



**INTENTION-TO-TREAT SURVIVAL BENEFIT OF LIVER
TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR
CANCER**

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INTENTION-TO-TREAT SURVIVAL BENEFIT OF LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CANCER

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Word count: 3801**Abstract:** 246**Pages:** 21**Tables:** 3**Figures:** 2**References:** 33**Abbreviations used in the text:**

AIC,	Akaike Information Criterion
AFP,	alpha-fetoprotein
CR,	complete response
DO,	drop-out
EurHeCaLT,	European Hepatocellular Cancer And Liver Transplantation
FU,	follow-up
HCC,	hepatocellular cancer
IQR,	interquartile ranges
ITT,	intention-to-treat
LRT,	loco-regional treatment
LT,	liver transplantation
MC,	Milan Criteria
MELD,	model for end-stage liver disease
MESIAH,	Model to Estimate the Survival In Ambulatory patients with HCC
mRECIST,	modified Response Evaluation Criteria in Solid Tumors
PR,	partial response
PD,	progression disease
SD,	stable disease
WL,	waiting list
WT,	waiting time

Conflict of interest

The authors have no conflicts of interest to declare in relation with this paper.

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Contributors

QL, AV and JL were responsible for the conception, design and analysis of the study and for writing the final report;

QL, AV, IS, AF, GM, GS, MHL, GV, TMM, DN, AWA and ACF were involved with the collection and interpretation of data;

UC, IG, MR, ET, GO, GME, GT and MV participated in data management and manuscript review.

ABSTRACT

The debate about the best approach to select patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) is still ongoing. This study aims to identify the best variables allowing to discriminate “high-” and “low-benefit” patients. To do so, the innovative concept of intention-to-treat (ITT) survival benefit of LT has been created. Data of 2103 adult HCC patients consecutively enlisted during the period 1987-2015 were analyzed. Three rigorous statistical steps were used in order to create the ITT survival benefit of LT: the development of an ITT LT and a non-LT survival model, and the individual prediction of the ITT survival benefit of LT defined as the difference between the median ITT survival with (based on the first model) and without LT (based on the second model) calculated for each enrolled patient. Four variables (MELD, alpha-fetoprotein, Milan-Criteria status and radiological response) displayed a high effect in terms of delta-benefit. According to these risk factors, four benefit groups were identified. Patients with three-four factors (“no-benefit group”, n=405/2103; 19.2%) had no benefit of LT compared to alternative treatments. Inversely, patients without any risk factor (“large-benefit group”, n=108; 5.1%) yielded the highest benefit from LT reaching 60 months. Conclusion: The here presented innovative ITT transplant survival benefit allows to better select HCC patients waiting for LT. The obtained stratification may lead to an improved and more equal way for organ allocation. Patients with no benefit should be delisted, whilst patients with large benefit ratio should be prioritized for LT.

INTRODUCTION

The debate about the best approach for selecting patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) is still ongoing. Recent literature has shown that outcome of HCC patients in which the selection for LT is based on specific restrictive tumor characteristics may generate survival rates comparable to those obtained after LT in non-HCC patients. Furthermore, LT may also represent an optimal treatment for HCC patients harboring tumors being out of conventional (Milan) criteria if morphological and biological tumor behavior is taken into account.¹ Consequently, the line between the need to justifiably transplant as many patients as possible and the necessity to select only patients having an effective benefit from LT is very thin and represents therefore an everyday clinical challenge.

Recently, the concept of “transplant benefit”, corresponding to the number of years gained by LT minus the number of years offered by alternative treatments, has been proposed in the field of liver transplantation.² In the context of non-HCC patients, the concept of transplant benefit has been efficaciously adopted. Indeed, patients with a model for end-stage liver disease (MELD) score <15 do not improve their survival if transplanted or if staying on the waiting list (WL).² When follow-up period is no longer than 10 years, transplant benefit estimation is equally influenced by pre- and post-LT variables, thus providing a balance between the concepts of pure urgency (“the sickest first”) and pure utility (the highest survival gain).³

However, the definitive answer on the best pre- and post-LT variables to be used for selecting HCC patients able to reach an effective benefit from LT is still needed. Apart from morphological aspects, biological and “time-dependent” variables have been recently added in the LT selection process.⁴ Among them, waiting time (WT), alpha-fetoprotein (AFP) values and radiological response after neo-adjuvant loco-regional treatment (LRT) have been largely explored.⁵⁻⁹

Moreover, transplant benefit values have been always evaluated from the moment of LT and not from the moment of WL inclusion. In the present study, the innovative concept of intention-to-treat (ITT) transplant benefit has been proposed. ITT survival is defined as the LT survival from the

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3 moment of patient enlistment and not from the day of LT,¹⁰ having been widely accepted in the LT
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5 community.^{11,12} The use of an ITT survival analysis allows the opportunity to analyze the results
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7 based on the initial treatment assignment and not on the treatment eventually received, thus
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9 avoiding various misleading artifacts and initial selection biases.

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11 The aim of the present study is then to analyze a large multicenter European collaborative Project,
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13 with the intent to identify the best variables able to discriminate high or low benefit patients. In
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15 order to do so, an ITT survival benefit has been developed, aiming at identifying different patient
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17 subgroups deserving or not LT.
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20 21 22 23 MATERIALS AND METHODS

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25 A retrospective analysis of data from 2103 adult (≥ 18 year-old) patients with radiological and/or
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27 pathological diagnosis of HCC was performed. All patients were listed for LT during the period
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29 from January 1, 1987 to December 31, 2015, and being dropped-out or undergoing a first LT during
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31 the same time period. Data were obtained from the prospectively collected databases of ten
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33 collaborative European Centers involved in the EUROpean HEpatocellular CANcer and Liver
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35 Transplantation (EurHeCaLT) Project. The participating centers were Padua, Italy (n=346);
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37 Brussels, Belgium (n=336); Innsbruck, Austria (n=330); Sapienza University Rome, Italy (n=243);
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39 Royal Free London, UK (n=193); Mainz, Germany (n=176); San Camillo Hospital Rome, Italy
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41 (n=142); Tor Vergata University Rome, Italy (n=140); Ancona, Italy (n=110); and, Catholic
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43 University Rome, Italy (n=87).
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47 Patients with incidental tumors, mixed hepatocellular-cholangiocellular tumors or cholangiocellular
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49 cancer misdiagnosed as HCC were excluded from the analysis.
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52 Of note is that all of the participating centers do not consider anymore Milan Criteria (MC) as the
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54 limit for inscription on the WL: consequently, 636 (30.2%) MC-OUT patients were enlisted.
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57 Despite different policies were used in the different centers, all the transplanted cases reported were
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59 within University of San Francisco California Criteria, Up-to-seven Criteria or Tokyo ("5+10 role")
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3 Criteria: so, the dimensional upper limit observed in the present study was 6.5 cm of diameter in the
4 target lesion and 10 nodules. A majority of patients (n=1754; 83.4%) had pre-LT multimodal LRT.
5 Such policy allowed an in-depth analysis of the response to LRT as a possible selection variable.
6
7 All analyzed patients were categorized in different groups according to the modified Response
8 Evaluation Criteria in Solid Tumors (mRECIST) criteria termed as Complete Response (CR),
9 Partial Response (PR), Stable Disease (SD) and Progression Disease (PD).¹⁰ Patients which did not
10 have LRT were considered as no-LRT group: the decision to not consider no-LRT patients with a
11 possible increase of the tumor burden before LT into the PD group derived from the consideration
12 that these patients do not fully correspond from a biological point of view to patients with a tumor
13 with a PD after a radiological treatment. In the treated patients, mRECIST status was defined after
14 comparison between initial imaging at WL inscription and the last available one before LT or drop-
15 out (DO).
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29 Patients listed before 1996 and 2010 were re-classified according to MC and mRECIST criteria
30 according to the retrospective evaluation of their imagings.^{1,13}
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33 The adopted cut-offs of 1000 ng/mL and 15 ng/mL/month for AFP and AFP slope were selected
34 according to literature data.^{6,7} The AFP slope was calculated using the two values at the moment of
35 WL inscription and the one immediately before LT or DO. The adopted WT cut-off of 120 days and
36 MELD cut-off of 13 were also chosen according to previous reports.^{5,11,14}
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43 Median patient follow-up (FU) from the moment of WL inscription was 3.7 years (interquartile
44 ranges [IQR]: 1.4-7.6).
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49 Statistical analysis

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51 Continuous variables were reported as medians and IQR. Dummy variables were reported as
52 numbers and percentages. Missing data relative to study covariates always involved less than 10%
53 of patients. Thus, they were estimated using the Maximum Likelihood Estimation method.¹⁵
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3 The statistical design of this study included three main steps: a) the development of an ITT LT
4 survival model; b) the development of a non-LT survival model and; c) the individual prediction of
5 the ITT survival benefit of LT defined as the difference between the median ITT survival with LT
6 (based on the first model) and median survival without LT (based on the second model) calculated
7 for each enrolled patient. The specific steps for the construction of the models are diffusely
8 explained in **Supplementary Data 1**. We briefly reported here the statistical steps we adopted.

