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Analysis of the survival of patients with hepatocellular carcinoma and indications for liver transplantation or hepatic resection

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Abstract

Background Hepatic resection (HR) and liver transplantation (LT) are potentially curative treatments for Hepatocellular carcinoma (HCC). The aim of this study was to analyze the survival of patients with HCC and indications for surgical treatment (HR or LT) in a high-volume center.

Methods This was a retrospective cohort study of consecutive patients with HCC and indications for LT or HR from May 2006 to July 2019. Analysis of overall survival (OS) and disease-free survival (DFS) rates, univariate analysis and construction of a multivariable model to identify risk factors were performed.

Results A total of 744 patients with HCC were evaluated, 563 (75.6%) of whom were enrolled in waiting list for LT and 181 (24.4%) of whom underwent HR. Among the patients enrolled in the waiting list, 362 (64.3%) underwent LT, whereas 201 (35.7%) remained on the waiting list (WL). From the group of 201 patients on the waiting list, 97 (48.2%) were removed from the list due to tumor progression beyond the Milan criteria (MC), and 83 (41.3%) died while waiting for the transplant. In the WL group, 97 (48.2%) patients were removed from the list due to tumor progression beyond the MC, another 83 (41.3%) patients died while waiting for the LT. The OS rates of the LT group were 77.4%, 67.5% and 56.8%, whereas those of the WL + LT (intention-to-treat) group were 59.9%, 47.3%, and 39.9%, and the HRs were 82.8%, 49.3%, and 33.4% at 1, 5 and 10 years, respectively ($p = 0.001$). Donor age ($p = 0.002$) and cold ischemia time ($p < 0.001$) were independent factors related to OS in the LT group, whereas the presence of significant portal hypertension ($p < 0.001$), alpha-fetoprotein (AFP) value ($p < 0.001$) and MC ($p = 0.002$) were independent factors for HR. The DFS rates for HR were 74.9%, 40.0% and 31.0%, and those for LT were 97.9%, 92.0% and 90.9% at 1, 5 and 10 years, respectively ($p < 0.001$). Higher AFP levels were identified as an independent factor for lower DFS in both groups.

Conclusions The present study revealed that the OS of patients listed for LT was greater in the first year than in the second year and that the results were similar to those of the HR in an intention-to-treat analysis. However, patients who achieve LT have better long-term outcomes, especially disease-free survival.

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Keywords Carcinoma, Hepatocellular, Liver transplantation, Hepatectomy, Survival analysis, Recurrence, Liver cirrhosis

Background

Hepatocellular carcinoma (HCC) is the most common primary malignant neoplasm of the liver, accounting for approximately 75% of cases [1]. HCC represents a global health issue associated with considerable morbidity and mortality. It is the sixth most common malignant neoplasm worldwide and the third leading cause of cancer-related death in 2020. In that same year, approximately 906,000 new cases and 830,000 deaths were reported [2].

HCC staging is an important step in defining treatment prognosis. Several staging systems have been proposed, with the most commonly used being the TNM [3] and Barcelona Clinic Liver Cancer (BCLC) criteria [4]. The BCLC criteria are widely validated and categorize patients with HCC into 5 stages, considering tumor morphology, vascular invasion, the presence of portal hypertension, the Child–Pugh score, and patient performance status [5]. However, the surgical community has heavily criticized this staging system. Points of contention include the grouping of all single nodules within stage A, whereas large nodules (> 5 cm) have a worse prognosis and are contraindicated for transplantation. Patients in stage B also have the potential for transplantation if lesion size reduction (downstaging) occurs after locoregional treatment. Furthermore, stage C patients can undergo locoregional treatment, especially those with tumoral invasion of portal branches [6].

Additionally, the algorithm is overly restrictive regarding indications for hepatic resection (HR). The use of portal hypertension as a contraindication for resection limits its application in patients with preserved liver function. Child A patients in stages B and C could also benefit from this procedure, as survival after HR is better than noncurative treatments in patients with more than one nodule (up to three) and advanced tumors with tumor thrombosis and/or involvement of extrahepatic structures adjacent to the liver. A recent study from Taiwan retrospectively evaluated 321 patients with BCLC stage C HCC with macrovascular invasion and/or metastatic tumors. The median survival of these patients was 7 months; however, among the 57 patients who underwent resection, survival was 67 months [7]. Additionally, some stage B and C patients could still benefit from transplantation or locoregional treatment. A previous study from our group including 30% of patients with BCLC stages B and C disease subjected to liver resection reported 5-year global and disease-free survival rates of 47.7% and 39.7%, respectively [8].

For patient selection for liver transplantation (LT), multiple criteria have been proposed; however, the Milan criteria (MC) [9] are still the most commonly used criteria to select patients with the greatest benefit. Cirrhotic patients with a single nodule up to 5 cm or up to 3 nodules, the largest up to 3 cm, without macrovascular invasion or detectable metastases, fall under the MC. The 5-year survival rate after transplantation for HCC patients within the MC is 65–78%, which is comparable to the 68–87% survival rate for those who underwent transplantation without HCC [9]. However, the MC is criticized for being overly restrictive, failing to benefit patients with a good prognosis. In Brazil, there was an adaptation of the MC by not considering nodules smaller than 2 cm (regardless of number), informally named the Milan–Brazil criteria (MBC). A cutoff point for AFP of 1,000 ng/mL was subsequently included. A multicenter Brazilian study evaluating 1059 patients who were transplanted for HCC demonstrated a global 5-year survival of 63% [10]. Disease-free survival at 5 years, compared with patients within the MC and patients outside the MC but within the MBC, was 94% and 82%, respectively ($p < 0.001$) [10]. Patients initially outside these criteria may still benefit from LT if they respond to systemic or locoregional treatments and return to the MBC, a situation termed downstaging.

In Brazil, patients on the waiting list for LT have been allocated following the MELD score since July 2006. Patients on the waiting list diagnosed with HCC within MBC receive MELD exception points; however, even with this advantage, long periods until LT are common, especially in more populous states and for patients with blood type O [11]. Patients within the MBC after downtaging receive the same priority. During the waiting list, patients are mainly subject to unfavorable outcomes, such as tumor progression beyond MBC, drop out, and death.

The purpose of this study was to evaluate the results of an academic university referral center for the treatment of HCC, comparing consecutive patients with indications for LT or HR for HCC.

Methods

Data from patients with HCC selected for LT or HR in our department from May 2006 to July 2019 were evaluated. The diagnosis of HCC was based on clinical data, mostly radiological criteria, and was later confirmed by histopathological evaluation of surgical samples. The studied variables were obtained from the prospective electronic database Research Electronic Data Capture (REDCap) [12]. To ensure patient data privacy, all information was anonymized, with restricted access

to the research team, all of whom were physicians. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) recommendations [13] were used for organizing and conducting this clinical protocol.

The study was approved by the Research Ethics Committee of our institution (number 294,198), which waived the need for individual patient consent due to the retrospective nature of the study.

Patients who were indicated for LT or HR for the treatment of hepatocellular carcinoma were included in the study. Preoperative examination assessments and indications for HR were decided upon at a weekly multidisciplinary meeting. Data from patients indicated for LT were sent to the State Collegiate Organ Committee Transplantation Center for confirmation of the patient's placement on the waiting list. All patients listed for transplantation were within the MBC. Alpha-fetoprotein (AFP) threshold of 1000 ng/mL was included in the criteria for selecting patients for liver transplantation in Brazil in 2019. However, as AFP was already recognized as a marker of poor prognosis, only 10 patients in our study, who were selected for transplantation, had AFP levels above this value. Moreover, all of these cases occurred prior to the institution of this new rule, as the last patient in our sample included in the waiting list with AFP greater than 1000 ng/mL was registered in 2018.

