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Survival After Liver Transplantation For Hepatocellular Carcinoma According To The Milan Criteria: A Single-Center Experience

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Abstract

Background: This study aimed to assess the long-term outcomes of liver transplantation (LT) for the treatment of hepatocellular carcinoma (HCC) according to the Milan Criteria (MC) in a university hospital.

Methods: A cohort study of 100 HCC patients transplanted between 2006 and 2020. Patients were grouped according to MC for survival analysis, based on explant findings. The median follow-up duration was 65 months.

Results: Perioperative mortality and recurrence rates were 5% and 9.5%, respectively. Recurrence appears within two years post-LT, and the median time until death was seven months (range 2-38). In univariate analysis, recurrence was more likely in the presence of Hepatitis B Virus (HBV), maximal tumor diameter > 50 mm, total tumor diameter > 70 mm, microvascular invasion, poor histological differentiation, and HCC stage beyond MC. The median alpha-fetoprotein (AFP) level and locoregional therapies (LRT) before LT showed no significant differences in recurrence rates. On multivariate analysis, factors associated with the recurrence rate were maximal tumor diameter > 50 mm, total tumor diameter > 70 mm, presence of microvascular invasion, and poorly differentiated tumors. The 5-year Overall Survival (OS) was 73.2% [95%CI 62.9-81]. According to explant biopsies, 70 patients were within MC (WMC) and 25 beyond MC (BMC), with significant differences in recurrence rates (2.8% vs. 28%, $p<0.05$) and 5-year OS rates (78.5% vs. 55.7%, $p=0.0091$).

Conclusion: In our center, the 5-year OS rate for LT in HCC is over 70%, with a recurrence rate of 9.5%. Significant differences were found between the patients with and without MC.

Keywords: Liver Transplantation, Hepatocellular Carcinoma, Recurrence, Survival

Introduction

Primary liver cancer is 7th in frequency and the second most common cause of cancer-related mortality, worldwide. The highest incidence rates have been reported in Asia and Africa. Hepatocellular carcinoma (HCC) is the dominant type of liver cancer, accounting for > 75% of all cases. The prognosis of HCC is poor in all regions of the world, with an estimated global incidence rate of 9.3 per 100,000 person-years and mortality rate of 8.5[1]. Risk factors include chronic hepatitis B and C, alcohol addiction, nonalcoholic fatty liver disease (NAFLD), and exposure to dietary toxins. Early-stage HCC can be treated with local ablation, surgical resection, or liver transplantation (LT). Treatment selection depends on the tumor characteristics, severity of underlying liver dysfunction, age, other medical comorbidities, available medical resources, and local expertise[2]. LT remains the optimal treatment for patients with early-stage HCC owing to the replacement of the diseased liver and restoration of normal hepatic function[3]. A landmark study by Mazzaferro in 1996 established LT as an effective treatment for early-stage HCC defined by the Milan Criteria (MC): one HCC lesion ≤5 cm or three lesions ≤3 cm without evidence of vascular invasion or extrahepatic spread. Patients with MC have a 5-year survival rate of 75% and recurrence rates of <10-15%[4]. For patients with HCC exceeding the MC, survival decreases with increasing tumor size and number, although modest expansion of the tumor size criteria to improve access to LT can achieve post-LT survival comparable to that of MC[3]. In addition, locoregional therapies (LRT) such as transcatheter arterial chemoembolization (TACE), radiofrequency or microwave ablation (RFA), and percutaneous ethanol injection (PEI) can potentially prevent tumor progression while on the waiting list (bridging therapy) or reduce tumor burden back to the Milan criteria (downstaging)[5].

The study aimed to assess the long-term outcomes of LT for the treatment of HCC in our center and perform a survival analysis according to MC.

Materials and Methods

Between January 2006 and December 2020, 100 consecutive patients with pathologically proven HCC underwent LT at our hospital. The cohort included patients diagnosed with HCC by CT or MRI based on the Liver Imaging Reporting and Data System (LI-RADS)[6]. The indication for LT was HCC without extrahepatic metastasis or macroscopic vascular invasion on conventional imaging. Patients with incidentally detected HCC in explant pathology were also included. On the waiting list, patients were treated with LRT according to the Barcelona Clinic Liver Cancer guidelines as a bridge to transplantation[7]. Patients outside the MC can undergo downstaging treatment and should be considered for LT according to local guidelines. The response after therapy was assessed using CT or MRI according to the Treatment Response algorithm of the LI-RADS (LR-TR).

Subsequently, a retrospective review of electronic medical records was performed. Clinical factors including age and comorbidities were reviewed. The Model for End-stage Liver Disease Sodium Score (MELD-Na) was calculated using the last available laboratory values before transplantation. Preoperative AFP levels, morphological characteristics of HCC on imaging, and treatment before transplantation were also reviewed. Patients were classified as within or beyond the MC, according to the final explant pathology. After transplantation, patients were followed up by routine clinic appointments and cross-sectional imaging, according to the local protocol.

All surgical procedures were performed by specialists with experience in liver transplantation using liver allografts obtained from brain-dead cadaveric donors (DBD). Organ donations and transplantations were performed strictly following the National Coordination of Organ and Tissue Procurement and Transplantation regulations of the Ministry of Health of Chile and the Declaration of Helsinki. The study was approved by the Ethics Committee of the University of Chile`s Hospital.

Postoperative complications were classified according to the Clavien-Dindo system, considering events within 90 days from LT. A team of specialized hepatologists performed post-transplant management, including an immunosuppressive regimen.

The final pathology reports were based on the American Joint Committee on Cancer Staging Manual. Pathological variables, including the maximal tumor size (maximal diameter of the most significant tumor in the resected specimen), total tumor size (sum of the diameters of all tumors), number of HCC lesions, histopathologic differentiation graded according to the Edmondson–Steiner criteria (grade I, well differentiated; II, moderately differentiated; and grade III, poorly differentiated), and microvascular invasion, were recorded.

