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RESEARCH ARTICLE

Unresectable Hepatoblastoma, Living Donation and Pre-Transplant Factors Associated with Event-Free Survival

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ABSTRACT

Background: The mainstays of irresectable hepatoblastoma (HB) treatment are surgical resection and cisplatin based (CB) chemotherapy (CHT). However, adequate patient selection is a key to achieve acceptable disease-free survival in patients with unresectable HB undergoing liver transplantation (LT).

Procedure: This single-center retrospective analysis of 28 children with HB submitted to LDLT from 1996 to 2019 aimed at determining the pre-transplant factors associated with worse post-transplant event-free survival. The clinical variables collected were gender, age, PELD score (Pediatric End-Stage Liver Disease scoring system), type of neoadjuvant CHT (CB versus other regimens), pre- and post- CHT AFP levels, %AFP reduction post CHT (AFP pre-CHT – AFP post- CHT /AFP pre- CHT), PRETEXT stage, primary versus rescue LDLT, time between diagnosis and LDLT, presence of metastases at diagnosis, follow-up time.

Results: Patients were divided in groups according to the occurrence of the event (recurrence/death) after LDLT – 10 patients in the event-yes and 18 patients in the event-no. Probability of 5-y event-free survival was 63.9%. AFP reduction $< 70\%$ (HR=4.33, 95%CI 1.1 to 16.95, p=0.03), and time from diagnosis to LT $\geq$ 12 months (HR=4.11, 95%CI 1.14 to 14.76, p=0.03) were associated with higher recurrence/death in the Cox regression analysis. Alpha-fetoprotein (AFP) reduction post-CHT $\geq 70\%$ had a good performance in determining disease-free survival, with a calculated AUC of 0.8.

Conclusion: LT for HB is the preferred treatment option for unresectable HB, with no distant metastasis and adequate response to CHT. AFP reduction $< 70\%$, and time from diagnosis to LT $\geq$ 12 months were associated with higher recurrence/death However, due to the limited number of patients in this study, a larger number of patients is required to corroborate these findings.

Keywords: liver transplantation, hepatoblastoma, children, outcomes, living donation.

ABBREVIATIONS

AFP	alpha-fetoprotein
AUC ROC	area under the receiver operating characteristic curve
HB	hepatoblastoma
LDLT	living donor liver transplantation
LT	liver transplantation
PELD	pediatric end-stage liver disease
SD	standard deviation
CHT	chemotherapy

INTRODUCTION

Hepatoblastoma (HB) is the most common primary hepatic neoplasm in children. The mainstays of irresectable HB treatment are surgical resection and cisplatin based (CB) chemotherapy (CHT). If the tumor is considered unresectable at diagnosis, neoadjuvant chemotherapy can make the lesion resectable in up to 80% of the patients [1]. For patients with PRETEXT III or IV that remain unresectable after neoadjuvant CHT, and do not present distant metastasis, liver transplantation (LT) is a treatment alternative. Current 10-year post-LT overall survival for unresectable HB is over 80% [2].

Although patients with HB receive exception points on the waiting list to compete with other children with end-stage liver disease for a liver graft, the timing to perform the LT is crucial for a better outcome. Usually, these patients have an optimal treatment window – after completion of the CHT – when the transplant can be performed. The importance of living donor liver transplantation (LDLT) in this context has been previously described [3, 4]. The majority of the reports on LDLT for HB are based on a limited number of cases, and most studies show recurrence rates from 20% to 37.5% [4-6].

It is well known that response to chemotherapy, manifested as either a decrease in tumor size or a significant decrease in alpha-fetoprotein (AFP) level, is an important prognostic factor for successful LT [7]. However, lengthy courses of preoperative chemotherapy while the tumor remains unresectable should be avoided due to diminishing effects on the tumor, combined with the substantial risk of inducing CHT resistance with the prolonged exposure [8].

