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Life Expectancy after Liver Transplantation for Non-Cirrhotic Hepatocellular Carcinoma

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Abstract:

Background: Hepatocelluar carcinoma typically occurs with underlying cirrhosis. However roughly 20% of cases arise in a non-cirrhotic liver. There is limited literature that addresses the long-term survival of the narrow subgroup who received transplantation. For such patients we sought to calculate life expectancies both at time of transplant and several years later, stratified by key risk factors, and to determine if survival has improved in recent years. Such information can be helpful in making treatment decisions.

Methods: Data on 4,373 non-cirrhotic HCC 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: Demographic and past medical history factors related to survival were patient age, donor age over 20, and the presence of ascites or severe hepatic encephalopathy. Survival did not vary by race or sex. HCC-specific factors significantly related to survival were the total number of tumors, extrahepatic spread, lymph node involvement, satellite lesions, micro- or macrovascular invasion, tumor differentiation (grade), and pre-transplant treatment. Survival improved over the study period, at 4% per calendar year during the first 5 years post transplant and 1% per year thereafter.

Conclusions: Life expectancy in non-cirrhotic HCC transplant patients is much reduced from normal, and varies according to tumor-related factors. Survival improved modestly over the study period.

Introduction

Hepatocellular carcinoma (HCC) typically occurs with underlying cirrhosis. However roughly 20% of cases arise in a non-cirrhotic liver (NC-HCC), with causes including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), viral hepatitis, genotoxic substances (eg alcohol, aflatoxin B1, iron overload, industrial carcinogens, and chronic anabolic androgen steroid abuse), inherited diseases or metabolic disorders, germline mutations, and hepatic adenomas.[1] The peculiar nature of these NC-HCC tumors has been described in detail.[2]

While survival of the larger group of HCC transplantation patients with cirrhosis has been studied, there are apparently few studies specific to the long-term survival of NC-HCC transplantation patients. A 5-year study by Mergental et al.[3] identified 105 European patients with unresectable NC-HCC, where transplantation was the primary treatment in 62 patients (59%) and was the rescue therapy in the other 43 (41%); only 12 initially met the Milan criteria. The authors identified factors related to survival, but did not report life expectancies nor stratify results by age or other factors, nor did Zakaria et al.[4] or Mehta et al.[5]

Prior studies on HCC transplant patients (without regard for cirrhosis status) have identified patient demographics (age, sex, year, race) and medical conditions (eg, diabetes, alcohol abuse, cirrhosis, and hepatitis B and C) as factors related to survival.[6] Tumor specific factors, including grade and stage,[7] have been suggested as well, though only early stages receive transplant under the Milan or UCSF criteria.[8] Several studies have also identified risk factors for resection patients. For example, Lewis et al.[9] reported on the overall survival of 42 patients (mean age 62, 67% male) who were treated by resection for NC-HCC. They found that disrupted/absent tumor capsule, vascular invasion, obesity, elevated alkaline phosphatase, and

possibly tumor size > 10 cm were significantly associated with survival, though the authors only reported the *P*-values without indicating the magnitudes of their effects on survival.

As noted, previous research has reported some survival probabilities in the NC-HCC group, but has not provided life expectancies (the average survival times). Life expectancy is increasingly used as a factor in medical decision making.[10-14] Its calculation requires long-term follow-up of patients and the use of life table methodology, the latter of which has thus far seen rather limited application in cancer research. The Organ Procurement and Transplantation Network (OPTN) data includes the requisite lengthy follow up, and the methods used here are standard. These enabled us to address our primary research goal: to calculate life expectancies for select patient subgroups, both from the time of initial transplant and conditioned upon patient survival to 1 or 5 years posttransplant. Secondarily, we also examined if survival improved over the study period (ie, if mortality rates decreased, all else being equal).

Design/Methods

Setting/Population

We analyzed de-identified data from the OPTN database,[15] 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 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.[15] 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, 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 (1) having NC- HCC as the reason for transplant (OPTN etiology code 4400), (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, and because mortality rates over this range in the general population are known to follow the same rough doubling pattern over a 10-year period, whereas rates increase more quickly at older ages. 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 4373 patients.

Data Analysis

The survival data were analyzed using Kaplan-Meier (empirical) survival curves and both univariate and multivariate Cox proportional hazard regression models.[16] Analyses 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 listing, as well as donor age and tumor related factors (which became available in OPTN in 2012) such as number of tumors, lymph node involvement, and existence of vascular invasion. The relatively small number of cases with missing values for any covariates were either excluded from various subanalyses or the values were coded as missing. The factors were first assessed independently in univariate models, and then in multivariate models. To aid comparisons with other literature, we included age, sex, and race in all models. Further, 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 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, we used a standard method to calculate the associated mortality rates at later/older ages.[17] Life expectancy was calculated as the area under the survival curve,[18] which is equivalent to constructing a life table.[19] 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 to 1- or 5-years post. We thus opted to use only the one Cox model rather than three; we did so because (a) the risk factors were measured only at time of transplant, (b) had we refit models at the later time points, using only the conditional data, we would have reduced the sample sizes and resulting accuracies of the results, (c) further investigation revealed that use of separate models did not materially affect the results, and (d) in any event, only the conditional survival data were used to compute the conditional results. Life expectancy was compared with that of the age- and sex-matched US general population.[19]

We analyzed secular trends in survival by separately considering patient follow-up time periods beginning at transplant, 1 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 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 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 4373 NC-HCC liver transplant recipients are shown in **Table 1**. The mean age at transplant was 59 years, 77% were male, and 66% were Caucasian. Follow-up times ranged from 0.0 to 16.5 years (mean 4.3) and there were 1227 deaths over the period.