Patients were regularly followed up according to the local protocol. Serum AFP levels and liver function were monitored at each follow-up visit. Abdominal cross-sectional imaging was performed every six months during the first two years and annually thereafter. In selected cases, HCC recurrence was diagnosed based on imaging findings or biopsy findings. For patients with incomplete EMR data, follow-up data were obtained via telephone inquiries. All patients completed at least two years of follow-up, and none of the patients had been lost.

Overall Survival was calculated from 90 days after LT until death or the last follow-up visit. The cutoff date for follow-up was April 30, 2024. The median follow-up period was 64.7 months (range 28.4–213.4).

Survival and recurrence analyses were performed for the complete cohort. In addition, a group analysis was performed according to HCC Staging on explant pathology (WMC or BMC), comparing survival and recurrence rates between the two groups.

Statistical analysis

Continuous variables were presented as medians and ranges, and categorical variables were presented as absolute numbers and percentages. Fisher's exact and Mann-Whitney U tests were used to compare categorical and continuous variables, respectively. Patient and tumor characteristics were compared between patients with and without recurrence, and univariate and multivariate analyses of recurrence rate were performed using logistic regression.

The Kaplan-Meier method was used for univariate survival analysis, and the difference between the WMC and BMC groups was assessed using the log-rank test. The Cox proportional hazards regression model was used for the multivariate survival analysis. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the STATA/IC version 16.0.

Results

The median age of the patients was 62 years, and 71% were male. Underlying liver disease was caused by NAFLD (48%), Hepatitis B or Hepatitis C virus infection (23%), and alcohol consumption (11%), followed by other causes (18%). The baseline characteristics of the cohort and the two groups according to MC are presented in Table 1. HCC was diagnosed before LT in 79 patients, and in 21 cases, it was incidentally detected by explant pathology. The characteristics of explant pathology are summarized in Table 2. Thirteen patients had nonviable HCC with 100% tumor necrosis, and all of them received preoperative treatment with LRTs. On the first 90 days after LT, 8% and 28% of patients had Grade III and IV complications according to the Clavien-Dindo classification, respectively. The perioperative mortality rate was 5%.

Locoregional therapies pre-transplant

Sixty-eight patients (86%) diagnosed with HCC before LT received preoperative treatment. LRTs were performed as a bridge to LT in 51 patients, mainly combining two or more modalities, with a median of 1 treatment session (range 1-5). The response to LRT was assessed using cross-sectional imaging according to the LR-TR criteria and was reported as non-viable in 56.9% (29/51) and viable in 33.3% (17/51). Nine patients who presented with HCC BMC were treated for downstaging using a combination of LRTs. The response was reported as non-viable in 66.7% (6/9) and viable in 22.2%

(2/9), and one patient did not receive image control. Finally, eight patients underwent salvage LT due to the development of HCC recurrence after being treated with liver resection (4), liver resection and LRT (2), and RFA for solitary resection (2). In total, 64 patients received LRTs: 51 (79.7%) bridge-to-LT, 9 (14.5%) for downstaging, and 4 (6.3%) as primary treatment. According to explant pathology, the response to LRT was complete (100% tumor necrosis) in 18.8% (12/64) and partial in 56.3% (36/64). No response to treatment was observed in 25% of the cases (16/64).

The concordance between imaging before LT and explant pathology findings (Table 3) to classify a patient as having MC was 82.3% (kappa 0.4).

Factors related to recurrence

Recurrence occurred in 9/95 (9.5%) patients during the follow-up period. Most recurrences were diagnosed within two years post-LT (88%); in six patients, recurrence occurred in the first year after LT, and in two cases, it appeared during the second year of follow-up. One patient presented with recurrence 38 months after transplantation. The median time between LT and HCC recurrence was seven months (range 2-38). The most common recurrence site was intrahepatic in three patients and extrahepatic in six. The lungs and bones were the most common sites of extrahepatic metastases (55%). The other recurrence sites were the brain, peritoneum, and para-aortic lymph nodes. These patients received different treatments for HCC recurrence according to their tumor behavior and functional status. At the latest follow-up, 100% of the patients with recurrence had disease.

Patient and tumor characteristics were compared between patients with and without recurrence (Table 4). In univariate analysis, recurrence was more likely in the presence of HBV, maximal tumor diameter > 50 mm, total tumor diameter > 70 mm, microvascular invasion, poor histological differentiation, and HCC stage beyond the Milan criteria. The median AFP level and LRT before LT showed no significant differences in recurrence rate. On multivariate analysis (Table 3), factors associated with the recurrence rate were maximal tumor diameter > 50 mm, total tumor diameter > 70 mm, presence of microvascular invasion, and poorly differentiated tumors on histology.

Factors Related to Survival

During follow-up, 38 patients died, with a median time between LT and death of 40 months (range 3-156). The cause of death was HCC recurrence in 24% (9/38) of patients (Figure 1). The 3-, 5-, and 10-year OS were 81.1% [CI95% 71.6 – 87.8], 73.2% [CI95% 62.9 – 81], and 53.1% [CI95% 40.2 – 64.5], respectively (Figure 2A).

Univariate and multivariate analyses were performed to identify factors that might affect the OS of patients who underwent transplantation for HCC (Table 5). A total tumor diameter > 7 cm, poor histopathologic differentiation beyond the Milan criteria, AFP level >15 ng/ml, and HCC recurrence were significantly associated with worse OS. In the multivariate Cox analysis, only tumor recurrence was significantly associated with OS.

Comparison according to Milan Criteria

Based on the pathological findings, the cases were classified according to the MC. The baseline characteristics were similar in both groups (Table 1). Five patients with MC died in the perioperative period, leaving 95 patients for survival analysis: 70 with WMC and 25 with BMC. The recurrence rates were significantly different between the groups, with 2.8% in the WMC group and 28% in the BMC group (P =0.001). The OS rates of patients WMC and BMC were 87.1% versus 64% at three years and 79.4% versus 55.7% at five years (Figure 2B., p=0.0091).