The ideal scenario when treating patients with unresectable HB should include response to CHT and the availability of liver graft for transplantation. However, how far to push the transplant indication in patients with a marginal response to chemotherapy (but no distant metastasis) and with an available living donor? In the present study, the outcome of 28 patients who received LDLT is reported with emphasis in the factors associated with recurrence/death after transplantation.

METHODS

A total of 28 primary pediatric LDLT for HB were performed in patients under 18 years of age at Hospital Sírio-Libanês and A. C. Camargo Cancer Center, São Paulo, Brazil, from 1996 to 2019. The same medical team was responsible for the clinical and surgical transplantation procedures in both hospitals. All patients were referred to our center by different pediatric oncology centers in the country and had received pre-transplant chemotherapy regimen as determined by each center. In this retrospective study, data was acquired through review of medical records and from a prospectively collected database. Patients with HB who received deceased donor liver transplants (n=2) were not included in this study. The hospitals' ethics committee approved this study.

The clinical variables collected were gender, age, PELD score (Pediatric End-Stage Liver Disease scoring system), type of neoadjuvant CHT (CB versus other regimens), pre- and post- CHT AFP levels, %AFP reduction post CHT (AFP pre-CHT – AFP post- CHT /AFP pre- CHT), PRETEXT stage, primary versus rescue LDLT, time between diagnosis and LDLT, presence of metastases at diagnosis, follow-up time. These variables were used for determining the factors associated with event-free and overall survival in this cohort. An event was defined as HB recurrence or patient death, whichever came first. The patients were then divided in two groups: Event-No and Event-Yes.

Rescue transplant was defined as transplant after a previous liver resection for HB. Pulmonary metastasis at the time of diagnosis was not considered a contra-indication for transplantation as long as it was treated either with surgery or achieved complete remission after CTH. Vascular invasion was studied in liver explant analysis. It was classified as macrovascular invasion, which is grossly recognizable (mostly in large to medium vessels), or microvascular invasion (MVI), which can be identified only by microscopic observation (mainly in small vessels such as portal vein branches in portal tracts, central veins in noncancerous liver tissue, and venous vessels in the tumor capsule and/or noncapsular fibrous septa) (https://documents.cap.org/protocols/cp-pediatric-hepatoblast-resection-19-4000.pdf).

Post-operative care

Patients with platelet count >50,000/mm^3 were kept on dipyridamole (1 mg/kg/day) or aspirin (3 mg/kg) for 3 months after the transplant. Tacrolimus (FK 506, Prograf) and steroids were used for immunosuppression. Details

of post-operative clinical management have been previously described and were equal to the care provided for children transplanted for other reasons (metabolic diseases and cirrhosis) [9, 10].

Statistical analysis

Continuous variables were tested for normality with the Kolmogorov-Smirnov and Shapiro Wilk tests. The values are expressed either as mean ± standard deviation (SD) or median, and 25 and 75 percentiles. The categorical data are presented as absolute values and percentages and were tested using Pearson $\chi 2$ test and Fischer's Exact Test. The comparison between groups was performed using the Kruskal Wallis test or Pearson $\chi 2$ test and Fischer's Exact Test, as appropriate. Event-free survival and patient survival analysis was conducted according to the Kaplan-Meier product-limit estimates, and patient subgroups were compared using a two-sided log-rank test.

A Cox-Regression analysis was conducted to evaluate the association of each clinically or statistically significant ($p<0.1$) variable with the outcome (event-free survival).

The area under the receiver operating characteristic curve (AUC ROC) was the tool used to evaluate the association of AFP reduction with the outcome (event-free survival). Therefore, AUC ROC ranges from 0 to 1, with 1 corresponding to a perfect score. AUC ROC ≤ 0.7 are considered to have very little predictive ability. The level of statistical significance adopted was $P \leq 0.05$. All analyses were performed using the SPSS 21.0 statistical package (IBM, Inc., Chicago, IL, USA).