Patients were divided into 3 groups: LT, patients who underwent liver transplantation; HR, patients who underwent hepatic resection; and WL, patients who entered the liver transplantation waiting list but did not undergo the procedure.

Patients with mixed tumors (hepatocholangiocarcinoma) or other histological types of hepatocellular lesions other than HCC were excluded. Patients who underwent a second HR due to HCC recurrence and patients with outpatient follow-up of less than 3 months, considered lost to follow-up in this situation, were also excluded.

During the study period, 203 patients underwent HR, and 598 patients were listed for LT, for a total of 801 patients. However, 22 patients who underwent HR were excluded: 13 due to histological identification of hepatocholangiocarcinoma, 4 who underwent a second hepatectomy due to HCC recurrence, 3 due to loss to follow-up, and 2 due to a diagnosis of another histological type other than HCC. Among patients who underwent LT, 17 were excluded: 16 due to identification of hepatocholangiocarcinoma in the explant and 1 patient due to the identification of only one regenerated nodule with dysplasia without evidence of HCC. Eighteen patients who had been listed were excluded because 8 underwent transplantation in another state and 10 were lost to follow-up (Fig. 1).

Ten patients had more than one outcome: 4 underwent HR and subsequently rescue LT due to HCC recurrence, 3 underwent HR and were listed for LT but did not undergo transplantation, 2 were listed twice and did not undergo transplantation either time, and finally, 1 patient who was listed, experienced tumor progression, and later returned for downstaging LT.

For each included patient, the following characteristics were studied: age, sex, body mass index (BMI), blood type, etiology of chronic liver disease, radiological staging according to the Milan–Brazil criteria, liver disease classification [14] according to the Model for End-Stage Liver Disease (MELD) and Child–Turcotte–Pugh (Child), bridging treatments, outcome date, and survival.

For patients who underwent HR and LT, the preoperative data assessed included the presence of ascites, esophageal varices, and significant portal hypertension

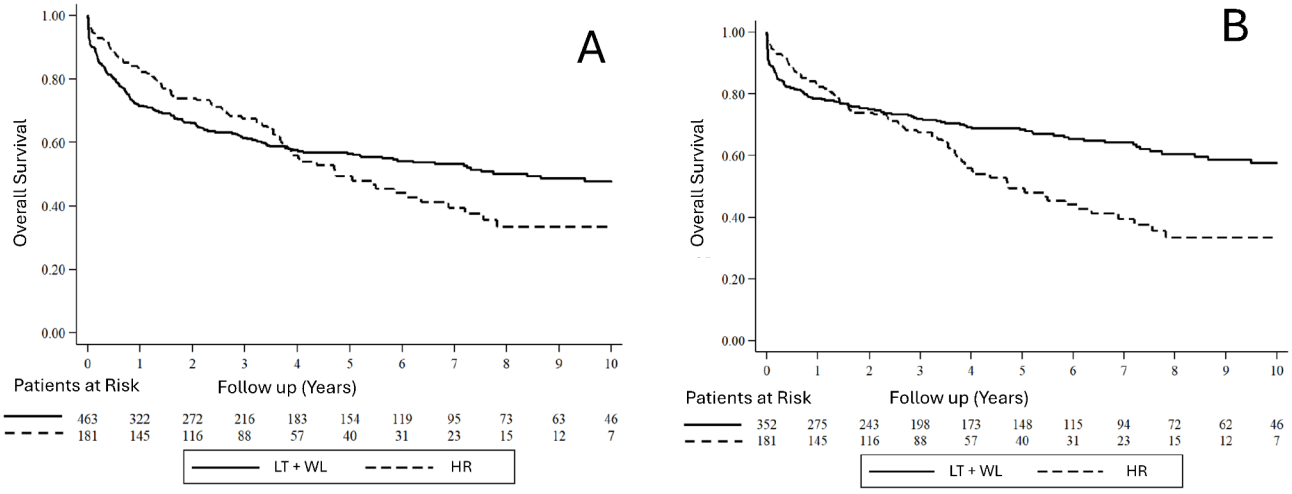

Fig. 1 Comparison of overall survival between patients listed for transplant and patients undergoing hepatic resection
TF liver transplant; WL waiting list; HR hepatic resection

(presence of esophageal varices, ascites, a platelet count less than 100,000/mm3 associated with splenomegaly, or a hepatic venous pressure gradient greater than 10 mmHg [17]). The presence of bilobar nodules or other neoplasms were also assessed. The nomenclature of the surgical procedures followed Brisbane terminology [16]. Major hepatectomy was defined as the resection of three or more liver segments.

Histological variables related to the tumor and whether preoperative locoregional treatment was performed were analyzed. Surgical data such as surgery time, ischemia time, and the need for red blood cell transfusion were collected. Preoperative AFP (ng/mL) and recurrence were also recorded. Patient staging and the Milan/Brazil criteria were evaluated preoperatively through abdominal and thoracic exams (CT and/or MRI). The surgical specimen was assessed through histopathological evaluation and termed the pathological Milan criterion.

For patients listed for LT, the data collected included the following: exception points in the MELD and waiting time, defined as the time from listing to transplantation or removal from the list. Whether the patient had previously undergone HCC resection and required LT was referred to as rescue transplantation. If the patient did not undergo transplantation, the reason for noncompletion was recorded. Among patients who underwent LT, the following data regarding the donor were evaluated: age, BMI, donor risk index (DRI) [15], and cold ischemia time. Patients who required retransplantation owing to clinical complications, early or late.

Overall survival (OS) analysis was performed via intention-to-treat analysis, thus considering all patients in the sample, i.e., patients from the WL, LT, and HR groups. The initial date was the time of listing or the time of surgery for the HR group. Disease-free survival (DFS) analysis was performed for the treated patients (LT and HR groups). Prognostic factors for global survival and disease-free survival (DFS) were analyzed among patients undergoing treatment.

Table 1 Characteristics of the study participants

Characteristic	*n* = 744 (%)	Mean (SD)	Median (min–max)
Age		59.0 (9.1)	60 (17–82)
Male Gender	548 (74.7)		
BMI (kg/m2)		26.3 (4.4)	25.8 (15.6–43.6)
Etiology			
HCV	454 (63.4)		
HBV	67 (9.4)		
Alcohol	156 (21.8)		
Other	113 (15.8)		
MELD		13.4 (8.3)	10 (6–58)
MELD ≤ 14	510 (71.3)		
MELD > 14	205 (28.7)		
CHILD A	309 (59.5)		
CHILD B	135 (26.0)		
CHILD C	75 (14.5)		

SD: standard deviation; min: minimum value; max: maximum value; HCV: hepatitis C virus; HBV: hepatitis B virus; alcohol: alcohol consumption

Statistical methodology

Qualitative variables are presented as absolute and relative frequencies (%). The mean, median, standard deviation, minimum, and maximum values were calculated for quantitative variables, and the values of the 25th and 75th percentiles were also calculated. Associations between qualitative variables were assessed via the Pearson chi-square test or Fisher's exact test. The normality of the quantitative variables was tested via the Kolmogorov–Smirnov test; hence, the Mann–Whitney test was used to compare the distributions of the quantitative variables according to the treatment group. Overall survival and disease-free survival were calculated in days. Kaplan–Meier curves were constructed for survival times according to treatment type (transplantation or resection). Hazard ratio values and 95% confidence intervals (95% CI) were calculated via Cox regression stratified by treatment. In multiple analyses, variables that were significant in univariate analysis were considered, as were other adjustment variables or clinically relevant variables. Models were constructed via the stepwise backward method (from the full model to the model with significant variables). The significance level adopted was 5%. Analyses were performed via SPSS for Windows v.25 and STATA/MP v.14 for Windows.

