The Effect of a Liver Transplant Program on the Outcomes of Resectable Hepatocellular Carcinoma: A Nationwide Multicenter Analysis

THE EFFECT OF A LIVER TRANSPLANT PROGRAM ON THE OUTCOMES OF RESECTABLE HEPATOCELLULAR CARCINOMA: A NATIONWIDE MULTICENTER ANALYSIS

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MINI-ABSTRACT:

Results of this study support the hypothesis that when hepatic resection is performed in a transplant hospital, treatments offered may be more conservative and liver transplantation is more frequently proposed in case of recurrence as compared to non-transplant hospitals.

STRUCTURED ABSTRACT

Objective: To evaluate the effect of a liver transplantation (LT) program on the outcomes of resectable hepatocellular carcinoma (HCC).

Summary Background Data: Surgical treatment of HCC includes both hepatic resection (HR) and LT. However, the presence of cirrhosis and the possibility of recurrence make the management of this disease complex and probably different according to the presence of a LT program.

Methods: Patients undergoing HR for HCC between January 2005 and December 2019 were identified from a national database of HCC. The main study outcomes were major surgical complications according to the Comprehensive Complication Index (CCI), post-hepatectomy liver failure (PHLF), 90-day mortality, overall survival (OS), and disease-free survival (DFS). Secondary outcomes were salvage liver transplantation (SLT) and post-recurrence survival (PRS).

Results: A total of 3202 patients were included from 25 hospitals over the study period. Three out of 25 (12%) had a LT program. The presence of a LT program within a center was associated with a reduced probability of PHLF (OR=0.38) but not with OS and DFS. There was an increased probability of SLT when HR was performed in a transplant hospital (OR=12.05). Among transplant-eligible patients, those who underwent LT had a significantly longer PRS.

Conclusions: This study showed that the presence of a LT program was associated with decreased PHLF rates and an increased probability to receive SLT in case of recurrence.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most frequent cause of cancer-related death worldwide. According to the Barcelona Clinic Liver Cancer (BCLC) algorithm, patients with a single, early-stage HCC and preserved liver function should be offered hepatic resection (HR)[1]. However, even after potentially curative and negative-margin resections, recurrence occurs in 30-50% of patients within 2 years after surgery.[2] In this regard, liver transplantation (LT) is able to provide better disease-free survival (DFS) rates, curing not only the cancer but also the underlying liver cirrhosis that generated it. However, the eternal debate on which is the best curative option for early HCC in cirrhosis still continues,[3] and the shortage of donors has led centers to consider LT eventually as a salvage procedure in case of hepatic recurrence after HR.[4] This decision may be guided however by institutional practices or hospital characteristics such as the presence of a LT program. Similarly, both short- and long-term outcomes may vary depending on whether hospitals where HR is carried out have experience also in LT, taking into account that HCC patients represent a very heterogeneous population with the possibility of different treatment strategies according to the extent of disease and underlying liver function.[5]

The aim of this study was therefore to evaluate the effect of being treated in a LT center on the outcomes of HR for HCC by analyzing a national representative database. Primary endpoints of the study were post-operative outcomes such as major surgical complications, 90-day mortality, overall survival (OS) and DFS. Secondary endpoints were salvage liver transplantation (SLT) and post-recurrence survival (PRS).

METHODS

Study Design and Data Sources

Data were identified from a multi-institutional national database of HCC promoted by the Hepatocarcinoma Recurrence in the Liver Study (He.Rc.O.Le.S.) group. Briefly, this database is a prospectively maintained national registry open to inclusion of cases from any Italian center performing HR for HCC, without any restriction criteria based on the number of procedures performed. Inclusion criteria are described in detail elsewhere.[6]

Study Population and Exposure

Adult patients (≥18 years) with histologically proven HCC, submitted to HR from January 2005 to December 2019 and followed-up until December 2020, were retrospectively analyzed. The exposure of interest was the presence of an accredited LT program in the hospital where the patient was surgically treated for HCC.

Outcomes and Covariates

The primary outcomes under study were the following:

- Major surgical complications, defined as scoring ≥26.2 in the Comprehensive Complication Index (CCI), which ranges from 0 (uneventful course) to 100 (death);[7]
- Post-hepatectomy liver failure (PHLF), defined according to the "50-50 criteria" (i.e. PT <50% and serum bilirubin >50 μmol/L on post-operative day 5);[8]
- Ninety-day mortality, defined as any death occurring within 90 days after HR;
- OS, defined as the time from surgery to the date of death or the last follow-up;
- DFS, defined as the time from surgery to the date of recurrence, death or the last follow-up.