Conclusion

Most patients in our series were men with a median age of 60 years. Similar to our findings, the SRTR reported in 2021 that 61.7% of LT recipients were men, with the primary age group being 50–64 years[8]. Regarding the etiology of liver disease, NAFLD was identified as the primary cause in 48% of our patients, followed by hepatotropic viruses and alcohol in the second and third place, respectively. This differs from what has been published in the literature, where the leading cause of HCC in cirrhotic patients is hepatitis C or B virus[1], [5], [9]. This could be associated with the high prevalence of obesity and metabolic syndrome in the Chilean population, associated with a low prevalence of the hepatitis C virus, reported at 0.01% in the National Health Survey of 2009-2010. Alcohol consumption continues to be a frequent cause of liver diseases and HCC worldwide[10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50]. Most patients had compensated cirrhosis (Childs A or B) with a median MELD-Na score of 16. Similar to our findings, other authors report mainly compensated patients, with some exceptions where Child-Pugh C patients reach up to 58% [11]. This finding could be related to a selection bias or the fact that HCC cases were diagnosed in the setting of a screening program. Not all of our patients had available pre-transplant AFP levels, but of the 66 patients who did, the majority had normal values (65%).

In the perioperative period, the prevalence of major complications (Clavien Dindo grade ≥ III) was 36%, and the operative mortality rate was 5%. In our series, the causes of perioperative mortality included hemorrhagic or septic shock, and one patient died intraoperatively. Other studies of patients transplanted for HCC reported perioperative mortality (between 30 and 90 days) ranging from 2.7% to 11% [10], [11], [16], [18], [19], [25], [30], [49], [51], [52]. A study from Portugal[41], with 231 patients transplanted for HCC between 1992 and 2014, reported an average ICU stay of 4±3 days and a total hospital stay of 19±11 days. The overall perioperative morbidity was 40.7%, with Clavien-Dindo grade III and IV complications in 19%, and no perioperative mortality. Another series of 76 cases of HCC transplanted in Belgium reported perioperative complications within 90 days in 47.4% of cases, with 26.3% being grade III/IV according to the Clavien-Dindo classification, and a mortality rate of 13.1%, mainly due to sepsis, ARDS, cerebral infarction, and sudden cardiopulmonary arrest[53]. Our results are similar to those of a previous report. However, concerning the significant complications (III/IV), an explanation for the slightly higher frequency might be that we transplanted ten patients in our series in an urgent setting.

Most studies evaluated the selection criteria for LT based on explant pathology. Of our patients, 71% met the Milan Criteria, a proportion like other studies[54]. A literature review including 58 articles reported a prevalence of HCC beyond the Milan criteria, ranging from 16% to 97% [55]. In our series, patients with BMC had a 44% rate of microvascular invasion compared to a 21% rate in those within Milan. However, the proportion of patients with poor histological differentiation grades was similar in both the groups. Mazzaferro et al. (2009) reported data on 1556 patients who underwent transplantation for HCC in 36 centers in Europe and the USA between 2006 and 2007, with 71% falling BMC. These patients had a 41% rate of microvascular invasion and a 27% rate of poor histological differentiation compared to 11% and 16%, respectively, in those with WMC ($p<0.005$) [22]. In a UCSF cohort of 211 patients, all beyond the Milan criteria, there was a 7.1% rate of microvascular invasion and a 4.3% rate of poor histological differentiation[56]. Patients beyond MC had a higher tumor burden, which might explain the association with a higher frequency of microvascular invasion and poor histological differentiation. These results are similar in all the series, including ours.

In our cohort, 21% of patients had incidental HCC (iHCC) diagnosed in the explant. Several studies have reported a percentage of incidental HCC between 1.4% and 34% [11], [12], [13], [15], [17], [26], [27], [28], [34], [36], [40], [57], [58], [59], [60], [61]. Perez et al. [62] characterized 25 iHCC cases, which had similar characteristics to known cases but had a higher prevalence of multinodular disease

and poor histological differentiation (55.6% and 70.4%, respectively); however, in the comparison of 5-year overall survival and disease-free survival, there were no differences with known HCC. Our cohort's recurrence rate was similar between incidental and known HCC (10%), with no differences in the 5-year overall or disease-free survival. Reports on the predictive value of incidental HCC have varied in the literature.

Bridge therapy aims to prevent disease progression and dropout from waiting lists. Despite the lack of data from controlled trials, recent European guidelines recommend neoadjuvant therapies with LRTs to reduce the risk of exclusion due to tumor progression. This strategy is suggested, especially when the expected waiting time is six months or longer[63]. The rationale is based on the dropout rate from the transplant waiting list related to HCC progression, reported in 10%-20% of cases. Additionally, improvements in long-term post-transplant outcomes have been reported in patients who respond to LRT[64]. Owing to the heterogeneity of populations and therapeutic criteria observed in different research protocols, it is difficult to reach a definitive conclusion on the net effect of bridge therapy for HCC. In our series, 64 patients underwent locoregional treatment, bridging, or downstaging, with the majority receiving one or two sessions (53%), combining TACE with RFA, PEI, or both. 69% showed a complete or partial radiological response, with no tumor progression in 14%. These results indicate that, at least during the waiting period, there was no radiological disease progression. There were no differences in OS between patients who received LRT before transplantation and those who did not.

Tumoral recurrence of HCC after liver transplant is a primary concern related to long-term morbidity and mortality. Even with strict adherence to the indication criteria for LT for HCC, the reported recurrence rate worldwide varies between 8% and 20%. Malignant cell release during surgery or the prevalence of hidden metastases after transplantation have been postulated as causes that can manifest as intrahepatic or distant recurrences. The most common extrahepatic sites include the lungs, lymph nodes, and bones. Factors recognized in the literature to increase the risk of recurrence include poor histological differentiation, vascular invasion, satellite nodules, and the quantity and size of tumors. The presentation time of recurrence varies and is categorized as early- or late-onset, with the latter occurring two years post-transplant. Early onset recurrence is associated with a poor prognosis and is likely the result of pre-existing extrahepatic malignant cells at the time of transplant[65].