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11 Firstly, the ITT LT survival model was constructed using a log-logistic model: the results of the
12 model are reported in **Supplementary Table 1**. The obtained results of the model were applied to
13 predict ITT median survival with LT of each enrolled patient.

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16 Non-LT survival model was built starting from some assumptions: the majority of WL patients are
17 censored by LT;^{16,17} median WT of HCC patients is relatively short, thus prediction of long-term
18 survival of these patients may be inaccurate.⁵ Several statistical techniques have been proposed for
19 resolving this problem.¹⁶⁻¹⁸ However, these methods are still insufficient to resolve the biases
20 related to the complexity of WL dynamics, often requiring arbitrary corrections.^{18,19} The Model to
21 Estimate the Survival In Ambulatory patients with HCC (MESIAH) was then adopted for resolving
22 this problem.¹⁴ This model, recently validated both in western and eastern countries,^{20,21} provides a
23 simple formula to translate the MESIAH score in individual survival predictions. Using patient
24 characteristics at the last evaluation before LT or DO, we used the MESIAH score to simulate the
25 median time to death that patients censored by LT would have had in the absence of LT. This
26 simulated time to death was therefore used to perform a second log-logistic parametric survival
27 model to find significant predictors of non-LT survival: the results of the model are reported in
28 **Supplementary Table 2**. Then, we used this second model to predict non-LT median survival of
29 each enrolled patient.

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32 Finally, The ITT LT and the non-LT survival log-logistic models generated two median survival
33 predictions for each enrolled patient. The ITT survival benefit of LT was, therefore, calculated for
34 each patient as the difference between ITT LT median and the non-LT median survival estimations.

All estimations were capped at 120 months, since this time horizon represents the ideal balance between utility and urgency allocation principles.⁴ A multivariate least square regression was finally used to find significant predictors of ITT LT benefit among studied variables.^{22,23} In all the

multivariable survival models, all variables with $p < 0.1$ at univariate model were included. In the final model only variables showing a significant impact on survival at the first multivariable model were maintained.

Since p-values can be biased from population size, results of survival benefit estimations in covariates subgroups were reported as effect size. Effect size is a standard measure that can be calculated from any number of statistical outputs. One type of effect size, the standardized mean effect, expresses the mean difference between two groups in standard deviation units. Typically, it is reported as Cohen's d, or simply referred to as d-value.²⁴

Variables with a $p < 0.05$ were considered statistically significant. The calculations were done with the JMP (1989–2003 SAS Institute Inc.) and Stata/IC 13.0 (1985–2013 StataCorp LP) packages.

RESULTS

Demographics of the entire population are displayed in **Table 1**. Two hundred forty-six (11.7%) of 2103 patients dropped-out during the WT period: 160/246 (65.0%) cases dropped-out due to HCC progression, with 143/246 (58.1%) patients dying during the WT period. Looking more in detail the reasons of DO, 69 patients were excluded due to HCC progression (patient alive at the moment of DO). In 91 cases, a tumor-related death on WL was observed; 52 patients showed a liver disease-related death on WL, 25 moved to another center, and 9 were excluded due to poor compliance.

A total of 1857 patients underwent LT: 242 (13.0%) patients recurred. When considering the 1504 patients having a minimum FU of 1 year after LT, the recurrence rate was 16.1%.

After the construction of the different models, a multivariate least square regression analysis finally identified eight variables as significant predictors for ITT transplant benefit. Five variables favored an increase of benefit: age at listing (β -coefficient=1.3; p -value=0.0006), MELD at LT or DO (β -

coefficient=1.1; p-value<0.0001), WT duration (β -coefficient=0.1; p-value=0.001), last radiological HCC assessment of the major lesion diameter (β -coefficient=10.9; p-value<0.0001), and of number of HCC lesions (β -coefficient=6.5; p-value<0.0001). In other terms, a higher benefit was reported in older patients, if MELD or WT increased, or if greater tumors were transplanted.

Three variables pointed towards a poor benefit: WL inscription before 2001 (β -coefficient=-25.3; p-value<0.0001), mRECIST PD (β -coefficient=-36.8; p-value<0.0001), and last available logAFP value (β -coefficient=-3.4; p-value<0.0001). In other terms, being listed before 2001, presence of radiological PD and progressive increase in AFP values were all linked to a poor benefit (**Table 2**).

ITT transplant benefit estimations in different clinically relevant subgroups were also looked at (**Table 3**). Five variables showed a moderate-to-high effect in terms of differences of median benefit: patients with last AFP value ≥ 1000 ng/mL (6.8 vs. 25.4 months in patients with AFP < 1000 ng/mL; D-value=0.69), lab-MELD ≤ 13 (19.8 vs. 39.1 months in patients with MELD > 13; D-value=0.81), mRECIST PD (10.6 vs. 29.2 months in patients without PD; D-value=0.78) and mRECIST CR (7.2 vs. 28.7 months in patients without CR; D-value=0.90) had very disappointing benefits. MC-IN status (22.8 vs. 34.5 months in patients exceeding MC; D-value=0.47) and WL inscription before 2001 (10.4 vs. 27.3 months in patients enlisted after 2001; D-value=0.49) presented only a moderate benefit discrimination (**Table 3, Figure 1**).

Based on these results, it was firstly decided to exclude the period of transplantation from further analyses because it was considered as useless when applying to patients transplanted nowadays. When doing so, four benefit groups could be identified according to the presence of the remaining four risk factors. Patients presenting a combination of three to four factors (no benefit group: n=405/2103; 19.2%) had no benefit in being transplanted compared to alternative therapies (median value of improved survival: zero months). Patients in the small (two risk factors: n=897; 42.7%) and moderate (one risk factor: n=693; 33.0%) groups displayed improved survival benefits of 20 and 40 months, respectively. Conversely, patients without any risk factor (large benefit group: n=108; 5.1%) had the highest benefit reaching 60 months (**Table 3, Figure 2**). Different contour

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3 plots deriving from the combination of the different risk factors are displayed in **Supplementary**
4
5 **Figure 1.**
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9 10 **DISCUSSION**

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12 Twenty years after its introduction, MC are not anymore considered to be the best criterion to select
13 HCC patients for LT.²⁵ However, the best compromise between the need to justifiably raise the
14 number of transplantable patients and the necessity to minimize the risk for recurrence, without
15 contemporaneously harming non-HCC patients on the WL, is still out.¹⁹
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19 Aiming at squaring the circle, a recent paper by Mazzaferro interestingly reported that the only way
20 to frame the complex scenario of LT for HCC is the ability to capture in a weighty manner tumor
21 evolution in relation to its treatment, aiming to modulate scores able to estimate the risk of pre-LT
22 DO and post-LT benefit.²⁶ So, morphology “per se” is insufficient to optimize selection and
23 allocation, and new criteria, possibly focused on “progression” instead than on static tumor
24 characteristics should be used in order to better identify those patients in real need for LT.⁴
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28 In Italy, a demanding effort has been made with the intent to build an algorithm based on the
29 principles of urgency, utility and transplant benefit, clearly underlying the inequity of a purely
30 MELD-based HCC allocation model. Different variables (response to LRT, WT, AFP) all have
31 been advocated as possible selection criteria to be used in such a “benefit scenario”.²⁷ However, the
32 main limit of their use in the setting of benefit is that no scientific evidence exists on their effective
33 contribution in terms of survival.
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37 In the present study, four different risk factors connected with poor ITT-benefit, have been
38 identified: radiological progression/complete response, AFP increase, MC-IN status and low MELD
39 score.
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43 Several previously published studies corroborate our findings. The recent paper by Metha reported a
44 selected population of HCC T2 patients waiting for LT with a very low 2-year probability of DO
45 (only 1-6%). Tumor morphology (1 tumor of 2-3 cm), radiological response to LRT (complete
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3 response after the first treatment), and biological behavior (AFP level stably normal after the first
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5 LRT) selected these patients.²⁸