Secondary outcomes were probability of SLT, defined as LT performed in patients with HCC recurrence after previous resection, and post-recurrence survival (PRS) defined as the time from the first relapse to the date of death or the last follow-up. PRS was evaluated only among patients <65 years at the time of relapse and meeting the Milan criteria.[9]

The following data were collected for each patient: age and sex; American Society of Anesthesiologists (ASA) classification and alpha-fetoprotein (AFP) levels before surgery; presence of cirrhosis (yes/no), and characteristics of HCC at explant pathology (number, size, Edmonson–Steiner grade, presence of microvascular invasion). Liver function was evaluated according to the Model for End-Stage Liver Disease (MELD) score[10] and the Albumin-Bilirubin (ALBI) score.[11] Portal hypertension was defined by the presence of esophageal varices and/or a platelet count $<100\times10^3$ /ml in association with splenomegaly.[12] Operative details included type of liver resection (major vs. minor hepatectomy) and approach (open vs. minimally-invasive).

All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Institutional review board gave ethical approval to perform this study. The study protocol was registered on ClinicalTrials.gov (identifier NCT04053231).

Statistical Analysis

Summary statistics were presented as frequencies and percentages. The association of relevant patient characteristics with the binary outcomes under study (post-operative complications, PHLF, 90-day mortality and LT after HCC recurrence) was assessed through random-effects multilevel logistic regression analysis: the effect size of covariates was expressed by odds ratios (ORs) with 95% confidence intervals (CIs), and the presence of systematic differences (i.e. statistical significance) was assessed using the 2-sided Wald test.

The association of relevant patient characteristics with OS and DFS was assessed through shared-frailty Cox proportional hazards regression analysis: the effect size of covariates was expressed by hazard ratios (HzRs) with 95% CIs, and statistical significance was assessed using the 2-sided Wald test. The proportional-hazards assumption was confirmed after checking for nonzero slope of scaled Schoenfeld residuals on time.[13] We adopted multilevel and frailty regression techniques to account for the hierarchical (correlated) structure of data, with patients "nested" within hospitals. In all the regression models, the regression coefficients of each explanatory variable were treated as fixed effects, while the hospitals were treated as random effects (i.e., random intercepts).

Due to the presence of missing covariate data, multiple imputation by chained equations was used to replace missing values with multiple sets of simulated values to complete the data (*m* = 30). [14,15] A sensitivity analysis using weighted regression estimates to test for local departures from the missing-at-random assumption gave results that closely agreed with those obtained under missing-at-random multiple imputation.[16]

A binary variable taking the value of 1 for hospitals with an accredited LT program (transplant hospitals) was included as a covariate in the aforementioned models in order to assess the impact of this structural characteristic on the study outcomes by adjusting for differences in patient case mix. Surgical caseloads, defined as performing >100 vs. ≤100 HRs per year (i.e., high vs. low/intermediate volumes[17]), were added as covariate in order to differentiate the independent (adjusted) association of LT center and volume of liver surgery with the study outcomes. The covariates included in the models were identified since known a priori to be strongly, or at least moderately, associated with the primary outcomes and/or because there was a strong clinical rationale for such an association.

All data were analyzed using Stata version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LP). The significance level was set at 5%. No

multi-collinearity issues were found, since the variance inflation factor was <5 and the condition index was <10 for each independent variable.

RESULTS

Three out of the 25 hospitals (12%) participating in the study had a LT program and accounted for 26.1% of all HRs; 8 hospitals (32%) were high-volume centers for liver surgery and accounted for 70% of all HRs; 2 hospitals (8%) were both high-volume and transplant hospitals. The baseline characteristics of the 3202 study patients, overall and in transplant vs. non-transplant hospitals, are shown in Supplementary Table 1 **(Table S1)**.

Short-Term Outcomes

Major complications following surgery (CCI ≥26.2) occurred in 423 patients (13.2%). The overall incidence of PHLF was 3.9% (*n* = 126), whereas 90-day mortality was 2.8% (*n* = 91).