After a median follow-up of 65 months, our cohort had a recurrence rate of 9.5%, with 89% diagnosed within the first two years after transplantation, classified as early recurrence. These results are similar to those reported in a systematic review that included 125 articles involving 55,333 HCC-transplanted patients, where the recurrence rate was 17%, ranging between 15% and 19%. The most common recurrence site was extrahepatic (70%), followed by the lung, bone, brain, peritoneum, and para-aortic lymph nodes[65]. Another meta-analysis of 218 patients who underwent transplantation for HCC reported a median time to recurrence of 15 months (range 1-118)[66]. A cohort study showed 32% of recurrences before 12 months post-transplant and 68% thereafter[67]. The 5-year overall survival rate in our patients with recurrence was 11% compared to 81% in patients without recurrence. Our results align with those published in the literature, such as an observational study of 311 confirmed HCC patients in the explant showing a significant decrease in the 5-year overall survival (22%) compared to patients without recurrence (64%)[68].

Serum AFP is a marker for HCC differentiation and vascular invasion. Higher AFP levels have consistently been identified as a negative predictor of post-LT outcomes. AFP levels > 1000 ng/mL have been associated with poorer outcomes (HR 4.9, [IC95% 1,3–18,6]; p=0.019)[69]. In our analysis, predictors of recurrence included being beyond the Milan criteria, maximal tumor diameter > 5 cm, total tumor diameter > 7 cm, microvascular invasion, and poor histological differentiation, which aligns with findings in the international literature.

Regarding the long-term outcomes of our transplant patients, the overall mortality rate in the cohort was 40% after a median follow-up of > five years. The leading causes of death were tumor recurrence (24%) and pulmonary sepsis. In a Brazilian study, tumor recurrence caused 38% of the deaths, followed by HCV recurrence, sepsis, graft dysfunction, and other factors [70]. Similarly, Piñero and colleagues in a multicenter Latin American study reported that tumor recurrence caused 15% of deaths, echoing the findings from our series[40].

The 5-year overall rate in our cohort was 73%, and recurrence was identified as the leading cause of mortality. Lai et al. identified independent risk factors for mortality as vascular macro-invasion, larger lesion diameter, poor histological differentiation, and AFP levels increasing by >15 ng/mL per month[50]. A meta-analysis of 25 articles involving nearly thousand patients reported a 5-year overall survival rate of 74%, encompassing studies with criteria beyond Milan[71].

When classifying patients based on the Milan criteria, those BMC had a 5-year overall survival of 55.7%, which was significantly lower than that of patients WMC (78.5%; p=0.0091). This difference was more pronounced in the disease-free survival at five years, where the WMC reached 96.5% compared to 71% for BMC (p=0.0008). In the original study by Mazzaferro, patients WMC showed a 4-year survival rate of 85% and a 92% disease-free survival rate, while those BMC had significantly lower rates of 50% and 59% [10]. A subsequent meta-analysis by the same center analyzing the results of patients BMC showed similar 5-year overall survival rates of at least 70%. In general, the 5-year overall survival predicted in liver transplants for HCC WMC varies between 65% and 78% [10], [63], [72], [73].

The observed 5-year overall survival for patients BMC in our cohort was below the expected threshold for non-HCC transplant patients, potentially impacting long-term outcomes. Due to organ scarcity, the minimum survival threshold for the expanded criteria is expected to be comparable to that of non-HCC patients. In the past three decades, more liberal selection criteria have been proposed, expanding BMC and exploring different size combinations, numbers of lesions, and tumor biology surrogates (such as AFP dynamics). Finally, while the extended criteria showed acceptable results, they must be balanced with other indications for transplantation.

The main limitations of this study included its single-center nature and possible selection bias, which may have influenced the results. Additionally, selection based solely on patients who reached transplantation excluded important data from the cohort of patients who dropped out of the study. The relatively small sample size compared with extensive database studies is another limitation. Retrospective data collection from the time of transplant can be prone to biases, memory issues, missing data, incomplete records in medical charts, etc., making it an essential limitation for generalizing the results.

Liver transplantation for HCC has yielded good results in our center, with a 5-year overall survival of>70% and recurrence of <10%. The survival rate of patients transplanted beyond the Milan Criteria was significantly lower but still >55%. This cohort of LT patients with HCC is the only one published in Chile to date.

Abbreviations

LT: Liver transplantation

HCC: Hepatocellular carcinoma

MC: Milan Criteria

HBV: Hepatitis B Virus

AFP: Alfa Feto Protein

LRT: Locoregional therapies

OS: Overall Survival

WMC: Within Milan Criteria

BMC: Beyond Milan Criteria

NAFLD: Nonalcoholic Fatty Liver Disease

TACE: Transcatheter Arterial Chemoembolization

RFA: Radiofrequency or Microwave ablation

PEI: Percutaneous Ethanol Injection

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

LI-RADS: Liver Imaging Reporting and Data System

LR-TR: Treatment Response algorithm of LI-RADS

MELD-Na: Model for End-Stage Liver Disease-sodium score

DBD: Donation after brain stem death

EMR: Electronic Medical Records

ICU: Intensive Care Unit

ARDS: Acute Respiratory Distress Syndrome

UCSF: University of California, San Francisco

iHCC: Incidental Hepatocellular carcinoma

Article Type: Original article.

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Authorship contributions:

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of the manuscript: All authors.

The authors equally contributed to this work.