Results

A total of 744 patients with HCC were evaluated, 563 (75.6%) corresponding to patients enrolled on the waiting list and 181 (24.4%) who underwent HR. Among patients at the waiting list, 362 (48.6%) were subjected to LT, whereas 201 (27%) remained at the WL, as they did not undergo transplantation. The median follow-up time for the entire sample was 4.02 years. Half of the participants were 60 years old or younger, and 74.7% were male. Other clinical characteristics are presented in Table 1.

Patient stratification according to the type of treatment performed revealed that those who underwent HR were significantly older than patients in the LT group were (median of 63 vs. 59 years, $p < 0.001$). Nodule dimensions were also greater in this group of patients (40 vs. 25 mm, $p < 0.001$), as was the frequency of vascular invasion (54.8% vs. 32.3%, $p < 0.001$). In the HR group, 56.9% of patients met the radiological Milan criteria. Patients who underwent LT had significantly higher MELD scores (median of 12 vs. 8, $p < 0.001$, with 34% having MELD > 14 vs. 3.7%, $p < 0.001$), as did more patients classified as Child–Pugh B (36.3% vs. 3.7%, $p < 0.001$) or C (20.8 vs. 0%, $p < 0.001$). Surgical time (median of 420 vs. 300 min, $p < 0.001$), the need for red blood cell transfusion (mean

of 2.2 vs. 0.5 units, $p < 0.001$), and the postoperative hospitalization period (median of 14 vs. 6 days, $p < 0.001$) were also significantly longer in the LT group than in the HR group.

Stratification was performed according to the number of nodules identified in the specimen: 152 (84%) patients had one nodule in the HR group, and 146 (40.3%) had one nodule in the TF group ($p < 0.001$). Among patients in the HR group with only one nodule, 91 (50%) patients had tumors smaller than 5 cm, 41 (22.6%) patients had tumors smaller than 3 cm, and 11 (6%) patients had tumors smaller than 2 cm. Other characteristics are shown in supplementary Table 1.

The median procedure time in hours was 7 h for LT patients and 5 h for HR patients. With respect to patients who entered the waiting list (LE and TF groups), we identified significantly more blood Rh type O patients in the WL group (53.2% vs. 40.6%, $p < 0.001$), as well as a longer wait time on the list (median 329 vs. 254, $p = 0.047$). The median MELD score for patients removed from the list or who underwent transplantation was 29.

Among the WL group patients, 97 (48.2%) were removed from the list due to tumor progression beyond Milan (drop out), which corresponds to 17.3% of all listed patients (LE and LT groups). Another 83 (41.3%) patients died while on the waiting list for LT. Fifteen (7.5%) patients achieved complete control of HCC through locoregional treatments and were removed from the list. Finally, 6 (3%) patients refused to undergo transplantation.

The majority of patients undergoing LT (81.5%) had HCC within the Milan criteria at diagnosis, while the remaining patients underwent downstaging to meet the criteria at the time of transplantation. The median waiting list time was 221.9 days. Thirty-five (9.7%) patients required retransplantation. Seven patients underwent rescue LT, 3 of whom underwent HR at another facility. The median cold ischemia time was 6 h and 54 min.

Among patients who underwent HR, 90.1% had chronic liver disease, and 95.4% achieved clear surgical margins. Almost half of the patients were approached by laparotomy (49.7%), and the other half (50.3%) were approached by some minimally invasive technique, of which 29.8% underwent the exclusive laparoscopic technique. Anatomical resection was performed in 61.3% of patients, and 30.4% of the resections were major hepatectomies.

Analysis of survival

During the entire follow-up, 171 (85%) deaths occurred in the WL group, 127 (35%) in the LT group, and 84 (46.4%) in the HR group. The overall survival rates at 1, 3, 5, and 10 years were 65.5%, 55.4%, 48.2%, and 39%, respectively.

Table 2 presents the values of median overall survival and disease-free survival times as well as actual survival at 1, 2, 3, 5, and 10 years according to the groups. There were significant differences in the overall survival curves according to the intention-to-treat (ITT) analysis ($p = 0.019$), as shown in Fig. 1A. In the analysis of overall survival (Fig. 1B) and disease-free survival (Fig. 2) for patients undergoing intervention (TF and HR), statistically significant differences were also found ($p = 0.008$ and < 0.001, respectively).

The prognostic factors for overall survival in patients in the TF group are presented in Supplementary Table 2. The variables MELD (1.02; 95% CI: 1.00–1.04, $p = 0.036$), corrected MELD (1.06; 95% CI: 1.02–1.09, $p = 0.001$), surgery time (1.003; 95% CI: 1.001–1.005, $p = 0.002$), intraoperative red blood cell concentrate transfusion (1.10; 95% CI: 1.04–1.15, $p < 0.001$), ICU days (1.032; 95% CI: 1.018–1.047, $p < 0.001$), and waitlist time (1.001; 95% CI: 1.0004–1.001, $p < 0.001$) were inversely proportional to overall survival. MELD categorized as greater than or less than 14 did not differ (1.02, 95% CI: 0.71–1.48, $p = 0.898$). Rescue transplantation (5.38; 95% CI: 1.70–17.00, $p = 0.004$) and retransplantation (2.11; 95% CI: 1.27–3.52, $p = 0.004$) resulted in lower overall survival. The downstaging condition (0.32; 95% CI: 0.11–0.97, $p = 0.043$) and shorter cold ischemia time (0.74; 95% CI: 0.70–0.78, $p < 0.001$) were better prognostic factors.

Table 2 Analysis of overall and disease-free survival at 10 years

Survival	Probability of survival					p[1]
	1-year	2-year	3-year	5-year	10-year	
Overall intention-to-treat						
Listed patients (WL + LT)	59.9%	55.3%	51.4%	47.3%	39.9%	0.019
Hepatic resection	82.8%	73.9%	67.5%	49.3%	33.4%	
Overall intervention						
Liver transplantation	77.4%	73.9%	71.0%	67.5%	56.8%	0.008
Hepatic resection	82.8%	73.9%	67.5%	49.3%	33.4%	
Disease-free						
Liver transplantation	97.9%	94.9%	93.6%	92.0%	90.9%	< 0.001
Hepatic resection	74.9%	56.7%	49.8%	40.0%	31.0%	

[1] Log-rank test for comparing survival curves. LE, transplant waiting list; TF, liver transplant