RESULTS

Twenty-eight patients underwent LDLT for HB during the study period. A total of 21 (75%) patients were classified as PRETEXT IV, 4 (14.3%) patients as PRETEXT III and 3 (10.7%) patients were rescue LT. All of them received pre-LT CHT: 13 (46.4%) received CB CHT, 10 (35.8%) received alternative regimens, and for 5 (17.8%) patients the CHT regimen was not informed. Eighteen patients were event-free, and were included in the Event-No group. A total of 10 patients experienced an event (recurrence or death), and were included in the Event-Yes group (Table 1).

Table 1. Differences of the studied variables between Event-No versus Event-Yes groups

Studied variables	Event-No (n=18)	Event-Yes (n=10)	P value
Age at diagnosis (mo), median (IQR)	15 (8.7 to 32.5)	15 (7.7 to 39.5)	0.88
Age at LT (mo), median (IQR)	27.7 (17.6 to 45.2)	29.6 (26 to 48.8)	0.38
Time from diagnosis to LT (mo), median (IQR)	7.5 (5 to 11)	13.5 (7.7 to 20)	0.11
Time from diagnosis to LT ≥12mo, n(%)	4 (22.2)	6 (60)	0.09
Weight at LT (kg), median (IQR)	11.6 (10.1 to 14)	12 (11.1 to 17.4)	0.42
PELD, median (IQR)	-3.5 (-8 to -2.7)	- 8 (-10 to -1.7)	0.38
PRETEXT, n(%)			0.38
III	2 (11.2)	2 (20)	
IV	15 (83.3)	6 (60)	
Rescue LT, n(%)	1 (5.5)	2 (20)	0.28
Lung Metastasis Pre CHT, n(%)	4 (22.2)	2 (20)	1
	N=15	N=8	
Type of PreLT CHT, n(%)			0.22
PLADO	10 (66.7)	3 (37.5)	
Other	5 (33.3)	5 (62.5)	
	N=18	N=10	
PostLT CHT, n(%)	15 (83.3)	10 (100)	0.28
AFP levels Pre CHT, median (IQR)	15684.5 (1099.7 to 104600.5)	3000 (836.7 to 210126.2)	0.48
AFP levels Post CHT, median (IQR)	2636 (107.9 to 12109)	15690.5 (2751.6 to 78516.5)	0.07
%AFP reduction Post CHT, n(%)			0.05
<70%	5 (27.8)	7 (70)	
≥70%	13 (72.2)	3 (30)	
Liver explant findings			
Vascular Invasion, n(%)			0.002
No	14 (77.8)	3 (30)	
Microvascular	3 (16.7)	3 (30)	

Macrovascular	1 (5.5)	4 (40)	

mo, months; IQR, interquartile range; LT, liver transplantation; CHT, chemotherapy.

Comparing the two groups, the statistically different pre-LDLT variables were: time from diagnosis to the LDLT ≥12 months (p=0.09), post- CHT AFP levels (p=0.07), and AFP post- CHT reduction ≥ 70% (p=0.05). The only statistically different post-LDLT variable among groups was the presence of vascular invasion in the explant analysis (p=0.002) (Table 1). Mean hospital stay was not different between groups. The median follow-up time in Event-Yes group was 3.8 months (2.3 to 6.6 months), and in the Event-No group it was 60.8 months (27.4 to 151.8 months). Ten patients, 4 in the Event-No and 6 in the Event-Yes were transplanted more than 12 months from diagnosis to LT due to logistic reasons related to timely referral to our transplant center.