Appendices

TABLES

Table 1. Baseline characteristics of patients with HCC transplanted (n=100), and according to the Milan Criteria

Variables	**Total N=100 Median [range] or N (%)**	**BMC N=25 Median [range] or N (%)**	**WMC N=75 Median [range] or N (%)**	**p-value***
Male sex, n (%)	71 (71%)	18 (72%)	53 (71%)	1
Age (years)	62 [42-74]	61.3 [41.8 – 68.8	62.1 [44.6 – 73.7]	0.6358
BMI (kg/m^2)	27.6 [19.4 - 41.8]	27.5 [19.4 – 31.5]	27.6 [20 – 41.8]	0.1917
Diabetes Mellitus, n (%)	45 (45%)	9 (36%)	36 (48%)	0.357
Hypertension, n (%)	43 (43%)	6 (24%)	37 (49.3%)	0.036
Etiology of cirrhosis, n (%) NAFLD HCV HBV Alcohol Autoimmune/ PSC / PBC Other	 48 (48%) 20 (20%) 3 (3%) 11 (11%) 9 (9%) 9 (9%)	 12 (48%) 6 (24%) 2 (8%) 2 (8%) 1 (4%) 2 (8%)	 36 (48%) 14 (18.7%) 1 (1.3%) 9 (12%) 8 (10.7%) 7 (9.3%)	0.618
MELD-Na score	16 [6-43]	17 [6-43]	14.5 [6-40]	0.1767
Child-Pugh class A B C	 23 (23%) 40 (40%) 36 (36%)	 5 (20%) 10 (40%) 10 (40%)	 18 (24%) 30 (40.5%) 26 (35%)	0.915
Preoperative AFP (ng/ml) Normal Value (≤7.5 ng/ml) 7.6-200 ng/ml ≥200 ng/ml	4.9 [1-869] 43 (65.26%) 18 (27.3%) 5 (7.6%)	6.8 [1.5 – 869]	4.5 [1 – 830.2]	0.1460
Incidental HCC	21 (21%)	5 (20%)	16 (25.8%)	0.783
LRT in Known HCC	64/79 (81%)	18/20 (90%)	46/59 (78%)	0.331
Time on List (months)	11 [0 – 110]	9.3 [0 – 40.8]	12.3 [0 – 110.9]	0.3537
Clavien–Dindo complications None IIIa / IIIb IV V	 21 (21%) 1 (1%) / 7 (7%) 28 (28%) 5 (5%)	 10 (40%) 2 (8%) 6 (24%) 0	 10 (16.1%) 6 (9.7%) 18 (29%) 4 (6.5%)	0.128
ICU days	4 [1-92]	6 [1 – 40]	4 [1-92]	0.3268
Hospital days	17 [8-158]	19 [10 – 101]	16 [8 – 158]	0.9115
Follow-up	64.7 [28.4 – 213.4]	59.3 [50.8 – 213.3]	67.7 [28.4 – 194.8]	0.9350

BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; MELD-Na model for end-stage liver disease; AFP, alpha-fetoprotein; LRT: Locoregional therapy. TN: tumor necrosis. ICU Intensive care unit. BMC: beyond Milan Criteria. WMC: Within Milan Criteria. *p-value of comparison between groups according to MC.

Table 2. Tumor characteristics in explant pathology

Variables	**Total N=87 Median [range] N (%)**	**BMC N=25 Median [range] or N (%)**	**WMC N=62* Median [range] or N (%)**	**p-value**
Tumor Number	1 [1-9]	4 [1-9]	1 [1-3]	0.0000
Single	45 (51.7%)	4 (16%)	46 (66.1%)	
Multiple	42 (48.3%)	21 (84%)	16 (25.8%)	
Max tumor size (mm)	25 [2-90]	43 [9 – 90]	20 [2-45]	0.0000
≤50	76 (87.4%)	14 (56%)	62 (100%)	
>50	11 (12.6%)	11 (44%)		
Total tumor size (mm)	32 [2-172]	71 [20 – 172]	25 [2-58]	0.0000
≤70	74 (85.1%)	12 (48%)	62 (100%)	
>70	13 (14.9%)	13 (52%)		
Microvascular invasion	24 (27.6%)	11 (44%)	13 (21%)	0.037
Histological differentiation				
I. Well	49 (55.42%)	12 (48%)	37 (60%)	0.525
II. Moderate	30 (34.94%)	10 (40%)	20 (32%)	
III. Poor	8 (9.63%)	3 (12%)	5 (8%)	

*In 13 cases, explant pathology revealed 100% tumor necrosis.
BMC: beyond Milan Criteria. WMC: Within Milan Criteria.

Table 3. Tumor characteristics in explants pathology in patients who received LRT before LT compared with explants pathologies findings (N=62)

Variables	**Pre LT N=62 Median [range] N (%)**	**Biopsies N=62 Median [range] N (%)**
Tumor Number	1 [0-4]	2 [1-9]
None	30 (48.4%)	13 (21%)
Single	15 (24.2%)	21 (33.8%)
Multiple	17 (27.4%)	28 (45.2%)
Max tumor size (mm)	23 [8-55]	28.5 [9-90]
≤50	31 (50%)	41 (66.1%)
>50	1 (1.6%)	8 (12.9%)
Total tumor size (mm)	26 [10-92]	40 [15-172]
≤70	30 (48.4%)	39 (62.9%)
>70	2 (3.2%)	10 (16.1%)
WMC	57 (91.9%)	46 (74.2%)

WMC: Within Milan Criteria.

Table 4. Risk factors for recurrence, univariate and multivariate analysis (n=95).