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7 Several European studies similarly confirmed the paramount role of radiological response,^{8,9,11} and
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9 AFP modification following LRT,^{6,7,11,18} as the better selection criterion of HCC patients awaiting
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11 LT. The multicentric EurHeCaLT study showed that the combination of radiological response and
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13 AFP slope allowed to better discriminate “low-risk” from “high-risk-for-recurrence” patients, and
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15 this independently from their MC-IN or OUT status.¹² Two recent scores, all focusing on the HCC
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17 selection process, further underlined the importance of combining biology and morphology in order
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19 to further improve results. Interestingly, the TRAIN score, based on the combination of AFP slope,
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21 radiological progression, inflammatory markers and WT, was superior respect to MC in predicting
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23 patient death during the WT in a long-WT population, whilst it was superior in predicting post-LT
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25 recurrence in case of short WT.¹¹ The MORAL score, incorporating inflammatory markers, AFP
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27 and tumor morphology, also showed to be significantly superior to MC, with an area under the
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29 curve of 0.82 vs. 0.63 for predicting post-LT HCC recurrence.²⁹

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34 Also the fact that MC-IN status was connected with poor survival benefit had been observed in a
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36 multicentre Italian study including 1328 patients: survival benefit was obtainable in patients having
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38 advanced HCC, and this was regardless of the “nodule number-size criteria” (as MC are).³⁰ In other
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40 terms, the benefit increases when the number of nodules and the dimensions of the tumor
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42 contemporaneously increase, on the condition that radiological findings and AFP do not progress.

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45 Various articles already focused on the role of MELD increase as a cause of increased benefit. A
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47 US study clearly observed that the increase in MELD points corresponds to a progressive survival
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49 benefit increase in HCC and non-HCC patients, ranging from just a few months in patients with
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51 MELD score of 6-8 to 4 years in patients with MELD score of 36-40.¹⁹ Another Italian study
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53 similarly reported that MELD score increase was associated with a better benefit both in HCC and
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55 non-HCC patients; interestingly enough, this study observed that an equation based on the
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57 combination of MELD and AFP (the “HCC-MELD” equation) allowed the calculation of a
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3 numerical score for HCC patients, with the intent to calibrate their transplant benefit with the one
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5 observed in non-HCC patients having the same MELD value.¹⁸ This finding was also observed in
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7 the present series, in which MELD and AFP were factors allowing to discriminate low- and high-
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9 benefit patients.

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11 Despite the fact that each risk factor has already been singularly investigated in other studies
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13 focusing on the prediction of survival in HCC patients, one should note that the present study
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15 presents several innovations. Firstly, a new concept of ITT survival benefit has been proposed, as
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17 well as a statistical methodology has been created for calculating it. The rationale for the proposal
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19 of this new concept is to further increase the balancing between pure priority and pure utility: the
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21 integration of two large populations of LT and non-LT patients in the creation of the ITT benefit
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23 statistical model allowed in fact to better calibrate the role of the evaluated variables in both
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25 settings.
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29 Secondly, radiological response to LRT has been investigated for the first time in a benefit-related
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31 analysis. The lack of studies investigating its role in the LT selection process may be explained by
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33 the fact that several large cohorts include a smaller number of LRT cases compared to our series;
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35 moreover, radiological response has not been systematically collected in large populations, so until
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37 now only small mono-centre studies (apart the reported EurHeCaLT study) have been
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39 investigated.¹²
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43 Thirdly, this is the first time that all of the investigated variables have been connected in order to
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45 create different ITT benefit groups, and to define categories of patients that would benefit from LT.

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47 In fact, when three to four of the analyzed risk factors are present in a single patient, ITT benefit
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49 was nil. Such a result is extremely important, because patients presenting three to four risk factors
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51 represented 19% of the investigated population. Interestingly enough, this specific “no benefit”
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53 group consisted of two main patient categories. On one side, MC-IN patients with low MELD
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55 showing radiological-biological progression were observed. These patients are similar to those
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3 patients already reported in the study by Metha, in which poor radiological response and increased
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5 AFP corresponded to higher percentages of DO.²⁸

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7 On the other hand, MC-IN patients with low MELD with complete radiological response
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9 corresponded to the Transplantable Tumor (TT)0 category reported by Mazzaferro, in which the
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11 cancer is “zeroed” by LRT/resection during the WT.²⁶ In both scenarios such patients should be
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13 delisted: in the first case because of the poor benefit connected with an advanced cancer, in the
14
15 second case due to a poor benefit associated with a completely healed tumor.

16
17 Conversely, when looking at the “high” ITT benefit group, an extraordinary benefit (5 years) in
18
19 comparison to not-transplanted patients presenting the same characteristics was observed. As a
20
21 consequence, it looks obvious that such a patient population should be surely considered for LT.
22
23 Despite the fact that this group consists of high-MELD MC-OUT patients (without any evidence of
24
25 radiological-biological progression), thus potentially being associated with more peri-operative
26
27 mortality and post-LT recurrence, the benefit in transplanting (and even prioritizing) them is clear.
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29 Moreover, it should be underlined that such a population is really small, representing no more than
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31 5% of the entire investigated population. Therefore, prioritization of such a population should only
32
33 marginally impact on the number of used grafts, mainly if we consider on the opposite the great
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35 number of potentially “preservable” livers if we delist the patients with no ITT benefit (as a
36
37 reminder, this group represents 19% of all the investigated cases!).

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39 When considering the group of patients presenting “low” ITT benefit (patients with two risk factors:
40
41 20 months of benefit), one should keep in mind that the decision to transplant these patients has to
42
43 be seen in the context of the opportunity to perform a LT without harming the group of listed non-
44
45 HCC patients (“concept of equity”).³¹ Such a concept has been very elegantly demonstrated by
46
47 Volk in the US population, in which the decision to transplant an HCC patient was justified only if
48
49 a minimal survival threshold was reached: only in this case, in fact, the benefit of transplanting
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51 tumor patients outweighed the harm for not transplanting non-HCC patients.³² Similar results were
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53 also reported in a monocentre experience from Italy.³³ As a consequence, patients presenting only
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3 small benefit (corresponding to 42.7% of our entire investigated population) should be carefully
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5 considered, mainly when evaluated in a low-volume center. As an example, a MC-OUT patient
6
7 with low MELD and AFP ≥ 1000 ng/mL should be closely evaluated in a low-volume centre in light
8
9 of his high recurrence risk.

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11 The present study did not explore the opportunity to propose a more equal organ allocation model
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13 among enlisted HCC and non-HCC patients in terms of priority score for LT, such the “HCC-
14
15 MELD” model did.¹⁸ Moreover, this latter score is based only on AFP and MELD and it was
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17 calculated only in T2 HCC patients, whilst the present score presents a higher complexity (AFP,
18
19 MELD, radiological response, initial MC status). The development of an equation able to
20
21 recalibrate the whole allocation process (i.e. including both selection of patients for listing and
22
23 prioritization of listed patients) among non-HCC and HCC patients should be further explored.
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27 The authors admit that the present study has some limitations. First of all, it is a retrospective
28
29 collaborative non-randomized study covering 30-year period. Consequently, some statistical and
30
31 methodological limits exist. However, we feel confident that the largeness of the investigated
32
33 population and the rigorous adherence to the statistical analysis guidelines may have counteracted
34
35 these negative parameters. Moreover, the introduction of the period of WL inscription as covariate
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37 in the multivariate models further minimizes the possible errors deriving from a “period-dependent”
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39 selection.
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43 Another possible limit derives from the fact that allocation disparities may be caused by not
44
45 investigated parameters other than tumor characteristics (i.e., blood group): unfortunately, the
46
47 retrospective character of the present study did not give the opportunity to fully investigate such
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49 aspects.
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51 52 53 54 CONCLUSIONS

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56 The innovative ITT survival benefit of LT allows to better discriminate HCC patients waiting for
57
58 LT in relation to their real need for transplantation. Such a stratification may lead to an improved
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3 and more equitable liver allocation. New aspects such as radiological response after LRT should be
4
5 implemented in clinical practice as a selection parameter to be used in HCC patients. The
6
7 combination of radiological and biological tumor characteristics should be considered as the gold
8
9 standard for HCC selection instead of the conventionally used “only morphological” criteria.
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For Peer Review

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29 liver transplantation. *Transplant Proc* 2010;42:1194–6.
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FIGURES

Figure 1. Benefit risk factors and benefit gains. For each of the 9 reported risk factors (section A), two median benefits are reported according to specific threshold values (section B). Median benefit gains are calculated for each factor by difference between the reported median benefits (section C). Benefit gains are arbitrary grouped in 4 levels (very small, small, moderate and large benefit).

Figure 2. Incidence of the 4 different “Benefit Groups” in the examined population.