Post-LDLT overall 5-y survival probability was 66% (Figure 1A) and 5-y event-free survival probability was 63.9% (Figure 1B). In those patients who achieved an AFP reduction post- CHT ≥ 70%, 5-y event-free survival was of 81.3% vs. 40% in those who did not (p=0.02) (Figure 2A). Patients in which the time from HB diagnosis to LDLT was ≥ 12 months had a 5-y event-free survival rate of 40% vs 77% for those who performed the LDLT in <12 months from the diagnosis (p=0.01; Figure 2B). Patients who received the pre-LDLT CB CHT (high-risk SIOPEL) had a 5-y event-free survival of 76.9% *versus* 50% for those who received other CHT regimens (p=0.14) (Figure 2C). The 5-y event-free survival in primary LDLT was 67.7% *versus* 33.3% for those who underwent rescue LT (p=0.04) (Figure 2D). In the liver explant analysis, the presence of vascular invasion also impacted in the 5-y event-free survival: no vascular invasion (82.4%) vs microvascular invasion (50%) vs macrovascular invasion (20%) (p=0.04).

Figure 1.

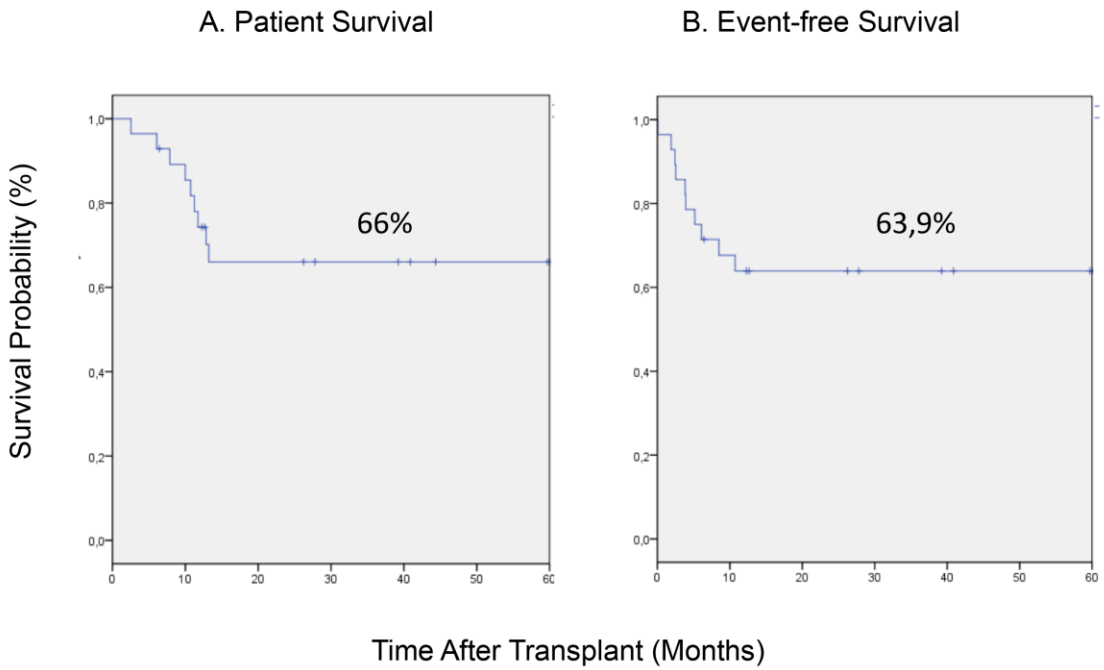

Figure 1: Kaplan-Meier product-limit estimates. Five-year patient survival probability (A), and 5-y event-free survival probability (B).

Figure 2.

