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Life Expectancy After Liver Transplantation for Hepatocellular Carcinoma With Cirrhosis

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Abstract

Background: Hepatocelluar carcinoma, the most common primary liver cancer, has a historically dire prognosis. For hepatic cancer patients with cirrhosis who underwent liver transplantation, we sought to calculate life expectancies both at time of transplant and several years later, stratified by some key variables, and to determine if survival has improved in recent years. **Methods:** Data on 13,797 hepatic cancer patients with cirrhosis who underwent liver transplantation in the MELD era (2002-2018) from the US Organ Procurement and Transplantation Network database were analyzed using the Cox proportional hazards regression model and life table methods. **Results:** The major factors related to survival were age, donor age, transplant year, diabetes, functional status, and the presence of severe hepatic encephalopathy. Survival was significantly worse with increasing age and decreasing functional status level. There was no significant difference in survival between males and females. Survival improved over the study period, at 5% per calendar year during the first 5 years post transplant, and 1% per year thereafter. **Conclusions:** Life expectancies were markedly reduced from normal, even among 5-year survivors with the most favorable characteristics. Survival improved modestly over the years 2002-2018.

Keywords

liver transplant recipient, survival, epidemiology, life table, mortality, OPTN

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer[1,2] and a leading cause of cancer-related death worldwide.[2] It is the fifth leading cause of cancer death in the United States.[3] Despite advances in prevention, screening, and new technologies in both diagnosis and treatment, both incidence and mortality continue to rise.[2,3] Incidence is expected to increase further as hepatitis C, nonalcoholic steatohepatitis (NASH), alcohol abuse, and obesity become more prevalent in the United States.[2]

While multiple treatment modalities for HCC exist, only orthotopic liver transplantation, surgical resection, and ablation may be curative.[2,3] Hepatocellular carcinoma is the only solid cancer that has been approved for treatment with transplantation,[2] which is available for patients who meet or are downstaged into the Milan or University of California San Francisco (UCSF) criteria.[2]

Prior studies have identified recipient age, sex, histology, diagnosis year, race, diabetes, alcohol abuse, cirrhosis, and hepatitis B and C as factors related to survival.[2] Other characteristics, including grade and stage,[2] have been suggested as well, though only early stages receive transplant under the Milan or UCSF criteria.[4] Functional status at the time of transplant as measured by the Karnofsky Performance Status (KPS), has also been shown to be associated with survival,[5-8] inasmuch as severity of disability has been similarly recognized in older adults[9] and those with brain injury.[10] Limitations regarding the KPS,[5,6] however, may preclude its use in prognosis. We return to this issue in the discussion.

Previous research has reported various survival probabilities or the median survival time but has not provided life expectancies (the average survival times). Life expectancy is increasingly used as a factor in medical decision making, including in ocular hypertension,[11] surgery and informed consent,[12] hospice settings,[13] palliative care patients receiving radiotherapy,[14] long-term care facilities,[15] screening for colorectal cancer,[16] prostate cancer,[17] and the type of cardiac replacement valve.[18]

Life expectancy calculations require lengthy follow-up survival times or the use of life table methodology, which thus far has seen limited application in cancer research. The Organ Procurement and Transplantation Network (OPTN) data includes the requisite lengthy follow up, and the methods used

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here are robust. These allowed us to calculate life expectancy based on specific patient characteristics. We performed these both from the time of initial transplant and also conditioned upon patient survival to 1- or 5-years posttransplant. We also investigated whether survival has improved in recent years, and if so whether the improvement was concentrated in the early period following surgery. The life expectancy estimates provide an alternative framework for discussion of individual prognosis that may be more intuitive than those based on survival probabilities.

Materials and Methods

The OPTN database,[19] managed and maintained by the United Network for Organ Sharing (UNOS) under contract with the US Department of Health and Human Services, contains all national data on the candidate waiting list, organ donation and matching, and transplantation occurring in the United States since October 1, 1987.

The UNOS Standard Transplant Analysis and Research (STAR) Files, released March 15, 2019, contains organ transplantation data, including liver cases, from 1987 to 2018.[19] Data collected at the time of recipient registration include transplant date, patient description (at time of transplant), 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.

There were 130 665 single-organ first-time liver transplants. We then restricted attention to patients (1) aged 35 to 74, (2) having HCC with cirrhosis as the reason for transplant, and (3) receiving transplants in years 2002 to 2018. The first condition was applied so as to consider only the most common age range for transplant, and also because mortality rates over this range are known to follow the same rough doubling pattern over a 10-year period, whereas rates increase more quickly at much older ages. The second was invoked because HCC with cirrhosis is the most common etiology for liver transplant. The last was used 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 13 797 patients. The relatively small number of cases with missing values were either coded as missing or the observations were excluded from the analysis.

