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Life Expectancy After Liver Transplantation for Alcoholic Cirrhosis

Robert M. Shavelle, PhD[1], Rachel C. Saur, BA[1], Ji Hun Kwak, BA, RN[1], Jordan C. Brooks, PhD, MPH[1], and Bilal Hameed, MD[2]

Abstract

Background: Alcohol-associated liver disease is the leading cause of liver transplantation in the western world. For these patients we calculated life expectancies both at time of transplant and several years later, stratified by key risk factors, and determined if survival has improved in recent years. **Methods:** Data on 14 962 patients with alcohol-associated liver disease who underwent liver transplantation in the MELD era (2002-2018) from the United States Organ Procurement and Transplantation Network database were analyzed using the Cox proportional hazards regression model and life table methods. **Results:** Demographic and past medical history factors related to survival were patient age, presence of diabetes or severe hepatic encephalopathy, and length of hospital stay. Survival improved over the study period, at roughly 3% per calendar year during the first 5 years posttransplant and 1% per year thereafter. **Conclusions:** Life expectancy in transplanted patients with alcohol-associated liver disease was much reduced from normal, and varied according to age, medical risk factors, and functional status. Survival improved modestly over the study period. Information on patient longevity can be helpful in making treatment decisions.

Keywords

survival, OPTN, epidemiology, life table, mortality, acute alcoholic hepatitis

Introduction

Alcohol-associated liver disease (ALD) is the leading cause of liver disease in the western world and has recently become the leading cause for liver transplantation in the United States.[1] ALD represents a spectrum of liver injury resulting from alcohol use, ranging from hepatic steatosis to more advanced forms including alcoholic hepatitis, alcohol-associated cirrhosis, and acute alcoholic hepatitis presenting as acute-on-chronic liver failure. As the prevalence of ALD continues to rise,[2] proper allocation of a limited supply of donor livers will become even more important. Patient life expectancy is a factor increasingly used in medical decision making.[3–10] In the context of liver allocation, the factors to identify appropriate candidates associated with potential recipient survival have been variously referred to as prognostic factors,[11] predictive factors,[12] selection criteria,[13] prioritization of organs,[14] and utility.[15] Without a formal metric for survival, such discussions may lack objectivity.

While there are many prior studies on survival after transplantation for ALD, these have two notable limitations. Firstly, reported survival percentages are difficult to interpret. For example, it is not clear which is preferable: a 5-year survival of 95% or an 8-year of 92%. A stated survival percentage over 10 years does not in itself indicate what is expected in future; that is, it is incomplete. Life expectancy is strictly defined as the average survival time among a group of similar persons; it is not meant to be a prediction of survival, nor is it a 5-year survival rate. Yet by construction it accounts for current and future mortality, neatly summarized in a single number that can be compared across ages, sexes, countries, and other factors.

Secondly, to our knowledge there are no detailed long-term follow up studies that report life expectancies stratified simultaneously by age, sex, race, and other factors. For example, the European Liver Registry routinely reports many survival figures, and trends,[16] but does not provide life expectancies.

Prior studies of liver transplant recipients have identified patient demographics (age, sex, year) and medical conditions (eg, diabetes, alcohol abuse, cirrhosis, and hepatitis B and C) as factors related to survival.[11,12,17,18] But, as noted, that research did not provide life expectancies. The calculation of life expectancy requires long-term follow-up of persons and the use of life table methodology, the latter having thus far seen rather limited application in transplant research.[19,20] The Organ Procurement and Transplantation Network (OPTN)

[1] Life Expectancy Project, San Francisco, California, USA
[2] Division of Gastroenterology, University of California, San Francisco, USA

Corresponding Author:
Robert Shavelle, Life Expectancy Project, 1439 – 17th Avenue, San Francisco, CA 94122-3402, USA.
Email: Shavelle@LifeExpectancy.org

data[21] includes the requisite lengthy follow up, and the methods used here are standard. In the present study we calculate life expectancy for select ALD patient subgroups, both from the time of initial transplant and also conditioned upon patient survival to 1- or 5- years posttransplant. We also examine if ALD survival improved over the study period.

Design/Methods

The methods are similar to our work in two prior studies.[19,20] We identified and followed a cohort of ALD liver transplant patients in the United States to identify factors related to survival and to calculate life expectancies for various subgroups. We used standard methods of survival analysis and life table construction.

