Published in final edited form as:

Clin Transplant. 2016 September ; 30(9): 1036–1045. doi:10.1111/ctr.12785.

Patient-Reported Outcomes in Liver Transplant Recipients with Hepatocellular Carcinoma

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Abstract

Background—The effect of awarding MELD exception points for Hepatocellular Carcinoma (HCC) on patient-reported outcomes (PROs) is unknown. We evaluated the physical and mental health-related quality of life (HRQOL), and symptoms of anxiety and depression in liver transplant recipients with HCC compared to patients without HCC.

Methods—The single-center sample measured PROs before and post-transplant, which included 1,521 multi-survey measurement points among 502 adults (67% male, 28% HCC, follow-up time: <1 to 131 months). Data were analyzed using multivariable mixed effects models.

Results—Longitudinal PRO values did not differ between persons who received HCC exception points and those who did not have HCC. Patients with HCC who didn't receive exception points had reduced physical HRQOL ($p=0.016$), a late decline in mental HRQOL, and delayed reduction in anxiety (time by outcome interaction $p<0.050$) compared to patients with HCC who received exception points.

Conclusion—Transplant recipients who received HCC exception points had PROs that were comparable to patients without HCC, and reported better physical HRQOL and reduced symptoms of anxiety compared to patients with HCC who did not receive exception points. These analyses demonstrate the impact of HCC exception points on PROs, and may help inform policy regarding HCC exception point allocation.

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The authors of this manuscript have no conflicts of interest to disclose.

Author Contributions: *Clark D. Kensinger*: Developed concept and design of study, data acquisition, data interpretation, drafting of manuscript, critical revision of manuscript, approval of final manuscript

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Keywords

health-related quality of life; exception points; Model for End-Stage Liver Disease; organ transplant; multivariable models

Introduction

The incidence of hepatocellular carcinoma (HCC), the most common primary liver cancer, has increased substantially over the past several decades. The age adjusted incidence rates of liver cancer rose from 2.6 per 100,000 in 1975 to 8.9 per 100,000 in 2012 (1). Due to the excellent five year survival, which is reported to be 77.2% (2), the optimal therapeutic option for HCC is liver transplantation as it treats both the underlying liver disease and the malignancy. Among patients with HCC, eligibility for liver transplantation depends on the number and size of the tumor burden. Hepatocellular carcinoma patients within the Milan Criteria are potential candidates for Model for End-Stage Liver Disease (MELD) exception points, which are awarded to account for the probability of tumor progression beyond transplant eligibility criteria.

In 2005, the threshold for HCC exception points was set to 22 (if the calculated MELD score was less than 22), which was estimated to be equivalent to a 15% probability of candidate death within three months as compared to a non-HCC patient. However, there is an increasing controversy surrounding the assignment of patients with HCC waitlist priority by awarding MELD exception points. Due to disproportionate waitlist deaths (3-5), reduced waitlist dropout rates (4, 6, 7), and increased rates of transplantation (3, 7) for patients awarded waitlist priority for HCC when compared to non-HCC patients, there is ongoing debate regarding equitable organ allocation.

Patient-reported outcomes (PROs) such as health-related quality of life (HRQOL) and symptoms of anxiety and depression provide important additional metrics that complement clinical outcomes such as adverse events on the waiting list and rates of transplantation. Additionally, these metrics add greater depth to policy discussions around liver allocation. There have been prior reports evaluating HRQOL in patients with HCC who were ineligible for transplantation and were treated with systemic or locoregional therapy (8-11); however, there have been no prior reports examining physical and mental HRQOL or symptoms of anxiety and depression among patients with HCC who were eligible for and received liver transplants.

Patient-reported outcomes in liver transplant recipients with a diagnosis of HCC compared to non-HCC recipients could provide unique and novel data given the concern that awarding HCC exception points is contributing to organ allocation inequality. In order to justify the continued practice of assigning waitlist priority for patients with HCC, PROs of recipients with HCC should be comparable to or better than those of non-HCC liver transplant recipients. Despite the disparity in waitlist outcome metrics reported in the literature (3-7), we hypothesize that patients with HCC have similar PROs compared to non-HCC transplant candidates. Our aim was to evaluate, among HCC and non-HCC liver transplant recipients,

the levels and trajectories of four PROs: physical HRQOL, mental HRQOL, symptoms of anxiety, and symptoms of depression.