We analyzed the survival data using Kaplan-Meier (empirical) survival curves and both univariate and multivariate Cox proportional hazard regression models.[20] Analyses were performed using SAS software version 9.4 (SAS Institute). Possible explanatory variables included recipient age, sex, race, transplant year, diabetes, functional status, ascites, hepatic encephalopathy, and the factors that underlie the MELD score, as well as donor age. All variables were first assessed independently in univariate models, and then in multivariate models.

Based on the fitted Cox models, we estimated survival functions for various combinations of the covariate values, thereby constructing customized survival curves for various representative patient groups. Because the empirical survival data extended for only up to 17 years, we used a standard method to calculate the associated mortality rates at later/older ages.[21] Life expectancy was then calculated as the area under the survival curve, which is equivalent to constructing a life table.[22] Life expectancies were obtained at 3 time points: immediately prior to transplantation (which includes operative mortality), and also at 1 and 5 years posttransplant. For the latter 2 time points, we used the results from the same Cox models as used for time 0 (at diagnosis), with survival conditioned upon surviving to 1- or 5-years post. We used only the 1 Cox model rather than 3 separate ones because (a) all covariates were measured only at time of transplant, (b) refitting models at the later time points would reduce the sample size and concomitant accuracy of the results, and (c) 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.[22]

To investigate the trend toward improved survival, we considered separately the patient follow-up time periods beginning at transplant, 1-year and 5-years posttransplant. For the latter 2, we thus excluded persons who had died in the interim, and measured survival only from the latter point in time. We then fit models including only 4 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 posttransplant, 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 posttransplant, we thus 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

Characteristics of the 13 797 HCC liver transplant recipients are shown in Table 1. The mean age at transplant was 59 years, 79% were male, and 66% were Caucasian. Follow-up times ranged from 0.0 to 17.0 years (mean 4.3) and 3714 deaths occurred over the period.

Table 2 shows the univariate Cox survival models. The hazard ratios (HRs) shown in the table are based on models where only one factor was considered at a time. For example, the HR for males was 1.03, indicating that males had 3% higher mortality than females, and this difference was not statistically significant ($P = 0.43$). Regarding the calendar year of transplant (ie secular trend), persons who underwent liver transplantation in years 2014 to 2018 had 39% lower risk (HR = 0.61, $P < 0.001$) compared with those in years 2002 to 2005. A similar pattern emerged when survival time was instead measured from 1-year post transplant. At 5 years posttransplant, however, the crude trend reversed, with higher mortality in later years

Table 1. Demographics of Liver Recipients With Hepatocellular Carcinoma (N = 13 797).

Variable	Categories	N	%
Age (years)	35-44	261	2
	45-54	2991	22
	55-64	7331	53
	65-74	3214	23
Sex	Male	10929	79
	Female	2868	21
Race	White	9141	66
	All other	4656	34
Transplant year	2002-2005	1263	9
	2006-2009	2996	22
	2010-2013	4063	29
	2014-2018	5475	40
MELD score	6-10	6180	45
	11-18	5623	41
	19-24	943	7
	25-40	677	5
	Missing	374	3
Donor type	Living	283	2
	Deceased	13514	98
Weight	Underweight (BMI < 18)	89	1
	Normal weight (18-25)	3098	22
	Overweight (25-30)	5388	39
	Obese (30+)	5219	38
Diabetes (Type I, II, or other/unknown type)	No	9460	69
	Yes	4249	31
Functional status at transplant as measured by the Karnofsky Performance Status	100% (normal)	284	2
	90%	1100	8
	80%	2585	19
	70%	2595	19
	60%	2220	16
	50%	1596	12
	40%	1351	10
	30%	453	3
	20%	616	4
	10%	134	1
	Missing	863	6
Prior Malignancy	Yes	5887	43
	No	5242	38
	Unknown	2668	19
Ascites	No	5612	41
	Yes	8185	59
Hepatic encephalopathy	No	7398	54
	Mild (1-2)	5805	42
	Severe (3-4)	523	4
	Unknown/missing	66	0
Donor age	0-19	1204	9
	20-49	7417	54
	50-79	5126	37
	80+	50	0
INR*	Normal (1.1 or less)	3288	24
	Undefined (1.1-2.0]	8842	64
	Therapeutic (2.0-3.0]	1263	9
	High risk (>3.0)	404	3
Sodium*	Low	2985	22
	Normal	9870	72
	High	191	1
	Missing	750	5
Creatinine*	Low	5662	41
	Normal	5379	39
	High	2756	20
Total bilirubin*	Normal	4761	35
	High	9036	65
Albumin	Low	8178	59
	Normal	5599	41
	High	20	0
CMV IgG	Positive	6237	45
	Negative	2776	20
	Missing	4784	35

All percentages are column percentages.
*Components of the MELD score.
Abbreviations: INR, international nomalized ratio; CMV, cytomegalovirus.