A. Univariate Analysis				
Variables	**Non-Recurrent (N=86)**	**Recurrent (N=9)**	**P-value**	**OR**
Male sex, n (%)	60 (69.8%)	6 (66.7%)	0.848	
Age (years)	62 [42-74]	62 [48-67]	0.986	
BMI (kg/m^2)	27.7 [20-41.8]	27.3 [19.4-30]	0.219	
Diabetes Mellitus, n (%)	41 (47.7%)	3 (33.3%)	0.417	
Hypertension, n (%)	36 (41.9%)	4 (44.4%)	0.881	
Etiology of cirrhosis, n (%) NAFLD HCV HBV Alcohol Autoimmune/ PSC / PBC Other	 42 (48.8%) 14 (17.4%) 1 (1.2%) 11 (12.8%) 8 (9.3%) 9 (10.5%)	 2 (22.2%) 4 (44.4%) 2 (22.2%) 0 1 (11.1%) 0	0.027 ref 0.068 0.013 . 0.452 .	 24.3 [1.95 – 302]
Incidental HCC, n (%)	18 (20.9%)	2 (22.2%)	0.928	
Child-Pugh class A B C	 22 (25.9%) 31 (36.5%) 32 (37.7%)	 0 6 (66.7%) 3 (33.3%)	 . ref 0.334	
Time on List (months)	12 [0-110.9]	9.1 [0-40.8]	0.342	
MELD-Na score	15 [6-40]	16 [9-43]	0.159	
AFP (ng/ml) ≤15 >15	4.7 [1-830.2] 48 (81.3%) 11 (18.6%)	23 [3.1-869] 2 (40%) 3 (60%)	0,1577	
LRT No Yes	 30 (34.9%) 56 (65.1%)	 4 (44.4%) 5 (55.6%)	0.717	
Maximal Diameter (mm) ≤50 >50	 67 (90.5%) 7 (9.5%)	 5 (55.6%) 4 (44.4%)	0.009	7.66 [1.7 – 35.3]
Total diameter (mm) ≤70 >70	 66 (89.2%) 8 (10.8%)	 4 (44.4%) 5 (55.6%)	0.002	10.3 [2.3 – 46.5]
Tumor Number ≤3 >3	 62 (83.8%) 12 (16.2)	 6 (66.7%) 3 (33.3%)	0.284	
Microvascular invasion No Yes	 58 (96.7%) 16 (21.6%)	 1 (1.7%) 8 (88.9%)	0.002	29 [3.4 – 249.3]
Histological differentiation High (I-II) Poor (III)	 71 (96%) 3 (4.1%)	 4 (44.4%) 5 (55.6%)	0.000	29.6 [5.1 – 170.2]
Milan Criteria BMC WMC	 18 (20.9%) 68 (79.1%)	 7 (77.8%) 2 (22.2%)	0.002	13.2 [2.5 – 69.2]

B. Multivariate Analysis				
Variables	**P-value**	**OR**	**95% CI**	
Etiology of cirrhosis HCV HBV	 0.132 0.551	 8.6 6.3	 0.7 – 114.9 0.1 – 336.2	
AFP >15 ng/ml	0.996	2.22	0.18-27.97	
LRT	0.685	1.81	0.10-32.17	
Maximal diameter >50 mm	0.045	10.7	1.05 – 109.5	
Total diameter >70 mm	0.039	37.6	1.2-1178.5	
Tumor number >3	0.438	6.11	0.13-289.62	
Microvascular invasion	0.047	15.7	1.03 – 149.4	
Poor differentiation	0.008	35.4	2.5 – 497.8	

BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; MELD-Na model, end-stage liver disease; AFP, alpha-fetoprotein; LRT: Locoregional therapy. BMC: beyond Milan Criteria. WMC: Within Milan Criteria. OR odds ratio, CI confidence interval

Table 5. Univariate and Multivariate analysis for OS (N=95)

A. Univariable Analysis	**OS**	
	5 years (%)	**P-value** **HR [CI95%]**
Sex Male Female	 74.7 69	 0.8647
Diabetes Mellitus No Yes	 70 76.9	 0.3439
Hypertension Arterial No Yes	 74 72.4	 0.3941
Etiology of cirrhosis NAFLD HCV HBV Alcohol Autoimmune/ PSC/ PBC Other	 74.3 56.8 33.3 81.8 88.9 50	 0.377
Incidental HCC No Yes	 72.9 74.3	 0.4318

AFP (ng/ml) ≤15 ng/ml >15 ng/ml	 85.4 47.6	0.0014 3.9 [1.6 – 9.4]
LRT No Yes	 64.3 75	 0.0713
Maximal Diameter (mm) ≤50 mm >50 mm	 74.3 54.6	0.0593
Total diameter (mm) ≤70 mm >70 mm	 76.3 46.2	0.0167 2.5 [1.15 – 5.3]
Tumor Number ≤3 >3	 74.3 60	 0.3954
Microvascular invasion No Yes	 77.2 58.3	 0.0731
Histological differentiation Alta (I-II) Poor (III)	 77.9 12.5	0.0000 6.76 [2.8 – 16.1]
Recurrence No Yes	 80.8 11.1	0.0000 17.1 [6.75 – 3.4]
Milan Criteria BMC WMC	 55.7 79.4	0.07 2.4 [1.3 – 4.6]
B. Multivariate Analysis	**OS**	
	HR [95%CI]	**P-value**
Etiology of cirrhosis HCV HBV	 2.3 [0.9 – 6.1] 0.7 [0.1 – 4.3]	 0.086 0.671
AFP (ng/ml) >15 ng/ml	2.9 [0.8 – 10.1]	0.097
Maximal Diameter >50mm	2.8 [0.36-22.00]	0.531
Total diameter >70 mm	4.9 [0.21-111.7]	0.667
Microvascular invasion	1.4 [0.5 – 3.9]	0.569
Poor differentiation	2.6 [0.8 – 8.9]	0.121
Beyond Milan Criteria	1.07 [0.4 – 2.79]	0.885
Recurrence	11 [2.3 – 52.2]	0.003

NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; AFP, alpha-fetoprotein; LRT: Locoregional therapy. BMC: beyond Milan Criteria. WMC: Within Milan Criteria. OS Overall survival. RFS Relapse-free Survival. HR Hazard Ratio. CI confidence interval

Table 6. Studies of patients with HCC transplanted were included in the analysis (n=41).

