | 27.4 ± 5.0 | 28.1 ± 5.2 | 28.4 ± 5.3 | 28.7 ± 5.3 | 29.0 ± 5.6 | <0.0001 | 28.5 ± 5.4 |
| Functional status (0–100) | 75.0 ± 20.9 | 68.6 ± 21.8 | 65.0 ± 22.0 | 62.4 ± 21.0 | 61.6 ± 20.5 | <0.0001 | 64.7 ± 21.6 |
| Most recent MELD score   | 19.0 ± 9.6 | 19.0 ± 9.6 | 20.2 ± 10.3 | 19.4 ± 10.3 | 18.5 ± 9.7 | <0.0001 | 19.2 ± 10.0 |
| Ascites                  | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Bacterial peritonitis    | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Hepatic encephalopathy  | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Portal vein thrombosis   | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| TIPS                     | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Type 2 diabetes          | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Any cancer               | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Prior transplant (non-liver) | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Liver retransplant       | 129 (4.5%) | 141 (3.7%) | 194 (3.4%) | 240 (2.7%) | 190 (2.3%) | 0.0078 | 833 (2.7%) |
| Primary listing diagnosis |           |           |           |           |           |         |         |
| CHB                      | 773 (26.7%) | 899 (23.4%) | 1405 (25.0%) | 2068 (24.5%) | 1399 (18.0%) | <0.0001 | 6544 (22.9%) |
| CHC                      | 380 (13.1%) | 964 (25.1%) | 1586 (28.2%) | 2762 (32.7%) | 3050 (39.1%) | <0.0001 | 8742 (30.6%) |
| NASH                     | 467 (16.2%) | 646 (16.8%) | 984 (17.5%) | 1551 (18.3%) | 1559 (20.0%) | <0.0001 | 5207 (18.2%) |
| Autoimmune hepatitis     | 36 (1.2%) | 85 (2.2%) | 128 (2.3%) | 224 (2.6%) | 224 (2.9%) | <0.0001 | 697 (2.4%) |
| ALD                      | 207 (7.2%) | 253 (6.6%) | 269 (4.8%) | 349 (4.1%) | 266 (3.4%) | <0.0001 | 1344 (4.7%) |
| PSC                      | 143 (4.9%) | 142 (3.7%) | 200 (3.6%) | 242 (2.9%) | 196 (2.5%) | <0.0001 | 923 (3.2%) |
| HCC                      | 477 (14.2%) | 1010 (23.4%) | 1800 (29.4%) | 3190 (35.7%) | 2845 (33.6%) | <0.0001 | 9322 (29.9%) |

**Note:** Data show percentage or mean ± SD.
**Abbreviation:** TIPS, transjugular intrahepatic portosystemic shunt.
HCC was found to be a primary or secondary diagnosis in approximately 1 in 3 elderly patients with a liver transplant, with a rapidly increasing rate over time (Table 2). Given that, we assessed trends in presentation and outcomes of elderly patients with a liver transplant and with HCC (Table S2). We found that the proportion of viral hepatitis in elderly patients with HCC decreased (hepatitis B from 14% in 2002–2005 to 4% in 2018–2020; hepatitis C from 45% in 2002–2005 to 39% in 2018–2020) while the proportion of NASH increased substantially (from 6% in 2002–2005 to 28% in 2018–2020) (p < 0.01). The crude transplant rate in that patient group has been decreasing (74% in 2002–2005 vs. 64% in 2014–2017), accompanied by an increase in removal from the list due to deterioration (7% in 2002–2005 vs. 17% in 2014–2017).
At the same time, there was a significant increase in posttransplant survival among elderly patients with HCC; 1-year mortality went from 20% in 2002–2005 to 6.6% in 2018–2019 and 3-year mortality from 34% in 2002–2005 to 18% in 2014–2017 (p < 0.0001) (Table S2).