Methods

Study Design

A retrospective analysis of prospectively-collected, pre- and post-transplant PRO data was conducted to compare physical and mental HRQOL and symptoms of anxiety and depression between transplant recipients with HCC and non-HCC patients. The patient sample with a diagnosis of HCC was a heterogeneous group consisting of patients who were awarded exception points for HCC and those who were not awarded HCC exception points. Because patients with HCC who were not awarded exception points did not experience the potential benefit of wait list priority they were clinically different from the HCC patients who received exception points and, for this reason, patients with HCC could not be treated as a single group. Our solution was to treat HCC status as a single variable having three mutually exclusive categories: 1) no HCC, 2) HCC without exception points awarded prior to transplantation, and 3) HCC with pre-transplant exception points. Study inclusion criteria were adult patients who underwent liver transplantation at a single transplant center between January 2003 and July 2014 who completed a battery of surveys before and after and who had PRO survey measurements within six months or less prior to transplantation and/or at least one post-transplant PRO measurement. Survey data were integrated with patient-level demographic and clinical information that was extracted from hospital and transplant center databases. This allowed an analysis of HCC patients with exception points compared to non-HCC patients and to patients with HCC who did not receive exception points.

PRO measures and data acquisition

Surveys were administered before transplant (at evaluation and while on the waiting list) and at targeted post-transplant time points (1, 3, 6 months, and annually) using a rolling enrollment process that permits transplant candidates and recipients to participate at any time point regardless of their prior participation (12). This process results in maximal subject inclusion and data capture and, importantly, allows for the number and timing of data points to vary among participants.

Patient-reported outcomes were measured using three survey instruments that have been widely validated and have norm-based interpretations. Details of the survey battery's psychometric characteristics and the complete data collection protocol have been reported previously (12). The Short Form Health Survey-36, (SF-36), version 1, is a generic health status survey that assesses health-related functioning and well-being as eight individual scales (13). Physical component summary (PCS) and mental component summary (MCS) scores are computed from the eight scales as differentially weighted HRQOL composites. The PCS and MCS scores can be referenced to a general population mean of 50 and standard deviation of 10, with scores between 40 and 60 being the general population normative range (13). Higher score represent better HRQOL. The Beck Anxiety Inventory (BAI) measures the severity of self-reported symptoms of anxiety (14). Each of 21 items is scored on a four-point ordinal scale (0, not at all affected by the symptom; to 3, severely

affected by the symptom). Total scores can range from 0 to 63, with higher scores indicating more severe symptoms of anxiety. Symptom severity is interpreted as: 0-7 (minimal), 8-15 (mild), 16-25 (moderate), and 26 (severe) (14). The Center for Epidemiologic Studies Depression Scale (CES-D) measures self-reported symptoms of depression (15). Twenty items are scored on an ordinal scale reflecting the duration each symptom was experienced over the past week: 0 (rarely or none of the time), 2 (1-2 days), 3 (3-4 days), and 4 (5-7 days). After reverse scoring four items, a total score is computed that can range from 0 to 60, with higher scores indicating more severe symptoms of depression. Symptom severity is interpreted as: 0-9 (none), 10-16 (mild), 17-24 (moderate), and 25 (moderate to severe) (15).

Data encoding

Hepatocellular carcinoma and HCC-related MELD exception point status were encoded as a single variable having three separate categories: 1) no HCC, 2) HCC without exception points awarded prior to transplantation, and 3) HCC with pre-transplant exception points (reference category). This approach allowed a single categorical variable to represent two key characteristics, HCC status and whether HCC exception points were awarded, which reflects three distinct patient “groups”. Etiology of end-stage liver disease was classified as 12 binary variables, which enabled records to be encoded based on patients having (present/not present) one or more of the following diagnoses: non-alcoholic steatohepatitis, hepatitis C virus, other (Non-C) viral hepatitis, alcoholic hepatitis, cryptogenic, metabolic, autoimmune, congenital liver disease, acute hepatic necrosis, non-HCC primary hepatic malignancy, benign tumor, and “other”. All liver transplants were performed after implementation of the MELD allocation system, and MELD era was classified as 2002-2004 (reference category) or 2005 to 2014 to capture temporal revisions to HCC exception point protocols. Demographic and clinical measures included age at transplant (years), gender, race (Caucasian, African-American, other), calculated MELD score at the time of transplant, and whether re-transplantation occurred prior to a given PRO data point. Duration of follow-up was computed at every PRO data point and expressed as a continuous variable (months), with pre-transplant data coded as zero months for the purpose of analysis. Duration of follow-up was also expressed as an ordinal variable for PRO observations that were temporally aligned with seven key monitoring points (pre-transplant, and post-transplant months 1, 3, 6, 12, 24, and 36).