The hazard ratios (HRs) from the univariate Cox survival models are presented in **Table 2**. It is important to note that these HRs are based on models where only one factor was considered at a time. For example, from time of transplant, the HR for persons with diabetes was 1.14, indicating that, overall, such persons had 14% higher mortality risk than those without diabetes. Also, patients transplanted in calendar years 2014 to 2018 had 36% lower risk (HR=0.64, $P<0.001$) from the time of transplant compared with those transplanted in years 2002 to 2005 (results not shown). A similar pattern emerged when survival time was measured from 1-year posttransplant. At 5 years posttransplant, however, the differences were much smaller (eg, HR=1.02 in 2006-2009 and 0.94 in 2010-2013 compared with 2002-2005) and were not statistically significant, $P=0.92$ and 0.75).

The multivariate Cox models of **Table 2** each included the first four factors (age, sex, race, transplant year). We chose to include several statistically and practically insignificant factors (eg, sex with HR = 1.02, $P = 0.77$) 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 ascites had 24% higher mortality risk (HR=1.24, *P<0.001*) compared with those without, after controlling for age, sex, race, and transplant year. Similarly, persons with severe hepatic encephalopathy had 37% higher mortality, all else being equal. As is evident in **Table 2**, the tumor related factors that came into use in 2012 (number of tumors, extrahepatic spread, lymph node involvement, satellite lesions, pre-transplant treatment, vascular invasion, and worst tumor differentiation) demonstrated relatively larger effects than the demographic or medical factors.

In our analyses of 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. For the model based on survival data beginning at the time of transplant, the HR for calendar year was 0.96 ($P<0.001$), indicating that mortality fell by 4% per year, on average, over the study period. When the analyses were begun at 1-year post, the HR was similarly 0.96 ($P<0.001$). At 5 years posttransplant, however, the HR was only 0.99, indicating a 1% annual decrease in mortality per calendar year for those who had already survived 5 years post, though it was not statistically significant from 1.00 ($P=0.75$). This 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 1-5 years posttransplant. For this the HR was 0.96 ($P<0.001$), again indicating a 4% 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 is thus largely restricted to the first 5 years posttransplant, and did not appear to vary by age, sex, or race ($P>0.05$ in all cases; results not shown).

Life expectancies are shown in **Tables 3 and 4**, stratified by time since transplant, age, sex, and various risk factors: diabetes, presence of ascites/hepatic encephalopathy, and some of

the 7 tumor related factors. We do not show tables for all the other factors for 4 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 (eg, INR >2.0 has an effect similar to that of ascites (see Table 2, HR = 1.21 cf. 1.24). Thirdly, in addition to tables for each factor singly, there could be tables for two factors at a time, three factors, etc. Finally, results are not shown stratified by the presence of lymph node involvement, as the fraction with such is only 1%, nor for those with extrahepatic spread (0.3%), no pretransplant treatment (2%), or satellite lesions (3%).

For consistency, all life expectancies were computed for Caucasian patients (though the results for other races are nearly identical). 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, to present clear and easily applicable results. Had we constructed more complicated models, the standard errors would have been larger and the applicability more limited. The basic results from Table 3a, which do not consider any medical or tumor 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 15 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) also be 15 years compared with 38. If he survives 5 years, his life expectancy at age 45 would be 13 additional years, compared with 34 years in the general population. If the same 40-year-old male had no vascular invasion (**Table 4a**), his life expectancy would be 18 years, and if he had such

invasion it would be 13 years. Notice that these two values, best and worst cases, properly straddle the overall value of 15 years.

The computed life expectancies summarize the reduced survival prospects for NC-HCC transplant patients. Even in persons with the most favorable characteristics displayed here (age 40 and complete tumor necrosis, **Table 4b**), the life expectancy at time of transplant is 21 years for both males and 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 2. For ease of comparison with other studies, **Table 5** shows survival probabilities for various combinations of age, sex, vascular invasion (micro or macro), and tumor differentiation.

Discussion

The fraction of HCC patients without cirrhosis has been reported variously as 12%,[20] 15%,[9] 16%,[21] and 36%[22] overall, and up to 37%[23] or 40%[24] in subgroups with NAFLD. A prior study of OPTN HCC transplant patients with cirrhosis[6] included 13 797 persons aged 35-74. The total herein for NC-HCC was 4373, of which 30% had a diagnosis of HBV. The overall percentage without cirrhosis between these two OPTN HCC transplant studies is thus 4,373 / 18,170 = 24%, well within the above reported range.

The overall survival percentages implicit in **Tables 3** and **4** and shown in **Table 5** are consistent with those of other studies on NC-HCC transplant patients. For example, Mergental et al.[3] reported 1- and 5-year survival rates of 84% and 49%, respectively, in 105 European patients. The corresponding figures (not shown) for the present sample for the same age range and calendar years are 86% and 62%. It bears noting that the patients in Mergental, while much younger (median age 40) than the present sample (average age 59), were transplanted in 1994-2005, mostly before the MELD era. Two more recent studies bear mention. Zakaria et al.[4]

reported 1- and 5-year rates of 89% and 67% in 62 Egyptian patients transplanted in 2003 to 2014, with average age 49, and Mehta et al.[5] reported 95% and 80% in 187 California patients of median age 58. Comparisons of this type are admittedly tentative, however, as they are may be confounded by differences in (*a*) era of transplant, (*b*) age and other demographics, (*c*) medical and tumor-related risk factors, and (*d*) various study selection criteria. Regarding items (*b*) and (*c*), it is thus important to stratify by key factors related to survival, as done in Tables 3-5 of the present study.