(eg, HR = 1.15 in 2010-2013 compared with 2002-2005, though this was not statistically significant, $P = 0.24$).

The multivariate Cox models are shown in Table 3. The first 4 factors (age, sex, race, transplant year) were included in all multivariate models. We chose to include several statistically and practically insignificant factors (eg, sex with HR = 1.04, $P = 0.31$) to document their modest effects and to allow for comparison with other studies. For example, the Cox model with survival measured from the time of transplant showed that persons with diabetes had 20% higher mortality risk (HR = 1.20, $P < 0.001$) compared with those without diabetes, after controlling for age, sex, race, and transplant year. Similarly, persons with severe hepatic encephalopathy had 60% higher mortality, all else being equal. The HR for high albumin was 2.8 ($P < 0.01$), though this was based on only 20 people.

In our specific analyses of the secular trend toward improved survival, we first accounted for 3 basic demographic factors: age, sex, and race. We then added calendar year of transplant to the Cox model. For the model beginning at the time of transplant, the HR for calendar year was 0.95 ($P < 0.001$), indicating that mortality fell by 5% per year, on average, over the study period. When the analyses were begun at 1-year post, the HR was similarly 0.95 ($P < 0.001$). At 5 years posttransplant, however, the HR was only 0.99 ($P = 0.63$), indicating a 1% annual decrease in mortality per calendar year for those who had already survived 5 years post. This 1% annual decrease is similar to what occurred in the general population over the same time period. Not shown in the table are 2 results of particular interest. Firstly, for the limited 1-year period immediately following transplant (and thus excluding any exposure after 1 year), the HR was 0.94 ($P < 0.001$), indicating a 6% decrease per calendar year. Secondly, for the period limited to 1 to 5 years post, the HR was 0.95 ($P < 0.001$), indicating a 5% decrease. As noted above, the HR was 0.99 for the period beginning 5 years posttransplant. The improvement in mortality is thus largely restricted to the first 5 years posttransplant.

Tables 4-7 show life expectancies stratified by time since transplant, age, sex, and various risk factors: diabetes,

Table 2. Univariate Hazard Ratios (*P*-Values) From Cox Proportional Hazards Regression Models With Only the One Stated Factor.