Statistical methods

Patient-level demographic and clinical data were analyzed using descriptive statistical methods. Analysis of variance methods with post-hoc tests and chi-square tests with column-wise tests of proportions were used to compare demographic and clinical data between the three HCC and exception point status conditions (No HCC, HCC without exceptions points, HCC with exceptions points). All post-hoc tests were adjusted for multiple comparisons. Summary data are reported as means, standard deviations, 95% confidence intervals, frequencies, and percentages. Data were analyzed using SPSS statistical software (IBM SPSS, version 22, IBM Corporation, Armonk, NY).

Four separate multivariable linear mixed effects models that included all available data points for each patient were used to evaluate the association between HCC and exception point status and time on the values and temporal trajectory of four PRO scores: 1) SF-36 PCS; 2) SF-36 MCS; 3) BAI; and 4) CES-D. Each model adjusted for age at transplant, gender, MELD era, the six most prevalent etiologies of end-stage liver disease, whether re-transplantation occurred prior to a PRO data point, and MELD score at the time of transplant. These variables were selected *a-priori* based on clinical hypotheses and previous research, and were applied consistently in all four models to permit direct comparison between the models. A time by HCC/exception point interaction term was included in each model to test whether the temporal trajectory of PRO scores differed on the basis of HCC and exception point status. Non-directional p-values less than 0.05 were considered statistically significant. Model-generated estimated values, which reflect the collective effects of all covariates, were computed for each outcome measure and these data were used to graphically depict the temporal trajectories of PRO scores.

Secondary two-way analyses of variance used the ordinal time metric to evaluate time point-specific average scores and focus on details of changes at post-transplant months 1, 3, 6, 12, 18, 24 and 36. These models were interpreted in relation to published norms and clinically meaningful differences in comparison to pre-transplant scores. Consistent with the general interpretation of HRQOL data, an effect size of a half standard deviation or more was considered to be a clinically meaningful difference (16) and, on this basis, the clinically meaningful effect threshold was considered to be five points or greater for all PRO measures.

Results

Demographic and Clinical Characteristics of the Sample

The study included 502 adult patients who underwent liver transplantation between January 2003 and July 2014. The rolling enrollment and longitudinal assessment processes resulted in 1,521 multi-survey data points (n=1,125 without HCC, n=116 with HCC and no exception points, n=280 with HCC and exception points). The number of multi-survey PRO data points per participant ranged from one to 11, with 88% of participants completing surveys on at least two occasions. Post-transplant follow-up time at each participant's final data point averaged 30±29 months, ranged from less than one to 131 months, and did not differ between the three HCC/exception point groups (p=0.147).

Demographic and clinical characteristics of the cohort are summarized in Table 1. Patients who did not have HCC were younger than those with HCC (column-wise comparison p<0.05) and comprised a higher proportion of female recipients (column-wise comparison p<0.05). The six most prevalent etiologies of end-stage liver disease were hepatitis C virus, alcoholic hepatitis, nonalcoholic steatohepatitis, autoimmune disorder, cryptogenic liver disease, and metabolic liver disease (which were included in the multivariable models). The majority of patients underwent liver transplantation after 2005, following the adjustment in the HCC exception point policy that set initial MELD exception scores to 22.

A diagnosis of HCC was confirmed based on pathology from hepatectomy specimens in 139 patients (28% of the cohort). Thirty-three of 139 patients, 24% of the HCC-sample, were not awarded exception points for HCC prior to transplant, and the majority of these (73%, 24 of 33) had HCC discovered on explant. Five (15%) of the 33 HCC patients who did not receive exception points had HCC diagnosed prior to liver transplant; however, because their calculated MELD scores were greater than 22, an application for exception points was not submitted. Two (6%) of the HCC patients who did not receive exception points were down staged with loco-regional therapy but were not awarded exception points prior to transplant. There was insufficient information in the medical record to determine why exception points were not awarded to two patients who were known to have HCC prior to transplant.

