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Life Expectancy after Liver Transplantation for NASH

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Abstract

Introduction: Non-Alcoholic Steatohepatitis is an increasing reason for liver transplantation in the western world. Knowledge of recipient life expectancy may assist in prudent allocation of a relatively scarce supply of donor livers. **Research Questions:** We calculated life expectancies for Non-alcoholic steatohepatitis (NASH) patients both at time of transplant and one year later, stratified by key risk factors, and examined whether survival has improved in recent years. **Design:** Data on 6635 NASH patients who underwent liver transplantation in the MELD era (2002-2018) from the United States OPTN database were analyzed using the Cox proportional hazards regression model and life table methods. **Results:** Factors related to survival were age, presence of diabetes or hepatic encephalopathy (HE), and whether the patient required dialysis in the week prior to transplant. Other important factors were whether the patient was working, hospitalization prior to transplant, ventilator support, and length of hospital stay (LOS). Survival improved over the study period at roughly 4.5% per calendar year during the first year posttransplant, though no improvement was observed in those who had survived one year. **Conclusion:** Life expectancy in NASH transplant patients was much reduced from normal, and varied according to age, medical factors, status at transplant, and post transplant course. Over the 17-year study period, patient survival improved markedly during the first year posttransplant, though not thereafter. The results given here may prove helpful in medical decision-making regarding treatment for both liver disease and other medical conditions, as they provide both clinicians and their patients with evidence-based information on prognosis.

Keywords

survival, OPTN, epidemiology, life table, mortality, cryptogenic cirrhosis

Introduction

Non-alcoholic steatohepatitis (NASH) as the indication for liver transplantation in the United States has increased from only 6% of all liver transplants in 2008% to 17% in 2018.[1] Obesity in the United States has similarly increased from 34% of adults in 2007–2008% to 42% in 2017–2018.[2] Non-alcoholic fatty liver disease (NAFLD), the precursor to NASH, is now the most common cause of liver disease in the United States.[3] NASH is already the leading indication for liver transplant in Asians and Hispanics, as well as in females in the United States,[4] and is predicted to become the most prevalent cause for liver transplant as the incidences of obesity and metabolic syndrome continue to rise. In light of the above, prudent allocation of a relatively scarce supply of donor livers will thus become even more important in future. Patient life expectancy is a factor increasingly used in medical decision-making. For example, testing for prostate cancer is often only performed in those with a longer life expectancy.[5] In liver allocation, US transplant centers now suggest that recipient life expectancy be at least as long as that of the graft.[6] And in the UK, the majority of adult transplants are currently based on the Transplant Benefit Score, a measure of the gain in patient survival conferred by potential transplant.[7]

As a scientific term, life expectancy is defined as the arithmetic mean survival time among a group of similar patients. It is thus not intended to be a prediction of the actual survival time of a given patient. Rather, it is an average, inasmuch as a 5-year survival percentage so commonly reported in cancer research is an average. Life expectancies derive from a life table, which is in turn based on age-specific mortality rates. A single life expectancy is thus a summary measure of current and future mortality. It can easily be compared across ages, sexes, countries, and other factors. Clinicians and patients alike have interest in what can be expected, and how it compares to others both with liver disease and without.

To our knowledge there are no detailed long-term follow up studies that report life expectancies in NASH patients stratified simultaneously by age, sex, race, and other factors. For example, while the European Liver Registry routinely

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reports many survival figures and trends,[8] it does not provide life expectancies.

The calculation of life expectancy requires long-term follow-up of patients and the use of life table methodology, the latter having thus far seen rather limited application in transplant research. The Organ Procurement and Transplantation Network (OPTN) data[1] includes the requisite lengthy follow up, and the methods used here are standard. These enabled us to calculate life expectancy for select patient subgroups, both from the time of initial transplant and also conditioned upon patient survival to 1-year post transplant. We also examined if survival improved over the study period, as this would indicate the effect of advances in treatment and post-op care.

Design/Methods

Design/Setting/Population

We analyzed de-identified data from the OPTN database,[1] which is managed and maintained by the United Network for Organ Sharing (UNOS) by contract with the US Department of Health and Human Services. This source contains information on all patients on the waiting list, organ donation and matching, and transplantation in the United States since late 1987. The population here thus mirrors that of transplant registries in other western democracies and represents all such patients rather than a subset.