For Peer Review

Brussels, 18 November, 2016

Dear Editor,

We hereby submit our original manuscript entitled **“INTENTION-TO-TREAT SURVIVAL BENEFIT OF LIVER TRANSPLANTATION IN PATIENTS WITH HEPATOCELLULAR CANCER”**

We report a retrospective analysis of data coming from 2103 adult patients with hepatocellular cancer (HCC) enlisted for liver transplantation (LT) during the period 1987-2015. Data were obtained from the prospectively collected databases of ten collaborative European Centers involved in the EUROpean HEpatocellular CAncer and Liver Transplantation (EurHeCaLT) Project.

The present study, based on a sophisticated statistical analysis, introduces the innovative concept of intention-to-treat (ITT) survival benefit of LT.

This new selection tool allowed to better select HCC patients waiting for LT. Four groups presenting different benefit gains were then identified, thus leading to an improved and more equal way for organ allocation. In fact, patients with no benefit ratio should be de-listed, whilst patients with large benefit ratio should be prioritized for LT.

We are of the opinion that the present paper represents an added value to surgeons, oncologists, and mainly gastroenterologists and transplant physicians dealing with HCC and indication or prioritization for LT.

All authors participated in the intellectual content, conception and design of the paper, took public responsibility for it and have agreed to have their name listed as contributors. Neither this manuscript nor parts of it have been previously submitted for publication.

None of the authors received any financial interest, direct or indirect, related to the achievement of this work.

If requested by the editors, we will provide the data and information on which the results of this manuscript are based.

We hope that this paper can be accepted for publication in the HEPATOLOGY Journal.

Sincerely Yours

Quirino LAI, MD PhD

Corresponding author

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3 HEP-16-2270

4 INTENTION-TO-TREAT SURVIVAL BENEFIT OF LIVER TRANSPLANTATION IN PATIENTS
5 WITH HEPATOCELLULAR CANCER
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8 *We thank the Editors of HEPATOLOGY for having the opportunity to revise the article with the intent to
9 improve its quality. We hope the revision work will be able to fully satisfy the requests of the reviewers.*

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12 **Reviewer: 1**

13
14 *We really thank the reviewer for the statistical suggestions and comments. To better answer to his/her
15 issues, we have performed a complete statistical revision of our study with the help of an expert
16 Statistician from Padua University.*

17
18 Lai et al. are proposing a transplant benefit model based on intention-to-treat (ITT) to assess the number
19 of life years gained/lost by transplanting patients with HCC. They suggest that ideal candidate for
20 transplant (with the highest transplant benefit) have high MELD (>13), reasonable AFP (<1000), no
21 progressive disease/complete response, and are outside Milan.

22
23 The concept is of interest, and represents a further adaptation from previous data. The proposed model
24 cannot be considered as final, but it helps understanding the expected benefit from transplant in specific
25 patients. The article is well written.
26

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28 1) One of the originality of the model is the ITT concept, and I would suggest better highlighting this
29 point, by better explaining the current model versus previous ones (especially the one in Vitale et al. J
30 Hepatology 2014).
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33 *ANSWER. We thank the reviewer for this important comment giving us the possibility to better explain
34 these important concepts. The following sentence has been added in the Introduction section of the paper:
35 "Moreover, transplant benefit values have been always evaluated from the moment of LT and not from
36 the moment of WL inclusion. In the present study, the innovative concept of intention-to-treat (ITT)
37 transplant benefit has been proposed. ITT survival is defined as the LT survival from the moment of
38 patient enlistment and not from the day of LT, having been widely accepted in the LT community. The use
39 of an ITT survival analysis allows the opportunity to analyze the results based on the initial treatment
40 assignment and not on the treatment eventually received, thus avoiding various misleading artifacts and
41 initial selection biases."*

42
43 *Regarding to the model by Vitale et al., it was actually proposed with the intent to create a more equal
44 organ allocation among enlisted HCC and non-HCC patients in terms of priority score for LT. The
45 present study did not explore such an aspect, focusing on the detection of variables able to discriminate
46 among high-benefit and low-benefit HCC patients and on the definition of the challenging clinical
47 decision about the patients to include vs. to exclude from the WL. The "HCC-MELD" score proposed by
48 Vitale et al. is based only on AFP and MELD and it was calculated only in T2 HCC patients, whilst the
49 present score presents a higher complexity (AFP, MELD, radiological response, initial MC status).*

50 *A sentence has been added in the Discussion section of the paper:*

51 *"The present study did not explore the opportunity to propose a more equal organ allocation model
52 among enlisted HCC and non-HCC patients in terms of priority score for LT, such the "HCC-MELD"
53 model did. Moreover, this latter score is based only on AFP and MELD and it was calculated only in T2
54 HCC patients, whilst the present score presents a higher complexity (AFP, MELD, radiological response,
55 initial MC status). The development of an equation able to recalibrate the whole allocation process (i.e.
56 including both selection of patients for listing and prioritization of listed patients) among non-HCC and
57 HCC patients should be further explored."*
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4 2) Please provide the number of missing data for each studied variable (potentially in Table 1). How were
5 they handled?
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8 *ANSWER. We really thank the reviewer for this comment because we actually forgot to specify one*
9 *important aspect of our statistical analysis in the methods.*

10 *“Missing data relative to study covariates always involved less than 10% of patients. Thus, they were*
11 *estimated using the Maximum Likelihood Estimation method.”*

12 *A reference was added accordingly: Baraldi AN, Enders CK. An introduction to modern missing data*
13 *analyses. Journal of school psychology 2010; 48(1): 5-37.*
14

15 3) Figure 2 suggests that patients without LRT have no risk factor, yet they could still present a PD.
16 Please explain and expand.
17

18 *ANSWER. We agree with the reviewer. However, when we defined PD or CR, we only considered the*
19 *cases with an effective post-treatment radiological response accordingly to the mRECIST criteria. These*
20 *criteria have been defined in accordance with the effective biological-morphological tumor response*
21 *evaluable at radiological assessment after any type of therapy (LRT, chemotherapy, sorafenib). In case of*
22 *no treatment, the possible increase of the tumor eventually represents its natural evolution, however not*
23 *fully corresponding from a biological point of view to a tumor with a PD after a treatment. Moreover, in*
24 *the great majority of cases, no-LRT cases presented a “fast-track” approach with short WT, thus*
25 *impeding the “factor time” to select tumors with an effective tumor dimensional increase.*

26 *We Added the following sentence in Material and Methods with the intent to explain this concept:*

27 *“the decision to not consider no-LRT patients with a possible increase of the tumor burden before LT into*
28 *the PD group derived from the consideration that these patients do not fully correspond from a biological*
29 *point of view to patients with a tumor with a PD after a radiological treatment.”*
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31

32 4) The authors state that “participating centers do not consider Milan Criteria as the limit”. Please be more
33 precise. Which selection criteria were used? In addition, and on a similar note, the best ITT benefit was
34 achieved in patients MC-OUT. Please be more precise in the description of the Milan out patients. How
35 far can we go beyond Milan? Size? Number?
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38 *ANSWER. We added in Table 1 information about the number of cases exceeding UCSFC, up-to-seven*
39 *and Tokyo (“5+10 role”) criteria. Only 76 on 2103 (0.4%) patients contemporaneously exceeding all of*
40 *these three criteria were eventually transplanted: all of these were transplanted before the introduction of*
41 *MC or were transplanted in Padua centre, in which morphological aspects are no more used as selection*
42 *tools but only biological features are commonly used for HCC selection.*

43 *In Materials and Methods, we added the following sentence:*

44 *“Despite different policies were used in the different centers, all the transplanted cases reported were*
45 *within University of San Francisco California Criteria, Up-to-seven Criteria or Tokyo (“5+10 role”)*
46 *Criteria: so, the dimensional upper limit observed in the present study was 6.5 cm of diameter in the*
47 *target lesion and 10 nodules.”*
48

49
50 5) “160/246 (65.0%) cases dropped-out due to HCC progression”. Please specify why the other patients
51 dropped-out. Did some patients improve/moved to another center? How were they handled?
52

53 *ANSWER. We added in Results the following sentence:*

54 *“Looking more in detail the reasons of DO, 69 patients were excluded due to HCC progression (patient*
55 *alive at the moment of DO). In 91 cases, a tumor-related death on WL was observed; 52 patients showed*
56 *a liver disease-related death on WL, 25 moved to another center, and 9 were excluded due to poor*
57 *compliance.”*
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6) How can an increased age be associated with an improved transplant survival (page 8)? This would mean that older patients should be favored compared to younger one. Please expend, and comment.