Variable	Categories	From transplant	For 1-year survivors	For 5-year survivors
Age (years)	(Continuous)	1.02 (<0.001)	1.02 (<0.001)	1.04 (<0.001)
Sex	Female	1 (ref)	1 (ref)	1 (ref)
	Male	1.03 (0.43)	1.06 (0.27)	1.05 (0.61)
Race	White	1.14 (<0.001)	1.24 (<0.001)	1.43 (<0.001)
	All other races	1 (ref)	1 (ref)	1 (ref)
Transplant year	2002-05	1 (ref)	1 (ref)	1 (ref)
	2006-09	0.88 (<0.01)	0.94 (0.31)	1.13 (0.18)
	2010-13	0.73 (<0.001)	0.78 (<0.001)	1.15 (0.24)
	2014-18	0.61 (<0.001)	0.66 (<0.001)	N/A
	(Continuous)	0.96 (<0.001)	0.97 (<0.001)	1.01 (0.46)
MELD score	6-10	1 (ref)	1 (ref)	1 (ref)
	11-18	0.95 (0.18)	0.88 (0.04)	0.83 (0.02)
	19-24	1.05 (0.47)	0.97 (0.75)	1.00 (0.98)
	25-40	1.22 (<0.01)	0.86 (0.17)	0.96 (0.83)
	Missing	1.19 (0.03)	0.91 (0.37)	0.21 (0.83)
Donor type	Living	1 (ref)	1 (ref)	1 (ref)
	Deceased	0.90 (0.35)	0.84 (0.18)	0.65 (0.03)
Weight	Underweight	1.26 (0.19)	1.09 (0.70)	0.96 (0.91)
	Normal weight	1 (ref)	1 (ref)	1 (ref)
	Overweight	0.98 (0.63)	1.06 (0.30)	1.03 (0.73)
	Obese	0.94 (0.16)	0.96 (0.44)	0.85 (0.10)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.21 (<0.001)	1.28 (<0.001)	1.61 (<0.001)
Functional status	100% (Normal)	1 (ref)	1 (ref)	1 (ref)
at transplant	90%	1.03 (0.84)	1.13 (0.42)	1.21 (0.44)
	80%	1.44 (0.27)	1.25 (0.11)	1.35 (0.19)
	70%	1.21 (0.10)	1.34 (0.38)	1.53 (0.06)
	60%	1.23 (0.98)	1.31 (0.06)	1.27 (0.31)
	50%	1.45 (<0.01)	1.44 (0.01)	1.47 (0.12)
	40%	1.27 (0.06)	1.29 (0.10)	1.46 (0.14)
	30%	1.39 (<0.001)	1.14 (0.50)	1.34 (0.39)
	20%	2.00 (<0.001)	1.59 (<0.01)	0.58 (0.11)
	10%	2.16 (<0.001)	1.74 (0.03)	2.87 (0.02)
	Missing	1.52 (<0.001)	1.4 (0.02)	1.23 (0.37)
Prior Malignancy	Yes	1.13 (0.04)	1.01 (0.95)	0.80 (0.16)
	No	1.18 (<0.01)	1.02 (0.77)	0.91 (0.55)
	Unknown	1 (ref)	1 (ref)	1 (ref)
Ascites	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.17 (<0.001)	1.06 (0.13)	1.12 (0.11)
Hepatic	No	1 (ref)	1 (ref)	1 (ref)
encephalopathy	Mild (1-2)	1.15 (<0.001)	1.10 (0.04)	1.12 (0.12)
	Severe (3-4)	1.55 (<0.001)	1.30 (0.01)	1.56 (0.01)
	Unknown	1.60 (<0.01)	1.46 (0.07)	1.33 (0.40)
Donor age	<20	1 (ref)	1 (ref)	1 (ref)
	20 and older	1.29 (<0.001)	1.30 (<0.001)	1.30 (0.03)
INR	$\leq$2.0	1 (ref)	1 (ref)	1 (ref)
	>2.0	1.15 (<0.01)	0.99 (0.88)	1.13 (0.28)
Sodium	Low	1.20 (<0.001)	1.27 (0.02)	1.28 (<0.01)
	Normal	1 (ref)	1 (ref)	1 (ref)
	High	1.31 (0.04)	1.15 (0.41)	1.11 (0.74)
	Missing	1.33 (<0.001)	1.17 (0.02)	1.03 (0.74)
Creatinine	Low	0.91 (0.02)	0.92 (0.07)	0.86 (0.05)
	Normal	1 (ref)	1 (ref)	1 (ref)
	High	1.38 (<0.001)	1.21 (<0.001)	1.27 (0.01)
Total bilirubin	Normal	1 (ref)	1 (ref)	1 (ref)
	High	1.00 (0.97)	0.91 (0.03)	0.85 (0.03)
Albumin	Low	1.13 (<0.001)	1.13 (<0.01)	1.19 (0.02)
	Normal	1 (ref)	1 (ref)	1 (ref)

(continued)

Table 2. (continued)

Variable	Categories	From transplant	For 1-year survivors	For 5-year survivors
CMV IgG	High	2.59 (<0.01)	1.82 (0.23)	3.9 (0.05)
	Negative	1 (ref)	1 (ref)	1 (ref)
	Positive	1.00 (0.97)	0.97 (0.55)	0.82 (0.01)
	Missing	0.89 (0.03)	1.04 (0.59)	1.09 (0.52)

functional status, and presence of ascites/hepatic encephalopathy. We do not show tables for all of the other factors for 3 reasons. Firstly, many of the factors were not both statistically and practically significant (eg, donor type, or patient weight) once the others were taken into consideration. Secondly, the effects of some factors can be inferred from the results shown (e., INR > 2.0 has an effect similar to that of diabetes (see Table 3, HR = 1.23 cf. 1.20). Thirdly, in addition to tables for each factor singly, there would be tables for 2 factors at a time, 3 factors, etc. For consistency, all life expectancies were computed for Caucasian patients (though the results for other races are nearly identical).

Consider a male age 40 who recently underwent transplantation (Table 4). His life expectancy from the time of transplant is approximately 16 additional years, rather than the 39 years that would obtain in the general population. At 1-year post, at age 41, it would be 17 years compared with 38. If he survives 5 years, his life expectancy at age 45 would be 15 additional years, compared with 34 years in the general population. The life expectancy increased from 16 years at age 40 to 17 years at age 41 because of the high initial mortality in the first-year post transplant. This rather high mortality is also reflected in Figure 1, where we see the survival curves as being relatively steep in the first few years posttransplant, and then becoming less steep over time. We return to this issue in the discussion.

However, if our 40-year-old male had diabetes, his life expectancies at transplant, 1 year, and 5 years post-transplant would instead have been modestly lower (Table 5) at 15, 15, and 14, years, respectively. The other scenarios of the Table show the same pattern. Namely, life expectancy after liver transplantation in HCC with cirrhosis is much reduced from normal, even among persons who survive 1- or 5- years post diagnosis.