The specific data were from the UNOS Standard Transplant Analysis and Research (STAR) File with release date March 15, 2019, which contained organ transplantation data, including liver cases, from 1987 to 2018.[1] This study met the criteria for exemption from Institutional Review Board (IRB) oversight. Variables obtained at the time of recipient registration include transplant date, patient descriptors, recipient's primary liver disease, pre-transplant serology, organ preservation information, and pre-transplant lab work pertaining to liver function. Follow-up data include vital status and cause of death.

Sampling/Data Collection

There were 130 665 first time, single organ liver transplants. We restricted attention to patients (*a*) having NASH as the reason for transplant (OPTN etiology code 4214), (*b*) aged 35 to 74 years, and (*c*) who received their transplant during calendar years 2002 to 2018. The second condition was applied to consider only the most common age range for transplant, to avoid possible spurious effects of outliers. The third was invoked to concentrate on patients in the period of the MELD system, which was implemented in 2002. Had we also used data from the pre-MELD era (1987-2001), any secular (time) trend in survival would have been confounded with selection effects due to the more restrictive recent MELD criteria. We did not exclude patients with hepatocellular carcinoma (HCC) or Hepatitis C, or those who received an organ from a living donor, though doing so would not have materially affected our results. The final sample included 6635 patients.

Because cryptogenic cirrhosis (CC) may be a manifestation of NASH, we also identified a separate group of patients with CC (OPTN etiology code 4213) and meeting the same other two criteria above. There were 3584 such patients, of whom 1065 died over the period. We compared survival between the CC and NASH groups.

Data Analysis

The survival data were analyzed using Kaplan-Meier (empirical) survival curves and both univariate and multivariate Cox proportional hazard regression models.[9] Analyzes were completed using SAS software version 9.4 (SAS Institute). Potential explanatory variables included patient age, sex, race, transplant year, diabetes, and MELD score at time of transplant, as well as donor age. The relatively small number of cases with missing or unknown values were coded as such. The factors were first assessed independently in univariate models, and then in multivariate models. We tested the proportional hazards assumption implicit in the Cox model. We used a significant level of $\alpha = 0.05$. To aid comparisons with prior and future studies, we included age, sex, and race (white versus others) in all models, even if the associated effects were modest and not statistically significant. We opted not to perform formal model selection with specified variable entry and exit criteria so that our resulting models would be more widely applicable and parsimonious. We return to this issue in the discussion.

The final fitted Cox models were used to compute survival curves for certain combinations of risk factors, to document survival for various representative patient groups. As the observed survival data extended for only up to 17 years, a standard method was used to calculate the associated mortality rates at older ages.[10] Life expectancy was calculated as the area under the survival curve,[11] which is equivalent to constructing a life table.[12] Life expectancies were obtained at two time points: at time of transplantation (which includes operative mortality), and at 1-year posttransplant. For the latter time point, we used the results from the same Cox models as used for time 0 but conditioned upon surviving 1 year. We opted to use only one model rather than two because (*a*) the risk factors were measured only up to the time of transplant, and (*b*) had we refit models at the later time point, using only the conditional data, we would have reduced the sample sizes and resulting accuracy of the results. Further, we found that use of separate models did not materially affect the results. Life expectancy in NASH transplant recipients was compared with that of the age- and sex-matched US general population.[12]

We analyzed secular trends in survival by separately considering patient follow-up time periods beginning at transplant and 1 year post transplant. In the latter case, we excluded any persons who had died prior to 1 year post, and measured survival only from the latter point in time. We fitted models including only four fixed demographic terms: age, sex, race, and calendar year of transplant. We also separately examined the limited time period from transplant to 1 year post transplant.

Table 1. Demographics and Risk Factors. Percentages are by Column. N = 6635.