Results of multivariable regression analysis investigating the association of patient case mix and structural characteristics with the probability of occurrence of short-term outcomes are presented in **Table 1**.

Independent factors significantly associated with major post-operative complications included major resection (OR = 2.13), ASA score ≥3 (OR = 1.86), MELD score ≥10 (OR = 1.61), portal hypertension (OR = 1.56) and cirrhosis (OR = 1.36), while laparoscopy was a protective factor (OR = 0.46).

Independent factors significantly associated with higher incidence of PHLF were major resection (OR = 2.92), cirrhosis (OR = 2.67) and MELD score ≥10 (OR = 1.90), while laparoscopy (OR = 0.57) was significantly associated with a lower incidence of PHLF. The

probability of PHLF was significantly lower in transplant hospitals as compared with non-transplant hospitals (OR = 0.38; 95% CI = 0.17-0.86; *P* = 0.02) (**Table 1**).

Independent factors significantly associated with increased mortality within 90 days of surgery were ASA score ≥3 (OR = 5.00), major resection (OR = 3.66), MELD score ≥10 (OR = 2.27) and female sex (OR = 1.72), whereas being treated in high-volume hospitals was significantly associated with decreased mortality (OR = 0.51).

Estimated average probability of experiencing a negative event when the patient was treated in transplant vs. non-transplant hospitals is graphically presented in **Figure 1**.

Overall and Disease-Free Survival

The estimated median OS was 9.9 years (95% CI = 8.6-11.1). Patients who survived were 91.0% after 1 year, 64.3% after 5 years, and 49.4% after 10 years. As shown in **Table 2**, risk factors for OS were >2 nodules (HzR = 1.89), size >5 cm (HzR = 1.72), Edmondson–Steiner grade ≥3 (HzR = 1.66), presence of microvascular invasion (HzR = 1.46), MELD score ≥10 (HzR = 1.46), age ≥65 years (HzR = 1.28), cirrhosis (HzR = 1.27) and ALBI grade ≥2 (HzR = 1.20). OS was significantly higher in hospitals with >100 liver resections per year as compared with hospitals below this threshold (HzR = 0.53; 95% CI = 0.35-0.82; *P* = 0.01). No significant differences were found between transplant and non-transplant hospitals (HzR = 1.23; 95% CI = 0.62-2.47; *P* = 0.54).

The estimated median DFS was 3.3 years (95% CI = 3.0-3.6). Patients who survived or did not experience disease recurrence were 76.2% after 1 year, 40.9% after 5 years, and 32.1% after 10 years. As shown in **Table 2**, factors significantly associated with shorter time to recurrence were multiple nodules (2 nodules, HzR = 1.23; >2 nodules, HzR = 2.10), microvascular invasion (HzR = 1.60), R1 resection margin (HzR = 1.30), largest nodule size >5 cm (HzR = 1.23) and Edmondson–Steiner grade ≥3 (HzR = 1.18). There was no

significant association between DFS and the presence of a LT program (HzR = 0.92; 95% CI = 0.62-1.38; *P* = 0.69).

Liver Transplantation after Recurrence (Salvage)

Information about post-recurrence treatment was available for 1251 (81.0%) of the 1544 patients with known disease relapse during the follow-up period; among these, 61 (4.9%) underwent SLT: 50 out of 340 (14.7%) patients had undergone HR in transplant hospitals whereas 11 out of 911 (1.2%) had been previously treated in non-transplant hospitals. As shown in **Table 3**, age ≥65 years was significantly associated with decreased probability of SLT (OR = 0.13), while cirrhosis (OR = 3.16) and meeting the Milan criteria[9](OR = 2.77) were significantly associated with increased odds. There was an increased probability of SLT when patients had undergone HR in transplant hospitals as compared with non-transplant hospitals (OR = 12.05; 95% CI = 5.83-24.88; *P* <0.001). More specifically, the estimated average probability of SLT was 7.4% (95% CI = 4.6%-11.7%) in transplant hospitals versus 0.7% (95% CI = 0.3%-1.3%) in non-transplant hospitals.

Post-Recurrence Survival

This analysis was restricted to transplant-eligible patients, i.e., subjects <65 years at the time of recurrence and meeting the Milan criteria (*n* = 250). The sample was further restricted to 134 patients (53.6%) with known survival status and censored time.