**DISCUSSION**

In this study, which used a nationwide registry of solid-organ recipients from the United States, we have reported substantial increases in both the absolute number and the proportion of patients 65 years of age or older who were listed for liver transplantation over the last 2 decades. The increase is consistent with both aging of the US population and also the rapid growth of liver disease etiologies that tend to progress to end stage later in life, such as NASH, or chronic liver disease complications, such as HCC. In fact, we observed a nearly 2.5-fold increase in the share of elderly liver transplant candidates (out of all adult candidates) that was driven primarily by the doubled rate of HCC and tripled rate of NASH as reasons for transplantation. Interestingly, in 2020, the share of elderly candidates slightly decreased for the first time since the mid 2000s, indicating a possible impact of the corona virus disease 2019 pandemic, which likely disrupted routine care primarily for older patients.

In comparison to younger patients, elderly liver transplant candidates had a lower chance of receiving a transplant despite similar on-list mortality. The reason for the different transplant rates was a substantially higher rate of removal from the list due to deterioration among elderly patients in comparison to the younger age group. The SRTR data set does not include more details about the reasons for removal from the list, so no conclusions could be made about the impact of any specific clinical criterion or management strategy to the outcome. Notably, a more recent year of listing was found to be independently associated with a higher chance of receiving a transplant among the elderly, indicating that the transplantation rate in that patient group is increasing even after adjustment for the changing clinical profile.

**TABLE 4** Comparison of outcomes of liver transplant candidates and recipients ≥65 vs. 18–64 years of age at listing or transplantation

|                         | Age ≥65     | Age 18–64   | p          | All ages 18+ |
|-------------------------|-------------|-------------|------------|--------------|
| Wait-listed candidates  |             |             |            |              |
| Received a transplant   | 16,912 (54.2%) | 103,124 (58.6%) | <0.0001    | 120,036 (57.9%) |
| Died on the list        | 3717 (11.9%)  | 21,261 (12.1%)  | 0.39       | 24,978 (12.1%)  |
| Removed from the list due to deterioration | 4215 (13.5%) | 15,111 (8.6%) | <0.0001 | 19,326 (9.3%) |
| Refused a transplant    | 491 (1.6%)   | 1005 (0.6%)   | <0.0001    | 1496 (0.7%)   |
| Improved, no longer in need | 1193 (3.8%) | 9010 (5.1%)   | <0.0001    | 10,203 (4.9%) |
| Removed for other reasons | 2222 (7.1%) | 17,102 (9.7%) | <0.0001 | 19,324 (9.3%) |
| Still listed            | 2455 (7.9%)  | 9359 (5.3%)   | <0.0001    | 11,814 (5.7%) |
| Transplant recipients   |             |             |            |              |
| Number                  | 18,855      | 100,388     |            | 119,243      |
| Single-organ liver transplant | 17,180 (91.1%) | 92,128 (91.8%) | 0.0028 | 109,308 (91.7%) |
| Length of inpatient stay after transplantation, days | 17.1 ± 0.2 | 16.4 ± 0.1 | 0.0001 | 16.5 ± 0.1 |
| Length of inpatient stay total, days | 22.4 ± 0.8 | 22.1 ± 0.2 | <0.0001 | 22.2 ± 0.2 |
| Discharged alive        | 17,448 (94.7%) | 93,513 (95.4%) | 0.0001 | 110,961 (95.3%) |
| 1-year mortality        | 2061 (12.5%) | 9068 (10.2%)  | <0.0001    | 11,129 (10.5%) |
| 3-year mortality        | 2853 (22.1%) | 13,848 (17.9%) | <0.0001 | 16,701 (18.5%) |
| 5-year mortality        | 2986 (30.4%) | 16,025 (24.3%) | <0.0001 | 19,011 (25.1%) |
| Experienced a graft failure | 743 (3.9%)  | 8082 (8.1%)  | <0.0001 | 8825 (7.4%) |

Note: Data show percentage or mean ± SD.
**TABLE 5** Independent predictors of time to receiving a transplant (Cox proportional hazards model) for elderly candidates (vs. wait-list dropout due to death or deterioration); the model was additionally adjusted for organ procurement organization region