Variable	Categories	N	%
Age (years)	35-44	395	6
	45-54	1430	22
	55-64	3065	46
	65-74	1745	26
Sex	Male	3538	53
	Female	3097	47
Race	White	5535	83
	All others	1100	17
Transplant year	2002-2005	317	5
	2006-2009	1038	16
	2010-2013	1517	23
	2014-2018	3763	57
MELD score at transplant	6-10	368	6
	11-18	1854	28
	19-24	1671	25
	25-40	2365	36
	Missing	377	6
Donor type	Living	319	5
	Deceased	6316	95
Weight	Underweight (BMI < 18)	11	0
	Normal weight (18-25)	554	8
	Overweight (25-30)	1695	26
	Obese (30+)	4372	66
Presence of Hepatitis C	No	6349	96
	Yes	158	2
	Missing	128	2
Diabetes (Type I, II, or other/ unknown type)	No	3065	46
	Yes	3516	53
	Missing	54	1
Functional status at transplant (Karnofsky Performance Status)	100% (normal)	60	1
	90%—Minor symptoms of disease	195	3
	80%—Normal activity with effort	753	11
	70%—Cares for self, but unable to carry on normal activity	828	12
	60%—Requires occasional assistance	827	12
	50%—Requires considerable assistance	994	15
	40%—Disabled	903	14
	30%—Severely disabled	676	10
	20%—Very sick	915	14
	10%—Moribund	246	4
	Missing	237	4
Ascites	No	936	14
	Yes	5699	86
Hepatic encephalopathy	No	1676	25
	Mild (1-2)	4139	62
	Severe (3-4)	795	12
	Missing	25	0
Donor age	0-19	535	8
	20-49	3460	52
	50-79	2599	39
	80+	41	1
Portal Vein Thrombosis	No	5554	84
	Yes	1023	15
	Missing	58	1
Time spent on waitlist	<180 days	4493	68
	181-365 days	973	15
	>365 days	1169	18
Length of Hospital Stay	0-10 days	3432	52
	11 to 30 days	2353	35
	31+ days	728	11
	Missing	122	2
Previous malignancy	No	3004	45
	Yes	713	11
	Missing	2918	44
Ventilator use at transplant	Yes	226	3
	No	6409	97
Working at time of transplant	Yes	925	14
	No	5406	81
	Missing	304	5
Dialysis within 1 week of transplant	No	5864	88
	Yes	764	12
	Missing	7	0
Hepatocellular carcinoma	No	3209	48
	Yes	331	5
	Missing	3095	47
Inpatient status immediately prior to transplant	Hospitalized, in ICU	770	12
	Hospitalized, not in ICU	1379	21
	Not hospitalized	4485	68
	Missing	1	0
Cold ischemic time	<6 hours	3475	52
	6-12 hours	2997	45
	12+ hours	163	2
	Missing	111	2
Treated for rejection within 1 year	No	3952	60
	Yes	437	7
	Missing	2246	34

We did so to determine if the improvement in survival was limited to the period immediately following surgery or if it extended longer term. For the period 0- to 1-year posttransplant, we censored all survival times at 1 year.

Results

Table 1 shows demographics and risk factors for the 6635 NASH liver transplant recipients. The mean age at transplant was 59 years, 53% were male, and 83% were white. Follow-up times ranged from 0.0 to 17.1 years (mean 3.6) and there were 1248 deaths over the 2002–2018 period. Not shown are the results of various investigations of subgroups of Table 1. Firstly, the 34% of patients with MELD scores of 6–18 were more likely to have HCC than the overall group (20% versus 5%), and more likely to have a living donor (10% versus 5%). Secondly, among the 557 (9%) of patients who were of normal weight (body mass index (BMI) 18-25), we found that 5 were underweight when placed on the transplant registration, 18 were overweight, and the remaining 534

Table 2. Univariate and Multivariate Hazard Ratios (*P*-values) from Cox Proportional Hazards Regression Models with Single or Multiple Factors[a].