The life expectancies given here for NC-HCC transplant patients are very similar to those given in a similar prior study on those with HCC and cirrhosis.[6] For example, for males aged 40 we reported 15 additional years, but the group with cirrhosis had a life expectancy of 16 years. As resection is the preferred initial treatment for NC-HCC patients, those who ultimately required transplantation were likely to include subsets with a failed attempt at resection, whose cancer recurred, or who otherwise have a more complex presentation. On the other hand, Gawrieh et al.[20] reported better survival in the NC-HCC group, as did Tobari et al.[24], who attributed this to a lower recurrence rate and the absence of liver failure for other reasons, though neither of these latter two study populations was restricted to transplant patients. Also, Bengtsson et al.[23] reported no difference in survival between the two groups, though their sample was a study mostly of resection patients. On a related note, Mergental et al.[3] found no statistically significant difference in survival when comparing primary transplant and rescue (salvage) transplant groups.

In the prior OPTN HCC study,[6] the life expectancy of a 60-year-old male was 12 additional years at time of transplant though increased to 13 years at age 61, one year later. Noted there was that his remaining life expectancy had increased even though he had aged a year; this

was due to his surviving the high initial mortality rate in the first-year posttransplant. This seeming paradox is commonly known as the healthy survivor effect, and indeed such conditional survival has been studied in this population.[25] We did not, however, observe as marked a trend in the present subgroup of NC-HCC patients.

That low weight (HR = 1.54 in the multivariate model) and Karnofsky Performance Scale (KPS) functional status (HRs ranging from 1.10 to 2.41) were highly related to survival is not surprising. Both can be viewed as proxies for frailty, comorbid conditions, or more dire need for transplant. Possible drawbacks to use of the KPS have been discussed elsewhere.[26,27]

Limitations in the present study include that patients in the OPTN database were not randomized to treatment. This may be relevant as more refined selection criteria in recent years may in fact have at least partially engendered the year-over-year 1% to 4% decrease in short-term mortality documented here. Further, we did not have patient HCC staging nor measurements of C-reactive protein[29] or AFP,[5,30] all three of which may be relevant to survival. In addition, OPTN does not provide details on what prior treatment (eg, ablation, chemoembolization) was afforded to patients.

Conclusions

Life expectancy after liver transplant in NC-HCC was significantly reduced from normal. As expected, the major demographic factors related to survival were age and calendar year of transplant, while sex and race were not practically or statistically significant. The seven tumor related factors, especially lymph node involvement, vascular invasion, and poor tumor differentiation, were significantly related to survival, with large hazard ratios and correspondingly large effects on life expectancy. These findings mirror those of Worns et al.[28] Zakaria et al.,[4] and Mergental et al.[3]

The methods used here are both standard and powerful. Under the assumption of proportional hazards, the Cox model based on the full group gives estimates that are more precise than that of the smaller narrow cohort approach of Kaplan-Meier. Also, importantly, under the Cox model one can calculate survival figures for various combinations of risk factors, perhaps even combinations not well represented 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 43-year-old non-white females who underwent transplant in 2013 for NC-HCC and had a longstanding history of diabetes. Survival information for such individual patients may prove helpful in medical decision-making regarding treatment for both liver and other conditions.

References

1. Desai A, Sandhu S, Lai JP, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: A comprehensive review. *World J Hepatol*. 2019;11(1):1–18. Doi: 10.4254/wjh.v11.i1.1.

2. Trevisani F, Frigerio M, Santi V, Grignaschi A, Bernardi M. Hepatocellular carcinoma in non-cirrhotic liver: a reappraisal. *Dig Liver Dis*. 2010;42(5):341-7. Doi: 10.1016/j.dld.2009.09.002.

3. Mergental H, Adam R, Ericzon BG, Kalicinski P, Mühlbacher F, Höckerstedt K, et al. Liver transplantation for unresectable hepatocellular carcinoma in normal livers. *J Hepatol*. 2012;57(2): 297-305. Doi: 10.1016/j.jhep.2012.03.022.

4. Zakaria HM, Sallam AN, Ayoub II, Saleh SM, Maher D, Omar H, et al. Predictors of outcome of living donor liver transplantation for hepatocellular carcinoma. *Indian J Surg*. 2017;79(4):299-307. Doi: 10.1007/s12262-016-1474-1.

5. Mehta N, Guy J, Frenette CT, Dodge JL, Osorio RW, Minteer WB, et al. Excellent outcomes of liver transplantation following down-staging of hepatocellular carcinoma to within Milan criteria: A multicenter study. *Clin Gastroenterol Hepatol*. 2018;16(6):955-964. Doi: 10.1016/j.cgh.2017.11.037.

6. Kwak JH, Shavelle RM, Brooks JC (2020). Life expectancy after transplantation for HCC with cirrhosis. *Prog Transplant*. in press. Cannot locate yet

7. Balogh J, Victor D 3rd, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. (2016). Hepatocellular carcinoma: a review. *J Hepatocell Carcinoma*. 2016;3:41-53. Doi: 10.2147/JHC.S61146.