The estimated median PRS was 9.6 years. After adjusting for sex, age, pattern of recurrence, cirrhosis and time between HR and recurrence, we found that the patients who underwent LT (*n* = 31) had longer PRS than those receiving redo-hepatectomy (*n* = 36; HzR = 0.28; 95% CI = 0.08-0.97; *P* = 0.04), RFA (*n* = 25; HzR = 0.19; 95% CI = 0.06-0.63; *P* = 0.006), trans-arterial chemoembolization (*n* = 24; HzR = 0.13; 95% CI = 0.04-0.39; *P* <0.001), sorafenib (*n*

= 8; HzR = 0.02; 95% CI = 0.004-0.09; *P* <0.001) or other unspecified therapeutic approaches (*n* = 10; HzR = 0.03; 95% CI = 0.01-0.20; *P* <0.001) (**Figure 2, Table S2**).

DISCUSSION

This cohort-based study examined the effect of a LT program on the outcomes of HR for HCC, using the data of a national representative registry. Interestingly, transplant hospitals were associated with decreased PHLF rates; we also found that in these centers the probability of SLT was higher, with resulting improved PRS after SLT than after other treatments. High-volume hospitals were significantly associated with lower risk of 90-day mortality and higher OS as compared with low-/intermediate-volume hospitals, in line with the findings of previous studies.

Hepatic resection represents the mainstay of treatments in the non-cirrhotic population in which healthy patients can tolerate also extended procedures with relative low morbidity and mortality.[18] On the other side, HR for HCC in the setting of chronic liver disease demands a careful patients' selection as well as a precise assessment of hepatic functional reserve.[19,20]Also, the presence of clinically relevant portal hypertension has to be ruled out by measurement of hepatic vein pressure gradient[21] or indirectly by liver stiffness measurement to decrease the risk of post-operative decompensation.[22]

Therefore, surgical decision making may be a very complex process, since the heterogeneous hepatic functional reserve may impact the actual treatment that a patient is eligible to receive. However, the choice of surgical therapy in HCC patients has been shown to depend not only on clinical factors but also on surgeon specialty.[23] Hence, our hypothesis was that there could be variations in the management of HCC also according to the presence of a LT program with possibly different outcomes between transplant and non-transplant hospitals.

Before the current study, only few papers have investigated the impact of a transplantation service on the outcomes of liver surgery [24,25,26] and even fewer have analyzed separately HCC [27,28]. None of these, however, have ever focused on PHLF, which is an important outcome also in light of its inevitable economic impact on healthcare systems[29], or on the treatment of HCC recurrence.

The significantly lower probability of PHLF in transplant hospitals as compared with non-transplant hospitals may represent the epiphenomenon of a certain number of patients who were evaluated at LT hospitals and offered to receive LT (or LRT bridge to LT) instead of HR, having been considered at high risk of PHLF.[30] Institution-related factors may play a role in the choice of therapy as demonstrated by Nathan et al.,[31] who showed that in the USA LT was proposed more frequently than HR or radiofrequency ablation (RFA) by LT surgeons but also by non-LT surgeons working in transplant hospitals[23], confirming in part our hypothesis. Nevertheless, the He.Rc.O.Le.S. registry includes only surgically treated patients and does not provide information regarding the intent of treatment thus limiting such an explanation for our results. Although the patients referred to transplant hospitals were younger and therefore supposed to have a greater hepatic functional reserve, cirrhosis and extent of hepatectomy were comparable between these two groups, bearing in mind that all the analyses were adjusted for several patient characteristics.

Such a difference, however, did not translate into a significantly decreased risk of 90-day mortality as described in other studies.[25,24] Conversely, Csikesz and colleagues [26] reported that hepatobiliary surgery performed at hospitals with a LT program reduced effectively the risk of perioperative (30-day) mortality by 21%. In another study[32], mortality after minor resection and RFA was not significantly different according to the transplant hospital status, whereas mortality after major hepatectomy was significantly lower at transplant vs. non-transplant centers, suggesting that patients who were anticipated to have complex surgical interventions