Setting/Population

We analyzed de-identified data from the OPTN database,[21] which is managed and maintained by the United Network for Organ Sharing 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 specific data were from the Standard Transplant Analysis and Research File with release date March 15, 2019, which contained organ transplantation data, including liver cases, from 1987 to 2018.[21] This study met the criteria for exemption from IRB oversight. Variables obtained at the time of recipient registration include transplant date, patient descriptors, recipient's primary liver disease, pretransplant serology, organ preservation information, and pretransplant lab work pertaining to liver function. Follow-up data included vital status and cause of death.

Sampling/Data Collection

There were 130 665 first time, single organ liver transplants. We restricted attention to persons (1) having alcoholic-associated cirrhosis with or without mention of hepatitis C as the reason for transplant (OPTN etiology codes 4215 or 4216), (2) aged 35 to 74 years, and (3) 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. The final sample included 14 962 patients.

There has been interest in whether acute alcoholic hepatitis patients have a prognosis similar to that of alcohol associated cirrhosis patients.[22–24] Until recently, adherence to the 6-month abstinence requirement by most liver transplant centers essentially excluded these patients from consideration for transplantation, though this has since changed. We thus also identified a separate group of patients with etiology of acute alcoholic hepatitis (OPTN etiology code 4217) and meeting the same other two criteria above. There were 163 such patients, of whom 25 died (18 males) over the period. We compared the survival of this group to that of the cirrhosis patients.

Data Analysis

The survival data were analyzed using Kaplan-Meier (empirical) survival curves and both univariate and multivariate Cox proportional hazard regression models.[25] Analyses were completed using SAS software version 9.4 (SAS Institute). Potential explanatory variables included those previously known to be related to survival: patient age, sex, race, transplant year, diabetes, and MELD score at time of transplant, as well as donor age and other possible factors. Standard categories for the variables were used (eg, ranges for the MELD scores). A detailed description of the variables were described in the UNOS database.[21] 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 used a significant level of $\alpha = 0.05$. To aid comparisons with prior and future studies, we included age, sex, and race (white vs 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 in order that our resulting models would be more widely applicable and parsimonious. We tested the proportional hazards assumption implicit in the Cox model. Where there were violations, we computed survival based on a subset containing only particular level (strata) of the variable.

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, we used a standard life table method to calculate the associated mortality rates at later/older ages.[26] Life expectancy was calculated as the area under the survival curve,[27] which is equivalent to constructing a complete life table.[28] Life expectancies were obtained at three time points: at time of transplantation (which includes operative mortality), and at 1- and 5- years posttransplant. For the latter two time points, we used the results from the same Cox models as used for time 0, but then conditioned upon surviving 1 or 5 years. We opted to use only one model rather than three because (a) the risk factors were measured only up to the time of transplant, and (b) had we refit models at the later time points, 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 was compared with that of the age- and sex-matched US general population.[28]

We analyzed secular trends in survival by separately considering patient follow-up time periods beginning at transplant, 1

Table 1. Patient Demographics and Medical Risk Factors (N = 14 962).

Variable	Categories	N	%
Age (years)	35 to 44	1961	13
	45 to 54	6004	40
	55 to 64	5591	37
	65 to 74	1406	9
Sex	Male	11588	77
Race	White	11763	79
Transplant year	2002 to 2005	3172	21
	2006 to 2009	3285	22
	2010 to 2013	2787	19
	2014 to 2018	5718	38
MELD score at transplant	6 to 10	714	5
	11 to 18	3807	25
	19 to 24	3337	22
	25 to 40	5914	40
	Missing/Other	1190	8
Donor type	Living	434	3
Weight	Underweight (BMI<18)	193	1
	Normal weight (18-25)	3863	26
	Overweight (25-30)	5678	38
	Obese (30 +)	5222	35
Presence of Hepatitis C	Yes	3596	24
Diabetes (Type I, II, or other/unknown type)	Yes	2721	18
Functional status at transplant (Karnofsky Performance Status)	100% (normal)	158	1
	90% - Minor symptoms of disease	391	3
	80% - Normal activity with effort	1394	9
	70% - Cares for self, but unable to carry on normal activity	1733	12
	60% - Requires occasional assistance	1543	10
	50% - Requires considerable assistance	1684	11
	40% - Disabled	1475	10
	30% - Severely disabled	1362	9
	20% - Very sick	2309	15
	10% - Moribund	578	4
	Missing/Other	2335	16
Ascites	Yes	13283	89
Hepatic encephalopathy	No	3150	21
	Mild (1-2)	9509	64
	Severe (3-4)	2168	15
	Unknown/missing	135	1
Donor age	0 to 19	1381	9
	20 to 49	8094	54
	50 to 79	5419	36
	80+	67	0
INR[a]	Normal (1.1 or less)	541	4
	Undefined (1.1 to 2.0]	8532	57
	Therapeutic [2.0 to 3.0]	4189	28
	High risk [>3.0]	1700	11
Sodium[a]	Low	5783	39
	Normal	6768	45
	High	281	2
	Missing	2126	14
Creatinine[a]	Low	3656	24
	Normal	4561	30
	High	6745	45
Total bilirubin[a]	Normal	1030	7
Albumin	Normal	4507	30
CMV IgG	Positive	5865	39
	Negative	3471	23
	Unknown/missing	5626	38