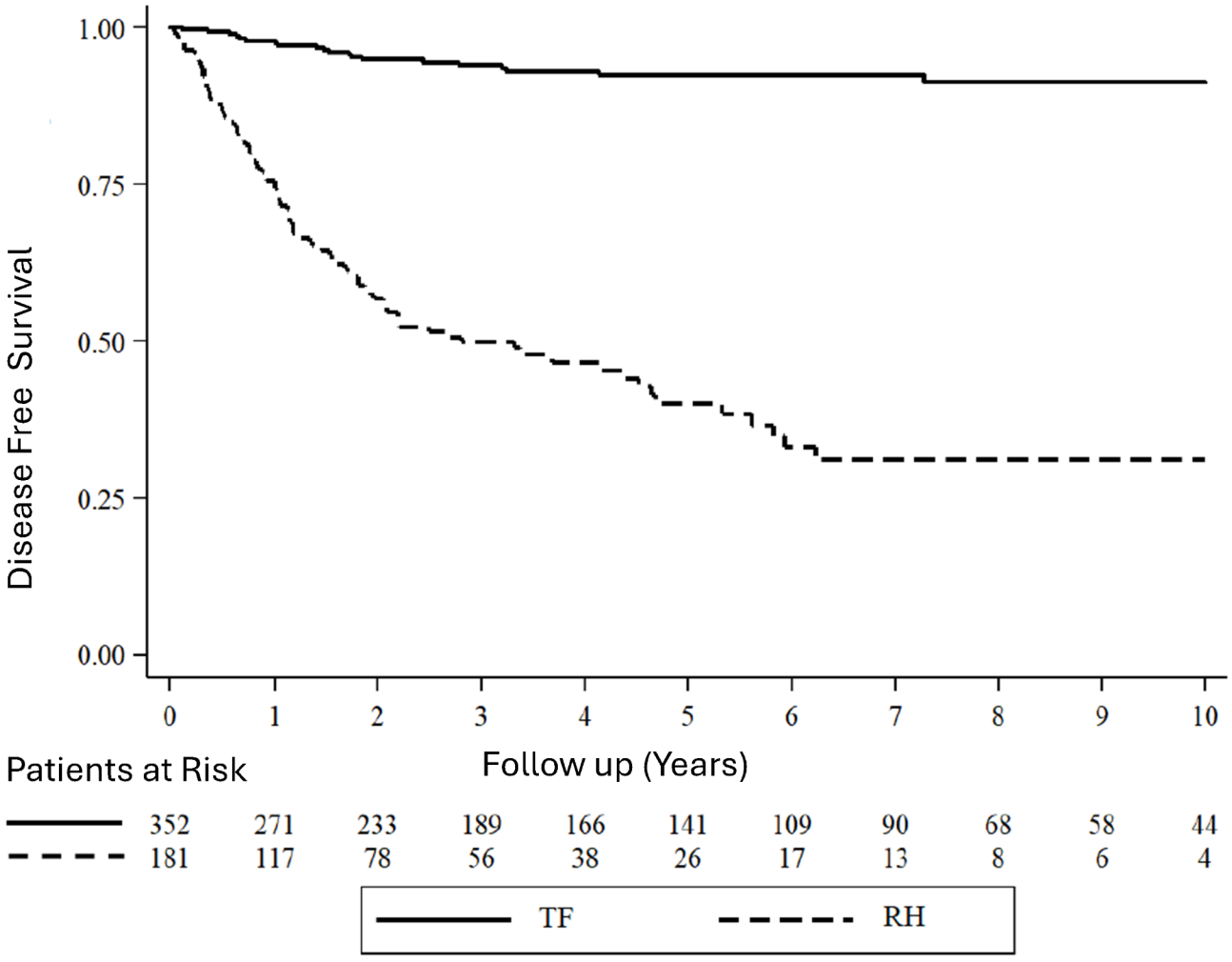

Fig. 2 Disease-free survival of patients undergoing surgical intervention: liver transplantation and hepatic resection
TF, liver transplant; HR, hepatic resection

For patients in the HR group, days in the hospital (1.043; 95% CI: 1.024–1.063, $p < 0.001$) and in the ICU (1.170; 95% CI: 1.098–1.248, $p < 0.001$), as well as preoperative INR values (8.71; 95% CI: 2.01–37.71, $p = 0.004$), were inversely proportional to overall survival. Two-stage hepatectomy (10.75; 95% CI: 1.43–81.05, $p = 0.021$), significant portal hypertension (1.92; 95% CI: 1.20–3.06, $p = 0.006$), and esophageal varices (1.94; 95% CI: 1.08–3.47, $p = 0.026$) were associated with lower survival. Conversely, preoperative ALB values were directly related to better overall survival (0.63; 95% CI: 0.43–0.94, $p = 0.022$). Supplementary Table 3 illustrates all variables associated with overall survival in the HR group. Both a MELD score greater than 14 (1.10; 95% CI: 0.35–3.50, $p = 0.872$) and Child B score (2.21; 95% CI: 0.89–5.48, $p = 0.088$) were not significant risk factors for lower overall survival.

The larger nodule was, the lower the overall survival for patients in both groups (TF 1.012; 95% CI: 1.001–1.022, $p = 0.025$; Hazard ratio 1.007; 95% CI: 1.003–1.011, $p = 0.002$). Similarly, the presence of macrovascular invasion negatively impacted overall survival (TF 2.16; 95% CI: 1.24–3.76, $p = 0.006$; HR 4.51; 95% CI: 2.42–8.39, $p < 0.001$). Patients in the HR group were negatively affected by microvascular invasion (2.09; 95% CI: 1.26–3.47, $p = 0.004$), which did not occur in the TF group (1.16; 95% CI: 0.77–1.75, $p = 0.478$). The higher the AFP value was, the lower the overall survival of HR patients (1.004; 95% CI: 1.003–1.006, $p < 0.001$). HR patients who were within the radiological (0.49; 95% CI: 0.32–0.76, $p = 0.001$) and pathological (0.39; 95% CI: 0.24–0.66, $p < 0.001$) Milan criteria had better overall survival. Other tumor-related factors for patients in the HR and TF groups are displayed in Table 3.

Table 4 shows the multiple variable analysis of patients who underwent surgical treatment and the construction of prognostic factor models for overall survival. For LT patients, we identified an association between a shorter cold ischemia time (0.74; 95% CI: 0.70–0.79, $p < 0.001$)

Table 3 Factors related to tumors associated with the overall survival of patients undergoing surgical treatment (liver transplantation and hepatic resection)

Characteristic	Liver Transplant		Hepatic Resection	
	Hazard Ratio (IC95%)	*p*	Hazard Ratio (IC95%)	*p*
Alpha-Fetoprotein	1.001 (0.998–1.004)	0.527	1.004 (1.003–1.006)	< 0.001
No. of Nodules	1.054 (0.996–1.116)	0.069	1.287 (1.061–1.561)	0.011
Within Radiological MC	-		0.49 (0.32–0.76)	0.001
Within Pathological MC	0.78 (0.55–1.11)	0.169	0.39 (0.24–0.66)	< 0.001
Largest Nodule Size	1.012 (1.001–1.022)	0.025	1.007 (1.003–1.011)	0.002
Well Differentiated	0.92 (0.43-2.00)	0.841	0.70 (0.19–2.63)	0.602
Moderately Differentiated	0.87 (0.52–1.46)	0.601	0.95 (0.38–2.37)	0.907
Poorly Differentiated	1.06 (0.58–1.94)	0.862	1.10 (0.41–2.98)	0.854
Microvascular Invasion	1.16 (0.77–1.75)	0.478	2.09 (1.26–3.47)	0.004
Macrovascular Invasion	2.16 (1.24–3.76)	0.006	4.51 (2.42–8.39)	< 0.001
Satellite Nodule	1.35 (0.83–2.19)	0.233	2.16 (1.34–3.47)	0.001
Inactive Tumor	0.90 (0.53–1.55)	0.714	-	-
Chronic Hepatopathy	-	-	1.34 (0.59–3.08)	0.488
Clear Margin	-	-	0.49 (0.20–1.21)	0.122
Margin Distance	-	-	1.002 (0.98–1.02)	0.85
Bilobar Nodules	-	-	1.93 (0.78–4.78)	0.155

95% CI: 95% confidence interval; MC: Milan criteria

Table 4 Prognostic factors according to multiple variable analysis for overall survival of patients undergoing transplantation