Author, year	Country	N	FU m	Mortality %	Recurrence %	BMC %	5-year OS	5-year OS WMC	5-year OS BMC
Mazzaferro, 1996[10]	Italy	48	26	17	8.3	27	4-y 75%	4-y 85%	4-y 50%
Yao et al, 2001[11]	USA	70	2 y	27	11.4	4	72.4	NR	NR
Leung, 2004[12]	USA	144	21	NR	NR	40	46.6	50.9%	NR
Duffy, 2007[13]	USA	467	79	NR	NR	63	52	86	NR
Millonig, 2007[14]	Austria	116	37	NR	NR	41	NR	NR	NR
Chen, 2009[15]	Australia	186	111	NR	NR	40	67.1	77.1	46.1
Halazun, 2009[16]	USA	150	37	31	19	33	60	NR	NR
Lai, 2009[17]	Italy	85	24	NR	NR	31	NR	NR	NR
Li, 2009[18]	China	148	13	NR	NR	84	32.1	NR	NR
Muscari, 2009[19]	France	110	46	8.2	5.5	34	72.8	77	NR
Toso, 2009[20]	Canada	6478	13	31.3	36.6	3	NR	NR	NR
Xiao, 2009[21]	China	224	60	NR	NR	70	51.5	3-y 88.4%	3-y 33.1 %
Mazzaferro, 2009[22]	36 centers: USA/Europa/LA	1556	53	38	20	71	59.1	73.3	53.6
Cescon, 2010[23]	Italy	283	42	24	12	27	75	NR	NR
Macaron, 2010[24]	USA	107	22	NR	12.1	34	76.6	NR	NR
Wang, 2010[25]	China	255	23	27.8	37.6	71	3-y 53%	3-y 86.1%	3-y 34.9 %
Koniaris, 2011[26]	USA	270	NR	NR	34	24	55	NR	NR
Raj, 2011[27]	New Zealand	95	68	18.9	13.6	39	IT: 73%	72.7	NR
Kashkoush, 2014[28]	Canada	115	60	NR	16.5	47	NR	NR	NR
Zhang, 2014[29]	China	203	57	33.9	22.6	44	NR	77.2	57.3
Marqués, 2015[30]	Portugal	146	33	12.4	14.4	32	58	NR	NR

Fu, 2016[31]	China	130	40	NR	46.15	65	58	NR	NR
Guerrini, 2016[32]	Italy	131	47	NR	14.5	30	68.2	NR	NR
León Díaz, 2016[33]	Spain	91	NR	NR	9.8	19	NR	66.7	21.4
O'Connor, 2016	Ireland	57	43	NR	14	28	73	NR	NR
Piñero, 2016[35]	15 centers LA	327	47	NR	15	39	62.7	NR	NR
Schraiber, 2016[36]	Brazil	206	50	44	15.5	NR	60.5	NR	NR
Grat, 2017[37]	Polonia	240	34	NR	13	40	68.8	71.6	65.4
Kornberg, 2017[38]	Germany	116	74	NR	25	43	75.6	81.7	62.7
Notarpaolo, 2017[39]	Italy	574	41	NR	13.5	25	NR	73.5	54.3
Piñero, 2018[40]	LA	527	37	29	14.2	33	64.8	NR	NR
Pinto-Marques, 2018[41]	Portugal	231	60	37.2	19	19	67	74.5	NR
Sternby Eilard, 2018[42]	Sweden	336	64	40.8	23.5	39	62	70	53
Al-Ameri, 2019[43]	China	589	280 días	12.4	9.3	38	NR	2-y 85.3%	2-y 75.8 %
Mirón Fernández, 2019[44]	Spain	105	Min. 60	NR	10.5	19	NR	59.4	30
Degroote, 2020[74]	Belgium	526	56.1	NR	WMC 12.3%	17	NR	71.3	60% - 71%
Grat, 2020[46]	Polonia	282	59	NR	17.4	40	NR	NR	NR
Meischl, 2021[47]	Austria	166	111	43.4	19.3	38	68.1	NR	NR
Víctor, 2020[48]	USA	220	60	17.3	7.3	37	NR	81	88%-80%
Chagas, 2020[49]	Brazil	1059	28	Periop-30d: 11%	8	19	75	78	69-65%
Lai 2022[50]	10 centers Europa	1854	46	31.5	13.1	NR	68.1	NR	NR
Present, 2024	**Chile**	**100**	**65**	**40**	**9.5**	**62**	**73**	**78.5**	**55.7**

FU: follow-up. m: months. BMC: beyond Milan Criteria. OS: overall survival. WMC within the Milan criteria. NR: not reported. Y: years. LA: Latin American.