(continued)

Table 1. (continued)

Variable	Categories	N	%
Portal Vein Thrombosis	Yes	1294	9
Time spent on waitlist	<180 days	11136	74
	181 to 365 days	1700	11
	> 365 days	2126	14
Length of Hospital Stay Post Transplant	0 to 7 days	3950	26
	8 to 30 days	9158	61
	31 + days	1669	11
	Missing	185	1
Previous malignancy	Yes	1165	8
Ventilator use at transplant	Yes	725	5
Working at time of transplant	Yes	1434	10
Dialysis within 1 week of transplant	Yes	1814	12

[a]Component of MELD score.

year, and 5 years posttransplant. In the latter two cases, we excluded any persons who had died prior, 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 periods (a) from transplant to 1 year post transplant, and (b) from 1 year to 5 years posttransplant. 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 post transplant, we censored all survival times at 1 year. For the period 1 to 5 years post, we took the group of 1-year survivors then censored their survival times at the 5-year mark.

Results

Table 1 shows demographics and risk factors for the 14 962 alcohol associated cirrhosis liver transplant recipients. The mean age at transplant was 54 years, 77% were male, 24% had a history of hepatitis C, and 79% were White. Follow-up times ranged from 0.0 to 17.1 years (mean 4.9) and there were 3871 deaths over the 2002 to 2018 period.

Table 2 shows hazard ratios (HRs) from the univariate and multivariate Cox survival models from time of transplant and 1- and 5- years posttransplant. As noted, the multivariate models each included the first four factors (age, sex, race, and transplant year). Noteworthy in Table 2 is that the effect of needing dialysis within a week of transplant was large at the outset (HR = 1.37, 95% CI 1.24-1.51, $P < 0.0001$) though much lower by years 1 (HR = 1.08, 0.94-1.24, $P = 0.28$) and 5 (HR = 1.02, 0.82-1.27, $P = 0.88$). A similar pattern was present for those who required ventilator support. The effect of diabetes was more durable, with HRs of 1.31, 1.34, and 1.26 respectively (all $P < 0.001$, 1.22-1.42, 1.22-1.47, 1.10-1.45,). As intimated by the above, the proportional hazards assumption was satisfied with respect to age, sex, race, and diabetes. It was not satisfied with dialysis, working at time of transplant, ventilator dependence, or length of hospital stay. We return to these findings in the discussion.

To examine secular trends in survival, we first accounted for three basic demographic factors: age, sex, and race. We then added calendar year of transplant to the Cox model. From the time of transplant, the model HR for calendar year was 0.97 (0.96-0.98, $P < 0.0001$), indicating that mortality fell by 3% per year, on average, over the study period. When the analyses were begun at 1-year post, the HR was 0.98 (0.97-0.99, $P = 0.003$). At 5 years posttransplant, however, the HR was only 0.993, indicating a 0.7% annual decrease in mortality per calendar year for those who had already survived 5 years, though it was not statistically significant from 1.00 (0.97-1.02, $P = 0.54$). This roughly 1% annual decrease is similar to what occurred in the general population over the same time period. Not shown in the table is the result for the period 1 to 5 years posttransplant. For this the HR was 0.98 (0.97-0.99, $P = 0.003$), indicating a 2% decrease in mortality per calendar year. As noted above, the HR was 0.99 for the period beginning 5 years posttransplant. The improvement in mortality was thus largely restricted to the first five years posttransplant and did not appear to vary by age (test for interaction, $P = 0.10$), sex ($P = 0.56$), or race ($P = 0.24$).