Characteristic	Hazard Ratio (IC95%)	*p*
Liver Transplant		
MELD ≤ 14	1.03 (0.99–1.06)	0.140
Child B	0.68 (0.43–1.08)	0.099
Child C	0.55 (0.24–1.30)	0.176
Surgery time (minutes)	1.001 (0.999–1.003)	0.267
Alpha-fetoprotein	0.9999 (0.9997–1.0002)	0.642
Cold ischemia time (minutes)	0.74 (0.70–0.79)	< 0.001
Rescue transplant	0.80 (0.22–2.82)	0.723
Donor age (years)	0.98 (0.96–0.99)	0.002
Donor risk index score	5.40 (2.56–11.42)	< 0.001
Time on the list until transplant (days)	1.0003 (0.9999–1.0007)	0.160
Hepatic Resection		
Child A	1	
Child B	1.86 (0.71–4.89)	0.206
Intraoperative red blood cell transfusion	1.04 (0.92–1.19)	0.534
Alpha-Fetoprotein	1.00005 (1.00003-1.00007)	< 0.001
Within radiological MC	0.45 (0.27–0.75)	0.002
Preoperative portal hypertension	2.32 (1.39–3.86)	0.001

95% CI: 95% confidence interval; MC: Milan criteria

and younger donors (0.98; 95% CI: 0.96–0.99, $p = 0.002$) with lower mortality. The DRI (5.40; 95% CI: 2.56–11.42, $p < 0.001$) was negatively associated. For patients who underwent HR, the AFP level (1.00005; 95% CI: 1.00003–1.00007, $p < 0.001$) and the presence of significant portal hypertension (2.32; 95% CI: 1.39–3.86, $p = 0.001$) were factors associated with worse survival, whereas being within the radiological MC (0.45; 95% CI: 0.27–0.75, $p = 0.002$) was a favorable prognostic factor.

Analysis of disease-free survival

Patients in the LT group had a disease-free survival (DFS) that was negatively affected when they underwent preoperative chemoembolization (2.98; 95% CI: 1.16–7.70, $p = 0.024$) and rescue transplantation (21.27; 95% CI: 2.76–164.02, $p = 0.003$). A lower DFS was also associated with a longer cold ischemia time (2.82; 95% CI: 2.01–3.97, $p < 0.001$) (Supplementary Table 4). Patients in this group had lower DFS rates among those who stayed in the ICU longer (1.13; 95% CI: 1.04–1.23, $p = 0.006$) and those who underwent two-stage hepatectomy (12.36; 95% CI: 1.62–94.46, $p = 0.015$). The INR (6.67; 95% CI: 1.46–30.49, $p = 0.014$) and BMI (0.94; 95% CI: 0.90–0.99, $p = 0.028$) were inversely proportional to DFS (Supplementary Table 5).

Variables associated with HCC were tested in both groups as prognostic factors for DFS (Table 5). Pathologically, being within the Milan criteria was a better predictor of DFS in both groups (LT: 0.32; 95% CI: 0.13–0.80, $p = 0.015$; Hazard ratio: 0.56; 95% CI: 0.35–0.88, $p = 0.012$). The number of nodules (LT: 1.12; 95% CI: 1.01–1.25, $p = 0.034$; Hazard ratio: 1.33; 95% CI: 1.10–1.61, $p = 0.004$) and the size of the largest nodule (LT: 1.03; 95% CI: 1.01–1.05, $p = 0.016$; Hazard ratio: 1.01; 95% CI: 1.001–1.01, $p = 0.027$) were inversely related to DFS. Both macrovascular (LT 5.65; 95% CI: 1.73–18.40, $p = 0.004$, Hazard ratio 3.93; 95% CI: 2.08–7.43, $p < 0.001$) and microvascular invasion (LT 2.69; 95% CI: 1.04–6.97,

Table 5 Tumor-related factors associated with disease-free survival in patients undergoing surgical treatment (liver transplantation and hepatic resection). Characteristics| transplantation| resection

Characteristics	Liver Trasnplantation		Hepatic Resection	
	Hazard Ratio (IC95%)	*p*	Hazard Ratio (IC95%)	*p*
Alpha-fetoprotein	1.003 (0.999–1.001)	0.274	1.005 (1.003–1.007)	< 0.001
Within radiological MC	-		0.69 (0.45–1.04)	0.077
Within pathological MC	0.32 (0.13–0.80)	0.015	0.56 (0.35–0.88)	0.012
Number of nodules	1.12 (1.01–1.25)	0.034	1.33 (1.10–1.61)	0.004
Largest nodule size	1.03 (1.01–1.05)	0.016	1.01 (1.001–1.01)	0.027
Moderately differentiated	1.48 (0.34–6.52)	0.604	1.58 (0.58–4.35)	0.374
Poorly differentiated	1.92 (0.37–9.91)	0.435	1.60 (0.54–4.72)	0.398
Microvascular invasion	2.69 (1.04–6.97)	0.042	1.76 (1.10–2.81)	0.018
Macrovascular invasion	5.65 (1.73–18.40)	0.004	3.93 (2.08–7.43)	< 0.001
Satellite nodules	1.86 (0.63–5.54)	0.263	1.49 (0.91–2.45)	0.117
Active tumor in the specimen	2.42 (0.32–18.01)	0.389	-	
Chronic liver disease	-	-	1.51 (0.66–3.47)	0.327
Clear margin	-	-	0.64 (0.24–1.76)	0.389
Margin distance	-	-	0.999 (0.978–1.019)	0.895
Bilobar nodules	-	-	1.59 (0.58–4.34)	0.367

95% CI: 95% confidence interval; -: not applicable; MC: Milan criteria

Table 6 Prognostic factors according to multiple variable analysis for disease-free survival of patients undergoing transplantation

Characteristic	Hazard Ratio (IC95%)	*p*
Liver transplantation		
Preoperative alpha fetoprotein	1.002 (1.001–1.004)	0.006
Downstaging	2.51 (0.43–14.55)	0.304
Cold ischemia (minutes)	41.20 (6.30-269.39)	< 0.001
Rescue transplantation	$1.01*10^{25}$($2.98*10^{12}$-$3.41*10^{37}$)	< 0.001
Time on liver transplant list	1.01 (1.00-1.01)	0.007
Hepatic resection		
Age (years)	0.99 (0.97–1.01)	0.206
BMI (kg/m2)	0.945 (0.895–0.998)	0.044
Intraoperative red blood cell transfusion	1.02 (0.88–1.18)	0.799
Preoperative chemoembolization	2.16 (0.85–5.43)	0.104
Pretreatment alpha-fetoprotein	1.00005 (1.0003–1.00007)	< 0.001
Within radiological Milan criteria	0.93 (0.57–1.53)	0.78

95% CI: 95% confidence interval; LT: liver transplant

$p = 0.042$, Hazard ratio 1.76; 95% CI: 1.10–2.81, $p = 0.018$) were associated with a worse prognosis. Patients in the HR group were negatively affected by higher AFP levels (1.005; 95% CI: 1.003–1.007, $p < 0.001$).

Prognostic models were created by evaluating multiple variables related to DFS in relation to the groups that underwent surgical treatment (Table 6). Patients in the LT group had a shorter DFS (1.002; 95% CI: 1.001–1.004, $p = 0.006$), longer cold ischemia time (41.202; 95% CI: 6.30–269.39, $p < 0.001$), and longer waiting time on the list (1.012; 95% CI: 1.00–1.01, $p = 0.007$). Rescue transplantation (1.01*1025; 95% CI: 2.982*1012 – 3.418*1037, $p < 0.001$) was also an independent risk factor for shorter DFS. Patients who underwent hepatic resection had better DFS among those with lower BMIs (0.945; 95% CI: 0.895–0.998, $p = 0.044$) and poorer performance among those with elevated AFP levels (1,00005; 95% CI: 1,0003–1,00007, $p < 0.001$).

Discussion

This study reports the experience of a large center in the surgical treatment of HCC over a long follow-up period, demonstrating that HR and LT are complementary treatment modalities, as they cater to patients with different characteristics. The therapeutic modalities often address patients with different oncological statuses and liver functions, resulting in equally different outcomes.