Consider another male age 40, who was at the 10-20% functional level at time of transplant (Table 6). His life expectancy is approximately 11 years, compared with 17 years in the healthiest patients at the 80-100% functional level and 39 years in the general population. Table 7 similarly shows results stratified by the presence of ascites and/or hepatic encephalopathy.

The computed life expectancies summarize the reduced survival prospects for HCC transplant patients who have cirrhosis. Even in persons with the most favorable characteristics displayed here (age 40 and 80-100% functional status), the life expectancy at time of diagnosis is only 17 years for males and 18 for females, compared with 39 and 43 in the general population. It is of course possible to calculate life expectancies for any other combinations of variable levels from the models shown in Table 3.

Discussion

Life expectancy after liver transplant in HCC is significantly reduced from normal. Also, as expected, age and functional status were major factors associated with survival. In addition, and consistent with the prior literature,[1,2,23,24] we found that persons who underwent transplant in more recent years, all else being equal, had better survival, and those with diabetes, ascites, and hepatic encephalopathy had worse survival.

In our initial presentation of results, we noted that the life expectancy of a 40-year-old male was 16 additional years at age 40 and 17 years at age 41. That the remaining life expectancy increased even though he aged a year is due to his surviving the high initial mortality rate in the first-year post transplant. This seeming paradox is commonly known as the "healthy survivor effect," and indeed such conditional survival has been studied in this population.[25]

The life expectancies reported here are consistent with the survival probabilities given in prior literature. For example, Bouami et al,[26(Figure 2A, p503)] shows median survival times of 9 years for patients aged 56 and over, and 14 years for those aged 47-55. Also, Pischke et al,[27(Figure 2A, p431)] indicates a median of 13 years for patients older than age 53. The corresponding life expectancies would be several years higher than these medians, and thus keeping with the results shown in Table 2, for example, though neither of the aforementioned studies is specific to HCC patients. Other studies such as Li et al[28] and Malik et al[29] do not report separately by age, so it is less feasible to compare with the age-specific figures given here.

It may be worth distinguishing a related group of 4358 OPTN patients aged 35-74 who also underwent liver transplant in 2002-2018 due to HCC, but in their case without mention of cirrhosis in the etiology. For this separate subset, the resulting life expectancies (not shown) were similar to, though lower than, those given in Table 4. This is perhaps not surprising, as resection (rather than transplant) is the preferred treatment for patients without cirrhosis and such patients would generally have a better prognosis than the present group; yet the 4358 patients who ultimately required transplant as well may represent a less favorable subset who had a prior failed resection, recurrence of cancer, multiple primaries, or other more complex presentation.[2] We hope to report separately on this comparison later.

Table 3. Multivariate Hazard Ratios (*P*-Values) From Cox Proportional Hazards Regression Models With Multiple Factors.*