ANSWER. We thank the reviewer for this comment. Actually, the data reported show that increased age was connected with an increased benefit, not an increased post-LT survival. In other terms, older patients obtained a higher benefit in being transplanted respect to being treated with other therapies respect to younger patients. However, when the cut-off value of ≥ 60 years of listing was used, a very small benefit of only 2 months was observed. So, the impact of such a result was neglectable and we decided not to describe it in discussion.

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7) The fact that the year of WL inscription has an impact on the transplant benefit suggests that practices/outcomes have changed over time, and that the proposed conclusions may not reflect current practice. Simply adding this variable in the multivariable model does not appear enough. Please use a more homogeneous population, covering a more restricted period.

ANSWER. We thank again the reviewer for this comment. With the intent to appropriately correct our study in light of the suggestions of the Reviewers, we performed a complete statistical revision of our study with the help of an expert Statistician from Padua University.

As suggested by the reviewer, we performed new multivariable models only evaluating patients listed after 01/01/2001 (n=1,802).

As you can see in new supplementary tables 3 and 4, variables estimates obtained from multivariable models (i.e. for ITT LT survival, non-LT survival, and benefit) resulted very similar to that of the whole population (Table 2, suppl. Tables 1, 2). This sub-analysis gave us, therefore, a strong statistical demonstration that the introduction of the variable "period of LT" in all the multivariable models (n=2,103) of the first version of the paper effectively represented a guarantee of solid statistical approach.

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Reviewer: 2

We really thank the reviewer for the positive comments. To better answer to his/her issues, we have performed a complete statistical revision of our study with the help of an expert Statistician from Padua University.

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1) Statistical methods must be checked by a statistician

ANSWER. As suggested, we performed a complete statistical revision of our study with the help of an expert Statistician from Padua University.

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2) It is not clear which is the study-period: 1984-2015 (abstract) or 1987-2015 (Materials and Methods).

ANSWER. We are sorry for this error. The first enlisted patient with the diagnosis of HCC was listed on February 12th, 1987. We have corrected the error in the abstract.

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Reviewer: 3

We really thank the reviewer for the statistical suggestions and comments. To better answer to his/her issues, we have performed a complete statistical revision of our study with the help of an expert Statistician from Padua University.

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1) Although the term "intention to treat" is well recognized in the clinical trial and statistical literature, it is not as common a term in observational designs. Please clarify in lay terms what is meant by ITT survival benefit during the introduction.

ANSWER. The following sentence has been added in the Introduction section of the paper:

"Moreover, transplant benefit values have been always evaluated from the moment of LT and not from the moment of WL inclusion. In the present study, the innovative concept of intention-to-treat (ITT) transplant benefit has been proposed. ITT survival is defined as the LT survival from the moment of patient enlistment and not from the day of LT, having been widely accepted in the LT community. The use of an ITT survival analysis allows the opportunity to analyze the results based on the initial treatment assignment and not on the treatment eventually received, thus avoiding various misleading artifacts and initial selection biases."

2) Methods: Please define the term MC-OUT (p 6 line 40).

ANSWER. According to the suggestions already reported by Reviewer 1, we added in Table 1 information about the number of cases exceeding UCSFC, up-to-seven and Tokyo ("5+10 role") criteria. Only 76 on 2103 (0.4%) patients contemporaneously exceeding all of these three criteria were eventually transplanted: all of these were transplanted before the introduction of MC or were transplanted in Padua centre, in which morphological aspects are no more used as selection tools but only biological features are commonly used for HCC selection.

In Materials and Methods, we added the following sentence:

"Despite different policies were used in the different centers, all the transplanted cases reported were within University of San Francisco California Criteria, Up-to-seven Criteria or Tokyo ("5+10 role") Criteria: so, the dimensional upper limit observed in the present study was 6.5 cm of diameter in the target lesion and 10 nodules."

3) The MESIAH score was used to simulate time to death in patients that were censored by LT. The simulated additional time they would have lived in absence of LT was then summed with their wl time. Given that this was essentially a missing data problem, there is uncertainty in this value from the imputation. Rather than giving this imputed value the same weight as an actual observed value, the imputation process should account for this uncertainty. Multiple imputation would be one way to account for this.

ANSWER. We understand the perplexities of the reviewer concerning our non-LT survival model. However, using a real HCC population waiting LT to predict long-term survival represents a great (and probably not solvable) statistical problem because the high proportion of patients censored for LT at a very low median time from listing as underlined in detail in the supplementary text.

Also the expert statistician from Padua University now reviewing our data confirmed that this peculiarity of waiting list populations cannot be resolved as a missing data imputation problem for some main reasons:

- 1. of the cohort of 2,103 patients included, 1,894 had the LT at a median time of 5.2 months from listing (90% censoring);*
- 2. the reason for censoring is informative rather than not informative, while missing data are supposed to be at random.*

For these reasons, we afforded the problem using the best predictive survival model for HCC patients (i.e. the MESIAH score) simulating the survival of patients if had they not been transplanted.

We sincerely hope that the reviewer could accept this original but also unavoidably biased methodological aspect of this study. The aim of this study is not to give extremely precise estimations of LT survival benefit, but only to obtain a qualitative stratification of the HCC population in different

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3 *subgroups (i.e. no, small, moderate, high benefit) in order to help clinicians in selecting HCC patients for*
4 *LT according to the innovative ITT transplant benefit principle.*

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6
7 4) Is the multivariate least squares regression a linear regression?

8
9 *ANSWER. Yes, it was.*

10
11 5) Please describe the steps for determining the significant factors in the multivariable analysis of survival
12 benefit. Provide clarity on the census of variables considered for the multivariable model and be specific
13 as to how the variables were selected for inclusion. (E.g. where they based on a univariate screening
14 process followed by inclusion of all significant factors in the model or some other selection procedure?).

15
16 *ANSWER. We really thank the reviewer for this comment underlying a missing aspect of our original*
17 *methods section. In the original paper, in fact, this explanation was only written below supplementary*
18 *tables. We now specified also in the methods that:*

19 *“In all the multivariable survival models, all variables with $p < 0.1$ at univariate model were included. In*
20 *the final model only variables showing a significant impact on survival at the first multivariable model*
21 *were maintained.”*

22
23
24 6) Specify the units of survival benefit in table 2.

25
26 *ANSWER. We now specified that the units of survival benefit were months.*

27
28 7) Please describe what the d-value is and how it's calculated in the methods.

29
30 *ANSWER. Again, we thank the reviewer for this comment giving us the possibility to better explain our*
31 *methods. We now specified that:*

32 *“Since p-values can be biased from population size, results of survival benefit estimations in covariates*
33 *subgroups were reported as effect size. Effect size is a standard measure that can be calculated from any*
34 *number of statistical outputs. One type of effect size, the standardized mean effect, expresses the mean*
35 *difference between two groups in standard deviation units. Typically, it is reported as Cohen's d, or*
36 *simply referred to as d-value.”*

37
38 *A new reference was added accordingly: Burnand B, Kernan WN, Feinstein AR. Indexes and boundaries*
39 *for "quantitative significance" in statistical decisions. J Clin Epidemiol 1990; 43: 1273–84.*

40
41 8) Can confidence intervals be added to the effect size (d-values) estimates in table 3?

42
43 *ANSWER. As requested, we added 95% confidence intervals in Table 3.*
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TABLES

Table 1. Patient- and tumor-related characteristics in the EURHECALT study population.