| Predictor                                           | aHR (95% CI)          | p     |
|-----------------------------------------------------|------------------------|-------|
| Calendar year, per year                             | 1.031 (1.026–1.035)    | <0.0001 |
| Age at listing, per year                            | 1.021 (1.014–1.029)    | <0.0001 |
| Male sex                                            | 1.06 (1.02–1.10)       | 0.0056 |
| Black race (ref. non-Hispanic white)                | 1.07 (0.99–1.15)       | 0.08   |
| Hispanic (ref. non-Hispanic white)                  | 0.91 (0.87–0.97)       | 0.0016 |
| Asian (ref. non-Hispanic white)                     | 1.07 (0.98–1.17)       | 0.15   |
| College degree                                      | 1.04 (1.00–1.08)       | 0.07   |
| Medicare (ref. private insurance)                   | 0.99 (0.96–1.03)       | 0.71   |
| Medicaid (ref. private insurance)                   | 0.92 (0.83–1.01)       | 0.09   |
| On life support                                     | 4.10 (3.64–4.63)       | <0.0001 |
| MELD score, per 1 point                             | 1.016 (1.014–1.019)    | <0.0001 |
| Ascites                                             | 1.06 (1.01–1.12)       | 0.0127 |
| Bacterial peritonitis                               | 1.25 (1.16–1.34)       | <0.0001 |
| Hepatic encephalopathy                              | 0.95 (0.91–1.00)       | 0.0294 |
| BMI, per kg/m²                                       | 0.997 (0.993–1.000)    | 0.08   |
| Type 2 diabetes                                     | 0.89 (0.85–0.92)       | <0.0001 |
| Prior solid organ transplant                        | 0.94 (0.73–1.23)       | 0.66   |
| Liver retransplant                                   | 1.41 (1.24–1.60)       | <0.0001 |
| CHB (ref. hepatitis C)                              | 1.09 (0.97–1.22)       | 0.14   |
| NASH (ref. hepatitis C)                             | 0.98 (0.93–1.03)       | 0.40   |
| Autoimmune hepatitis (ref. hepatitis C)             | 0.96 (0.85–1.08)       | 0.52   |
| ALD (ref. hepatitis C)                              | 1.05 (1.00–1.11)       | 0.08   |
| ALD + hepatitis C (ref. hepatitis C)                | 0.97 (0.87–1.08)       | 0.57   |
| PBC                                                  | 0.89 (0.82–0.97)       | 0.0108 |
| PSC                                                  | 0.88 (0.80–0.97)       | 0.0120 |
| HCC                                                  | 1.14 (1.09–1.19)       | <0.0001 |

Abbreviation: ref., reference.

**FIGURE 2** Posttransplant survival in elderly transplant recipients by the year of transplantation
use posttransplant mortality as well as wait-list dropout (death or removal due to deterioration, considered too sick for transplantation) of those who did not receive a transplant as a competing risk.[7] On the other hand, the rate of graft failure was significantly lower among patients of older age even after adjustment for the difference in liver disease etiologies, year of transplantation, duration of posttransplant survival, and clinical factors. The exact reasons behind this phenomenon are unknown but may be related to decreased rates of rejection with advancing age or greater access to routine and/or continuous health care among older Americans who, with few exceptions, are eligible for universal health care coverage.[14]

The limitations of this study include its retrospective observational nature and also a limited number of parameters available in the SRTR data set. Owing to the lack of formal data entry monitoring, there could be inconsistencies across different transplant centers and/or over time. Nonetheless, our findings are not only consistent with other reports but also expand our understanding of recent liver transplantation trends in the elderly population.

In conclusion, we found that elderly patients in need of a liver transplant are increasingly being considered for the procedure. The primary etiology of end-stage liver disease among elderly patients is NASH, which tripled in prevalence during the study period and is currently responsible for more than one in three listings in that demographic group. The outcomes of both wait-list candidates and recipients of older age have been steadily improving so that 3 in 4 recipients of a transplant are currently able to reach at least the 5-year posttransplant survival mark. Further research is needed to improve both on-list and posttransplant management of patients of advanced age in order to meet the growing demand for this complex treatment among the aging population with liver disease.

