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ORIGINAL ARTICLE

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).[1,2] 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.[2] However, by the early 1990s, growing evidence suggested that patients older than 60 years can have reasonably high posttransplant survival, so these limits were gradually reconsidered and then largely abandoned.[3] In fact, multiple studies to date have shown that elderly patients, including those over 75 or 80 years of age, can tolerate the procedure well with reasonable safety and 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.[2,4–7]

Over the last 2 decades, the demand for liver transplantation among the elderly has been increasing[4] 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.[8–11] The increase in the prevalence of HCC,[12,13] 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 $p \le 0.05$ was considered statistically significant.

All analyses were run in SAS, version 9.4 (SAS Institute, Cary, NC). The study was granted a nonhuman 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/m^2, 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 ($p \le 0.01$) (Table S1). In this context, improvement of the transplantation rate over

TABLE 1 Comparison of clinicodemographic characteristics of liver transplant candidates ≥65 versus 18–64 years of age at listing

	Age ≥65	Age 18–64	*p*	All Candidates 18+
Number	31,209	175,977		207,186
Sociodemographic parameters				
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/m^2	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.

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 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	2526 (75.0%)	3153 (73.0%)	4431 (72.4%)	6489 (72.7%)	6157 (72.7%)	0.06	22,756 (72.9%)
Non-Hispanic black	129 (3.8%)	226 (5.2%)	388 (6.3%)	671 (7.5%)	482 (5.7%)	<0.0001	1896 (6.1%)
Asian	243 (7.2%)	327 (7.6%)	385 (6.3%)	440 (4.9%)	379 (4.5%)	<0.0001	1774 (5.7%)
Hispanic	440 (13.1%)	577 (13.4%)	866 (14.1%)	1248 (14.0%)	1357 (16.0%)	<0.0001	4488 (14.4%)
Other race/ethnicity	28 (0.8%)	35 (0.8%)	52 (0.8%)	81 (0.9%)	99 (1.2%)	0.16	295 (0.9%)
US citizen	3230 (96.0%)	4139 (95.9%)	5884 (96.1%)	8522 (95.5%)	7983 (95.7%)	0.29	29,758 (95.8%)
College degree	625 (26.7%)	905 (26.7%)	1713 (30.3%)	2634 (30.7%)	2479 (30.7%)	<0.0001	8356 (29.8%)
Employed	140 (9.4%)	557 (14.0%)	805 (13.5%)	1228 (13.9%)	1218 (14.8%)	<0.0001	3948 (13.9%)
Private insurance	995 (30.2%)	1333 (31.0%)	1684 (27.6%)	2199 (24.7%)	1935 (23.2%)	<0.0001	8146 (26.3%)
Medicare	2104 (63.9%)	2696 (62.7%)	3982 (65.3%)	5973 (67.2%)	5740 (68.9%)	<0.0001	20,495 (66.3%)
Medicaid	134 (4.1%)	191 (4.4%)	254 (4.2%)	353 (4.0%)	312 (3.7%)	0.39	1244 (4.0%)
Other insurance	38 (1.2%)	59 (1.4%)	153 (2.5%)	345 (3.9%)	338 (4.1%)	<0.0001	933 (3.0%)
Uninsured	23 (0.7%)	18 (0.4%)	23 (0.4%)	24 (0.3%)	11 (0.1%)	<0.0001	99 (0.3%)
Clinical parameters							
BMI, kg/m^2	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 (laboratory value)	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
On life support	115 (3.5%)	112 (2.6%)	176 (2.9%)	240 (2.7%)	190 (2.3%)	0.0078	833 (2.7%)
Ascites	2720 (80.9%)	3187 (73.8%)	4332 (70.8%)	6152 (68.9%)	5868 (69.3%)	<0.0001	22,259 (71.3%)
Bacterial peritonitis	129 (4.2%)	212 (5.1%)	294 (4.9%)	500 (5.6%)	573 (6.9%)	<0.0001	1708 (5.6%)
Hepatic encephalopathy	2317 (68.9%)	2668 (61.8%)	3656 (59.7%)	5285 (59.2%)	4965 (58.6%)	<0.0001	18,891 (60.5%)
Portal vein thrombosis	85 (2.8%)	157 (3.8%)	361 (6.0%)	720 (8.1%)	774 (9.3%)	<0.0001	2097 (6.9%)
TIPS	235 (7.7%)	304 (7.2%)	447 (7.4%)	639 (7.3%)	638 (7.9%)	0.53	2263 (7.5%)
Type 2 diabetes	313 (11.9%)	1110 (27.3%)	1961 (33.1%)	3302 (37.5%)	3108 (37.6%)	<0.0001	9794 (33.0%)
Any cancer	331 (10.7%)	621 (14.8%)	1343 (22.6%)	2687 (30.2%)	2789 (33.4%)	<0.0001	7771 (25.5%)
Prior transplant (non-liver)	19 (0.6%)	24 (0.6%)	38 (0.6%)	41 (0.5%)	40 (0.5%)	0.65	162 (0.5%)
Liver retransplant	182 (5.4%)	163 (3.8%)	201 (3.3%)	225 (2.5%)	215 (2.5%)	<0.0001	986 (3.2%)
Primary listing diagnosis							
CHB	129 (4.5%)	141 (3.7%)	194 (3.4%)	205 (2.4%)	161 (2.1%)	<0.0001	830 (2.9%)
CHC	773 (26.7%)	899 (23.4%)	1405 (25.0%)	2068 (24.5%)	1399 (18.0%)	<0.0001	6544 (22.9%)
NASH	380 (13.1%)	964 (25.1%)	1586 (28.2%)	2762 (32.7%)	3050 (39.1%)	<0.0001	8742 (30.6%)
Autoimmune hepatitis	95 (3.3%)	114 (3.0%)	162 (2.9%)	208 (2.5%)	195 (2.5%)	0.07	774 (2.7%)
ALD	467 (16.2%)	646 (16.8%)	984 (17.5%)	1551 (18.3%)	1559 (20.0%)	<0.0001	5207 (18.2%)
ALD + CHC	36 (1.2%)	85 (2.2%)	128 (2.3%)	224 (2.6%)	224 (2.9%)	<0.0001	697 (2.4%)
PBC	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.