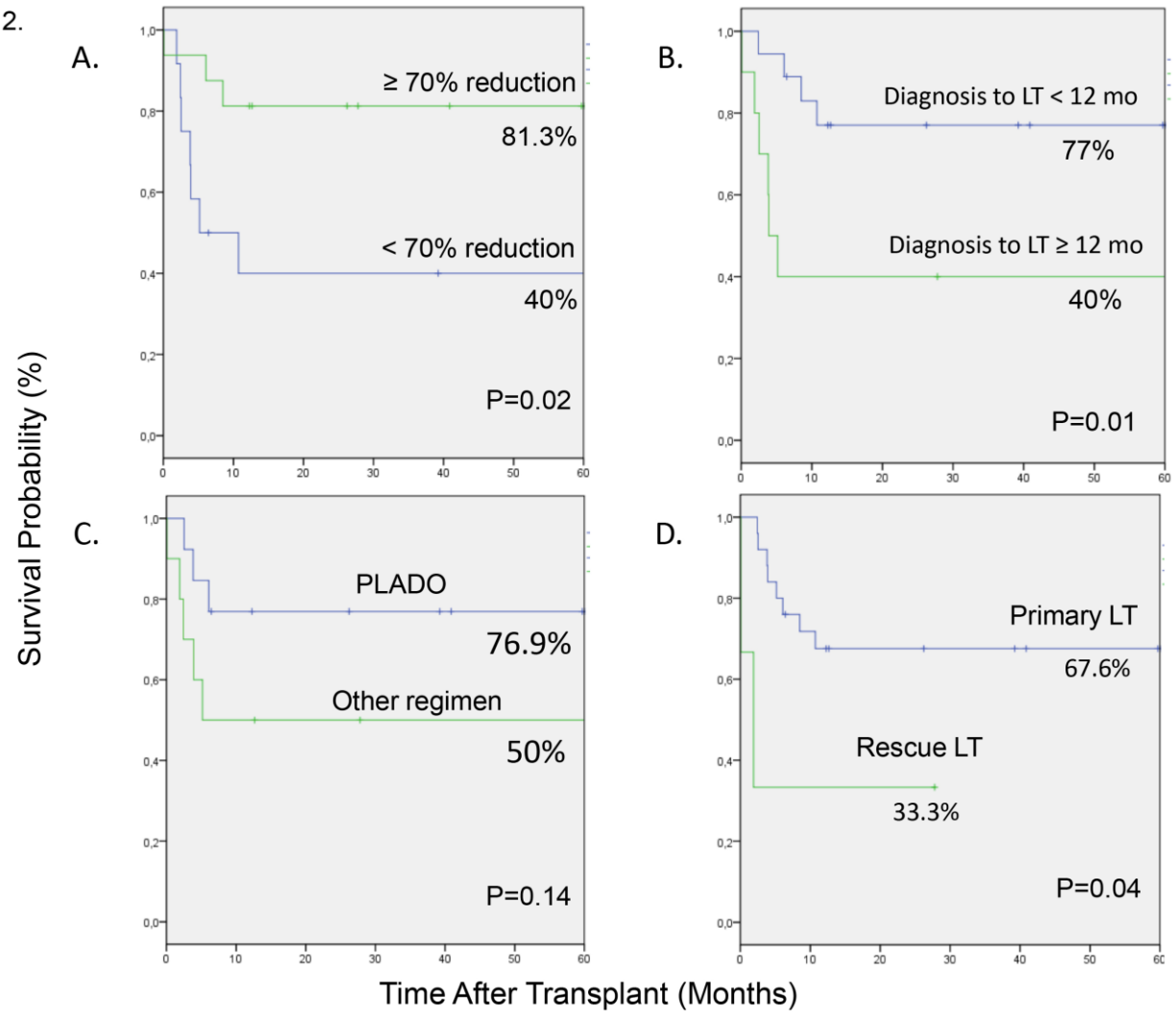

Figure 2: Kaplan-Meier product-limit estimates / 5-y event-free survival: (A) ≥ 70% reduction in AFP levels (81.3%) vs. < 70% reduction (40%), P=0.02, (B) Time from HB diagnosis to LDLT, t ≥ 12 mo. (40%) vs. t < 12 mo (77%), P=0.01, (C) PLADO CHT regimen (76.9%) vs. other CHT regimens (50%), P=0.14, (D) primary LDLT (67.7%) vs. rescue LT (33.3%), P=0.04.

The area under the receiver operating characteristic curve (AUC ROC), used to evaluate the performance of the test (AFP reduction ≥70%) with event-free survival showed a calculated AUC of 0.8 (Figure 3).