Multivariable Model of Physical HRQOL

Pre-transplant PCS scores were substantively impaired (<40) in all three HCC/MELD exception point groups. Persons with HCC who received exception points had impaired, but higher, pre-transplant PCS scores (33 ± 12 ; 95%CI: 30-37) compared to those who had HCC and did not receive exception points (25 ± 7 ; 95%CI: 21-29) ($p=0.005$) and compared to those who did not have HCC (26 ± 8 ; 95%CI: 25-28) ($p<0.001$). The longitudinal multivariable mixed effects model (Table 2; Figure 1, panel A) demonstrated that PCS improved significantly with time post-transplant ($p=0.001$) and that re-transplantation, increased age, hepatitis C virus, and transplantation in the earliest MELD cohort were associated with lower PCS scores (all $p \leq 0.033$). However, longitudinal PCS scores differed between the three groups. In comparison to having HCC and receiving exception points, having HCC and *not* receiving exception points was associated with substantively (5 points) lower PCS scores over time (unstandardized coefficient = -5.00, $p=0.016$). In contrast, the PCS scores of patients who did not have HCC did not differ substantively over time (difference <5 points, unstandardized coefficient = 2.50, $p=0.051$) compared to patients with HCC who received exception points.

The unadjusted time point-specific PCS data depicted through post-transplant month 36 (Figure 2, panel A) are consistent with the multivariable model. While all three groups average PCS scores were well below general population norms before transplant, patients who received exception points improved substantively (5 points) by month three, those without HCC improved substantively by month one, and both were within general population norms by month six. In contrast, those with HCC who did not receive exception points improved substantively by month three but averaged below general population norms through month 36 (Figure 2, panel A).

Multivariable Model of Mental HRQOL

Pre-transplant MCS scores averaged within general population norms (40-60) before transplant in all three groups. Persons with HCC who did not receive exception points had pre-transplant scores (49 ± 10 ; 95%CI: 43-54) that were comparable to those without HCC (43 ± 12 ; 95%CI: 42-45) and to those with HCC who received exception points (44 ± 11 ; 95%CI: 41-47) (ANOVA $p=0.174$). The multivariable model demonstrated that overall MCS scores remained statistically stable and within general population norms over the full follow-up period (effect of time $p=0.089$). However, the main effect of time does not reflect the

finding that, after adjusting for the significant positive association between age and MCS scores ($p=0.009$), persons with HCC who did not receive exception points had a statistically significant downward temporal trajectory of MCS *in the later follow-up period* compared to those who received exception points (time by group interaction contrast, $p=0.006$) (Table 2; Figure 1, panel B). Persons who did not have HCC had a stable long-term temporal trajectory for MCS scores that was comparable to those who received HCC exception points (time by group interaction contrast, $p=0.496$). The unadjusted time point- specific analysis demonstrated that an overall improvement in average MCS scores through the first 3 post-transplant years ($p=0.001$) was well within general population norms and the temporal trajectories in the multivariable model of the three groups do not vary significantly *over the first 3 years* (time point by group interaction $p=0.300$) (Figure 2, panel B).

Multivariable Model of Symptoms of Anxiety

Pre-transplant BAI scores averaged just within the moderate severity level (16 ± 10) and did not differ significantly between the three groups ($p=0.415$). The multivariable model (Table 3) indicated that overall BAI scores improved significantly over time (unstandardized coefficient = -0.08 , $p=0.001$). However, in contrast to those who received exception points for HCC, who had a downward (improved) temporal trajectory, persons with HCC who did not receive exception points had statistically stable BAI scores over the full follow-up period (time by group interaction contrast, $p=0.042$) (Figure 1, panel C). Persons who did not have HCC had a temporal improvement in post-transplant BAI scores that was comparable to those patients who received HCC exception points (time by group interaction contrast, $p=0.308$). Unadjusted time point-specific analyses that focused on the early post-transplant period through year three (Figure 2, panel C) demonstrated that overall BAI scores were significantly improved by post-transplant month one ($p=0.004$) and substantively improved by month three (average reduction = 5.4 points, $p<0.001$ vs. pre-transplant). Persons without HCC and those who received exception points had scores that were in the minimal to lower limit of mild severity levels at post-transplant months 6, 12, 24 and 36. However, consistent with the multivariable model, persons who had HCC and did not receive exception points had BAI scores that consistently averaged within the mild severity level at months 6 through 36.