Life expectancies are shown in Table 3, all stratified by age, sex, and time since transplant, and then by various risk factors: diabetes, hepatitis C, presence of severe hepatic encephalopathy, and length of hospital stay. We do not show tables for all the other factors for several reasons. Firstly, many of the factors were not both statistically and practically significant (eg, INR >2.0, HR = 1.06, $P = 0.11$) once the others were taken into consideration. Secondly, the effects of some factors can be inferred from the results shown (eg, the effect of high creatinine [HR = 1.22] is similar to the presence of hepatitis C [HR = 1.21]). Thirdly, in addition to tables for each factor singly, 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

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	For 5-year survivors
Age (years)[a]	(Continuous)	1.02 (<0.0001)	1.03 (<0.0001)	1.02 (<0.0001)	1.03 (<0.0001)
Sex[a]	Female	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Male	1.07 (0.10)	1.02 (0.59)	1.00 (0.99)	0.99 (0.89)
Race[a]	White	1.01 (0.12)	1.02 (0.56)	1.07 (0.21)	1.31 (0.0004)
	All others	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Transplant year[a]	(Continuous)	0.97 (<0.0001)	0.97 (<0.0001)	0.98 (0.003)	0.99 (0.54)
MELD score at transplant	6 to 10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	11 to 18	0.80 (0.002)	0.82 (0.007)	0.81 (0.009)	0.79 (0.03)
	19 to 24	0.85 (0.02)	0.90 (0.15)	0.83 (0.03)	0.73 (0.006)
	25 to 40	0.88 (0.06)	1.00 (0.98)	0.80 (0.008)	0.73 (0.0043)
	Other	0.99 (0.87)	1.13 (0.16)	0.85 (0.14)	0.71 (0.02)
Donor type	Living	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Deceased	1.17 (0.11)	1.20 (0.08)	1.08 (0.51)	1.13 (0.46)
Weight	Underweight	0.98 (0.85)	1.02 (0.91)	0.88 (0.01)	1.20 (0.37)
	Normal weight	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Overweight	0.85 (<0.0001)	0.82 (<0.0001)	0.84 (0.0003)	0.81 (0.003)
	Obese	0.85 (<0.0001)	0.85 (<0.0001)	0.88 (0.01)	0.92 (0.25)
Presence of Hepatitis C	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.19 (<0.0001)	1.21 (<0.0001)	1.22 (<0.0001)	1.09 (0.18)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.38 (<0.0001)	1.31 (<0.0001)	1.34 (<0.0001)	1.26 (0.001)
Functional status	70 to 100%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
at transplant	0 to 60%	1.19 (<0.0001)	1.30 (<0.0001)	1.03 (0.52)	1.0 (0.97)
	Other	1.25 (<0.0001)	1.05 (0.35)	0.94 (0.31)	0.94 (0.47)
Ascites	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.03 (0.62)	1.03 (0.52)	0.96 (0.50)	0.91 (0.27)
Hepatic	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
encephalopathy	Mild (1-2)	1.10 (0.02)	1.01 (0.03)	1.06 (0.25)	1.05 (0.45)
	Severe (3-4)	1.35 (<0.0001)	1.39 (<0.0001)	1.13 (0.08)	1.15 (0.15)
	Unknown	1.48 (0.07)	1.45 (0.08)	1.23 (0.43)	1.27 (0.51)
Donor age	<20	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	20 and up	1.28 (<0.0001)	1.28 (<0.0001)	1.31 (<0.0001)	1.33 (0.002)
INR[b]	2.0 or under	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	>2.0	0.97 (0.35)	1.06 (0.11)	0.92 (0.05)	0.90 (0.09)
Sodium[b]	Low	0.91 (0.01)	0.91 (0.07)	0.86 (0.002)	0.91 (0.17)
	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	1.6 (<0.0001)	1.63 (<0.0001)	1.16 (0.35)	1.12 (0.66)
	Missing	1.10 (0.03)	0.91 (0.07)	0.89 (0.06)	0.88 (0.21)
Creatinine[b]	Low	0.99 (0.78)	1.03 (0.59)	1.00 (0.97)	1.05 (0.48)
	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	1.21 (<0.0001)	1.22 (<0.0001)	1.09 (0.07)	1.02 (0.77)
Total bilirubin[b]	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	0.77 (<0.0001)	0.83 (0.0007)	0.76 (<0.0001)	0.70 (<0.0001)
Albumin	Low	0.10 (0.88)	0.98 (0.48)	0.949 (0.24)	0.90 (0.08)
	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	1.06 (0.84)	1.09 (0.75)	1.17 (0.65)	0.34 (0.28)
CMV IgG	Negative	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Positive	1.05 (0.23)	1.04 (0.32)	1.04 (0.44)	1.05 (0.41)
	Unknown/missing	0.96 (0.96)	1.11 (0.05)	1.14 (0.05)	1.12 (0.25)
Portal Vein Thrombosis	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.09 (0.16)	1.12 (0.07)	1.02 (0.81)	0.97 (0.81)
	Unknown	1.25 (0.02)	1.17 (0.09)	1.15 (0.19)	1.08 (0.58)
Time spent on waitlist	<180 days	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	180 to 365 days	1.04 (0.44)	1.01 (0.84)	1.08 (0.20)	1.04 (0.66)
	>365 days	1.08 (0.06)	1.03 (0.49)	1.07 (0.23)	0.97 (0.73)