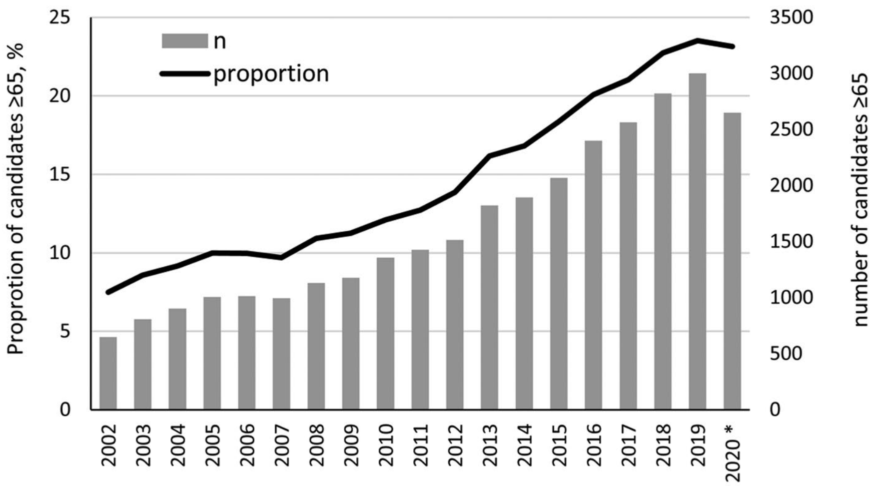

FIGURE 1 Proportion and absolute number of liver transplant candidates ≥65 years old in 2002–2020. *Year 2020 includes January 1-December 2 period only

TABLE 3 Outcomes of elderly liver transplant candidates and recipients by the period of listing/transplantation