Multivariable Model of Symptoms of Depression

Pre-transplant CES-D scores did not differ between the three groups ($p=0.146$) and averaged just within the moderate severity level (17 ± 10) overall. The multivariable model indicated that CES-D scores were statistically stable over the full follow-up period (effect of time, $p=0.210$) and that there was no difference between the three HCC/exception point groups scores ($p=0.278$) or their temporal trajectories (time by group interaction contrasts, $p=0.352$) (Table 3; Figure 1, panel D). The unadjusted time point-specific analysis demonstrated that there was an early, statistically significant overall improvement at month one ($p<0.001$) that was substantive (average reduction = 5.9 points, $p<0.001$ vs. pre-transplant) by month three. Consistent with the multivariable model that showed no significant temporal effect over the full follow-up period, this overall early improvement was sustained through month 36, reflecting a stable long-term trajectory.

Discussion

The current study used a long-standing, multi-survey PRO protocol to prospectively evaluate the effect of HCC on the values and trajectories of four PROs in liver transplant recipients. Patient-reported health-related quality of life and symptoms of anxiety and depression are important components of the evaluation of outcomes following liver transplantation, and are specifically relevant to ongoing discussions regarding organ allocation and policies for awarding MELD exception points for HCC. By assigning exception points, patients with HCC are awarded wait list priority; therefore, it is important to demonstrate that they have both clinical and patient-reported outcomes that are comparable to those being transplanted for other etiologies without wait list priority. Our study showed that, patients with HCC who received exception points and patients with other etiologies of liver disease had similar PROs after liver transplantation. These findings, which focus on *patient-reported* outcomes, complement our understanding of the effects of HCC exception points on clinical outcomes such as patient survival and add depth to policy discussions regarding the continued application of exception points for patients with HCC.

Patients with a diagnosis of HCC who did not receive exception points had PCS scores after transplant that were both statistically and substantively lower compared to patients with HCC who received exception points. In addition, patients with HCC not awarded exception points showed a downward trajectory in MCS scores in the later post-transplant period, beginning approximately at year three, and had levels of anxiety that remained statistically stable while those who received exception points and those without HCC showed reduced levels of anxiety over time after transplantation. These findings are significant for both persons with notably lower calculated MELD scores for HCC patients who received MELD exception points, as well as patients with comparable pre-transplant MELD scores who do not have HCC. Patients transplanted with incidental HCC on explant (73% of the HCC group that did not receive exception points) receive organs based on their laboratory MELD scores. For this reason they would be anticipated to have pre-transplant PRO scores in some domains that were comparable to the non-HCC group and lower than those who were awarded HCC exception points. This point is illustrated in Figure 2 panel A. Patients without HCC and those with HCC who did not receive exception points had substantively impaired and comparably low pre-transplant PCS scores. However, while the PCS scores of patients without HCC recovered to the general population norm within the first six months of transplant, patients with HCC who did not receive exception points had attenuated post-transplant improvement and their PCS scores remained below the general population norm through the first three years post-transplant. Undiagnosed HCC in the group that did not receive exception points could be related to variability in pre-operative imaging and waiting list surveillance, which could be due to a multitude of reasons, such as renal insufficiency preventing the acquisition of high quality, contrast enhanced axial imaging. It is not possible to test this possibility from the present data as our database was constructed by querying the MELD scores at the time of transplant, not the individual laboratory values and dialysis-related parameters used to calculate the MELD score. However, we suspect that the presence of undiagnosed HCC contributed to both the decrement in pre-transplant PCS and attenuated improvement in post-transplant physical health-related quality of life in the HCC group that

did not receive exception points. Future studies would be required to prospectively test this possibility. Likewise, it is also unknown whether the PCS scores of this group would follow the trajectory and values of the HCC group who received exception points if HCC had been diagnosed pre-operatively with subsequent application of waitlist priority. Further research is indicated to investigate patient-reported outcomes in patients with both progressed end-stage liver disease with elevated laboratory MELD scores and associated undiagnosed cancer.