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### TABLE 6

| Predictor                                      | aHR (95% CI)       | p     |
|------------------------------------------------|--------------------|-------|
| Calendar year, per year                        | 0.954 (0.946–0.962) | <0.0001 |
| Age at listing, per year                       | 1.049 (1.036–1.062) | <0.0001 |
| Male sex                                       | 1.19 (1.11–1.29)    | <0.0001 |
| Black race (ref. non-Hispanic white)           | 1.11 (0.97–1.27)    | 0.12  |
| Hispanic (ref. non-Hispanic white)             | 0.84 (0.76–0.93)    | 0.0011 |
| Asian (ref. non-Hispanic white)                | 0.68 (0.58–0.79)    | <0.0001 |
| College degree                                 | 0.88 (0.82–0.95)    | 0.0009 |
| Medicare (ref. private insurance)              | 1.03 (0.96–1.11)    | 0.45  |
| Medicaid (ref. private insurance)              | 1.12 (0.92–1.37)    | 0.25  |
| On life support                                | 1.18 (1.02–1.38)    | 0.0283 |
| MELD score, per 1 point                        | 1.010 (1.006–1.014) | <0.0001 |
| BMI, per kg/m²                                  | 0.985 (0.979–0.992) | <0.0001 |
| Type 2 diabetes                                | 1.27 (1.17–1.37)    | <0.0001 |
| Prior solid organ transplant                   | 1.25 (0.82–1.91)    | 0.30  |
| Liver retransplant                              | 1.49 (1.24–1.78)    | <0.0001 |
| CHB (ref. hepatitis C)                         | 0.78 (0.61–1.01)    | 0.06  |
| NASH (ref. hepatitis C)                        | 1.10 (1.00–1.22)    | 0.05  |
| ALD (ref. hepatitis C)                         | 1.09 (0.98–1.21)    | 0.12  |
| PBC                                            | 0.94 (0.79–1.13)    | 0.53  |
| PSC                                            | 0.79 (0.65–0.97)    | 0.0248 |
| HCC                                            | 1.19 (1.09–1.29)    | <0.0001 |
| Donor without heart beat                       | 1.08 (0.94–1.24)    | 0.26  |
| Recurrence of HCC                              | 4.06 (3.65–4.52)    | <0.0001 |

Abbreviation: ref., reference.
CONFLICT OF INTEREST
Dr. Ong received grants from Gilead Sciences. The other authors have nothing to report.

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REFERENCES
1. Starzl TE, Brettschneider L, Groth CG. Liver transplantation. Bull Soc Int Chir. 1967;26:474–88.
2. Dolnikov S, Adam R, Cherqui D, Allard MA. Liver transplantation in elderly patients: what do we know at the beginning of 2020? Surg Today. 2020;50:533–9.
3. Stieber AC, Gordon RD, Todo S, Tzakis AG, Fung JJ, Casavilla A, et al. Liver transplantation in patients over sixty years of age. Transplantation. 1991;51:271–3.
4. Su F, Yu L, Berry K, Liou IW, Landis CS, Rayhill SC, et al. Aging of liver transplant registrants and recipients: trends and impact on waitlist outcomes, post-transplantation outcomes, and transplant-related survival benefit. Gastroenterology. 2016;150:441–53.e6.
5. Aduen JF, Sujay B, Dickson RC, Heckman MG, Hewitt WR, Stapelfeldt WH, et al. Outcomes after liver transplant in patients aged 70 years or older compared with those younger than 60 years. Mayo Clin Proc. 2009;84:973–8.
6. Gómez Gavara C, Esposito F, Gurusamy K, Salloum C, Lahat E, Feray C, et al. Liver transplantation in elderly patients: a systematic review and first meta-analysis. HPB (Oxford). 2019;21:14–25.
7. Goldberg DS, Charlton M. Usefulness of liver transplantation in the elderly: the converging impact of risk and benefit. Gastroenterology. 2016;150:306–9.
8. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73–84.
9. Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. Transplantation. 2019;103:22–7.
10. Younossi ZM, Stepanova M, Younossi Y, Golabi P, Mishra A, Rafiq N, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. Gut. 2020;69:564–8.
11. Younossi ZM, Stepanova M, Ong J, Trimble G, AlQuahtani S, Younossi I, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol. 2021;19:580–9.e5.
12. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology. 2021;73(Suppl. 1):4–13.
13. Younossi Z, Stepanova M, Ong JP, Jacobson IM, Bugianesi E, Duseja A, et al.; Global Nonalcoholic Steatohepatitis Council. Nonalcoholic nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019;17:748–55.e3.
14. Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. J Hepatol. 2019;70:745–58.

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