Variable	Categories	Univariate model from time of transplant	Multivariate models	
			From transplant	For 1-year survivors
Age (years)[a]	(Continuous)	1.04 (<0.0001)	1.04 (<0.0001)	1.04 (<0.0001)
Sex[a]	Female	1 (ref)	1 (ref)	1 (ref)
	Male	0.92 (0.16)	0.96 (0.51)	1.04 (0.66)
Race[a]	White	1.14 (0.12)	1.02 (0.44)	0.99 (0.94)
	All others	1 (ref)	1 (ref)	1 (ref)
Transplant year[a]	(Continuous)	0.98 (0.002)	0.97 (0.0008)	1.01 (0.64)
MELD score at transplant	6-10	1 (ref)	1 (ref)	1 (ref)
	11-18	0.93 (0.54)	0.98 (0.89)	0.94 (0.69)
	19-24	0.86 (0.26)	0.95 (0.69)	0.80 (0.18)
	25-40	1.16 (0.25)	1.38 (0.01)	1.12 (0.50)
Donor type	Living	1 (ref)	1 (ref)	1 (ref)
	Deceased	1.09 (0.55)	1.16 (0.30)	1.07 (0.74)
Weight	Underweight	1.38 (0.48)	1.66 (0.27)	1.98 (0.19)
	Normal weight	1 (ref)	1 (ref)	1 (ref)
	Overweight	0.75 (0.01)	0.70 (0.01)	0.76 (0.04)
	Obese	0.75 (<0.01)	0.69 (<0.01)	0.74 (0.02)
Presence of hepatitis C	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.29 (0.13)	1.30 (0.12)	1.04 (0.88)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.25 (0.0001)	1.18 (0.004)	1.23 (0.009)
Functional status at transplant	70-100%	1 (ref)	1 (ref)	1 (ref)
	0-60%	1.42 (<0.0001)	1.57 (<0.001)	1.33 (0.002)
Ascites	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.15 (0.11)	1.15 (0.10)	1.02 (0.89)
Hepatic encephalopathy	No	1 (ref)	1 (ref)	1 (ref)
	Mild (1-2)	1.21 (0.007)	1.20 (0.009)	1.10 (0.30)
	Severe (3-4)	1.78 (<0.0001)	1.79 (<0.0001)	1.72 (<0.0001)
Donor age	<20	1 (ref)	1 (ref)	1 (ref)
	20 and up	0.99 (0.90)	1.01 (0.95)	1.09 (0.53)
Portal vein thrombosis	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.22 (0.01)	1.22 (0.01)	0.99 (0.93)
Time spent on waitlist	<180 days	1 (ref)	1 (ref)	1 (ref)
	180-365 days	0.94 (0.47)	0.93 (0.36)	0.90 (0.35)
	>365 days	1.02 (0.76)	1.02 (0.83)	1.03 (0.77)
Length of hospital stay	0-10 days	1 (ref)	1 (ref)	1 (ref)
	11-30 days	1.23 (0.002)	1.22 (0.002)	1.28 (0.004)
	31+	2.98 (<0.0001)	2.40 (<0.0001)	2.18 (<0.0001)
Previous malignancy	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.00 (0.98)	0.95 (0.59)	0.94 (0.66)
Ventilator use at transplant	Yes	1.89 (<0.0001)	2.05 (<0.0001)	1.43 (0.10)
	No	1 (ref)	1 (ref)	1 (ref)
Working at time of transplant	Yes	1 (ref)	1 (ref)	1 (ref)
	No	1.90 (<0.0001)	1.78 (<0.0001)	1.49 (0.003)
Dialysis within 1 week of transplant	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.67 (<0.0001)	1.86 (<0.0001)	1.606 (0.07)
Hepatocellular carcinoma	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.0 (1.0)	0.89 (0.52)	0.28 (0.03)
Inpatient status immediately prior to transplant	Not hospitalized	1 (ref)	1 (ref)	1 (ref)
	Hosp, not in ICU	1.41 (<0.0001)	1.50 (<0.0001)	1.36 (0.001)
	Hosp, in ICU	1.95 (<0.0001)	2.23 (<0.0001)	1.74 (<0.0001)
Cold ischemic time	<6 hours	1 (ref)	1 (ref)	1 (ref)
	6-12 hours	1.09 (0.17)	1.09 (0.17)	1.01 (0.88)
	12+ hours	1.37 (0.02)	1.28 (0.08)	1.29 (0.15)

(continued)

Table 2. (continued).