Variables	Study group (n=2103) Median (IQR) or n (%)
Period of WL inscription (1987-2000 vs. 2001-2015)	301/1802 (14·3/85·7)
WT days	137 (57-284)
≥120 days	963 (45·8)
Male gender	1763 (83·8)
Recipient age at WL inscription (years)	56·8 (49·7-62·0)
≥60 years	731 (34·8)
Cause of underlying cirrhosis (*)	
HCV	1001 (47·6)
HBV	391 (18·6)
Alcohol	631 (30·0)
Laboratory MELD at LT or DO	12 (9-16)
MELD ≤13	1395 (66·3)
Laboratory albumin (g/dl) at LT or DO	4·0 (3·8-4·0)
HCC at WL inscription	
Major lesion diameter (cm)	3·0 (2·0-4·0)
Number of lesions	2 (1-3)
MC-OUT status	636 (30·2)
Last radiological HCC assessment	
Major lesion diameter (cm)	2·0 (0·0-3·0)
Number of lesions	1 (1-3)
MC-OUT status	476 (22·6)
University of San Francisco California Criteria status	349 (16·6)
Up-to-seven Criteria status	253 (12·0)
Tokyo Criteria ("5+10 role") status	114 (5·4)
LRT (**)	1754 (83·4)
Total number of procedures	2 (1-3)
Complete response	380 (18·1)
Progressive disease	491 (23·3)
AFP	
At listing (ng/mL) §	10·0 (4·8-37·3)
Last available AFP (ng/mL)	9·7 (4·4-34·9)
≥1000 ng/mL	63 (3·0)
Slope ≥15 ng/mL/month §	228 (12·6)
DO	246 (11·7)
HCC-related DO	160 (7·6)
Death during WT	143 (6·8)
Recurrence (***)	242/1504 (16·1)
Within 1 year after LT	76/1504 (5·1)
Within 2 years after LT	138/1504 (9·2)
Within 3 years after LT	172/1504 (11·4)
Within 5 years after LT	213/1504 (14·2)
(*) multiple causes in the same patient: HCV + alcohol=101; HCV + HBV=29; HBV + alcohol=22; HCV + HBV + alcohol=6; alcohol + other=6; HCV + other cause=5; alcohol + NASH=5; HCV + alcohol + other cause=3; HBV + other cause=3; HCV + HBV + alcohol + NASH=1.	
(**) percentages calculated only on patients undergoing LRT.	
(***) percentages calculated only on transplanted patients with FU > 1 year.	
§ medians, IQR and percentages calculated on 1804 (85·8%) cases with available data.	

Abbreviations: WT, waiting time; IQR, interquartile ranges; WL, waiting list; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, non-alcoholic steato-hepatitis; MELD, model for end-stage liver disease; LT, liver transplantation; DO, drop-out; HCC, hepatocellular cancer; MC, Milan Criteria; LRT, loco-regional treatment; AFP, alpha-fetoprotein; FU, follow-up.

Table 2. Multivariate least square regression evaluating significant predictors of ITT transplant benefit.

Variables	Multivariable model	
	Coefficient \pm SE (months)	p value
Constant	-14.7 \pm 2.7	<0.0001
WL inscription before 2001	-25.3 \pm 1.0	<0.0001
Age at listing (per year) / 10	1.3 \pm 0.4	0.0006
MELD at LT or DO	1.1 \pm 0.1	<0.0001
WT (per month)	0.1 \pm 0.03	0.001
mRECIST progression disease	-36.8 \pm 0.9	<0.0001
Last radiological HCC assessment		
Major lesion diameter (cm)	10.9 \pm 0.4	<0.0001
Number of lesions	6.5 \pm 0.3	<0.0001
Last available logAFP	-3.4 \pm 0.2	<0.0001

The constant term in the final model represents the estimated ITT survival benefit of LT in the mean patient. The covariates effects for the estimated ITT benefit are assumed to be additional to the constant term.

Abbreviations: SE, standard error; WL, waiting list; MELD, model for end-stage liver disease; LT, liver transplantation; DO, drop-out; WT, waiting time; mRECIST, modified response evaluation criteria in solid tumors; HCC, hepatocellular cancer; AFP, alpha-fetoprotein.

Table 3. ITT transplant benefit estimations in months in different subgroups.

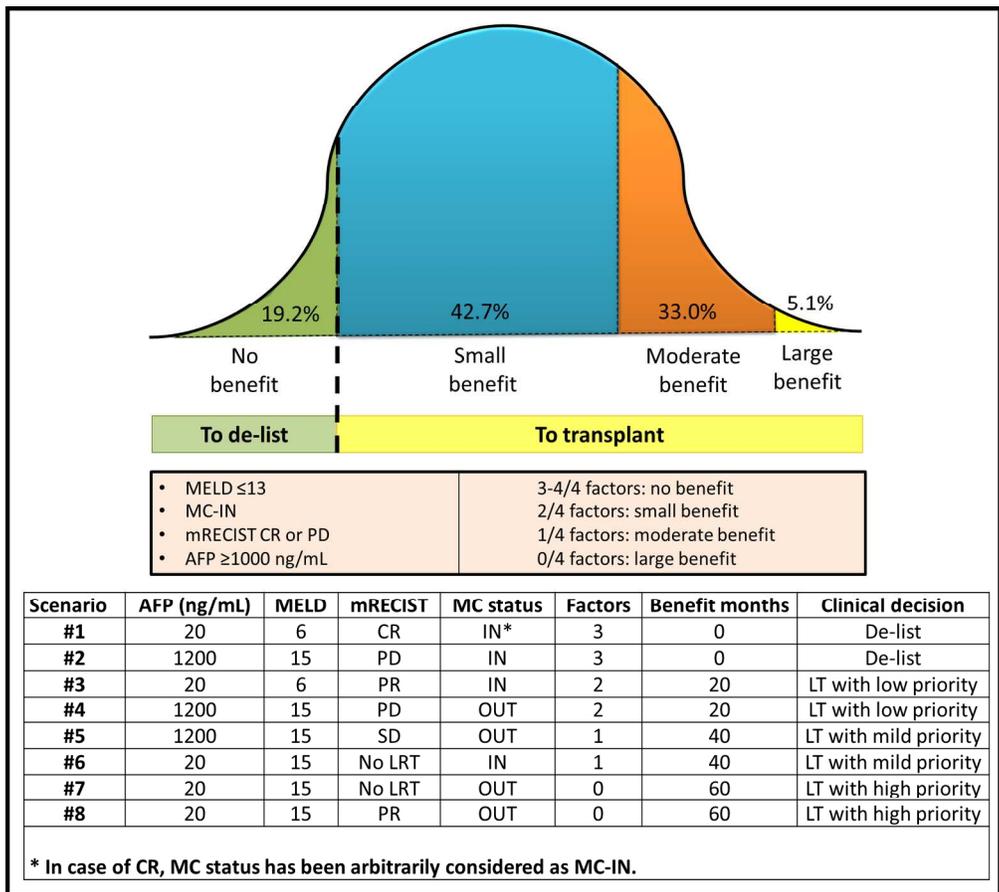
Variables	Benefit in months (n of patients)		D value between Groups (95% CI)	Difference
	No	Yes		
WT \geq 120 days	25.5 (1140)	24.0 (963)	0.06 (0.01-0.13)	Very small
Age at listing \geq 60 years	25.5 (1372)	23.6 (731)	0.07 (0.02-0.16)	Very small
Last AFP \geq 20 ng/mL	27.0 (1439)	20.3 (664)	0.26 (0.17-0.36)	Small
MC-IN at LT or DO	34.5 (496)	22.8 (1607)	0.47 (0.37-0.57)	Moderate*
WL inscription before 2001	27.3 (1802)	10.4 (301)	0.69 (0.57-0.81)	Large§
Last AFP \geq 1000 ng/mL	25.4 (2040)	6.8 (63)	0.74 (0.49-0.99)	Large*
mRECIST progression disease	29.2 (1612)	10.6 (491)	0.78 (0.67-0.88)	Large*
MELD at LT or DO \leq 13	39.1 (708)	19.8 (1395)	0.81 (0.73-0.90)	Large*
mRECIST complete response	28.7 (1723)	7.2 (380)	0.90 (0.79-1.01)	Large*
Benefit Groups (*)				
Group	Benefit in months	n of patients (%)		
No benefit	0	405 (19.2)	3-4 negative factors	
Small benefit	20	897 (42.7)	2 negative factors	
Moderate benefit	40	693 (33.0)	1 negative factor	
Large benefit	60	108 (5.1)	No negative factors	
<p>Continuous variables in Table 4 were dichotomized using relevant cut-off values used in the literature (5,6,11,12).</p> <p>Results are reported as means; D-value (effect size) values <0.1 indicate very small differences; between 0.1 and 0.3 and between 0.3 and 0.5 indicate small and moderate differences, respectively, and > 0.5 indicate large differences.</p> <p>(*) Four risk factors were considered for constructing the benefit groups: MELD \leq13; MC-IN; mRECIST progression disease or complete response; AFP \geq1000 ng/mL. Benefit values in the groups were rounded to the nearest whole number.</p> <p>(§) WL inscription before or after 2001 was not considered in the final group stratification because the period of WL inscription showed a very poor effect on survival benefit estimates (supplementary Tables 3-4) and it was not considered useful for the evaluation of the benefit in patients enlisted now.</p> <p>Abbreviations: CI, confidence interval; WL, waiting list; WT, waiting time; AFP, alpha-fetoprotein; MC, Milan Criteria; LT, liver transplantation; DO, drop-out; MELD, model for end stage liver disease; mRECIST, modified response evaluation criteria in solid tumors.</p>				

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A. Benefit risk factors	B. Median benefit	C. Median benefit gain	Months	
WT <120 days	25.5		1.5	Very small
WT ≥120 days	24.0			
Age at listing <60 years	25.5		1.9	
Age at listing ≥60 years	23.6			
<hr/>				
Last AFP < 20 ng/mL	27.0		6-7	Small
Last AFP ≥ 20 ng/mL	20.3			
<hr/>				
MC-OUT at LT or DO	34.5		11.7	Moderate
MC-IN at LT or DO	22.8			
WL inscription after 2001	27.3		16.9	
WL inscription before 2001	10.4			
<hr/>				
Last AFP <1000 ng/mL	25.4		18.6	Large
Last AFP ≥1000 ng/mL	6.8			
mRECIST no progression disease	29.2		18.6	
mRECIST progression disease	10.6			
MELD at LT or DO >13	39.1		19.3	
MELD at LT or DO ≤13	19.8			
mRECIST no complete response	28.7		21.5	
mRECIST complete response	7.2			
		0	10	20

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Supplementary Data 1

The statistical design of this study included three main steps: a) the development of an ITT LT survival model; b) the development of a non-LT survival model and; c) the individual prediction of the ITT survival benefit of LT defined as the difference between the median ITT survival with LT (based on the first model) and median survival without LT (based on the second model) calculated for each enrolled patient.