The pre-LDLT factors identified that were associated with the occurrence of the event (recurrence/death) underwent a Cox-Regression analysis. The calculated hazard-ratios (HR) for AFP reduction < 70% was HR=4.33, 95%CI 1.1 to 16.95 (p=0.03), and time from diagnosis to LDLT ≥ 12 months HR=4.11, 95%CI 1.14 to 14.76 (p=0.03). The only post-LDLD variable associated with Event-Yes was macrovascular vascular invasion (HR=5.66, 95% CI 1.25 to 25.49, p=0.02).

Figure 3.

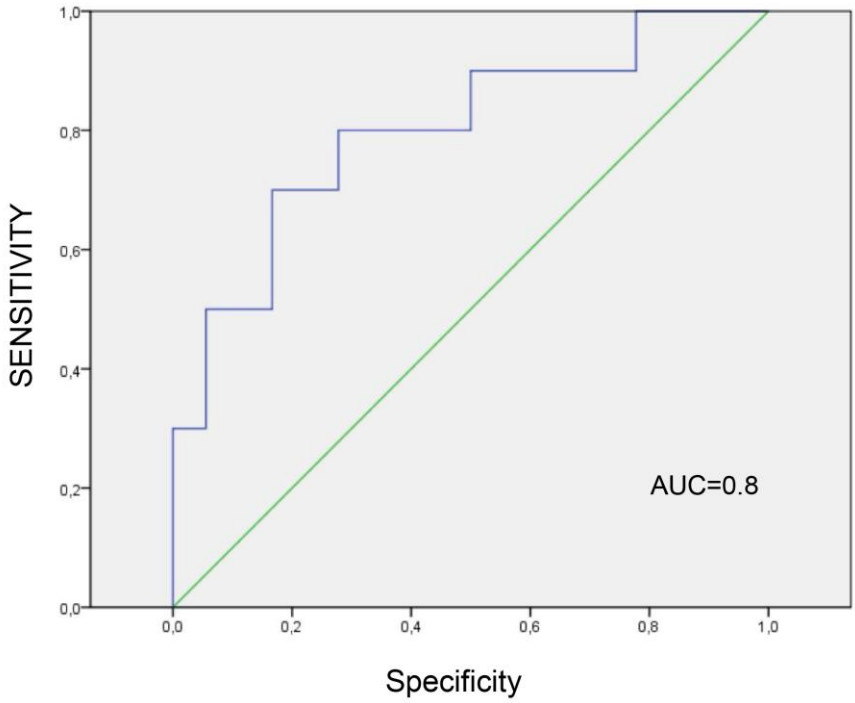

Figure 3: ROC curve analysis: performance AFP reduction ≥ 70% with Event-free survival. The calculated AUC was 0.8.

DISCUSSION

The outcome of patients with HB changed dramatically after the establishment of CHT protocols associated with liver resection, pioneered by the SIOPEL [11] and COG [12] study groups. The 10-y expected overall survival with primary LT was 85%, and 40% in patients who underwent LT as a "rescue therapy"[13] in the SIOPEL-1 study. After the initial studies, and others that followed, the absolute indication for LT, and the basis for considering a tumor unresectable after neoadjuvant CHT, is POST-TEXT IV or POST-TEXT III with major vascular tumor involvement [14, 15]. Five-year patient survival in the present report is similar to event-free survival, since recurrence meant fatality in almost all patients.

Determining the risk factors associated with patient survival is paramount to an improved selection of patients for LT, but efforts to identify such prognostic factors in the setting of a rare tumor have been hampered by extensive fragmentation resulting in relatively small patient cohorts [16]. In the report of the Children's Hepatic tumors International Collaboration (CHIC), advanced PRETEXT group, macrovascular venous or portal involvement, contiguous extrahepatic disease, primary tumor multifocality and tumor rupture at enrollment, higher age (>8 years), low AFP (<100 ng/ml), and metastatic disease were associated with the worst outcome; however, patients in all stages of HB were included.