LT is recognized by international consensus as the best curative option for HCC and underlying cirrhosis [18]. However, patient selection is a critical point since it is a procedure linked to the limitation of donor availability, requiring rigorous evaluation regarding postoperative outcomes, the risk of patient loss at the WL, and possible alternative treatments. On the other hand, HRs usually follow more cautious Western consensuses [18] than broader Eastern consensuses [17]. The final decision for HR candidates is highly dependent on institutional experience and the surgical team, primarily considering patient performance, the number of tumor nodules, the volume of residual liver, the assessment of residual liver function, and the presence of significant portal hypertension. These selection criteria can be observed in the sample of this study; for example, patients who underwent HR presented more advanced tumors. While all

patients listed for transplantation were within the Milan criteria, only 56.9% of patients who underwent HR met this criterion. Furthermore, compared with patients who underwent LT, those in the HR group had larger tumors, a greater incidence of vascular invasion, and greater AFP levels. Conversely, LT patients had more severe liver dysfunction, with more Child B and C patients and more patients with MELD scores of 14 or higher.

Additionally, the disparity in HR versus LT patient numbers is attributed to the distribution of care; less complex HR cases are often managed at secondary hospitals, while LT referrals are concentrated at tertiary centers, including ours, which specializes in transplantation, since not all tertiary centers performs LT in Brazil, whereas HR is almost always available. The timing of HCC treatment is highly dependent on effective screening protocols, as early-stage tumors have a greater potential for undergoing HR. The scarcity of donors justifies HR whenever feasible. Furthermore, in recent years, there has been an expansion of HR indications relative to liver transplantation, driven by the dissemination of minimally invasive surgery and the demonstration of satisfactory results even in patients with advanced oncological status. It's important to acknowledge that we are a referral center within a well-functioning public health program, which also presents limitations. These include occasional delays in patient referrals, limitations in radiological resources for screening, and a long waiting list for transplantation.

Overall, the first treatment option for uninodular HCC should always be HR; however, it is contraindicated in most cases because of its strict selection. In our study, the number of patients selected for transplantation ($n = 563$) exceeded the number of candidates for HR ($n = 181$). The number of HCC nodules is a factor to be considered in the decision of therapeutic modality, as recurrence after HR of multinodular tumors tends to be high. A Chinese study compared Child A patients within the Milan criteria with more than one nodule and no previous treatment who underwent HR ($n = 33$) or LT with a living donor ($n = 34$) and who had significantly reduced 5-year DFS (19.8% vs. 72%, $p < 0.001$) [19]. In our case series, the number of nodules was a criterion used in patient selection, with more patients with only one nodule in the HR group (84% vs. 40.3%, $p < 0.001$).

The 5-year survival of patients undergoing HR reported in the literature can reach 70% in highly selected patients [20]. However, large series present lower results when patients with borderline liver function and more advanced stages are included. A New Zealand study evaluated 190 patients who underwent HR, with 21% having significant portal hypertension, and the 5-year survival rate was 54% [21]. The reported 5-year survival in our study was 49%; however, 34% of our patients had significant portal hypertension. The New Zealand study reported recurrence rates of 55% and 62% at 3 and 5 years, respectively [21]. Our patients had DFS rates of 49.8% and 40% in the same period, representing recurrence rates of 50.2% and 60%, respectively.

The survival of patients who undergo HR is negatively affected in the short and medium term in patients with significant portal hypertension [22]. Xia et al. [23] reported the results of 224 patients with early-stage HCC (BCLC A) who underwent HR and reported that significant portal hypertension had a negative effect on the median survival of patients (35 vs. 75 months, $p < 0.001$). This study, like others, concluded that patients with significant portal hypertension have a significant risk of postoperative liver dysfunction and a 5-year survival of less than 50%, even among patients with normal preoperative liver function. Our univariate and multivariate analyses also revealed that significant portal hypertension was a risk factor for lower survival among patients who underwent HR ($p = 0.006$ and 0.001, respectively). On the other hand, more severe liver disease identified as Child B and a MELD score greater than 14 were not identified as risk factors for survival in our study. Even in the multivariate regression model, Child B classification was not a significant risk factor, which is consistent with the literature [24-26] and reinforces that these characteristics are not contraindications for HR and can be safely performed in (super)selected patients.

A multicenter European study evaluated over a thousand patients with HCC and metabolic syndrome who underwent HR and revealed a high risk of morbidity (34.6%) and mortality (2.9%) in these patients [27]. This study identified obesity, diabetes mellitus, coronary artery disease, significant portal hypertension, major hepatectomy, and open access as risk factors for increased morbidity. In our analysis, BMI did not impact survival, but it was identified as an independent prognostic factor for DFS, resulting in a better prognosis at lower values.

LT is more comprehensive regarding patient liver function; however, it follows much stricter oncological criteria and depends on the waiting time on the transplant list, so many listed patients do not undergo the procedure. For this reason, it is interesting to observe the results not only of transplanted patients but also of patients who were included in the transplant list and did not undergo the procedure; the ITT analysis covers this need. A multicenter European [28] study retrospectively evaluated 579 patients listed for LT due to HCC and revealed that after a median wait of 7 months, tumor progression occurred in 67 (11.5%) patients. However, tumor progression is not the only risk for patients awaiting LT. Mehta et al. [29] evaluated 2092 patients listed for LT due to HCC in the US in an area with a long WL; after a median wait of 7

months, 25% of patients did not undergo transplantation due to tumor progression, critical clinical worsening, or death on the list. In our series, of the 563 listed patients, 32% did not undergo LT due to death (14.7%) or tumor progression on the list (17.3%), after a median wait time of 329 days (10.9 months). Patients who underwent LT had a median wait time of 254 days (8.5 months), and this difference in waiting time between WL patients and LT patients was significant. A possible explanation for the longer wait time could be the greater number of blood type O patients among WL patients than among LT patients, as this blood type presents a much higher recipient/donor ratio in our setting [11].

A meta-analysis comparing HR and LT for patients within the Milan criteria yielded 9 publications totaling 570 patients who underwent HR and 861 who underwent LT, identifying similar 1-year survival rates of 84.5% and 84.4% ($p = 0.8$) and 5-year survival rates of 47.9% and 59.3%, respectively ($p = 0.06$) [30]. Compared with the results obtained in our study, the 1-year survival rates in the HR and LT groups were 82.8% and 77.4%, and the 5-year survival rates were 49.3% and 67.5%, respectively. The log-rank test revealed significant differences between the two curves, probably due to long-term analysis, where LT offered a clear advantage over HR, as the 10-year survival rates were 56.8% and 33.4%, respectively. However, there is a clear crossover at 2 years when both have survival rates of 73.9%, and at 3 years, the curves are still quite close (LT 71% vs. HR 67.5%). This allows us to observe that the results were similar for approximately this period, highlighting the importance of both therapeutic options for HCC treatment. It is important to acknowledge that our analysis did not stratify patients based on the Milan versus Milan-Brazil criteria. Since the MBC represent an expanded selection protocol, it is conceivable that the inclusion of patients meeting these less stringent criteria could have influenced the overall study outcomes. Indeed, a large Brazilian database analysis demonstrated a significantly reduced 5-year DFS in patients exceeding the Milan criteria but fulfilling the Milan-Brazil criteria (94% vs. 72%, $p < 0.001$) [10]. Future research should consider a stratified analysis to fully elucidate the impact of these criteria on treatment efficacy.