Variable	Categories	Univariate model from time of transplant	Multivariate models	
			From transplant	For 1-year survivors
Treated for rejection within 1 year[b]	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.39 (0.006)	1.45 (0.002)	1.43 (0.004)
	Missing	4.84 (<0.0001)	4.87 (<0.0001)	1.19 (0.097)

[a]The univariate results were based on models with only the 1 stated factor. The multivariate results were based on multiple models, each of which includes terms for age, sex, race and transplant year. For example, the hazard ratios for MELD scores were based on a model with 5 factors. Of course, the multivariate hazard ratios for age, sex, race, and transplant year each vary by model. For simplicity, the values shown here are the ones for the model with MELD score.
[b]Because this factor was measured during the follow-up period, there is an inherent immortal time bias in these results. Notably, the patient had to survive long enough to be measured. Those with missing values had a higher mortality rate primarily because missing was a proxy for having died prior to being measured. Notice that the magnitude of the effect among persons with missing values abated after the first year (from 4.87 to 1.19).

were of normal weight. Thirdly, the 5% of patients with HCC were found to have lower MELD scores than the overall group (for example, 26% had scores 6-10% and 39% had scores 11-18), though this finding should be viewed with caution as 47% of patients had missing information with respect to the presence of HCC. Fourthly, there were too few patients of other races (12% Hispanic, 2% Black) to report results separately by race, and indeed a detailed study of the effect of race is outside the scope of the present work. See the recent comprehensive review article by Nephew and Serper.[13] Table 2 shows hazard ratios (HRs) from the univariate and multivariate Cox survival models from time of transplant and at 1-year posttransplant. For example, the univariate HR from time of transplant for patients who had concurrent Hepatitis C was 1.29, indicating that such patients had 29% higher mortality than those who did not.

The multivariate Cox models of Table 2 each included the first 4 factors (age, sex, race, and transplant year). As noted, these 4 factors were included in all models to document clearly their effects (even if modest) and also to allow for comparison with other studies. For example, the model with survival measured from the time of transplant showed that persons with diabetes had 18% higher risk than those without (HR = 1.18, $P = .004$) after controlling for age, sex, race, and transplant year, whereas the effect of being male was an HR of only 0.96 ($P = .51$).

Of note in Table 2 are the HRs reflecting patient status at the time of transplant. Those not working at the time of transplant had 78% higher risk than those who were (HR = 1.78, $P < .0001$). Those hospitalized in the intensive care unit (ICU) prior to transplantation had 2.23 times the risk ($P < .0001$), and those who required dialysis within the prior week had 1.86 times the risk ($P < .0001$). Similarly, factors reflecting events during transplant had large effects. The need for ventilator use was associated with 105% higher mortality (HR = 2.05, $P < .0001$), though this was attenuated among 1-year survivors (HR = 1.43, $P = .10$). Also, the length of hospital stay (LOS) was strongly associated with posttransplant survival. For example, those in the hospital 31 days or longer had 2.40 times the risk of death ($P < .0001$), and even those who survived the first year had 2.18 times the risk ($P < .0001$).

In our analyzes of secular trends in survival, we first accounted for 3 basic demographic factors: age, sex, and race. We added calendar year of transplant to the Cox model. For the model based on survival data beginning at the time of transplant, the HR for calendar year was 0.973 ($P = .0008$), indicating that mortality fell by 2.7% per year, on average, over the study period, and over the entire patient follow-up time. During the first year posttransplant, the HR was 0.955 ($P < .0001$), indicating the mortality fell by 4.5% per year over the study period. At 1-year post, however, the HR was 1.01, suggesting that mortality instead increased by 1% per calendar year, though this increase was not statistically significant ($P = .64$). The improvement in mortality thus appears to be restricted to the first year post transplant. It did not appear to vary by age, sex, or race ($P > .05$ in all cases).