8. Unek T, Karademir S, Arslan NC, Egeli T, Atasoy G, Sagol O, et al. Comparison of Milan and UCSF criteria for liver transplantation to treat hepatocellular carcinoma. *World J Gastroenterol*. 2011;17(37):4206-12. Doi: 10.3748/wjg.v17.i37.4206.

9. Lewis RH, Glazer ES, Bittenbinder DM, O'Brien T, Deneve JL, Shibata D, et al. Outcomes following resection of hepatocellular carcinoma in the absence of cirrhosis. *J Gastrointest Cancer*. 2019;50(4): 808-815. Doi: 10.1007/s12029-018-0152-x.

10. Kymes SM, Plotzke MR, Kass MA, Boland MV, Gordon MO. Effect of patient's life expectancy on the cost-effectiveness of treatment for ocular hypertension. *Arch Ophthalmol*. 2010;128(5):613-8. Doi: 10.1001/archopthamol.2010.83.

11. Pino M, Parry R. How and when do patients request life-expectancy estimates? Evidence from hospice medical consultations and insights for practice. *Patient Educ Couns*. 2019;102(2): 223-237. Doi: 10.1016/j.pec.2018.03.026.

12. Chiu N, Chiu L, Lutz S, Zhang N, Lechner B, Pulenzas N, et al. Incorporation of life expectancy estimates in the treatment of palliative care patients receiving radiotherapy:

treatment approaches in light of incomplete prognostic models. *Ann Palliat Med*. 2015;4(3):162-8. Doi: 10.3978/j.issn.2224-5820.2015.07.05.

13. Daskivich TJ, Lai J, Dick AW, Setodji CM, Hanley JM, Litwin MS, Saigal C; Urologic Diseases in America Project. Variation in treatment associated with life expectancy in a population-based cohort of men with early-stage prostate cancer. *Cancer*. 2014;120(23):3642-50. Doi: 10.1002/cncr.28926.

14. Tillquist MN, Maddox TM. Cardiac crossroads: deciding between mechanical or bioprosthetic heart valve replacement. *Patient Prefer Adherence*. 2011;5:91-9. Doi: 10.2147/PPA.S16420.

15. Organ Procurement and Transplantation Network (2019). About Data: OPTN Database. Accessed December 24, 2020. Available at https://optn.transplant.hrsa.gov/data/about-data/optn-database/

16. Collett D (1994). Modelling survival data in medical research. London: Chapman and Hall.

17. Strauss DJ, Vachon PJ, Shavelle RM. Estimation of future mortality rates and life expectancy in chronic medical conditions. *J Insur Med*. 2005;37(1):20-34.

18. Rohatgi VK (1976). An introduction to probability theory and mathematical statistics. New York: John Wiley and Sons, p.84.

19. Arias E, Xu JQ, Kochanek KD (2019). United States life tables, 2016. National Vital Statistics Reports; vol 68 no 4. Hyattsville, MD: National Center for Health Statistics.

20. Gawrieh S, Dakhoul L, Miller E, Scanga A, deLemos A, Kettler C, et al. Characteristics, aetiologies and trends of hepatocellular carcinoma in patients without cirrhosis: a United States multicentre study. *Aliment Pharmacol Ther*. 2019;50(7):809-821. Doi: 10.1111/apt.15464.

21. Carvalho KSD, Fonseca LE, Cotrim HP. Hepatocellular carcinoma in patients without cirrhosis: relevance and clinical characteristics. *Hepatoma Res*. 2018;4:15. Doi: 10.20517/2394-5079.2018.13.

22. Witjes CDM, de Man RA, Eskens FALM, Dwarkasing RS, Zondervan PE, Verhoef C, et al (2010). [Hepatocellular carcinoma: the significance of cirrhosis for treatment and prognosis--retrospective study]. *Ned Tijdschr Geneeskd*. 2010;154:A1747.

23. Bengtsson B, Stål P, Wahlin S, Björkström NK, Hagström H. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. *Liver Int*. 2019;39(6):1098-1108. Doi: 10.1111/liv.14087.

24. Tobari M, Hashimoto E, Taniai M, Kodama K, Kogiso T, Tokushige K, et al. The characteristics and risk factors of hepatocellular carcinoma in nonalcoholic fatty liver disease without cirrhosis. *J Gastroenterol Hepatol*. 2020;35(5):862-869. Doi: 10.1111/jgh.14867.

25. Dong J, Zhu Y, Ma F, Ren Y, Lu J, Wang Z, et al. Conditional disease-free survival after liver transplantation for hepatocellular carcinoma: A two-center experience. *Medicine*. 2016;95(31):e4383. Doi: 10.1097/MD.0000000000004383.

26. Wang CW, Lai JC. Reporting functional status in UNOS: The weakness of the Karnofsky Performance Status Scale. *Clin Transplant*. 2017;31(7). Doi: 10.1111/ctr.13004.

27. Tapper EB, Su GL. Does Karnofsky performance status of patients with cirrhosis on the transplant waitlist meet the eyeball test? *Clin Gastroenterol Hepatol*. 2016;14(8):1196-8. Doi: 10.1016/j.cgh.2016.04.024.