Variable	Categories	From transplant	For 1-year survivors	For 5-year survivors
Age (years) *	(Continuous)	1.02 (<0.001)	1.02 (<0.001)	1.04 (<0.001)
Sex *	Female	1 (ref)	1 (ref)	1 (ref)
	Male	1.04 (0.31)	1.06 (0.24)	1.08 (0.37)
Race *	White	1.14 (<0.001)	1.24 (<0.001)	1.43 (<0.001)
	All other races	1 (ref)	1 (ref)	1 (ref)
Transplant year *	(Continuous)	0.95 (<0.001)	0.95 (<0.001)	0.99 (0.63)
MELD score	6-10	1 (ref)	1 (ref)	1 (ref)
	11-18	0.94 (0.11)	0.87 (<0.01)	0.84 (0.02)
	19-24	1.07 (0.34)	1.98 (0.82)	1.04 (0.77)
	25-40	1.31 (<0.001)	0.91 (0.38)	1.04 (0.84)
	Missing	1.00 (0.99)	0.80 (0.03)	0.85 (0.28)
Donor type	Living	1 (ref)	1 (ref)	1 (ref)
	Deceased	0.91 (0.38)	0.85 (0.23)	0.67 (0.05)
Weight	Underweight	1.19 (0.31)	1.05 (0.84)	0.89 (0.76)
	Normal weight	1 (ref)	1 (ref)	1 (ref)
	Overweight	0.97 (0.47)	1.03 (0.53)	0.99 (0.97)
	Obese	0.95 (0.28)	0.95 (0.37)	0.82 (0.04)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.20 (<0.001)	1.26 (<0.001)	1.55 (<0.001)
Functional status at transplant	90-100%	1 (ref)	1 (ref)	1 (ref)
	70-80%	1.18 (<0.01)	1.19 (0.01)	1.21 (0.11)
	50-60%	1.35 (<0.001)	1.28 (<0.01)	1.14 (0.31)
	30-40%	1.39 (<0.001)	1.22 (0.03)	1.25 (0.17)
	10-20%	2.14 (<0.001)	1.58 (<0.001)	1.64 (0.01)
	Unknown	1.16 (0.06)	1.04 (0.70)	1.06 (0.73)
Prior Malignancy	Yes	1.15 (0.02)	1.02 (0.78)	0.83 (0.23)
	No	1.21 (0.001)	1.05 (0.55)	0.93 (0.65)
	Unknown	1 (ref)	1 (ref)	1 (ref)
Ascites	No	1 (ref)	1 (ref)	1 (ref)
	Yes	1.15 (<0.001)	1.05 (0.27)	1.12 (0.14)
Hepatic encephalopathy	No	1 (ref)	1 (ref)	1 (ref)
	Mild (1-2)	1.14 (<0.001)	1.09 (0.04)	1.15 (0.06)
	Severe (3-4)	1.60 (<0.001)	1.32 (<0.01)	1.59 (0.01)
	Unknown	1.52 (0.02)	1.41 (0.11)	1.35 (0.38)
Donor age	<20	1 (ref)	1 (ref)	1 (ref)
	20 and older	1.31 (<0.001)	1.30 (<0.001)	1.26 (0.06)
INR	$\leq$2.0	1 (ref)	1 (ref)	1 (ref)
	>2.0	1.23 (<0.001)	1.05 (0.48)	1.21 (0.10)
Sodium	Low	1.21 (<0.001)	1.13 (0.01)	1.29 (<0.01)
	Normal	1 (ref)	1 (ref)	1 (ref)
	High	1.29 (0.05)	1.13 (0.46)	1.08 (0.81)
	Missing	1.00 (0.96)	0.92 (0.32)	1.13 (0.37)
Creatinine	Low	0.94 (0.12)	0.95 (0.30)	0.90 (0.18)
	Normal	1 (ref)	1 (ref)	1 (ref)
	High	1.39 (<0.001)	1.22 (<0.001)	1.27 (0.01)
Total bilirubin	Normal	1 (ref)	1 (ref)	1 (ref)
	High	0.99 (0.88)	0.91 (0.02)	0.86 (0.05)
Albumin	Low	1.13 (<0.001)	1.13 (<0.01)	1.23 (<0.01)
	Normal	1 (ref)	1 (ref)	1 (ref)
	High	2.80 (<0.01)	2.00 (0.17)	4.9 (0.02)
CMV IgG	Negative	1 (ref)	1 (ref)	1 (ref)
	Positive	1.02 (0.71)	1.01 (0.92)	0.84 (0.03)
	Unknown/missing	1.05 (0.34)	1.13 (0.08)	1.09 (0.51)

* The results shown here are based on multiple Cox models, each of which included terms for age, sex, race, and transplant year. For example, the hazard ratios for MELD score are based on a model with 5 factors. The hazard ratios for age, sex, race, and transplant year of course varied by model. For simplicity, the values shown here are the ones from the model with MELD score.

Abbreviations: INR, international normalized ratio; CMV, cytomegalovirus.

Patients in the OPTN database were not randomized to receiving transplantation, and indeed not all waitlist patients received an offer. Treatment decisions were made on a case-by-case basis, as determined by the Milan or the UCSF criteria.[4] These criteria are known to be highly successful in selecting patients who will yield favorable outcome after transplant,[4] as attested to by the year-over-year 5% decrease in short-term mortality documented here.

As noted in the Introduction, weaknesses in the KPS have been discussed.[5,6] In the present context, it is important to note that any measurement error (ie, additional variability) in obtaining patient KPS scores, such as would be demonstrated by poor test-retest or inter-rater reliability, would tend to dilute the putative effects of this factor. That is, if this is true, the relative risks we observed here are too small, and the true effect of KPS is larger. In addition, any low sensitivity of the scale or systematic bias on the part of some centers or evaluators would also similarly dilute the effects. That is, the resulting hazard ratios would tend toward 1.0, or a null effect. That the hazard ratios here are quite large indicates that KPS is highly associated with survival. Whether this factor is confounded with others, or represents an unobserved/latent factor, such as being correlated with outcome, is beyond the scope of the present work. We would note, however, that any systematic bias in the assignment of KPS scores would make application of the results here problematic, as one would need to use the same criteria in practice in order to obtain the corresponding life expectancy.

Table 4. Life Expectancies Based on the "From Transplant" Model of Table 3: Overall.