FIGURES

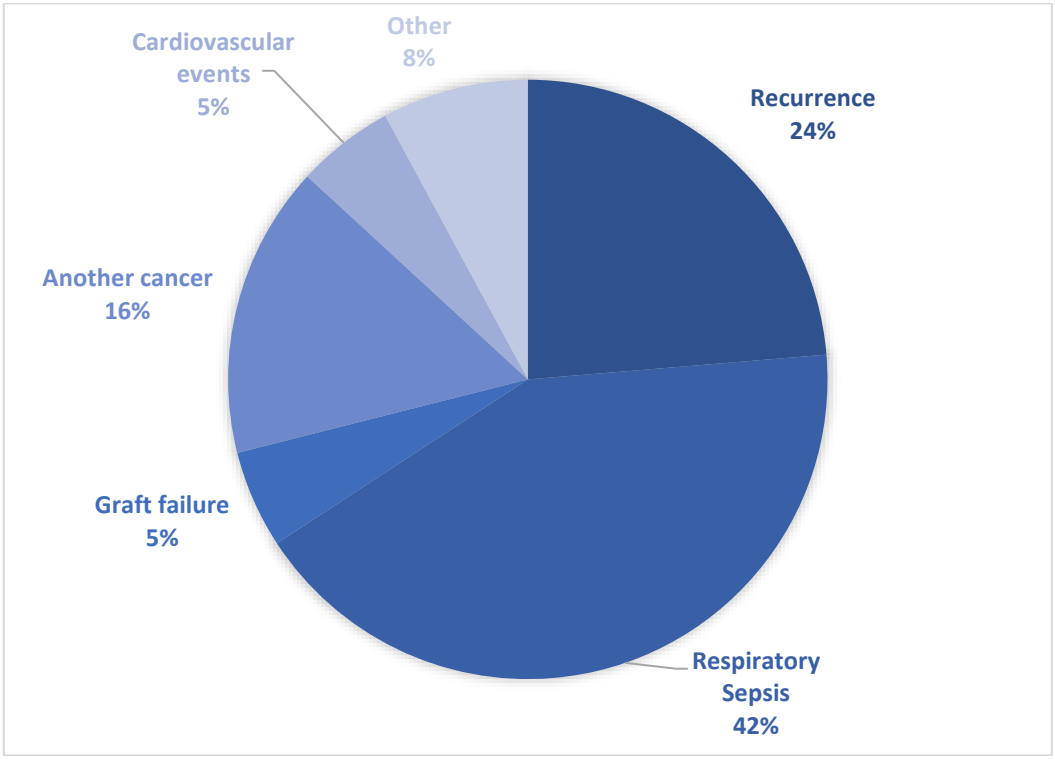
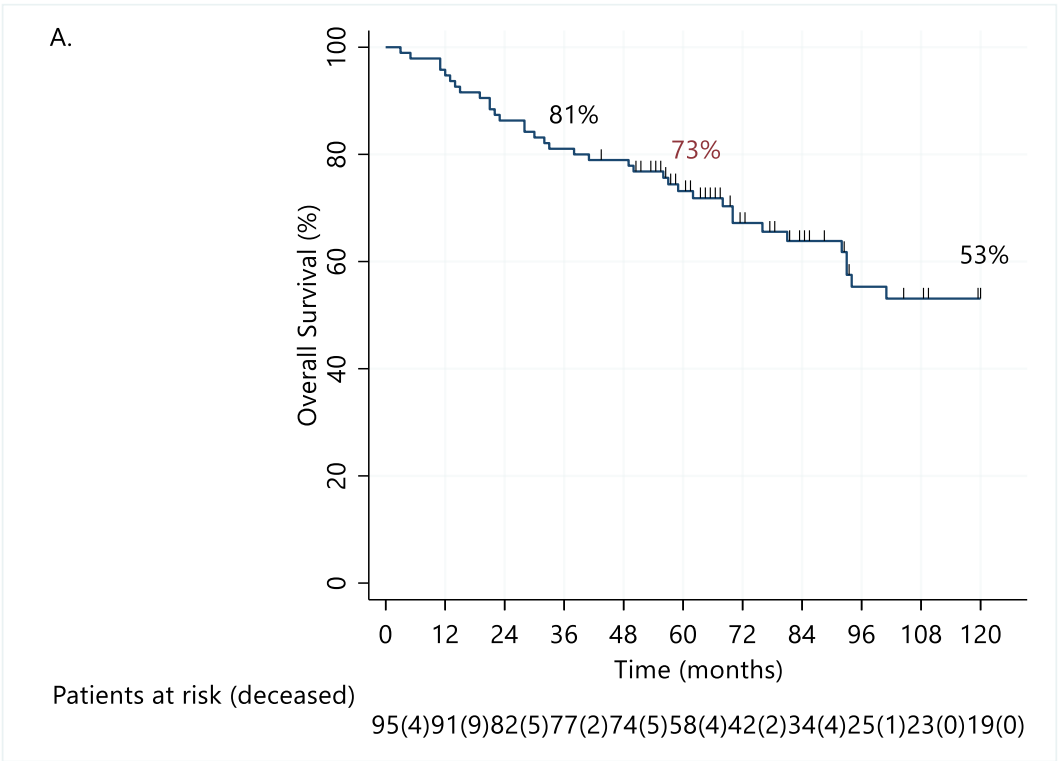


Figure 1. Graph of causes of death of patients after LT.



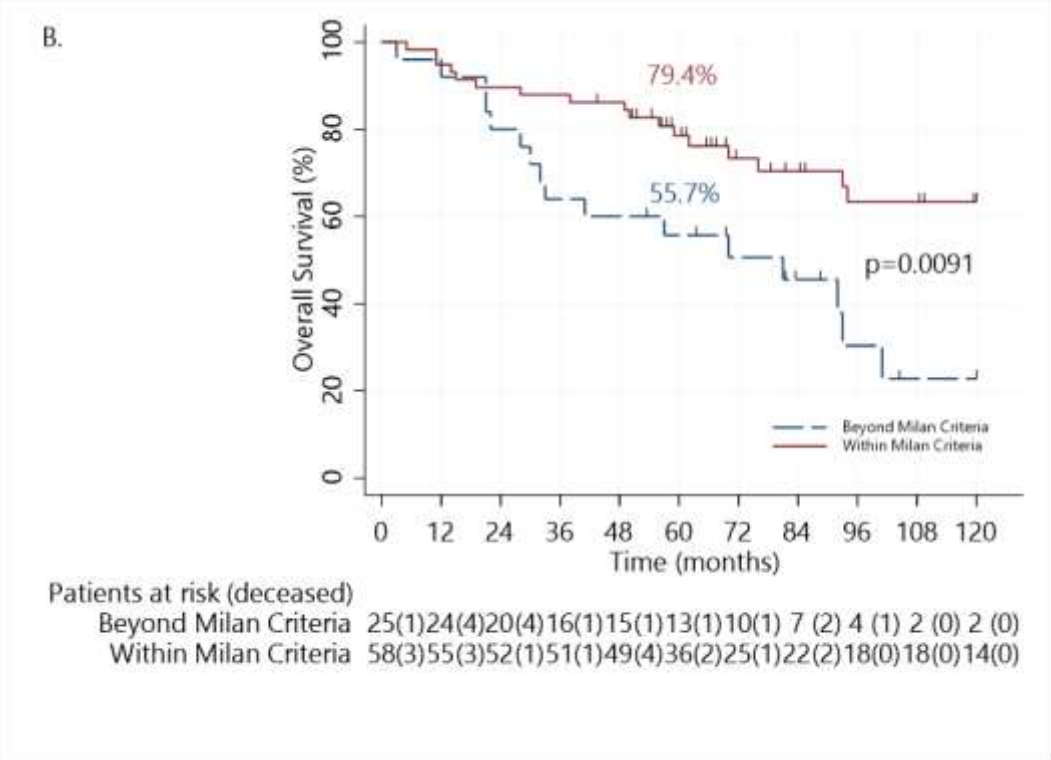


Figure 2. Kaplan-Meier Overall Survival estimation plot. **A**. Survival outcomes of cohort, overall survival rates at 3, 5, and 10 years. **B**. Comparison between patients Within Milan Criteria and Beyond Milan Criteria (5-year overall survival rates 79.4% vs. 55.7%, p=0.0091).

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