Life expectancies are shown in Table 3, all stratified by age, sex, and time since transplant. The tables are arranged chronologically: first the basic table, next the tables reflecting pretransplant conditions, and finally those reflecting posttransplant factors. Not shown are tables for the many other factors listed in Table 2. We have omitted these for several reasons. Many of the factors were not both statistically and practically significant (eg, deceased donor, HR = 1.16, $P = .30$) once the others were taken into consideration. The effects of some factors can be inferred from the results shown (eg, the effect of portal vein thrombosis [HR = 1.22] is similar to that of diabetes [HR = 1.18]). In addition to tables for each factor individually, there could be tables for two or more factors at a time, and space does not permit these. While all life expectancies were computed for Caucasian patients, results for the combined group of non-Caucasians were nearly identical when rounded to the nearest integer. Standard errors of the life expectancies are not shown. As noted, we opted not to derive a single model through a rigid model selection procedure, but rather instead to present clear and easily applicable results. More complicated models would have had larger standard errors and perhaps more limited applicability.

The basic results from Table 3, which do not consider any medical factors, are repeated in the other tables to allow for comparison of the relative effects. For example, consider a male, age 40, who recently underwent transplantation (Table 3a). His life

Table 3. Life Expectancies Based on the Multivariate Models of Table 2 from Time of Transplant.

a. Overall

		Male		Female	
Starting time	Current age	All transplant	GP	All transplant	GP
From transplant	40	20	39	20	43
	50	16	30	16	33
	60	13	22	13	25
	70	10	15	10	17
1-yr posttransplant	41	20	38	20	42
	51	17	29	16	33
	61	13	21	13	24
	71	11	14	11	16
5-yrs posttransplant	45	18	34	17	38
	55	14	26	14	29
	65	11	18	11	21
	75	9	11	9	13

b. Diabetes

		Male				**Female**			
Starting time	**Current age**	**Yes**	**No**	**All**	**GP**	**Yes**	**No**	**All**	**GP**
From transplant	40	19	21	20	39	19	21	20	43
	50	16	17	16	30	15	17	16	33
	60	12	14	13	22	12	13	13	25
	70	10	11	10	15	10	11	10	17
1-yr posttransplant	41	19	21	20	38	19	21	20	42
	51	16	17	17	29	15	17	16	33
	61	13	14	13	21	13	14	13	24
	71	10	11	11	14	10	11	11	16
5-yrs posttransplant	45	17	18	18	34	16	18	17	38
	55	13	14	14	26	13	14	14	29
	65	10	11	11	18	10	11	11	21
	75	8	9	9	11	8	9	9	13

c. Hepatic Encephalopathy (HE)

		Male					**Female**				
Starting time	**Current age**	**Severe**	**Mild**	**No**	**All**	**GP**	**Severe**	**Mild**	**No**	**All**	**GP**
From transplant	40	16	20	22	20	39	16	20	22	20	43
	50	13	16	18	16	30	13	16	18	16	33
	60	10	13	14	13	22	10	13	14	13	25
	70	8	10	12	10	15	8	10	11	10	17
1-yr posttransplant	41	17	20	22	20	38	16	20	22	20	42
	51	13	16	18	17	29	13	16	18	16	33
	61	11	13	15	13	21	11	13	14	13	24
	71	9	11	12	11	14	9	11	12	11	16
5-yrs posttransplant	45	14	17	19	18	34	14	17	19	17	38
	55	11	14	15	14	26	11	11	15	14	29
	65	9	11	12	11	18	9	9	12	11	21
	75	7	9	10	9	11	7	7	9	9	13

d. Dialysis within one week of transplant

		Male				**Female**			
Starting time	**Current age**	**Yes**	**No**	**All**	**GP**	**Yes**	**No**	**All**	**GP**
From transplant	40	15	21	20	39	15	21	20	43
	50	12	17	16	30	12	16	16	33
	60	9	13	13	22	9	13	13	25

(continued)

Table 3. (continued).