Over the past several years, evidence has accumulated regarding PROs following transplantation (17-22) and patients with HCC not eligible for transplantation (9,10), but there are no reports specifically evaluating PROs for patients with HCC following transplant. The importance of this study is highlighted by the lack of data describing PROs in patients with and without HCC. Additionally, our study provides opportunities for future research to evaluate PROs of HCC patients transplanted with relatively low calculated MELD scores compared to those transplanted at higher values who had been on the waiting list for a longer time despite having received exception points, particularly in the context of the revised guidelines proposed by The Liver and Intestinal Organ Transplantation Committee to delay HCC exception point assignment for six months following approval (23,24).

Strengths of our study include the well-documented and comprehensive survey methodology and the large cohort of 502 transplant recipients who provided 1,521 multi-survey data points over a 12-year period. In addition to the primary multivariable models that examined relationships between the three cohort groups and the PRO measures over each participants full follow-up period, data were analyzed from the perspective of detailed, norm-based interpretations of scores and over the first three post-transplant years.

Limitations of our study include the single center design, the relatively low MELD scores and short waiting list times at which patients are transplanted in our UNOS region. At our institution, patients with MELD exception points are rarely transplanted at a calculated MELD greater than 25. The generalizability of our findings may be limited, particularly for centers in regions with longer waiting list times where wait list priority afforded by exception points does not offer a significant advantage in reducing transplant times for patients with HCC. In addition, the new policy advocating delayed assignment of HCC exception points may limit the general applicability of our findings if the improved PRO is a result of being transplanted within the first six months of being on the waiting list. Other limitations include the previously mentioned lack of granularity in our database to sufficiently evaluate the effect of the individual parameters of the MELD score at the time of transplant as well as the potential for participation and survivorship biases that are inherent to survey research.

In conclusion, this study provides important insight into the levels and long-term trajectory of PROs in liver transplant recipients with and without HCC, and those with HCC who do and do not receive HCC exception points. Our study demonstrated that patients who received exception points for HCC had similar post-transplant physical and mental HRQOL and symptoms of anxiety and depression compared to those patients without HCC. Since there have been no prior data reporting the effect of HCC on PROs after liver

transplantation, these analyses may help inform policy regarding exception point allocation for patients with hepatocellular carcinoma.

Acknowledgments

Clark Kensinger received salary support from the Renal Biology and Disease Training Program grant: NIH/NIDDK 5T32DK007569.

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Figure 1. Multivariable linear mixed effects models of the effect of HCC and exception point status on the values and temporal trajectories of four patient-reported outcomes

Panel (A) SF-36 PCS: All three HCC/exception point groups averaged below general population norms before transplant and demonstrated improvement to within the normal range after transplantation. However, in comparison to patients with HCC who received exception points, patients with HCC who did not receive exception points had significantly lower PCS scores overall, which resulted in a delay in reaching general population values. *Panel (B) SF-36 MCS:* All three HCC/exception point groups MCS scores averaged within general population norms before and after transplant, however patients with HCC who did not receive exception points had a late decline in mental HRQOL beginning approximately three years following liver transplantation. *Panel (C) BAI:* Pre-transplant BAI scores were in the mild to moderate severity class overall. Following liver transplantation, patients without HCC and those who received exception points for HCC had substantive reductions in symptoms of anxiety over time; however, patients with HCC who did not receive exception points showed less long-term change in the severity of anxiety. *Panel (D) CES-D:* All three HCC/exception point groups averaged within the range of mild to moderate symptoms before transplant and remained statistically stable over the full follow-up period. (Abbreviations: SF-36: Short Form 36 Health Survey; PCS: Physical Component Summary;

HRQOL: HRQOL: Health-related quality of life. HCC: Hepatoceluar Carcinoma; BAI: Beck Anxiety Inventory; CES-D: Center for Epidemiologic Studies Depression Scale)

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Figure 2. Unadjusted time point-specific PRO data through post-transplant year three
Panel (A) SF-36 PCS: Pre-transplant physical HRQOL scores were below general population norms (as indicated by the reference lines) for all three groups. As expected, the highest average pre-transplant scores were among patients with HCC who received exception points. In contrast with HCC patients who received exception points and patients without HCC, both of whose scores improved to within general population levels by month six, PCS scores of persons with HCC who did not receive exception points averaged below general population norms through month 36. *Panel (B) SF-36 MCS:* MCS scores averaged within general population norms before and after transplantation and the early trajectory of scores did not differ between groups through month 36. *Panel (C) BAI:* Pre-transplant BAI scores averaged within the mild to moderate severity classes for the three individual groups. Substantive early reductions in symptom severity were observed but the response was attenuated in person with HCC who did not receive exception points. *Panel (D) CES-D:* Pre-transplant symptoms of depression averaged within the mild to moderate severity classes for the three individual groups. Scores improved in the very early follow-up period then remained statistically stable overall. (Abbreviations: SF-36: Short Form 36 Health Survey; PCS: Physical Component Summary; HRQOL: Health-related quality of life)