28. Wörns MA, Bosslet T, Victor A, Koch S, Hoppe-Lotichius M, Heise M, et al. Prognostic factors and outcomes of patients with hepatocellular carcinoma in non-cirrhotic liver. *Scand J Gastroenterol*. 2012;47(6):718-28. Doi: 10.3109/00365521.2012.677952.

29. An HJ, Jang JW, Bae SH, Choi JY, Yoon SK, Lee MA, et al. Serum C-reactive protein is a useful biomarker for predicting outcomes after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl*. 2012;18(12):1406-14. Doi: 10.1002/lt.23512.

30. Guerrini GP, Pinelli D, Marini E, Corno V, Guizzetti M, Zambelli M, et al. (2018). Value of HCC-MELD score in patients with hepatocellular carcinoma undergoing liver transplantation. *Prog Transplant*. 2018;28(1):63-69. Doi: 10.1177/1526924817746686.

Table 1. Demographics and Risk Factors of Study Participants.
Percentages are by column, N=4373.

Variable	Categories	n	%
Age (years)	35-44	108	2
	45-54	909	21
	55-64	2301	53
	65-74	1055	24
Sex	Male	3386	77
Race	White	2900	66
Transplant year	2002-2005	498	11
	2006-2009	1023	23
	2010-2013	1116	26
	2014-2018	1736	40
MELD score	6-10	2076	48
	11-18	1722	39
	19-40	438	10
Weight	Overweight/Obese (BMI = 25+)	3340	77
Diabetes (Type I, II, or other/unknown type)	Yes	1367	31
Functional status at transplant (Karnofsky Performance Status)	100% (normal)	180	4
	90% - Minor symptoms of disease	402	9
	80% - Normal activity with effort	939	21
	70% - Cares for self, but unable to carry on normal activity	770	18
	60% or less- Requires occasional or more assistance	1692	39
Prior Malignancy	Yes	1578	36
Ascites	Yes	2340	54
Hepatic encephalopathy	Yes	1784	41
Donor age	0-49	2603	60
	50+	1770	40
INR	Normal (1.1 or less)	1173	27
Sodium	Normal	3170	72
Creatinine	Normal	1763	40
Total bilirubin	Normal	1734	40
Albumin	Normal	1990	46
CMV IgG	Positive	1964	45
Number of tumors*	1	752	17
Extrahepatic spread*	No	1585	36
Lymph node involvement*	No	1573	36
Satellite lesions*	No	1483	34
Pre-transplant treatment*	No	86	2
Vascular Invasion*	None	1249	29
Worst tumor differentiation*	Moderate to poor	1001	23

Full list of variables is available as supplement
INR, international normalized ratio
CMV, cytomegalovirus

* Came into use in 2012

Table 2. Effects of risk factors, hazard ratios with associated *P*-values from Cox Proportional Hazards Regression models. §

Variable	Categories	Univariate Model From time of tx	Multivariate Models From tx	Multivariate Models For 1-year survivors	Multivariate Models For 5-year survivors
Age (years)§	(Continuous)	1.02 (<0.001)	1.02 (<0.001)	1.02 (<0.001)	1.04 (<0.001)
Sex§	Female	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Male	1.00 (1.00)	1.02 (0.77)	1.07 (0.40)	1.09 (0.55)
Race§	White	1.10 (0.11)	1.08 (0.22)	1.09 (0.25)	1.45 (<0.01)
Transplant year§	(Continuous)	0.97 (<0.001)	0.96 (<0.001)	0.96 (<0.001)	0.99 (0.75)
MELD score	6-10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	11-18	1.00 (0.97)	1.00 (0.95)	0.96 (0.59)	0.95 (0.70)
	19-24	1.07 (0.62)	1.11 (0.43)	1.06 (0.70)	0.57 (0.13)
	25-40	1.43 (0.01)	1.51 (<0.01)	1.25 (0.24)	1.19 (0.64)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.14 (0.04)	1.12 (0.07)	1.22 (<0.01)	1.43(<0.01)
Functional status at transplant	90-100%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	70-80%	1.14 (0.18)	1.16 (0.12)	1.10 (0.38)	1.15 (0.44)
	50-60%	1.37 (<0.05)	1.47 (<0.001)	1.22 (0.11)	1.26 (0.30)
	30-40%	1.44 (<0.05)	1.60 (<0.001)	1.18 (0.29)	0.94 (0.84)
	10-20%	2.27 (<0.0001)	2.41 (<0.001)	1.15 (0.53)	0.58 (0.36)
Ascites	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.25 (<0.001)	1.24 (<0.001)	1.21 (<0.01)	1.01 (0.95)
Hepatic encephalopathy	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Mild (1-2)	1.21 (<0.01)	1.21 (<0.01)	1.14 (0.08)	1.08 (0.56)
	Severe (3-4)	1.34 (0.07)	1.37 (0.06)	1.10 (0.68)	0.79 (0.60)
Extrahepatic spread*	No	1 (ref)	1 (ref)	1 (ref)	-
	Yes	2.22 (0.08)	2.27 (0.07)	1.81 (0.41)	-
Vascular invasion*	None	1 (ref)	1 (ref)	1 (ref)	-
	Microvascular	1.66 (<0.01)	1.65 (<0.01)	2.03 (<0.01)	-
	Macrovascular	2.35 (<0.01)	2.29 (<0.01)	1.82 (0.20)	-
Worst tumor differentiation*	Complete necrosis	0.82 (0.48)	0.85 (0.55)	0.78 (0.58)	-
	Well	1 (ref)	1 (ref)	1 (ref)	-
	Moderate	1.43 (0.05)	1.44 (0.05)	1.96 (0.02)	-
	Poor	2.97 (<0.001)	3.06 (<0.001)	4.89 (<0.001)	-

Full list of variables and results is available as supplement

§ 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.

tx, transplant

* Came into use in 2012. Results are thus not shown for the relatively few persons who survived to 5 years posttransplant.