(continued)

Table 2. (continued)

Variable	Categories	Univariate Model From time of transplant	Multivariate Models From transplant	For 1-year survivors	For 5-year survivors
Length of Hospital Stay Post Transplant	0 to 7 days	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	8 to 30 days	0.93 (0.06)	0.93 (0.05)	1.14 (0.005)	1.06 (0.40)
	31 +	1.89 (<0.0001)	1.85 (<0.0001)	1.60 (<0.001)	1.32 (0.006)
Previous malignancy	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.08 (0.19)	1.03 (0.68)	1.12 (0.11)	1.00 (1.00)
	Unknown	0.83 (0.0002)	0.96 (0.47)	0.97 (0.71)	0.81 (0.09)
Ventilator use at transplant	Yes	1.52 (<0.0001)	1.59 (<0.0001)	1.00 (0.99)	0.93 (0.67)
	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Working at time of transplant	Yes	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	No	1.41 (<0.0001)	1.41 (<0.0001)	1.36 (0.0001)	1.17 (0.16)
	Unknown/missing	1.43 (<0.0001)	1.22 (0.01)	1.22 (0.03)	1.08 (0.53)
Dialysis within 1 week of transplant	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.26 (<0.0001)	1.37 (<0.0001)	1.08 (0.28)	1.02 (0.88)

[a]The univariate results are based on models with only the one stated factor. The multivariate results are based on multiple models, each of which includes terms for age, sex, race and transplant year. For example, the hazard ratios for MELD scores are based on a model with five 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]Component of MELD score.

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 3a**, 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 expectancy from the time of transplant is approximately 17 additional years, rather than the 39 years that would obtain in the general population. At 1 year post, at age 41, it would (rounded to the nearest integer) be 18 years compared with 38. If he survives 5 years, his life expectancy at age 45 would be 16 additional years, compared with 34 years in the general population. If the same 40-year-old male did not have diabetes (**Table 3b**), his life expectancy would be 18 years, and if he did it would be 15 years. Notice that these two values, best and worst cases, properly straddle the overall value of 17 years.

In our comparison of the survival of alcoholic hepatitis patients with that of alcohol associated cirrhosis patients (results not shown), we found only modest differences. After controlling for age, sex, race, and calendar year in the Cox model, the hazard ratio was 0.92 (P = 0.65), suggesting slightly lower mortality in the former group. We additionally found that the HR was 1.0 for males ($P = 0.93$) and 0.78 for females ($P = 0.30$) and was 0.84 ($P = 0.80$) for transplants in years 2002 to 2012 and 1.13 for 2013 to 2018 ($P = 0.38$). **Table 4** shows various univariate results for the present study, with comparison to prior works.

Discussion

The overall survival percentages implicit in Table 3 and explicitly shown in Table 4 are consistent with those of other studies on ALD transplant patients. For example, Thuluvath et al.[17] reported a 10-year survival of 60%, and Adam et al.[16] reported 59%, whereas our overall figure was 61%. Comparisons of this type are admittedly tentative as they may be confounded by differences in (1) era of transplant, (2) age and other demographics, (3) medical and other risk factors, and (4) various study selection criteria. Regarding items (2) and (3), it is thus important to stratify by key factors related to survival, as done in Tables 3 and 4 of the present study. As Table 3 makes clear, life expectancy can vary greatly by age and other factors.