HCC: Hepatocellular Carcinoma; BAI: Beck Anxiety Inventory; CES-D: Center for Epidemiologic Studies Depression Scale)

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Table 1

Demographic and clinical characteristics of sample

	Total Sample 502	No HCC n=363 (72%)	HCC without Exception Points n=33 (7%)	HCC with Exception Points n=106 (21%)	p-value
Age (years)	54±10	53±10 ^a	54 ±7	57±7 ^a	0.001
Gender					0.003
Male	334(67)	226(62) ^{a,b}	28(85) ^a	80 (76) ^b	
Female	168(33)	137(38)	5(15)	26(25)	
Race					0.153
White	456 (91)	334	31 (94)	91 (86)	
African American	25(5)	18(5)	1(3)	6(6)	
Other	21(4)	11 (3)	1(3)	9(8)	
Etiology of End-Stage Liver Disease (whether present) ^c					
Non-Alcoholic Steatohepatitis	61(12)	47(13)	5(15)	9(9)	0.402
Hepatitis C Virus	210 (42)	153 (42)	17(52)	40 (38)	0.365
Alcoholic Hepatitis	118(24)	94(26)	7(21)	17(16)	0.103
Cryptogenic	39(8)	32 (9)	3(9)	4(4)	0.223
Metabolic	35(7)	29(8)	2(6)	4(4)	0.318
Autoimmune	61(12)	56 (15) ^{a, b}	2 (6) ^a	3(3) ^b	0.001
Other viral hepatitis	15(3)	8(2)	0(0)	7(7)	0.037
Congenital ^d	3(1)	3(1)	0(0)	0(0)	--
Acute Hepatic Necrosis ^d	9(2)	8(2)	1(3)	0(0)	--
Malignancy (non-HCC) ^d	3(1)	3(1)	0(0)	0(0)	--
Benign tumor ^d	1 (<0.1)	1 (0.3)	0(0)	0(0)	--
Other ^d	6(1)	6(2)	0(0)	0(0)	--
MELD cohort	85 (17)	67(18)	5(15)	13 (12)	0.314

	Total Sample 502	No HCC n=363 (72%)	HCC without Exception Points n=33 (7%)	HCC with Exception Points n=106 (21%)	p-value
2005-2014	417 (83)	296(82)	28(85)	93(88)	
Calculated MELD at transplant	22 ±8	24±7 ^a	24±6 ^b	14±5 ^{a,b}	<0.001
Required re-transplantation	7(1)	5(1)	0(0)	2(2)	0.721
Follow-up time (months)	30 ±29	31(30)	35 (29)	25 (27)	0.147

Table entries are mean ± standard deviation or frequency (% cohort or % HCC/Exception points group).

Superscript notation: ^avs. ^aand^b vs. ^b, pairwise<0.05.

^c Etiologies were coded as binary variables and persons could have multiple etiologies of end-stage liver disease (e.g., hepatitis C virus and alcoholic hepatitis).

^d Between-group proportions were not tested due to small cell frequencies.

Table 2

Multivariable mixed effects models of physical and mental health-related quality of life.