a. Overall

		Male		Female					
Starting time	Current age	All transplant	GP	All transplant	GP				
	70	7	10	10	15	7	10	10	17
1-yr posttransplant	41	15	21	20	38	15	21	20	42
	51	12	17	17	29	12	17	16	33
	61	10	14	13	21	10	13	13	24
	71	8	11	11	14	8	11	11	16
5-yrs posttransplant	45	13	18	18	34	13	18	17	38
	55	10	14	14	26	10	14	14	29
	65	8	11	11	18	8	11	11	21
	75	6	9	9	11	6	9	9	13

e. Working at time of transplant

		Male				**Female**			
Starting time	**Current age**	**Yes**	**No**	**All**	**GP**	**Yes**	**No**	**All**	**GP**
From transplant	40	25	19	20	39	25	19	20	43
	50	20	15	16	30	20	16	16	33
	60	17	12	13	22	17	12	13	25
	70	13	10	10	15	14	10	10	17
1-yr posttransplant	41	25	19	20	38	25	19	20	42
	51	20	16	17	29	20	16	16	33
	61	17	13	13	21	17	13	13	24
	71	14	10	11	14	14	11	11	16
5-yrs posttransplant	45	21	16	18	34	22	17	17	38
	55	17	13	14	26	17	13	14	29
	65	14	10	11	18	14	10	11	21
	75	11	8	9	11	11	8	9	13

f. Inpatient status (hospitalized yes/no) prior to transplant

		Male				**Female**			
Starting time	**Current age**	**Yes**	**No**	**All**	**GP**	**Yes**	**No**	**All**	**GP**
From transplant	40	17	21	20	39	17	22	20	43
	50	13	17	16	30	13	17	16	33
	60	10	14	13	22	10	14	13	25
	70	8	11	10	15	8	11	10	17
1-yr posttransplant	41	17	21	20	38	17	21	20	42
	51	13	17	17	29	13	17	16	33
	61	11	14	13	21	11	14	13	24
	71	9	11	11	14	9	11	11	16
5-yrs posttransplant	45	14	18	18	34	14	19	17	38
	55	11	14	14	26	11	14	14	29
	65	9	11	11	18	9	11	11	21
	75	7	9	9	11	7	9	9	13

g. Length of Hospital Stay (LOS)

		Male				**Female**			
Starting time	**Current age**	**0-30 days**	**31+ days**	**All**	**GP**	**0-30 days**	**31+ days**	**All**	**GP**
From transplant	40	21	12	20	39	21	12	20	43
	50	17	10	16	30	17	10	16	33
	60	14	7	13	22	14	7	13	25
	70	11	6	10	15	11	5	10	17
1-yr posttransplant	41	21	13	20	38	21	13	20	42
	51	17	10	17	29	17	10	16	33

(continued)

Table 3. (continued).

a. Overall

		Male		Female					
Starting time	Current age	All transplant	GP	All transplant	GP				
	61	14	8	13	21	14	8	13	24
	71	11	7	11	14	11	6	11	16
5-yrs posttransplant	45	18	11	18	34	18	10	17	38
	55	15	8	14	26	14	8	14	29
	65	12	7	11	18	11	6	11	21
	75	9	5	9	11	9	5	9	13

Abbreviation: GP, general population.

Table 4. Empirical Survival Percentages (%) for Select Groups of the Present Sample, and Comparison with Two Previously Published Results.

		Survival time (Years)			
Factor	Subgroup	1	5	10	15
All	(None)	90	79	63	48
Sex	Male	91	80	63	52
	Female	89	79	63	45
Age	35-44	95	85	77	67
	45-54	93	86	70	61
	55-64	90	79	63	48
	65-74	87	71	53	32
Thuluvath et al[14]	NASH	89	77	63	—
Haldar et al[15]	NASH; non-HCC	84	73	62	—

— Results not given in the cited study.

expectancy from the time of transplant is approximately 20 additional years, rather than the 39 years that would obtain in the general population (GP). At 1 year post, at age 41, it would (rounded to the nearest integer) also be 20 years compared with 38. If he survives 5 years, his life expectancy at age 45 would be 18 additional years, compared with 34 years in the GP. If the same 40-year-old male did not have diabetes (Table 3b), his life expectancy would be 21 years, and if he did it would be 19 years. Notice that these two values, best and worst cases, properly straddle the overall value of 20 years. Table 4 shows our univariate survival results, and values from two prior NASH studies.