The computed life expectancies summarized the reduced survival prospects for ALD transplant patients. Even in persons with the most favorable characteristics displayed here (age 40 and no hepatitis C, Table 3c), the life expectancy at time of transplant was 18 years for males and 19 for females, compared with 39 and 43 in the general population. It is 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 ALD patients are similar to those given in two prior studies on life expectancy after transplant for HCC.[19,20] For example, for males aged 40 we report 17 years, while the two prior studies indicated 15 (HCC with cirrhosis), and 16 (NC-HCC), respectively.

After adjusting for demographics, we found that alcoholic hepatitis patients had survival similar to that of those with alcohol associated cirrhosis. Al-Saeedi et al.[22] and Singal et al.[23] similarly found no statistically significant difference. Lee et al.[24] documented that only roughly 35% of true alcoholic hepatitis patients were classified as cirrhotic. As alcoholic hepatitis is a small subset of overall ALD, these findings do not materially affect our results for those with alcohol associated

Table 3. Life Expectancies Based On The Multivariate Models Of Table 2 From Time Of Transplant, Including Comparison With The General Population.

a. Overall

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

b. Diabetes

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

Table 3. (continued)

c. Hepatitis C

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

d. Severe Hepatic Encephalopathy (HE)

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

(continued)

Table 3. (continued)

e. Length of Hospital Stay (LOS)

		Male				Female			
Starting time	Current Age	0 to 7 days	LOS 8 to 30 days	31 + days	All Transplants	General Population	0 to 7 days	LOS 8 to 30 days	31 + days	All Transplants	General Population
	40	19	16	14	17	39	19	17	14	18	43
From transplant	50	17	14	11	15	30	16	15	11	15	33
	60	14	12	9	13	22	14	13	9	13	25
	70	12	11	7	11	15	12	11	7	11	17
	41	20	16	16	18	38	19	17	16	18	42
1-yr posttransplant	51	17	14	13	15	29	17	15	13	15	33
	61	15	12	11	13	21	15	13	11	13	24
	71	13	11	9	11	14	13	11	9	11	16
	45	18	14	14	16	34	17	15	14	16	38
5-yrs posttransplant	55	15	12	12	13	26	15	13	12	14	29
	65	13	10	10	11	18	13	11	10	11	21
	75	11	9	8	9	11	11	9	8	10	13

cirrhosis. It does make more tentative our putative HR of 0.92 comparing the two, as those correctly coded may represent a biased subset of the larger group. Our finding that the hazard ratio differed by sex could also be viewed as tentative, as this may have been due to low power (due to few number of deaths) to find any such differences. Finally, we comment on why the difference in survival between the two groups appeared to vary by calendar year of transplant. We surmise that this reflects that getting a transplant as an alcoholic hepatitis patient in 2002 to 2012 was much more challenging than in more recent years, and thus that those who qualified in that period were, naturally, in better overall health.

We found that a history of hepatitis C was a statistically and practically significant risk factor (HR = 1.2, $P < 0.0001$). This finding mirrors that of many others, including Schaubel et al.[29] Legaz et al.[30] and Burra et al.[31] From Table 3c, the presence of hepatitis C affected the life expectancy by some 1 to 3 years, depending on patient age.

We also found that the need for dialysis within a week of transplant or ventilator support at time of transplant were associated with increased short-term mortality (37% and 59%, respectively). Both allocation and posttransplant treatments teams should be mindful of these findings. The development of acute kidney injury before liver transplantation has been shown to be associated with higher risk of chronic kidney disease after transplantation and associated with increased risk of mortality,[32] though the risk appears to be mostly short-term, as a separate study found that only 9% of such patients had kidney nonrecovery and needed chronic kidney replacement therapy within 6 months after transplantation.[33] Diabetes, older age, and post exposure to calcineurin inhibitors were important factors for renal non-recovery.[33]