Effect	Outcome = SF-36 PCS				Outcome = SF-36 MCS			
	Estimate	p-value	95% Confidence Interval		Estimate	p-value	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Age (years)	-0.25	<0.001	-0.34	-0.17	0.12	0.009	0.03	0.21
Male gender (ref: female)	-1.36	0.139	-3.17	0.44	-1.22	0.200	-3.10	0.65
MELD cohort (ref: 2002-2004)	2.24	0.033	0.18	4.30	0.65	0.551	-1.49	2.79
Hepatocellular carcinoma (ref: HCC with exception points)								
No HCC	-2.50	0.051	-5.01	-0.01	2.51	0.058	-0.100	5.10
HCC without exception points	-5.00	0.016	-8.89	-0.92	4.38	0.037	0.27	8.49
Etiology of End Stage Liver Disease (ref: no)								
Non-Alcoholic Steatohepatitis	-0.63	0.662	-3.47	2.21	-0.57	0.701	-3.52	2.37
Hepatitis C Virus	-2.51	0.014	-4.50	-0.52	-1.29	0.219	-3.36	0.77
Alcoholic Hepatitis	-0.13	0.906	-2.25	1.99	-1.87	0.094	-4.07	0.32
Cryptogenic	0.06	0.969	-3.29	3.32	0.40	0.812	-2.95	3.77
Metabolic	0.14	0.931	-3.13	3.42	1.12	0.517	-2.27	4.51
Autoimmune	0.06	0.968	-2.77	2.88	2.44	0.103	-0.50	5.37
Re-transplant (ref: no)	-8.51	0.017	-15.48	-1.53	2.13	0.552	-4.91	9.28
Calculated MELD score at transplant	-0.09	0.125	-0.21	0.03	-0.06	0.332	-0.18	0.06
Time since transplant (months)	0.10	0.001	0.04	0.16	0.05	0.089	-0.01	0.11
Interaction Term (ref: Time since transplant × HCC with exception points)								
Time since transplant × No HCC	0.02	0.538	-0.04	0.08	-0.02	0.496	-0.09	0.04
Time since transplant × HCC without exception points	0.03	0.569	-0.07	0.13	-0.14	0.006	-0.24	-0.04
Intercept	52.20	<0.001	46.10	58.31	41.94	<0.001	35.61	48.27

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Effect	Outcome = SF-36 PCS				Outcome = SF-36 MCS			
	Estimate	p-value	95% Confidence Interval		Estimate	p-value	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Covariance Parameter	43.73	<0.001	34.81	54.93	49.45	<0.001	39.37	62.13

Table 3
Multivariable mixed effects models of symptoms of anxiety and depression

Effect	Outcome = BAI				Outcome = CES-D			
	Estimate	p-value	95% Confidence Interval		Estimate	p-value	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Age (years)	0.02	0.505	-0.05	0.10	-0.04	0.285	-0.11	0.03
Male gender (ref: female)	0.29	0.704	-1.22	1.81	0.92	0.255	-0.66	2.49
MELD cohort (ref: 2002-2004)	-0.55	0.535	-2.28	1.18	-1.05	0.249	-2.82	0.74
Hepatocellular carcinoma (ref: HCC with exception points)								
No HCC	-0.48	0.649	-2.54	1.59	-0.79	0.478	-2.97	1.39
HCC without exception points	-2.52	0.139	-5.87	0.82	-1.87	0.278	-5.25	1.51
Etiology of End Stage Liver Disease (ref: no)								
Non-Alcoholic Steatohepatitis	0.77	0.527	-1.62	3.15	0.06	0.961	-2.45	2.58
Hepatitis C Virus	2.10	0.013	0.44	3.77	1.50	0.085	-0.21	3.22
Alcoholic Hepatitis	0.98	0.282	-0.81	2.77	1.01	0.278	-0.82	2.85
Cryptogenic	0.57	0.678	-2.15	3.30	-1.27	0.377	-4.09	1.55
Metabolic	-1.05	0.444	-3.77	1.65	-1.61	0.263	-4.43	1.21
Autoimmune	-1.50	0.210	-3.86	0.85	-1.54	0.216	-3.97	0.90
Re-transplant (ref: no)	3.49	0.215	-2.03	9.00	2.31	0.440	-3.56	8.18
Calculated MELD score at transplant	0.12	0.024	-0.02	0.22	0.07	0.209	-0.04	0.17
Time since transplant (months)	-0.08	0.001	-0.12	-0.03	-0.03	0.210	-0.08	0.02
Interaction Term (ref: Time since transplant × HCC with exception points)								
Time since transplant × No HCC	0.02	0.308	-0.02	0.07	-0.01	0.663	-0.06	0.04
Time since transplant × HCC without exception points	0.08	0.042	0.00	0.15	0.04	0.352	-0.04	0.12
Intercept	7.78	0.003	2.65	12.91	13.18	<0.001	7.89	18.47

Effect	Outcome = BAI				Outcome = CES-D			
	Estimate	p-value	95% Confidence Interval		Estimate	p-value	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Covariance Parameter	34.02	<0.001	27.43	42.19	34.33	<0.001	27.33	42.87