Table 3. Life expectancies with average number of additional years for the entire sample and by medical condition pretransplant. Life expectancies are based on the multivariate models of Table 2.

a. Overall figures

Starting Time	Current Age	Male		Female	
		All Recipients	General Population	All Recipients	General Population
		Additional years			
From transplant	40	15	39	16	43
	50	14	30	14	33
	60	12	22	12	25
	70	10	15	11	17
1-yr posttransplant	41	15	38	16	42
	51	14	29	14	33
	61	12	21	12	24
	71	11	14	11	16
5-yrs posttransplant	45	13	34	14	38
	55	12	26	12	29
	65	11	18	11	21
	75	10	11	10	13

b. Diabetes

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

c. Ascites/Hepatic Encephalopathy (HE)

		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
		Additional years											
	40	14	15	16	16	15	39	15	16	16	17	16	43
From transplant	50	13	13	14	15	14	30	13	14	14	15	14	33
	60	11	12	12	13	12	22	11	12	12	13	12	25
	70	10	10	11	10	10	15	10	10	11	11	11	17

	41	14	15	16	16	15	38	15	16	16	17	16	42
1-yr posttransplant	51	13	14	14	15	14	29	13	14	14	15	14	33
	61	11	12	12	13	12	21	12	12	12	13	12	24
	71	10	11	11	11	11	14	10	11	11	12	11	16
	45	13	13	14	14	13	34	13	13	14	14	14	38
5-yr posttransplant	55	11	12	12	13	12	26	11	12	12	13	12	29
	65	10	11	11	11	11	18	10	11	11	11	11	21
	75	9	9	10	10	10	11	9	10	10	10	10	13

Rec, recipients
GP, general population

Table 4. Life expectancies with average number of additional years for tumor related outcomes. Life expectancies are based on the multivariate models of Table 2.

a. Vascular Invasion									
		Male				Female			
Starting time	Current Age	None	Micro or Macro	All Rec	GP	None	Micro or Macro	All Rec	GP
		Additional years							
	40	18	13	15	39	18	14	16	43
From transplant	50	16	12	14	30	16	12	14	33
	60	14	10	12	22	14	10	12	25
	70	12	9	10	15	13	9	11	17
	41	18	14	15	38	18	14	16	42
1-yr posttransplant	51	16	12	14	29	16	12	14	33
	61	14	11	12	21	14	11	12	24
	71	13	9	11	14	13	10	11	16
	45	15	12	13	34	15	12	14	38
5-yr posttransplant	55	14	11	12	26	14	11	12	29
	65	12	10	11	18	12	10	11	21
	75	11	9	10	11	11	9	10	13

b. Worst Tumor Differentiation													
		Male						Female					
Starting time	Current Age	Necro	Well	Mod	Poor	All Rec	GP	Necro	Well	Mod	Poor	All Rec	GP
		Additional years											
	40	21	19	16	11	15	39	21	19	16	11	16	43
From transplant	50	18	17	14	9	14	30	18	17	14	9	14	33
	60	16	15	13	8	12	22	16	15	13	8	12	25
	70	14	13	11	7	10	15	15	13	11	7	11	17
	41	20	19	16	11	15	38	20	19	16	11	16	42
1-yr posttransplant	51	18	17	14	10	14	29	18	17	14	10	14	33
	61	16	15	13	8	12	21	16	15	13	9	12	24
	71	14	13	11	7	11	14	14	14	11	7	11	16
	45	18	16	14	10	13	34	18	17	14	10	14	38
5-yr posttransplant	55	16	14	12	9	12	26	16	15	13	9	12	29

	65	14	13	11	8	11	18	14	13	11	8	11	21
	75	12	12	10	7	10	11	12	12	10	7	10	13

Rec, recipients
GP, general population
Necro, complete tumor necrosis
Well, well differentiated tumor
Mod, moderately differentiated tumor
Poor, poorly differentiated tumor

Table 5. Empirical survival percentages (%) for the entire population and stratified by several risk factors.

		Survival Time (Years)				
Factor	Level (posttransplant time)	1	3	5	10	15
		Percent				
All		90	80	72	57	42
Sex	Male	90	80	72	57	41
	Female	89	80	72	58	44
Ages 35-54	All	92	80	74	62	52
	By vascular invasion – Yes	88	80	67	-	-
	– No	95	89	86	-	-
	By tumor differentiation – Low	97	95	86	-	-
	– High	92	82	79	-	-
Ages 55-74	All	90	79	71	55	36
	By vascular invasion – Yes	89	77	68	-	-
	– No	92	86	80	-	-
	By tumor differentiation – Low	92	88	84	-	-
	– High	91	81	73	-	-

Supplemental Table 1. All Variables of Study Participants Demographic and Risk Factors. Percentages are by column, N=4373.