Patients undergoing LT are directly impacted by factors exclusive to this modality, such as organ ischemia and donor-related variables. Grat et al. [31] stratified 1402 liver recipients according to the MELD score and reported that in patients with MELD scores greater than 10, cold ischemia time was an independent risk factor for worse 5-year survival. Additionally, donor age is the main donor-related risk factor for graft function and recipient mortality [15, 32]. Patients who underwent LT in the present study received organs from donors with a median age of 43 years (ranging from 5 to 81 years) and a median cold ischemia time of 6 h and 54 min; these two variables were identified in the multivariate regression model as inversely related factors to survival. These variables are important for calculating the donor risk index (DRI), which is a score created through the analysis of over 20,000 livers harvested in the US. It is capable of predicting the risk of the liver being discarded, the risk of graft loss, and recipient mortality, employing different weighted variables. According to this study, each hour of cold ischemia increases the risk of graft loss by 1%. Furthermore, donors over 40 years old have an additional risk of graft nonfunction for each additional year, with donors aged 60 years or older being the main risk factor identified in the entire study (relative risk of 1.53 for donors aged 61–70 years and 1.65 for those aged over 70 years, both with $p < 0.0001$) [15]. The lower the DRI is, the greater the chance of organ utilization and graft survival; donors with DRIs greater than 1.5 have more than double the chance of the liver being discarded compared to a donor with a DRI less than 1.1. According to graft survival analyses, a donor with a DRI less than or equal to 1 had a 3-year graft survival of 81.2%, whereas donors with a DRI between 1.5 and 1.6 had a DRI of 70.6%, and those with a DRI greater than 2 had a DRI of 60% [15]. In our sample, the DRIs had a mean and median of 1.5, and the mean 3-year survival rate after transplantation was 71%, indicating good correlation with the proposed score. Furthermore, it was identified as an independent factor for overall survival. The use of DRIs in Brazil is subject to pertinent criticisms, especially regarding the inclusion in this score of the donor's ethnic origin, since for a mixed population such as ours, this factor should be irrelevant. However, these similar results are likely due to the strong correlation of age and cold ischemia time with the survival of our patients.

Regardless of the type of treatment, HCC is a neoplasm with a considerable risk of recurrence. In addition to the previously mentioned factors, the pretreatment serum level of AFP is an important prognostic factor. An Asian study involving 568 HCC patients identified AFP as an independent prognostic factor for OS, with 5-year OS rates of 75% and 46% ($p < 0.001$) when patients with low and high AFP levels, respectively, were compared. AFP also had a significant effect on DFS, with 5-year DFS rates of 42% vs. 21% ($p < 0.001$), respectively. Interestingly, the threshold value for determining whether AFP is high or low was 10 ng/mL [33]. Similarly, our data corroborate these findings, as AFP significantly impacted OS and DFS according to the multivariable assessment model of patients undergoing HR. Patients who underwent LT had a lower DFS associated with higher AFP values, but this difference was not significant for the multivariable analysis of OS. This finding is similar to those of other studies of patients who underwent LT for HCC [34].

Another significant factor for lower DFS in our study was cold ischemia time. This variable has been identified as a risk factor for recurrence when the duration is greater than 10 h; although this fact has not been fully elucidated, it is attributed to the mechanisms of injury and sinusoidal repair caused by ischemia/reperfusion [35]. This finding is interesting because, in the context of LT, many variables cannot be controlled, such as waiting time on the list and donor availability, unlike cold ischemia time, which can and should be systematically controlled with the aim of reducing it, as it is directly related to the allocation process, surgical tactics employed, and interaction between the recipient's team and organ extraction.

The main limitations of this study are the observational and retrospective design, so we chose a strategy to minimize possible biases through data collection from a prospective database, as well as statistical analysis of different groups of patients with multiple variables. Another limitation is the heterogeneity of tumor staging and degree of hepatic dysfunction among patients undergoing HR and LT; however, the aim of this study was to evaluate the most frequent outcomes of candidates for these treatments in reality. Other point of attention is the retrospective collection of a single AFP level per patient. This precluded the analysis of AFP slope, which is a recognized prognostic factor in HCC. However, when sequential AFP measurements are unavailable to assess the prognostic value of AFP dynamics, the AFP level closest to the time of transplantation provides the most relevant prognostic information, and this is the AFP level that was collected in our study. Additionally, we did not compare HCC-related characteristics between WL and LT patients; however, the inclusion of patients on the list aimed to identify the proportion of patients who underwent LT after being included in the waiting list with a diagnosis of HCC. Similarly, we analyzed the outcomes of patients undergoing each type of treatment to identify specific prognostic factors for these different populations rather than comparing the results of each type of treatment. It is noteworthy that the study presents inherent limitations due to its long-term scope. These include advancements in imaging modalities leading to improved diagnostic accuracy. Importantly, there were no significant changes in HCC management. These factors, while potentially confounding, are limitations inherent to any study spanning an extended period. Finally, it could be questioned whether some patients indicated for HR did not undergo the procedure or were not referred for LT during the study period. It was not possible to collect these data reliably, but on the basis of the service's experience, this situation must have occurred in a small proportion of patients. Furthermore, similar studies published in international journals do not address this outcome. Thus, this study represents the largest series in the national literature of patients with HCC indicated for surgical treatment; few studies include patients who entered the transplant list but did not undergo it. Another highlight of our study is the long follow-up time for patients, with a median of over 4 years.

In conclusion, HR and LT are complementary (and synergic) therapeutic options. Moreover, the overall survival of patients listed for transplantation is higher in the early years, but long-term outcomes are better. Disease-free survival was better among patients who underwent LT; however, a significant proportion of the listed patients did not undergo LT because of death or tumor progression after WL. For patients with HR, independent factors for better overall and disease-free survival are being within the Milan criteria and presenting lower levels of alpha-fetoprotein. Among patients who underwent LT, a shorter cold ischemia time was associated with better overall and disease-free survival as an independent factor.

Supplementary Information

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Supplementary Material 1

Author contributions

R.S.P., G.M.F. and W.A. made substantial contributions to the conception of the work.M.S.R., L.A.C.A. and P.H. made substantial contributions to the design of the work.F.F.C., V.R.S. and J.A.P.K. made the acquisition and analysis of data.V.J., R.B.M. and F.F.M. made interpretation of data.L.D., R.M.A.J. and R.O.F.B. have drafted the work.J.A.R.F. and D.R.W. substantively revised the work.ALL AUTHORS approved the submitted version (and any substantially modified version that involves the author's contribution to the study).ALL AUTHORS agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

All authors have participated in the realization of this paper. The authors are responsible for the intellectual content, conception, and design of this work; they take public responsibility for it and have agreed to have their name listed as contributors. Neither this manuscript nor one with substantially similar content under our authorship has been previously published. None of the authors did receive any financial interests (direct or indirect) related to the achievement of this work.

Human ethics and consent to participate

This study adhered to the principles of the Declaration of Helsinki and followed Good Clinical Practice guidelines. The study received ethics approval from the Ethics Committee for Research Project Analysis– CAPPesq of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (HC FMUSP), under the number 294,198. The same Committee waived the need for consent to participate.

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The authors declare no competing interests.