Studies in children with HB undergoing LT, despite the limited number of patients enrolled in each cohort, seem to point to the same direction. Umeda et al. [6], in a retrospective analysis of 24 children with unresectable HB submitted to LT, showed that the response to CHT at LT, evaluated by the decline (>95%) in serum AFP levels, could predict post-LT relapse for patients receiving both primary and rescue LT. Browne et al. [17], in a cohort with 14 patients, demonstrated that a drop of 99% in peak AFP levels was associated with 100% survival following LT. Other authors also have correlated the trends in AFP levels [18] or pretransplant

AFP values with outcome [2, 19]. In our study, a drop ≥70% in AFP levels was associated with improved survival at 5-years (81.3% versus 40%). It showed that it is still safe to indicate LT for patients with a more modest, but still significant drop in AFP levels post- CHT. The ROC curve analysis (Figure 3) presented an AUC of 0.8, demonstrating a good performance/correlation between the studied variable and event-free (event-No group) outcome.

Salvage or rescue LT has been associated with tumor recurrence and worse patient survival since the SIOPEL-1 report [13]. Many other studies replicated those results [7, 17, 20-22], and the present study corroborates worst patient survival with rescue transplantation, where all primary tumors were assumed to be resected during the first operation, however, in the present manuscript the number of patients who received rescue LT is too limited. Time between diagnosis and LT $\geq$ 12 months was also associated with decreased patient survival (Figure 2b, 77% <12 mo. vs. 40% >12 mo., P=0.01). Indeed, lengthier CHT regimens are often required in high-risk subgroups, and are characterized by marked chemoresistance and poor outcome [23, 24].

The two **pre-operative** risk factors associated with increased risk of tumor recurrence/death (AFP reduction < 70%, and time from diagnosis to treatment ≥ 12 months) may be able to help families and physicians during the decision-making process, especially in the context of live donation. The advantage of timely LT must be weighted at all times against the risks of the surgical procedure in the living donor and the chances of cure of the children with unresectable HB. In our own experience, Candido et al. [25] reported a rate of post-operative complication of 4.8% (29/601) in left liver segment donors used in pediatric LDLT with no patient mortality; however, the estimated rate of donor death "definitely" related to donor surgery has been reported to be 0.15% [26].

Vascular invasion has been associated with increased risk of recurrence [27-29], and the explant analysis with presence of vascular invasion in the present study was also associated with recurrence/death [patient survival with no vascular invasion (82.4%) vs. microvascular invasion (50%) vs. macrovascular invasion (20%) (p=0.04)]. However, explant analysis is not adequate and helpful for pre-transplant decision making, but they may eventually guide the indication for adjuvant or extended post-transplant CHT.

The present report shows the experience of a transplant center. The majority of the patients were referred to us from different oncology groups in the country, after the pretransplant chemotherapy regimens had already been defined. Despite the limitation in sample size, one should keep in mind that the study was designed to determine the risk factors for recurrence in a rare disease scenario, over a relatively long period of time. Also, chemotherapy regimens have changed over the study period, even the one used in the CB group. The authors recognize these shortcomings but they are inherent of the retrospective nature of this series.

In conclusion, LDLT for HB is a treatment option for unresectable HB, with no distant metastasis and adequate response to CHT. The following pre-transplant factors - AFP reduction < 70%, time from diagnosis to LT $\geq$ 12 months - were associated with higher recurrence/death risk and should be critically evaluated and discussed with the patient's family and the multidisciplinary team in order to move forward with the LDLT in a timely fashion in order to avoid drug toxicity and chemoresistance. However, due to the limited number of patients enrolled in this study, a larger number of patients is required to corroborate these findings.

CONFLICTS OF INTEREST STATEMENT

There was no external funding for this work. The authors do not have any commercial or financial connections that would pose a conflict of interest to the findings of this manuscript.

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