Variable	Categories	n	%
Age (years)	35-44	108	2
	45-54	909	21
	55-64	2301	53
	65-74	1055	24
Sex	Male	3386	77
	Female	987	23
Race	White	2900	66
	All others	1473	34
Transplant year	2002-2005	498	11
	2006-2009	1023	23
	2010-2013	1116	26
	2014-2018	1736	40
MELD score	6-10	2076	48
	11-18	1722	39
	19-24	273	6
	25-40	165	4
	Missing	137	3
Donor type	Living	123	3
	Deceased	4250	97
Weight	Underweight (BMI<18)	28	0
	Normal weight (18-25)	1005	23
	Overweight (25-30)	1692	39
	Obese (30+)	1648	38
Diabetes (Type I, II, or other/unknown type)	No	3006	69
	Yes	1367	31
Functional status at transplant (Karnofsky Performance Status)	100% (normal)	180	4
	90% - Minor symptoms of disease	402	9
	80% - Normal activity with effort	939	21
	70% - Cares for self, but unable to carry on normal activity	770	18
	60% - Requires occasional assistance	548	13
	50% - Requires considerable assistance	474	11
	40% - Disabled	363	8
	30% - Severely disabled	125	3
	20% - Very sick	146	3
	10% - Moribund	36	1
	Missing	390	9
Prior Malignancy	Yes	1578	36
	No	2704	62
	Unknown	91	2
Ascites	No	2033	46
	Yes	2340	54
Hepatic encephalopathy	No	2548	58
	Mild (1-2)	1655	38
	Severe (3-4)	129	3
	Unknown/missing	35	1
Donor age	0-19	372	9
	20-49	2231	51
	50-79	1718	39

	80+	52	1
INR	Normal (1.1 or less)	1173	27
	Undefined (1.1-2.0]	2762	63
	Therapeutic (2.0-3.0]	323	7
	High risk (>3.0)	115	3
Sodium	Low	802	18
	Normal	3170	72
	High	68	2
	Missing	333	8
Creatinine	Low	1735	40
	Normal	1763	40
	High	875	20
Total bilirubin	Normal	1734	40
	High	2639	60
Albumin	Low	2379	54
	Normal	1990	46
	High	4	0
CMV IgG	Positive	1964	45
	Negative	858	20
	Missing	1551	35
Number of tumors*	1	752	17
	2	400	9
	3	199	5
	4	102	2
	5	53	1
	>5	85	2
	Infiltrative	9	0
	Missing	2773	63
Extrahepatic spread*	No	1585	36
	Yes	15	0
	Missing	2773	63
Lymph node involvement*	No	1573	36
	Yes	26	1
	Missing	2774	63
Satellite lesions*	No	1483	34
	Yes	116	3
	Missing	2774	63
Pre-transplant treatment*	No	86	2
	Yes	1565	36
	Missing	2722	62
Vascular Invasion*	None	1249	29
	Microvascular	297	7
	Macrovascular	53	1
	Missing	2774	63
Worst tumor differentiation*	Complete necrosis	247	6
	Well	350	8
	Moderate	874	20
	Poor	128	3
	Missing	2774	63

* Came into use in 2012

Supplemental Table 2. Effects of Risk Factors, Hazard Ratios with Associated *P*-Values from Cox Proportional Hazards Regression models,§ expanded version.

		Univariate Model	Multivariate Models		
Variable	Categories	From time of tx	From tx	For 1-year survivors	For 5-year survivors
Age (years) §	(Continuous)	1.02 (<0.001)	1.02 (<0.001)	1.02 (<0.001)	1.04 (<0.001)
Sex§	Female	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Male	1.00 (1.00)	1.02 (0.77)	1.07 (0.40)	1.09 (0.55)
Race§	White	1.10 (0.11)	1.08 (0.22)	1.09 (0.25)	1.45 (<0.01)
	All other races	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Transplant year§	(Continuous)	0.97 (<0.001)	0.96 (<0.001)	0.96 (<0.001)	0.99 (0.75)
MELD score	6-10	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	11-18	1.00 (0.97)	1.00 (0.95)	0.96 (0.59)	0.95 (0.70)
	19-24	1.07 (0.62)	1.11 (0.43)	1.06 (0.70)	0.57 (0.13)
	25-40	1.43 (0.01)	1.51 (<0.01)	1.25 (0.24)	1.19 (0.64)
	Missing	1.41 (<0.01)	1.22 (0.13)	0.98 (0.88)	0.92 (0.74)
Donor type	Living	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Deceased	1.03 (0.89)	1.04 (0.83)	1.04 (0.86)	0.83 (0.60)
Weight	Underweight	1.72 (0.06)	1.54(0.13)	1.36(0.39)	0.80 (0.75)
	Normal weight	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Overweight	1.02 (0.75)	1.00(0.99)	0.99 (0.87)	0.82 (0.20)
	Obese	1.00 (0.99)	1.01(0.94)	0.96 (0.64)	0.97 (0.84)
Diabetes	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.14 (0.04)	1.12 (0.07)	1.22 (<0.01)	1.43(<0.01)
Functional status at transplant	90-100%	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	70-80%	1.14 (0.18)	1.16 (0.12)	1.10 (0.38)	1.15 (0.44)
	50-60%	1.37 (<0.05)	1.47 (<0.001)	1.22 (0.11)	1.26 (0.30)
	30-40%	1.44 (<0.05)	1.60 (<0.001)	1.18 (0.29)	0.94 (0.84)
	10-20%	2.27 (<0.0001)	2.41 (<0.001)	1.15 (0.53)	0.58 (0.36)
	Unknown	1.43 (<0.01)	1.10 (0.42)	1.08 (0.58)	1.28 (0.30)
Prior Malignancy	Yes	0.93 (0.24)	0.97 (0.64)	0.96 (0.64)	0.87 (0.36)
	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Unknown	1.26 (0.12)	1.17 (0.31)	1.30 (0.12)	1.29 (0.32)
Ascites	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Yes	1.25 (<0.001)	1.24 (<0.001)	1.21 (<0.01)	1.01 (0.95)
Hepatic encephalopathy	No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Mild (1-2)	1.21 (<0.01)	1.21 (<0.01)	1.14 (0.08)	1.08 (0.56)
	Severe (3-4)	1.34 (0.07)	1.37 (0.06)	1.10 (0.68)	0.79 (0.60)
	Unknown	0.77 (0.38)	0.77 (0.39)	0.71 (0.34)	0.87 (0.78)
Donor age	<20	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	20 and up	1.36 (<0.01)	1.42 (<0.01)	1.50 (<0.01)	1.75 (0.01)
INR	2.0 or under	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	>2.0	1.17 (0.08)	1.22 (0.03)	1.07 (0.58)	1.21 (0.35)
Sodium	Low	1.15 (0.05)	1.18 (0.03)	1.17 (0.09)	1.05(0.80)
	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	1.00 (0.99)	0.96 (0.87)	0.86 (0.63)	0.91 (0.85)
	Missing	1.27 (<0.01)	0.98 (0.83)	0.97 (0.83)	1.13 (0.60)
Creatinine	Low	0.93 (0.27)	0.95 (0.44)	0.98 (0.75)	0.89 (0.42)
	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	1.30 (<0.001)	1.30 (<0.001)	1.16 (0.12)	1.28 (0.13)
Total bilirubin	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	1.01 (0.85)	1.02 (0.77)	1.01 (0.93)	0.92 (0.50)