A longer hospital stay portended significantly reduced long-term survival. For example, at age 40 the life expectancy was 19 years for males or females discharged within 7 days though only 14 years among those whose stay was 31 days or longer. Length of stay (LOS) is a surrogate for either past medical history or the presence of short-term complications, rather than a controllable variable (we would thus not recommend that all patients be discharged within 7 days to increase their survival prospects). This LOS correlated with recipient factors (such as age, sex, liver disease severity, prolonged pre-transplant admission, ICU stay, retransplantation, pretransplant nutritional status, pretransplant renal support), donor factors (such as the donor risk index) and early posttransplant complications and graft dysfunction.[34–36] Cardiac disease and congestive cardiac failure were two comorbidities with a strong impact on increased LOS,[37] though we were not able to examine these in the present study. On a related note, that the Karnofsky Performance Scale (KPS) functional status (HR of 1.30) and working status (HR of 1.41) were both highly related to survival was not surprising. These can be viewed as proxies for frailty, comorbid conditions, or more dire need for transplant. Potential drawbacks with the use of KPS have been discussed elsewhere.[19]

Liver transplant extends life expectancy and enhances quality of life[38] though there is significant shortage of available

Table 4. Empirical Survival Percentages For Select Groups Of The Present Sample And Comparison With Two Previously Published Results.

		Survival Time (Years)				
Factor	Subgroup	0	1	5	10	15
All	(None)	100%	91	78	61	46
Sex	Male	100%	91	77	61	45
	Female	100%	92	79	62	46
Age	35 to 44	100%	94	81	67	51
	45 to 54	100%	92	79	64	51
	55 to 64	100%	90	76	59	41
	65 to 74	100%	87	70	49	24
Adam et al.[16]	Alcoholic Cirrhosis	100%	86	75	59	43
Thuluvath et al.[17]	Alcoholic Cirrhosis	100%	90	78	60	-

organs for transplantation. The probability of a good outcome must be emphasized to achieve the maximum benefit for all transplants. Age alone does not contraindicate transplantation; however, evaluation of cardiopulmonary comorbidities, asymptomatic malignancies, nutritional status, and frailty, is crucial to ensure optimal results and avoid futile transplantation. The improvement in short- and long-term survival documented here is a testament to the medical community's increasing ability to make these judgements.

In the United States, most transplant centers believe that the recipient's life expectancy should not be much shorter than that of the graft (https://optn.transplant.hrsa.gov/resources/ethics/general-considerations-in-assessment-for-transplant-candidacy/). In the United Kingdom, allocation for the majority of adult patients is now based on the Transplant Benefit Score (TBS) -- the difference between (a) predicted posttransplant survival, and (b) survival on the transplant waiting list over a 5 year period, where survival is calculated based on 21 recipient and 7 donor criteria.[39] The TBS is thus a measure of the improvement in survival conferred by transplant. It is important to notice that if survival were calculated over the lifetime, rather than only over 5 years, the TBS would be equal to the improvement in life expectancy due to transplant.

Although we have documented improvements in survival after transplant for ALD, clinicians must continue to improve and focus on identifying patients who can have poor outcomes. It is necessary to have discussions with patients and families about overall survival and factors that can be modified to have better outcomes, as most ALD patients are relatively younger at the time of transplant. Patients with HCV infection should be treated either before or soon after transplant. It is also important to identify patients at risk of kidney failure, and who qualifies for safety net kidney transplant with no renal recovery after liver transplant. Adjustment of immunosuppression affecting kidney function and aggressive management of diabetes are also relevant considerations. The present study provides information that can be important for transplant centers especially in understanding overall life expectancy after transplant. In addition, with the increasing prevalence of transplant for alcoholic hepatitis, this study has shown that such patients can have equally good outcomes as other ALD patients.

Limitations in the present study include that we did not have information on smoking status, type of prior treatment, the amount of prior alcohol consumption, or on relapse status, all of which may be relevant to survival.[40–42] Also, this is an observational study; patients were not randomized to treatment. This may influence interpretation and application of the results. Further, the results given here may require adjustment for other factors, such as the presence of heart disease or cancer. A final limitation is that we did not have information on several social determinants of health, such as socio-economic status and health literacy.

Conclusion

Life expectancy after liver transplant in ALD is significantly reduced from normal. As expected, the major demographic factors related to survival were age, medical risk factors, and measures of overall health (such as the ability to work), while sex and Caucasian race were not practically or statistically significant. The results given here may prove helpful in medical decision-making regarding treatment for both liver and other conditions.

Disclaimer

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ORCID iD

Robert M. Shavelle https://orcid.org/0000-0001-5601-0759

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