Starting Time	Current Age	Male		Female	
		All Tx	GP	All Tx	GP
Tx	40	16	39	17	43
	50	14	30	15	33
	60	12	22	13	25
	70	11	15	11	17
1-yr post tx	41	17	38	17	42
	51	15	29	15	33
	61	13	21	13	24
	71	11	14	12	16
5-yrs post tx	45	15	34	16	38
	55	13	26	14	29
	65	12	18	12	21
	75	10	11	10	13

The HCC staging system[30] was not available in the OPTN data. However, only patients who have early stage (most stage I and some stage II in the tumor, nodes, and metastases system) HCC are eligible for liver transplantation.[3] Moreover, the OPTN database does not currently provide information on whether the patient was treated with any form of chemotherapy, radiation, or other neoadjuvant therapy. This is a notable limitation, as such therapy is now known to be increasingly advantageous, especially in special cases or in concert with other therapies.[2,3] The results given here are therefore not specific to the presence of auxiliary treatments.

Guerrini et al[23] showed that HCC-MELD—a prognostic score developed by combining alpha-fetoprotein, MELD, and tumor size to derive the probability of dropping from a wait list—was significantly associated with survival. However, the OPTN database does not have alpha-fetoprotein; we therefore could not examine this potential explanatory variable.

The methods used here are standard and robust. The Cox model (using all the data) gives estimates that are more precise than that of the (smaller) cohort approach of Kaplan-Meier. That is, under model assumptions of proportional hazards, the

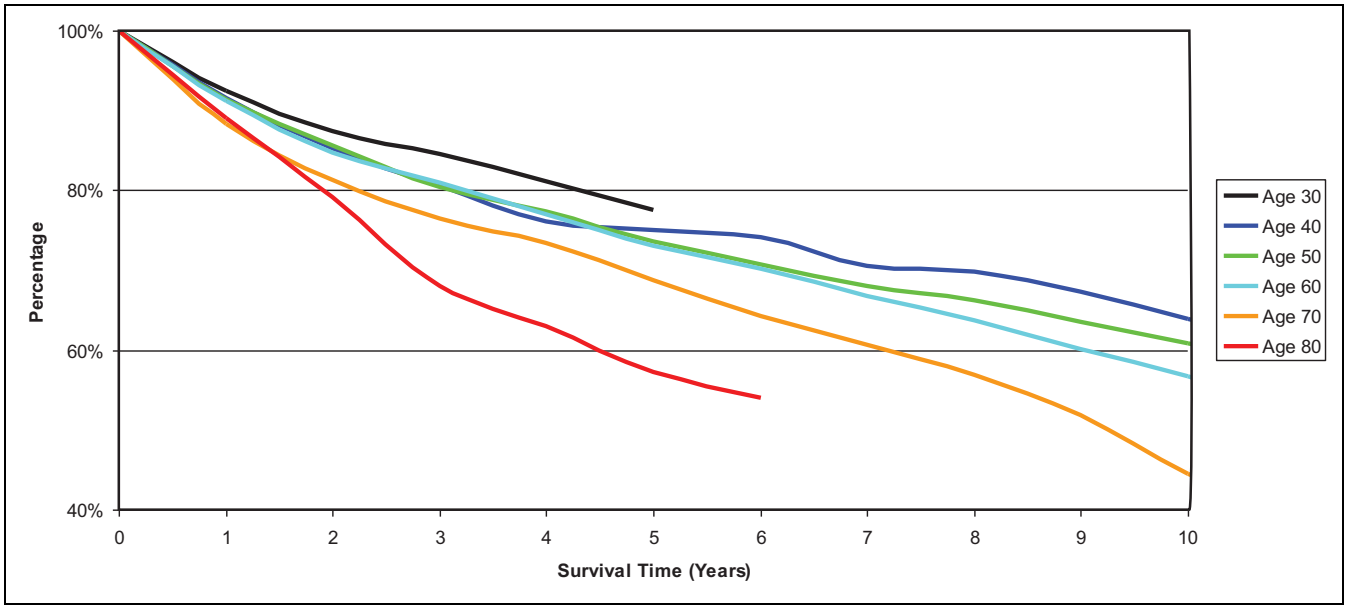

Figure 1. Empirical survival curves by age at transplant.

standard errors of the estimates are smaller. As well, the Cox model allows calculation of survival figures for various combinations of risk factors that might otherwise result in rather small (Kaplan-Meier) cohorts with large standard errors, or possibly even combinations not present in the existing data. The results can be applied to reflect a particular patient's clinical profile and may provide some reasonable guidance even for transplant recipients whose medical history is quite different from the norm. For example, one could consider non-white females, age 43, who underwent transplant in 2013 for HCC and cirrhosis, and had a longstanding history of diabetes.