Step a) ITT LT survival model

Length of follow-up and survival were expressed as medians (IQR). Overall survival was calculated from date of WL inclusion until death from any cause (before or after LT) or latest follow up. HCC patients dropping-out from the WL were followed until death or last follow-up. Survival curves were estimated using the Kaplan Meier method, whereas the statistical significance between survival curves was tested by the Log Rank test.

Several survival models (the semi-parametric Cox model, and parametric exponential, log-normal, Weibull, and log-logistic models) were tested; since the aim of this study was to develop a model able to give precise estimation of individual median survival after WL inclusion, it was decided to use an accelerated failure time parametric model. Among the different models available (gamma, log-logistic, lognormal), the log-logistic model was selected since it showed the lowest value of Akaike Information Criterion (AIC) at final multivariable model.

Finally, this model was applied to predict ITT median survival with LT of each enrolled patient.

Step b) Non-LT survival model

The prediction of non-LT survival using a WL population is controversial. The main statistical problem is that WL patients have relatively few failure events (death before LT) since the majority of them are censored by LT. Censoring related to LT, however, is an informative or dependent censoring since it depends on prioritization criteria used in each center.^{1,2} Moreover, median WT of

HCC patients is relatively short, usually less than one year, thus prediction of long-term survival of these patients may be inaccurate.³

Some statistical techniques such as competing risk analysis,^{1,4} or inverse probability censoring weight have been used to overcome these problems.² However, these methods seem still insufficient to resolve all the biases related to the complexity of WL dynamics and further corrections, sometime quite arbitrary, are necessary.^{4,5}

Since it was aimed to predict median long-term survival of enrolled HCC patients (n=2103) without LT, these statistical solutions were judged unsuitable for the present analysis.

The Model to Estimate the Survival In Ambulatory patients with HCC (MESIAH) has been recently developed with the specific aim to predict individual HCC patient survival.⁶ This model, proven to have a higher prognostic ability than that of available HCC prognostic systems, has been externally validated both in western and eastern countries.^{7,8}

More importantly, the authors of this score provided a simple formula to translate the MESIAH score in individual survival predictions. Using patient characteristics at the last evaluation before LT or DO, we used the MESIAH score to simulate the median time to death that patients censored by LT would have had in the absence of LT. So, time to death of enrolled patients censored by LT (n=1857) was calculated as the sum of their true WL time (from listing to LT) and the simulated additional time they would have lived in the absence of LT.

This simulated time to death was therefore used to perform a second log-logistic parametric survival model to find significant predictors of non-LT survival.

Finally, we used this second model to predict non-LT median survival of each enrolled patient.

Step c) ITT transplant benefit model

The ITT LT and the non-LT survival log-logistic models generated two median survival predictions for each enrolled patient. The ITT survival benefit of LT was, therefore, calculated for each patient as the difference between ITT LT median and the non-LT median survival estimations. All

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3 estimations were capped at 120 months, since this time horizon represents the ideal balance
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5 between utility and urgency allocation principles.⁹ A multivariate least square regression was finally
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7 used to find significant predictors of ITT LT benefit among studied variables.^{10,11}
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For Peer Review

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Supplementary Table 1

Multivariate log-logistic parametric survival analysis evaluating significant predictors of ITT LT survival.

Variables	Univariate analysis		First multivariable model (*)		Final multivariable model (**)	
	Coefficient ± SE, p value		Coefficient ± SE, p value		Coefficient ± SE, p value	
WL inscription before 2001	-0.45 ± 0.14	0.002	-0.59 ± 0.15	<0.0001	-0.61 ± 0.14	<0.0001
Male gender	0.14 ± 0.14	0.35	-	-	-	-
Age at listing (per year) / 10	-0.26 ± 0.06	<0.0001	-0.25 ± 0.06	<0.0001	-0.25 ± 0.06	<0.0001
HCV positivity	-0.17 ± 0.11	0.12	-	-	-	-
HBV positivity	0.07 ± 0.14	0.60	-	-	-	-
Alcohol abuse history	0.10 ± 0.12	0.39	-	-	-	-
MELD at LT or DO	-0.07 ± 0.01	<0.0001	-0.17 ± 0.09	0.07	-0.07 ± 0.01	<0.0001
Albumin at LT or DO	0.75 ± 0.14	<0.0001	-1.17 ± 1.10	0.28	-	-
WT (per month)	0.02 ± 0.01	0.0001	0.02 ± 0.01	<0.0001	0.02 ± 0.01	<0.0001
HCC at WL inscription						
Major lesion diameter (cm)	-0.09 ± 0.04	0.01	-	-	-	-
Number of lesions	0.05 ± 0.03	0.08	-	-	-	-
No LRT	-0.08 ± 0.14	0.59	-	-	-	-
Total number of LRT	-0.01 ± 0.02	0.92	-	-	-	-
mRECIST complete response	0.35 ± 0.15	0.02	-0.06 ± 0.18	0.76	-	-
mRECIST progression disease	-1.07 ± 0.12	<0.0001	-1.13 ± 0.13	<0.0001	-1.14 ± 0.13	<0.0001
Last radiological HCC assessment						
Major lesion diameter (cm)	-0.27 ± 0.05	<0.0001	-0.06 ± 0.07	0.38	-	-
Number of lesions	-0.09 ± 0.04	0.02	0.10 ± 0.05	0.05	0.08 ± 0.04	0.05
AFP						
LogAFP at listing	-0.12 ± 0.03	0.0004	-	-	-	-
Last available logAFP	-0.22 ± 0.03	<0.0001	-0.17 ± 0.03	<0.0001	-0.18 ± 0.03	<0.0001
Slope ≥ 15 ng/mL/month	-0.62 ± 0.08	<0.0001	-	-	-	-

The negative sign indicates a negative impact on survival.

(*) In the first multivariable model all variables with $p < 0.1$ at univariate model were included. The model showing the lowest AIC value was finally chosen.

(**) In the final model only variables showing a significant impact on survival at the first multivariable model were maintained. The model showing the lowest AIC value was chosen.

Abbreviations: SE, standard error; WL, waiting list; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; LT, liver transplantation; DO, drop-out; WT, waiting time; HCC, hepatocellular cancer; LRT, loco-regional therapies; mRECIST, modified response evaluation criteria in solid tumors; AFP, alpha-fetoprotein.

Supplementary Table 2

Multivariate Log-logistic parametric survival analysis evaluating significant predictors of non-LT-survival.