	2002–2005	2006–2009	2010–2013	2014–2017	2018–2020	*p*	All
Wait-listed candidates							
Received a transplant	1841 (54.7%)	2443 (56.6%)	3197 (52.2%)	5182 (58.0%)	4249 (50.1%)	<0.0001	16,912 (54.2%)
Died on the list	688 (20.4%)	631 (14.6%)	846 (13.8%)	938 (10.5%)	614 (7.2%)	<0.0001	3,717 (11.9%)
Removed from the list due to deterioration	285 (8.5%)	538 (12.5%)	1099 (18.0%)	1454 (16.3%)	839 (9.9%)	<0.0001	4215 (13.5%)
Refused a transplant	64 (1.9%)	75 (1.7%)	107 (1.7%)	172 (1.9%)	73 (0.9%)	<0.0001	491 (1.6%)
Improved, no longer in need	158 (4.7%)	231 (5.3%)	307 (5.0%)	344 (3.9%)	153 (1.8%)	<0.0001	1193 (3.8%)
Removed for other reasons	327 (9.7%)	397 (9.2%)	547 (8.9%)	614 (6.9%)	337 (4.0%)	<0.0001	2222 (7.1%)
Still listed	0 (0.0%)	2 (0.0%)	19 (0.3%)	225 (2.5%)	2209 (26.1%)	<0.0001	2455 (7.9%)
Transplant recipients							
Number	2031	2596	3262	5432	5534		18,855
Single-organ liver transplant	1937 (95.4%)	2395 (92.3%)	2986 (91.5%)	4900 (90.2%)	4962 (89.7%)	<0.0001	17,180 (91.1%)
Length of inpatient stay after transplantation, days	19.4 ± 0.6	17.7 ± 0.5	17.7 ± 0.5	16.7 ± 0.4	15.7 ± 0.3	<0.0001	17.1 ± 0.2
Length of inpatient stay total, days	23.4 ± 1.0	21.4 ± 0.7	22.2 ± 0.6	21.3 ± 0.5	23.7 ± 2.6	<0.0001	22.4 ± 0.8
Discharged alive	1803 (90.9%)	2402 (93.7%)	3036 (94.2%)	5137 (95.2%)	5070 (96.4%)	<0.0001	17,448 (94.7%)
1-year mortality	376 (19.3%)	397 (15.7%)	437 (13.7%)	554 (10.4%)	297 (8.4%)	<0.0001	2061 (12.5%)
3-year mortality	570 (29.2%)	653 (25.8%)	736 (23.1%)	894 (17.1%)	NA	<0.0001	2853 (22.1%)
5-year mortality	717 (36.8%)	828 (32.7%)	944 (29.6%)	497 (23.0%)	NA	<0.0001	2986 (30.4%)
Experienced a graft failure	174 (8.6%)	156 (6.0%)	165 (5.1%)	126 (2.3%)	122 (2.2%)	<0.0001	743 (3.9%)

Note: Data show percentage or mean ± SD.

Abbreviation: NA, not available.

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).

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.

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.

In this study, we have shown that elderly patients after a transplant have relatively high and, importantly, steadily improving survival rates, with the 5-year survival being as high as 77% in patients who received a transplant in 2014–2015 (increased from 63% in 2002–2005). Although crude posttransplant survival rates in elderly patients were lower than the same rates seen in younger patients, it has been argued that posttransplant survival alone may be inadequate in reflecting the comprehensive outcomes of patients with end-stage liver disease. Rather, survival benefit, which is a measure of the combined impact of transplantation on wait-list mortality and posttransplant survival, should

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/m^2	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.

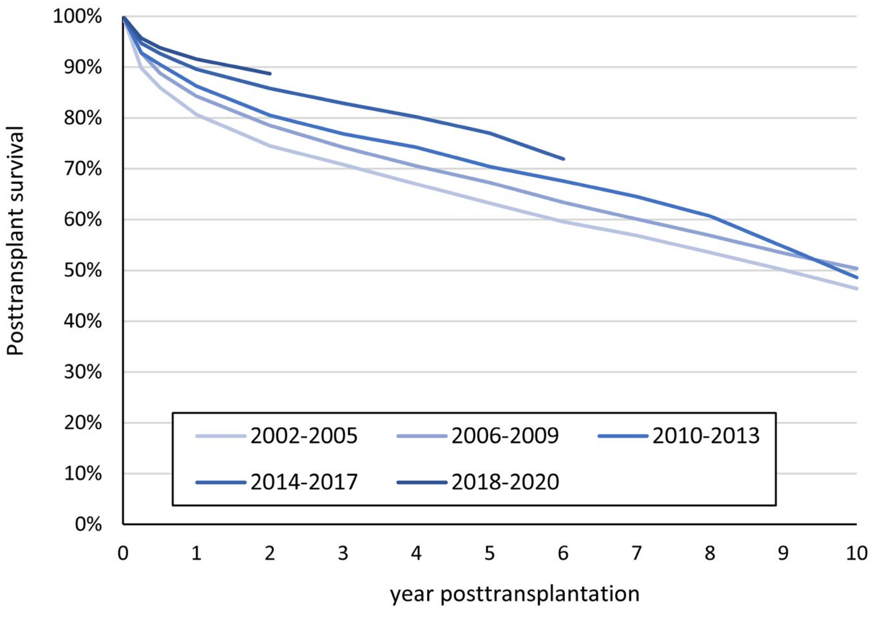

FIGURE 2 Posttransplant survival in elderly transplant recipients by the year of transplantation

TABLE 6 Independent predictors of time to posttransplant mortality (Cox proportional hazards model) in liver transplant recipients ≥65 years of age at transplantation

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/m^2	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.

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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CONFLICT OF INTEREST

Dr. Ong received grants from Gilead Sciences. The other authors have nothing to report.

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