Albumin	Low	1.10 (0.10)	1.10 (0.11)	1.13 (0.13)	1.06(0.65)
	Normal	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	High	0.89 (0.91)	0.89 (0.91)	1.43 (0.72)	7.12 (0.05)
CMV IgG	Negative	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Positive	1.02 (0.83)	1.01 (0.89)	1.07 (0.42)	0.94 (0.67)
	Unknown/missing	0.86 (0.10)	0.98 (0.85)	1.09 (0.50)	1.08 (0.76)
Number of tumors*	1	1 (ref)	1 (ref)	1 (ref)	-
	2	0.79 (0.20)	0.79 (0.19)	1.22 (0.45)	-
	3	1.13 (0.57)	1.10 (0.64)	1.49 (0.20)	-
	4	1.10 (0.72)	1.10 (0.72)	1.78 (0.10)	-
	5	1.73 (0.06)	1.69 (0.08)	2.77 (<0.01)	-
	>5	1.80 (0.02)	1.83 (0.01)	3.32 (<0.001)	-
	Infiltrative	1.85 (0.29)	1.90 (0.27)	2.95 (0.14)	-
	Missing	1.51 (<0.001)	1.38 (<0.01)	1.95 (<0.001)	-
Extrahepatic spread*	No	1 (ref)	1 (ref)	1 (ref)	-
	Yes	2.22 (0.08)	2.27 (0.07)	1.81 (0.41)	-
	Missing	1.46 (<0.001)	1.34 (<0.01)	1.45 (<0.01)	-
Lymph node involvement*	No	1 (ref)	1 (ref)	1 (ref)	-
	Yes	3.37 (<0.001)	3.44 (<0.001)	4.49 (<0.01)	-
	Missing	1.50 (<0.001)	1.37 (<0.001)	1.47 (<0.01)	-
Satellite lesions*	No	1 (ref)	1 (ref)	1 (ref)	-
	Yes	1.91 (<0.01)	1.92 (<0.01)	2.31 (<0.01)	-
	Missing	1.55 (<0.001)	1.43 (<0.001)	1.57 (<0.001)	-
Pre-transplant treatment*	No	1 (ref)	1 (ref)	1 (ref)	-
	Yes	1.67 (0.11)	1.63 (0.13)	2.42 (0.08)	-
	Missing	2.38 (<0.01)	2.16 (0.02)	3.43 (0.02)	-
Vascular invasion*	None	1 (ref)	1 (ref)	1 (ref)	-
	Microvascular	1.66 (<0.01)	1.65 (<0.01)	2.03 (<0.01)	-
	Macrovascular	2.35 (<0.01)	2.29 (<0.01)	1.82 (0.20)	-
	Missing	1.68 (<0.001)	1.54 (<0.001)	1.71 (<0.001)	-
Worst tumor differentiation*	Complete necrosis	0.82 (0.48)	0.85 (0.55)	0.78 (0.58)	-
	Well	1 (ref)	1 (ref)	1 (ref)	-
	Moderate	1.43 (0.05)	1.44 (0.05)	1.96 (0.02)	-
	Poor	2.97 (<0.001)	3.06 (<0.001)	4.89 (<0.001)	-
	Missing	1.95 (<0.001)	1.80 (<0.001)	2.45 (<0.001)	-

Tx, transplant
INR, international normalized ratio
CMV, cytomegalovirus

§ 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.

* Came into use in 2012. Results are thus not shown for the relatively few persons who survived to 5 years posttransplant.