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References

1. Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, et al. International trends in hepatocellular carcinoma incidence, 1978–2012. Int J Cancer. 2020;147(2):317–30. https://doi.org/10.1002/ijc.32723. Epub 20191105.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660. Epub 20210204.
3. Amin MB, Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. Eighth edition. ed. Switzerland: Springer; 2017. xvii, 1024 pages p.
4. Forner A, Hessheimer AJ, Isabel Real M, Bruix J. Treatment of hepatocellular carcinoma. Crit Rev Oncol Hematol. 2006;60(2):89–98. https://doi.org/10.1016/j.critrevonc.2006.06.001. Epub 20060724.
5. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern cooperative oncology group. Am J Clin Oncol. 1982;5(6):649–55. PubMed PMID: 7165009.
6. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022;400(10360):1345–62. Epub 20220906. https://doi.org/10.1016/S0140-6736(22)01200-4. PubMed PMID: 36084663.
7. Yen YH, Cheng YF, Wang JH, Lin CC, Chen YY, Yong CC, et al. Real world clinical practice in treating advanced hepatocellular carcinoma: when East Meets West. PLoS ONE. 2020;15(3):e0230005. https://doi.org/10.1371/journal.pone.0230005. Epub 20200312.
8. Barros AZA, Fonseca GM, Kruger JAP, Coelho FF, Herman P. Liver resection for hepatocellular carcinoma beyond the BCLC: are multinodular disease, portal hypertension, and portal system invasion real contraindications? J Gastrointest Oncol. 2022;13(6):3123–34.
9. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl. 2011;17(Suppl 2):S44–57. https://doi.org/10.1002/lt.22365. PubMed PMID: 21695773.
10. Chagas AL, Mattos AA, Diniz MA, Felga GEG, Boin IFSF, Silva RCMA, et al. Impact of Brazilian expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a multicenter study. Ann Hepatol. 2021;22:100294. https://doi.org/10.1016/j.aohep.2020.100294. Epub 20201201.
11. Andraus W. Liver transplantation in Brazil: the urgent need of a new allocation system for the exceptions in meld score. Arq Gastroenterol. 2020;57(1):1–2. https://doi.org/10.1590/S0004-2803.202000000-01. PubMed PMID: 32294727.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf. 2009;42(2):377–81. PubMed PMID: 18929686; PubMed Central PMCID: PMC2700030.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7. https://doi.org/10.1016/S0140-6736(07)61602-X. PubMed PMID: 18064739.
14. Nicoll A. Surgical risk in patients with cirrhosis. J Gastroenterol Hepatol. 2012;27(10):1569-75. https://doi.org/10.1111/j.1440-1746.2012.07205.x. PubMed PMID: 22694313.
15. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am J Transplant. 2006;6(4):783– 90. https://doi.org/10.1111/j.1600-6143.2006.01242.x. PubMed PMID: 16539636.
16. Strasberg SM, Phillips C. Use and dissemination of the Brisbane 2000 nomenclature of liver anatomy and resections. Ann Surg. 2013;257(3):377–82. https://doi.org/10.1097/SLA.0b013e31825a01f6. PubMed PMID: 22895397.
17. Korea KLCaKNCCN. 2022 KLCA-NCC Korea Practice Guidelines for the Management of Hepatocellular Carcinoma. Korean J Radiol. 2022;23(12):1126– 240. doi: 10.3348/kjr.2022.0822. PubMed PMID: 36447411; PubMed Central PMCID: PMC9747269.
18. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67(1):358–80..29086. PubMed PMID: 28130846.
19. Jiang L, Liao A, Wen T, Yan L, Li B, Yang J. Living donor liver transplantation or resection for Child-Pugh A hepatocellular carcinoma patients with multiple nodules meeting the Milan criteria. Transpl Int. 2014;27(6):562–9. Epub 20140402. https://doi.org/10.1111/tri.12297. PubMed PMID: 24606007.
20. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg. 2002;235(3):373–82. https://doi.org/10.1097/00000658-200203000-00009. PubMed PMID: 11882759; PubMed Central PMCID: PMC1422443.
21. Wu L, Swan P, McCall J, Gane E, Holden A, Merrilees S, et al. Intention-to-treat analysis of liver transplantation, resection and thermal ablation for hepatocellular carcinoma in a single centre. HPB (Oxford). 2018;20(10):966–76. https://doi.org/10.1016/j.hpb.2018.04.006. Epub 20180526.
22. Ito T, Tanemura A, Kuramitsu T, Murase T, Kaluba B, Noguchi D et al. Spleen volume is a predictor of posthepatectomy liver failure and short-term mortality for hepatocellular carcinoma. Langenbecks Arch Surg. 2023;408(1):297. Epub 20230807. https://doi.org/10.1007/s00423-023-03025-w. PubMed PMID: 37548783.
23. Xia F, Huang Z, Zhang Q, Ndhlovu E, Chen X, Zhang B, et al. Clinically significant portal hypertension (CSPH) on early-stage HCC following hepatectomy: what's the impact? Eur J Surg Oncol. 2023;49(4):771–9. PubMed PMID: 36372619.
24. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology. 1996;111(4):1018–22. https://doi.org/10.1016/s0016-5085(96)70070-7. PubMed PMID: 8831597.
25. Choi SB, Kim HJ, Song TJ, Ahn HS, Choi SY. Influence of clinically significant portal hypertension on surgical outcomes and survival following hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. J Hepatobiliary Pancreat Sci. 2014;21(9):639–47. https://doi.org/10.1002/jhbp.124. Epub 20140527.
26. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008;134(7):1908–16. https://doi.org/10.1053/j.gastro.2008.02.091. Epub 20080308.
27. Berardi G, Ratti F, Sposito C, Nebbia M, D'Souza DM, Pascual F, et al. Model to predict major complications following liver resection for HCC in patients with metabolic syndrome. Hepatology. 2023;77(5):1527–39. Epub 20230103. https://doi.org/10.1097/HEP.0000000000000027. PubMed PMID: 36646670; PubMed Central PMCID: PMC10121838.
28. Di Sandro S, Sposito C, Ravaioli M, Lauterio A, Magistri P, Bongini M, et al. Surgical treatment of hepatocellular carcinoma: multicenter Competing-risk analysis of Tumor-related death following liver resection and transplantation under an Intention-to-treat perspective. Transplantation. 2023;107(9):1965–75. Epub 20230821. https://doi.org/10.1097/TP.0000000000004593. PubMed PMID: 37022089.
29. Mehta N, Dodge JL, Roberts JP, Yao FY. A novel waitlist dropout score for hepatocellular carcinoma - identifying a threshold that predicts worse post-transplant survival. J Hepatol. 2021;74(4):829–37. https://doi.org/10.1016/j.jhep.2020.10.033. Epub 20201111.
30. Menahem B, Lubrano J, Duvoux C, Mulliri A, Alves A, Costentin C, et al. Liver transplantation versus liver resection for hepatocellular carcinoma in intention to treat: an attempt to perform an ideal meta-analysis. Liver Transpl. 2017;23(6):836–44. https://doi.org/10.1002/lt.24758. PubMed PMID: 28295992.

31. Grąt M, Wronka KM, Patkowski W, Stypułkowski J, Grąt K, Krasnodębski M, et al. Effects of donor age and cold ischemia on liver transplantation outcomes according to the severity of recipient status. Dig Dis Sci. 2016;61(2):626–35. https://doi.org/10.1007/s10620-015-3910-7. PubMed PMID: 26499986; PubMed Central PMCID: PMC4729807.
32. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. Am J Transplant. 2008;8(2):419– 25. Epub 20080107. https://doi.org/10.1111/j.1600-6143.2007.02086.x. PubMed PMID: 18190658.
33. Kudo A, Matsumura S, Ban D, Irie T, Ochiai T, Tanaka S, et al. Does the preoperative alpha-fetoprotein predict the recurrence and mortality after hepatectomy for hepatocellular carcinoma without macrovascular invasion in patients with normal liver function? Hepatol Res. 2014;44(14):E437–46. https://doi.org/10.1111/hepr.12335. Epub 20140506.
34. Hameed B, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level > 1000 Ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. Liver Transpl. 2014;20(8):945–51. https://doi.org/10.1002/lt.23904. Epub 20140712.
35. Nagai S, Yoshida A, Facciuto M, Moonka D, Abouljoud MS, Schwartz ME, et al. Ischemia time impacts recurrence of hepatocellular carcinoma after liver transplantation. Hepatology. 2015;61(3):895–904. Epub 20150130. doi: 10.1002/hep.27358. PubMed PMID: 25099130.

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