In our comparison of the survival of NASH patients with that of CC patients (results not shown), we found at most modest differences. After controlling for age, sex, race, and calendar year in the Cox model, the overall hazard ratio for CC to NASH was 1.00 ($P = .94$). We additionally found that the HR was 1.07 for males and 0.93 for females (the difference was not statistically significant, $P > .05$). When we stratified the CC group by obesity, the HRs were 1.02 for those with BMI < 30 and 0.98 for those with BMI ≥ 30.

Discussion

The overall survival percentages implicit in Table 3 are consistent with those of other studies on NASH transplant patients. For example, the European study by Haldar et al.[15] reported a 10-year survival of 62% in NASH, non-HCC patients. The US study by Thuluvath et al.[14] reported a 10-year survival of 63%. The present study reports 63% as well, though this is seen to vary from 53% in older ages to 77% in younger ones. Such reinforces the obvious point that age, sex, era of transplant, and other factors should be taken into consideration when making these comparisons.

The computed life expectancies summarize the reduced survival prospects for NASH transplant patients. Even in persons with the most favorable characteristics displayed here (age 40 and working at time of transplant, Table 3e), the life expectancy at time of transplant is 25 years for males and 25 for females, compared with 39 and 43 in the GP. It is of course possible to calculate life expectancies for any other combinations of variable levels from the models shown in Table 2. In addition, it is worth noting that the values shown represent averages over the composite groups; results for subgroups may differ.

The life expectancies given here for NASH patients were modestly higher than those given in prior studies on life expectancy after transplant for HCC[16,17] or alcohol related liver disease (ALD).[18] For example, for males aged 40 we report 20 years, while the three prior studies indicated 16 (HCC with cirrhosis), 15 (HCC without cirrhosis), and 17 (ALD), respectively. It makes biologic sense that NASH liver transplant patients would have superior survival, as HCC patients can develop other cancers and ALD patients may relapse into alcoholism. Many other studies have reported on related comparisons more directly. For example, Thuluvath et al.[14] reported rather similar adjusted HRs by etiology: CC (1.00), NASH (0.96), alcoholic cirrhosis (1.02) and autoimmune hepatitis (1.13), with all P-values greater than 0.10. Also, Wong et al.[19] reported multivariate HRs of: hepatitis C virus (HCV) (1.00), NASH (0.69), ALD (0.76), and HCC (1.09). Haldar et al.[15] concluded that prognosis with NASH is comparable to that of other indications. Conversely, Burra et al.[20] found that ALD was worse than that of other etiologies but only if accompanied by Hepatitis C, though even then the HR was rather modest at 1.14. Also, Boumani et al.[21] suggested that primary sclerosing cholangitis has a better prognosis. Finally, Nagai et al.[22] reported that mortality was higher in NASH patients that in ALD or HCV.

After adjusting for demographics, we found that CC patients had survival similar to that of NASH patients. This is not surprising for 3 reasons. Firstly, as documented above, etiology in general does not appear to be a major factor for long-term survival in liver transplant recipients. Secondly, some have suggested that most patients with CC may have what is considered burned out NAFLD.[23] Thirdly, being overweight was not a major factor for survival in this population. In fact, lean NAFLD patients had somewhat higher mortality than those who were overweight or obese. This finding mirrors that of Bambha et al.,[24] who found that underweight liver recipients with BMI less than 18.5 had 43% and 28% increased risk of 1-year-posttransplant death and graft failure, respectively. Also, Pelletier et al.[25] found that short-term mortality was doubled in patients with BMI less than 20. Conversely, Hagström et al.,[26] looking at lean NAFLD patients in general, not specific to transplantation, found no increased overall mortality in the group (HR = 1.06, $P = .73$).

The main limitations in the present study were that patients were not randomized to treatment, nor do we have information on prior treatment efforts. Moreover, the results given here do not account for other medical risk factors, such as concomitant heart disease.

Conclusions

As documented herein, life expectancy after liver transplant for NASH was significantly reduced from normal. The major demographic factors related to survival were age and whether the patient was healthy enough to work, while sex and Caucasian race were not practically or statistically significant. Notable other factors were the need for ventilator support and length of posttransplant hospitalization, both of which indicate more severely involved patients. The results given here may prove helpful in medical decision-making for liver patients regarding treatments for both their liver disease and other conditions.

Disclaimer

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