Variables	Univariate analysis		First multivariable model (*)		Final multivariable model (**)	
	Coefficient ± SE,	p value	Coefficient ± SE,	p value	Coefficient ± SE,	p value
WL inscription before 2001	-0.01 ± 0.05	0.89	-0.03±0.02	0.25	0.05±0.02	0.01
Male gender	0.04±0.14	0.35	-	-	-	-
Age at listing (per year) / 10	-0.13±0.02	<0.0001	-0.17±0.01	<0.0001	-0.17±0.01	<0.0001
HCV positivity	-0.01±0.04	1.00	-	-	-	-
HBV positivity	0.02±0.04	0.59	-	-	-	-
Alcohol abuse history	0.02±0.01	0.59	-	-	-	-
MELD at LT or DO	-0.12±0.01	<0.0001	-0.11±0.01	<0.0001	-0.11±0.01	<0.0001
Albumin at LT or DO	1.36±0.05	<0.0001	0.05±0.24	0.83	-	-
WT (per month)	0.01±0.01	<0.0001	0.01±0.01	<0.0001	0.01±0.01	<0.0001
HCC at WL inscription						
Major lesion diameter (cm)	-0.07±0.01	<0.0001	-	-	-	-
Number of lesions	-0.13±0.01	<0.0001	-	-	-	-
No LRT	-0.24±0.05	<0.0001	-0.05±0.02	0.02	-	-
Total number of LRT	0.01±0.01	0.63	-	-	-	-
mRECIST complete response	0.55±0.04	<0.0001	-0.16±0.03	<0.0001	-	-
mRECIST progression disease	-0.67±0.04	<0.0001	-0.19±0.03	<0.0001	-0.32±0.02	<0.0001
Last radiological HCC assessment						
Major lesion diameter (cm)	-0.35±0.01	<0.0001	-0.22±0.01	<0.0001	-0.20±0.01	<0.0001
Number of lesions	-0.22±0.01	<0.0001	-0.10±0.01	<0.0001	-0.06±0.01	<0.0001
AFP						
LogAFP at listing	-0.06±0.01	<0.0001	-	-	-	-
Last available logAFP	-0.13±0.01	<0.0001	-0.07±0.01	<0.0001	-0.07±0.01	<0.0001
Slope ≥ 15 ng/mL/month	-0.35±0.03	<0.0001	-	-	-	-

The negative sign indicates a negative impact on survival.

(*) In the first multivariable model all variables with $p < 0.1$ at univariate model were included. The model showing the lowest AIC value was finally chosen. WL inscription was maintained in the model for homogeneity with the ITT-LT survival model.

(**) In the final model only variables showing a significant impact on survival at the first multivariable model were maintained. The model showing the lowest AIC value was finally chosen.

Abbreviations: SE, standard error; WL, waiting list; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; LT, liver transplantation; DO, drop-out; WT, waiting time; HCC, hepatocellular cancer; LRT, loco-regional therapies; mRECIST, modified response evaluation criteria in solid tumors; AFP, alpha-fetoprotein.

Supplementary Table 3

Multivariate log-logistic parametric survival analyses evaluating significant predictors of ITT LT and non-LT - survival in patients listed after 01/01/2001 (n=1802).

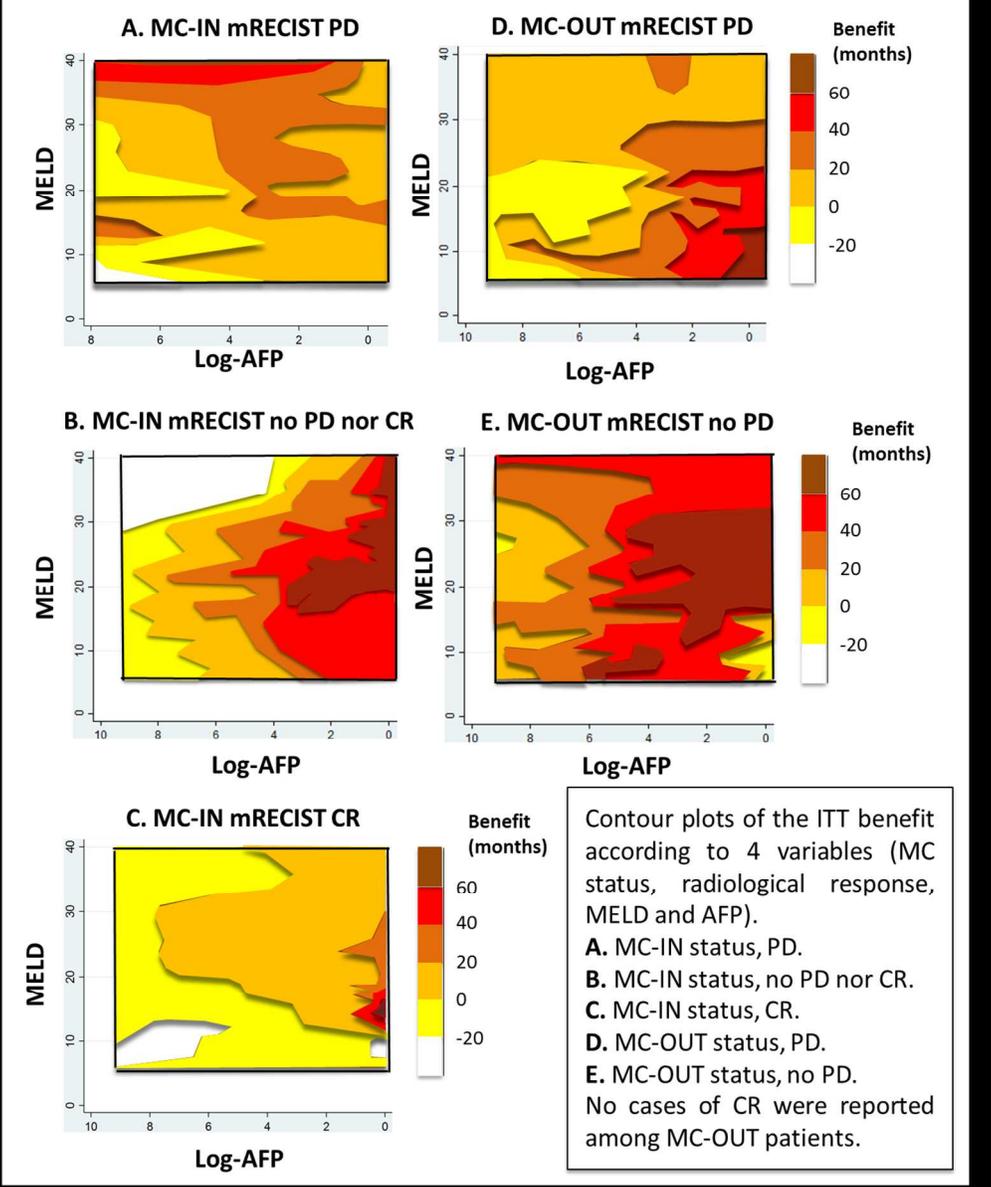
Variables	ITT LT multivariable model (*)		Non-LT multivariable model (**)	
	Coefficient ± SE, p value		Coefficient ± SE, p value	
Age at listing (per year) / 10	-0.21±0.07	<0.0001	-0.17±0.01	<0.0001
MELD at LT or DO	-0.08±0.01	<0.0001	-0.11±0.01	<0.0001
WT (per month)	0.02±0.01	0.0017	0.01±0.01	<0.0001
mRECIST progression disease	-1.26±0.14	<0.0001	-0.47±0.02	<0.0001
Last radiological HCC assessment				
Major lesion diameter (cm)	-	-	-0.19±0.01	<0.0001
Number of lesions	0.13±0.04	0.0034	-0.04±0.01	<0.0001
Last available logAFP	-0.19±0.03	<0.0001	-0.08±0.01	<0.0001
<p>The negative sign indicates a negative impact on survival. Abbreviations: SE, standard error; WL, waiting list; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, model for end-stage liver disease; LT, liver transplantation; DO, drop-out; WT, waiting time; HCC, hepatocellular cancer; LRT, loco-regional therapies; mRECIST, modified response evaluation criteria in solid tumors; AFP, alpha-fetoprotein.</p>				

Supplementary Table 4

Multivariate least square regression evaluating significant predictors of ITT transplant benefit in patients listed after 01/01/2001 (n=1802).

Variables	Multivariable model	
	Coefficient \pm SE	p value
Constant	-26.7 \pm 3.0	<0.0001
Age at listing (per year) / 10	3.0 \pm 0.4	<0.0001
MELD at LT or DO	1.1 \pm 0.1	<0.0001
WT (per month)	0.1 \pm 0.04	0.001
mRECIST progression disease	-37.6 \pm 1.0	<0.0001
Last radiological HCC assessment		
Major lesion diameter (cm)	11.1 \pm 0.5	<0.0001
Number of lesions	6.6 \pm 0.4	<0.0001
Last available logAFP	-2.8 \pm 0.2	<0.0001
<p>The constant term in the final model represents the estimated ITT survival benefit of LT in the mean patient. The covariates effects for the estimated ITT benefit are assumed to be additional to the constant term.</p> <p>Abbreviations: SE, standard error; WL, waiting list; MELD, model for end-stage liver disease; LT, liver transplantation; DO, drop-out; WT, waiting time; mRECIST, modified response evaluation criteria in solid tumors; HCC, hepatocellular cancer; AFP, alpha-fetoprotein.</p>		

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236x285mm (150 x 150 DPI)