benefited more from referral to specialized centers. In our study, the high quality of care provided by non-transplant hospitals which comprised also many high-volume hospitals (6 out of 22), and the low 90-day mortality rate compared to other national series[33] may have helped in reducing this difference to a non-significant level. Being operated in high-volume hospitals was instead protective against 90-day mortality, in line with the existing literature.[34,35,36,37,38,39] This finding, confirmed also in our study, has been recently related to the different failure-to-rescue (FTR) rates of centers.[37] In fact, probability of major complications according to the CCI score[40] was not significantly different according to hospital type, demonstrating that treating patients in centers with a lower number of HRs per year (in most cases due to the fact that these centers do not perform exclusively hepatobiliary surgery) or without a LT program, is not a technical expertise issue. Similarly, Ghaferi et al.[41] showed that hospitals with high and low mortality had comparable rates of complications and that low-volume hospitals had only slightly higher complications rates compared to high-volume hospitals but with, on the contrary, significantly higher FTR and mortality rates.[42,43] All these findings confirm that it may be more about an institution's ability to rescue patients who develop complications rather than avoiding complications per se.

Adequate technical skills together with appropriate indications for surgery may have also led to comparable DFS rates, although patients submitted to HR in transplant hospitals had a significantly higher rate of R1 resections. These results are likely to be explained by more advanced disease in these patients[44], taking into account however that the type of R1 resections performed (parenchymal or vascular) was not known and that reasons for significant differences between centers should not be searched among the covariates included in the regression model. Conversely, OS was found to be significantly associated with the volume of liver surgery. Such a difference in OS, higher in high-volume hospitals compared to low-/intermediate-volume hospitals, is a more reliable quality indicator of the structural

characteristics of the centers where the patients are treated rather than DFS which is more related to technical factors. In fact, improved long-term outcomes at high volume hospitals have already been demonstrated to be a surrogate marker also for several conditions associated with HCC including better management of chronic liver disease, post-resection cancer surveillance and more aggressive treatment in case of recurrence. [45,27,30] Among all the available surgical therapies to treat tumor recurrence, salvage liver transplantation (SLT) can be offered within transplantable criteria, thus removing at the same time the cancer and the underlying cirrhosis that generated it.[46,47] However, due to the scarcity of organs, every attempt to rescue these patients without affecting the donor pool should be made and repeat hepatectomy (RH) represents nowadays a more attractive alternative to SLT. A recent meta-analysis comparing SLT with RH showed that SLT was inferior to RH with regard to perioperative outcomes but with better results in terms of OS and DFS.[48] However, more recent papers have demonstrated that complications in SLT can be significantly reduced thanks to the increasingly high number of HRs approached with a minimally-invasive technique which may reduce adhesions and intraoperative bleeding during LT.[49] Nevertheless, the decision to proceed with SLT or other treatments is always difficult to make and it may be biased by institutional practices. Our study showed for the first time, adjusting for case-mix and surgical volumes, that when HR had been performed in transplant hospitals, recurrences were treated more frequently with SLT. Surprisingly, volumes of liver surgery did not influence that choice of treatment, confirming that access to LT even in the case of transplantable recurrence may be limited outside of transplant hospitals and suggesting the absence of a uniform pattern of referral for HCC patients even in a country where presentation of cases at multidisciplinary team is routine. Furthermore, in our study, among those who were eligible for SLT, PRS was significantly higher as compared to other treatments, confirming a clear survival benefit in these patients.[50] For this reason, transplant surgeons or

hepatologists should always be included in multidisciplinary liver tumor boards to optimize HCC management not only at the diagnosis but also in case of recurrence after HR.

This study has some limitations. First, 12% of all centers were defined as transplant hospitals however we do not know whether such a percentage reflect the real proportion of transplant hospitals in Italy. Nevertheless, the majority of hepato-pancreato-biliary surgery is being performed by non-transplant surgeons in Italy as in other countries.[26] Moreover, although the number of patients treated at each hospital type was disproportionate, proper case-mix adjustments limited this bias. A second limitation to our study was the occurrence of missing data in the He.Rc.O.Le.S. registry. However, the power of the analysis was preserved with multiple imputation of missing values by means of chained equations, and no relevant departures from the missing-at-random assumption were found. Furthermore, in contrast with most of existing large administrative database, more information on patients (e.g. tumor burden and severity of liver disease) and treatment factors were available to account for differences in the severity of HCC. Another limitation was the small number of hospitals investigated, which prevented us from assessing the role of other potential "structural" predictors of health outcomes and from providing estimates of the proportion of total outcome variance lying at the hospital level.