Relatively simple main effects multivariate models were fitted here. More complicated models are possible, including those both using a subset of the data, perhaps also based on time since diagnosis, and including various interaction terms. The model fitting process allows for the adjustment for many risk factors, and omnibus testing of their possible effects. For example, as reported here, we tested for and documented a secular trend in survival while simultaneously accounting for possible calendar-year differences in patient age, sex, and race.

A limitation of the analyses here is that we used only information collected at the time of transplant listing and initial transplant. We did not rely on medical status at future time points. The results given here are thus unbiased at time of transplant, but only unbiased at later time points (eg, at 5 years post diagnosis) if the patient is average with respect to the extant survivors. A further limitation is that data on certain widely known comorbid factors (eg, smoking status, hypertension) are not presently available at time of transplant in the OPTN data. Nevertheless, numerous key factors are available—such as age and functional status—and relevant clinical distinctions can thus be made, which together allow accurate computations of life expectancy.

Table 5. Life Expectancies Based on the "From Transplant" Model of Table 3: Diabetes.

		Male				Female			
		Diabetes				Diabetes			
Starting Time	Current Age	Yes	No	All Tx	GP	Yes	No	All Tx	GP
Tx	40	15	17	16	39	15	17	17	43
	50	13	15	14	30	14	15	15	33
	60	11	13	12	22	12	13	13	25
	70	10	11	11	15	10	12	11	17
1-yr post tx	41	15	17	17	38	16	17	17	42
	51	13	15	15	29	14	15	15	33
	61	12	13	13	21	12	14	13	24
	71	10	12	11	14	11	12	12	16
5-yrs post tx	45	14	16	15	34	15	16	16	38
	55	12	14	13	26	13	14	14	29
	65	11	12	12	18	11	12	12	21
	75	10	11	10	11	10	11	10	13

Table 6. Life Expectancies Based on the "From Transplant" Model of Table 3: Functional Status.

		Male						Female					
		Functional Status						Functional Status					
Starting time	Current Age	10-20%	30-50%	60-70%	80-100%	All Tx	GP	10-20%	30-50%	60-80%	80-100%	All Tx	GP
	40	11	15	17	17	16	39	12	16	17	18	17	43
Tx	50	10	14	15	15	14	30	10	14	15	15	15	33
	60	9	12	13	13	12	22	9	12	13	13	13	25
	70	7	10	11	11	11	15	8	11	11	12	11	17
	41	12	16	17	17	17	38	12	16	18	18	17	42
1-yr	51	10	14	15	15	15	29	11	14	15	15	15	33
Post	61	9	12	13	13	13	21	9	12	13	13	13	24
	71	8	11	11	11	11	14	8	11	12	12	12	16
	45	11	14	16	16	15	34	11	15	16	16	16	38
5-yr	55	10	13	14	14	13	26	10	13	13	14	14	29
Post	65	8	11	12	12	12	18	9	11	12	12	12	21
	75	7	10	10	10	10	11	8	10	11	11	10	13

10%—Moribund, fatal processes progressing rapidly
20%—Very sick, hospitalization necessary, active treatment necessary
30%—Severely disabled, hospitalization is indicated, death not imminent
40%—Disabled, requires special care and assistance
50%—Requires considerable assistance and frequent medical care
60%—Requires occasional assistance but is able to care for needs
70%—Cares for self, unable to carry on normal activity or active work
80%—Normal activity with effort, some symptoms of disease
90%—Able to carry on normal activity, minor symptoms of disease
100%—Normal, no complaints, no evidence of disease

Table 7. Life Expectancies Based on the "From Transplant" Model of Table 3: Presence of Ascites/Hepatic Encephalopathy.

		Male						Female					
Starting time	Current Age	Both Yes	Ascites Only	HE Only	Both No	All Tx	GP	Both Yes	Ascites Only	HE Only	Both No	All Tx	GP
	40	16	17	16	18	16	39	16	17	17	19	17	43
Tx	50	14	15	14	16	14	30	14	15	14	16	15	33
	60	12	13	12	13	12	22	12	13	13	14	13	25
	70	10	11	10	12	11	15	11	11	11	12	11	17
	41	16	17	16	18	17	38	17	18	17	19	17	42
1-yr	51	14	15	14	16	15	29	14	15	15	16	15	33
post	61	12	13	12	14	13	21	13	13	13	14	13	24
	71	11	11	11	12	11	14	11	12	11	12	12	16
	45	15	16	15	17	15	34	15	16	16	17	16	38
5-yr	55	13	14	13	15	13	26	13	14	14	15	14	29
post	65	11	12	11	13	12	18	12	12	12	13	12	21
	75	10	10	10	11	10	11	10	11	10	11	10	13

Authors' Note

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