In conclusion, transplant hospitals were more likely to offer LT in case of high-risk patients thus decreasing PHLF rates and especially in case of recurrent disease. However, referring complex patients to high-volume centers still remains of central importance to improve the management as well as the survival of such complex patients.

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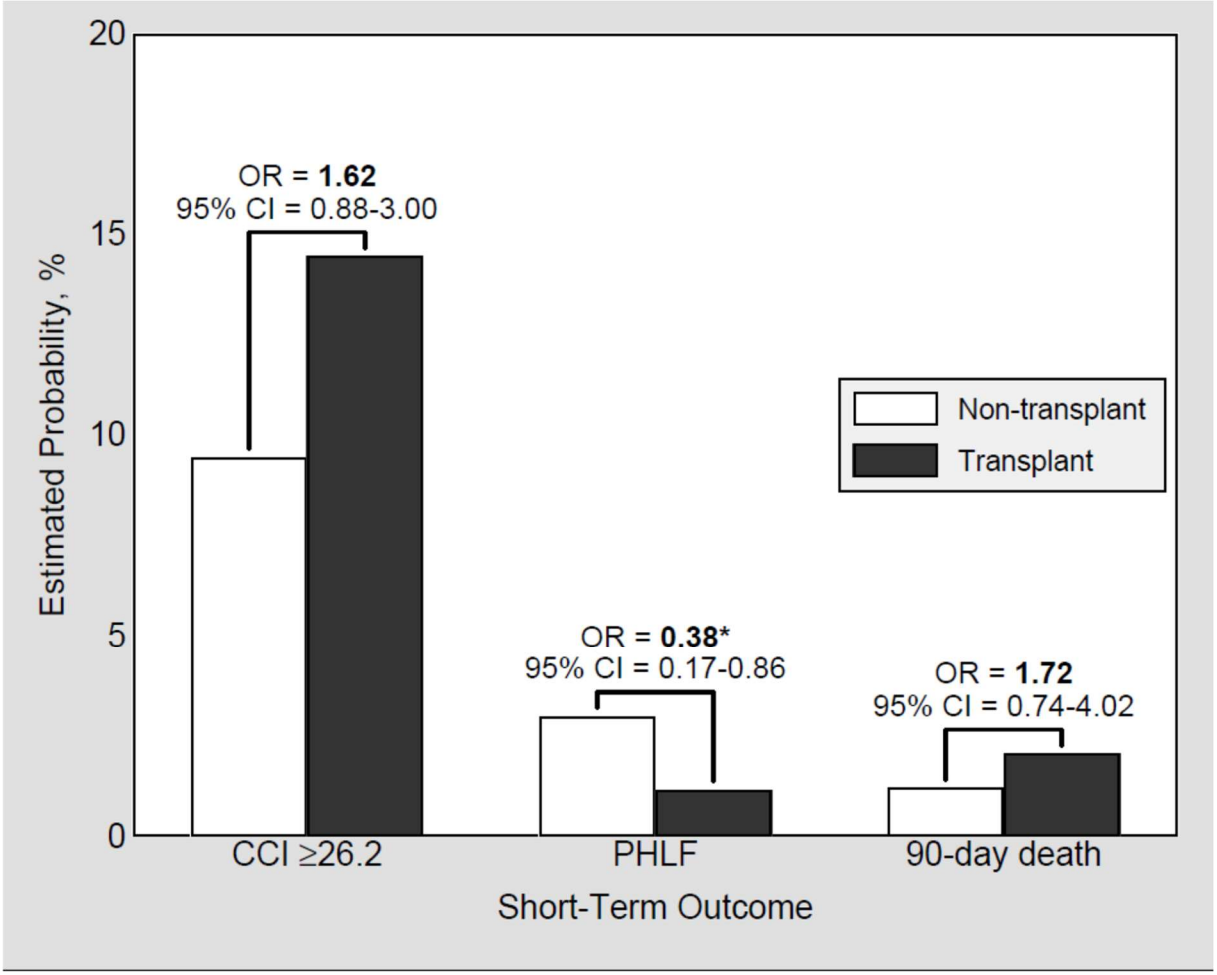
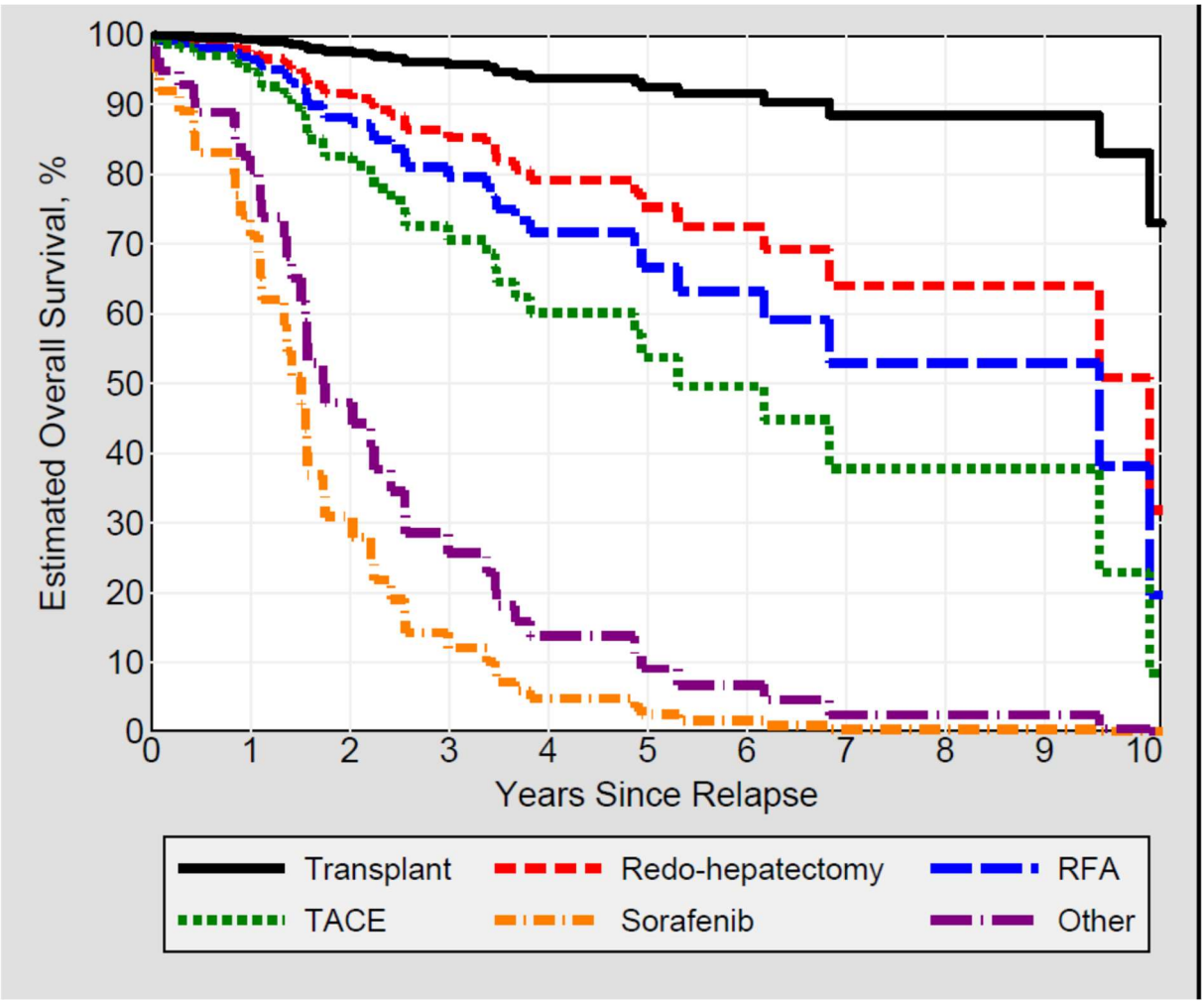
FIGURE LEGENDS

Figure 1. Estimated average probability (%) of experiencing a negative event when the patient was treated in transplant vs. non-transplant hospitals. All estimates were adjusted for the patient case mix via multilevel regression modelling.



*P value ≤0.05; **P value ≤0.01; ***P value ≤0.001.
PHLF, post-hepatectomy liver failure.

Figure 2. Estimated post-recurrence survival (PRS) in patients aged <65 years at the time of relapse and meeting the Milan criteria (n = 134), by treatment. All estimates were adjusted for sex, age, pattern of recurrence, cirrhosis and time between first surgery and recurrence via shared-frailty proportional hazards modelling.



RFA, radiofrequency ablation; TACE, trans-arterial chemoembolization.