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LIVER TRANSPLANTATION FOR PAEDIATRIC MALIGNANCIES

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Summary

Liver transplantation (LT) has become a fundamental therapeutic option for pediatric patients with unresectable liver malignancies, particularly hepatoblastoma (HB) and hepatocellular carcinoma (HCC). HB is the most common primary hepatic tumor in children and typically responds well to chemotherapy and surgical resection; however, a subset of tumors remains unresectable due to anatomical constraints or major vascular involvement. In such cases, LT represents the only curative treatment. In contrast, pediatric HCC is less frequent but presents significant clinical challenges, owing to its frequent association with underlying liver disease and its limited response to chemotherapy.

This article reviews current evidence regarding indications, prognostic factors, and outcomes of LT in pediatric liver cancers. It also reports the experience of the Pediatric Liver Transplant Center in Turin, which managed 21 cases of HB and 6 cases of HCC. The outcomes observed are consistent with published survival data and underscore the importance of timely referral, multidisciplinary assessment, and rigorous patient selection.

In addition, a brief review of rare oncologic indications for LT in children – such as giant hemangioma, cholangiocarcinoma, and inflammatory myofibroblastic tumor – is included to highlight less common but clinically significant scenarios. The article concludes with a case report that exemplifies the complexity and individualized nature of pediatric liver transplantation, emphasizing its unique challenges and therapeutic potential.

Key words: pediatric transplantation, pediatric oncology, hepatoblastoma, hepatocarcinoma

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INTRODUCTION

Liver transplantation (LT) represents a cornerstone in the management of pediatric liver malignancies, especially in cases of hepatoblastoma (HB) and hepatocellular carcinoma (HCC) that are not amenable to curative surgical resection. HB, the most common primary hepatic malignancy in children, accounts for approximately 79% of pediatric liver tumors [1]. With incidence rates ranging from 0.5 to 1.5 cases per million children annually, and a higher

prevalence in males, HB is typically diagnosed in children under 3 years of age [2,3]. In contrast, pediatric HCC remains rare but carries a poorer prognosis due to underlying cirrhosis and chemoresistance [4].

Complete surgical resection remains the mainstay of curative therapy. However, due to anatomical constraints or tumor burden – particularly in centrally located tumors or those involving major vasculature – only 60%-80% of HB cases are resectable after neoadjuvant chemotherapy. LT becomes the only curative option for unresectable disease. Data from the SPLIT registry show that HB patients who underwent LT had a 10-year overall survival (OS) of 85.5%, compared to 41.7% for pediatric HCC, underscoring the therapeutic effectiveness of LT in HB [5]. Additionally, the International Society of Pediatric Oncology (SIOP) has outlined criteria – such as PRETEXT III/IV stage with vascular involvement (V+/P+), multifocality, or recurrence post-resection – as strong indications for LT [6].

Several prognostic indicators have emerged from retrospective and registry analyses. Elevated pre-transplant alpha-fetoprotein (AFP) levels above 13,686 ng/mL, presence of metastatic disease at diagnosis, and vascular invasion have been linked to increased risk of recurrence and mortality [7,8]. In a single-center series by Okur et al. [9], involving 10 HB patients undergoing LT, the 90% survival rate at a median of 32 months was tempered by the occurrence of post-transplant lung metastasis in one case. Vascular invasion was present in 30% of patients and correlated with poorer outcomes. AFP levels, which ranged from 20 to 484,000 ng/mL pre-transplant, dropped significantly post-LT and were confirmed as a reliable marker for post-operative surveillance. Data from Wu et al. [10] using the SRTR database further illustrate systemic barriers in transplant access. Among 122 children listed for LT due to HB, 11% died on the waitlist and another 13% were delisted due to clinical deterioration. Those who received MELD/PELD exception scores were significantly more likely to be transplanted (HR = 2.37; p = 0.008), and early transplantation within 90 days from diagnosis and the use of mTOR inhibitors were associated with better long-term survival (5-year OS = 84%). In addition, Kastenberg et al. [11] emphasized critical elements in surgical planning, including the use of PRETEXT/POST-TEXT staging, multidisciplinary tumor boards, and intraoperative guidance tools like ICG-NIR imaging. Their review highlights that resectability decisions must consider not only tumor location but also potential for margin-negative resection and residual liver volume. LDLT plays an increasingly prominent role, particularly in countries with limited access to deceased donor organs. HCC in pediatric patients presents additional challenges. A study by Özçay et al. [12] analyzing 14 children with HCC undergoing LT reported a 10-year OS of 83%, though recurrence-free survival was 72.2%. HCC is less responsive to chemotherapy, and current outcomes remain inferior to those for HB, demanding careful patient selection and long-term follow-up strategies. Overall, evidence from multicenter registries and single-center studies consistently supports the efficacy of LT in appropriately selected pediatric patients with HB and, to a lesser extent, HCC. Outcomes have significantly improved over the last decades, due in part to standardized staging systems, aggressive chemotherapy regimens, early transplant evaluation, and advances in surgical technique. Future directions should focus on optimizing timing for LT, refining indications in the context of tumor biology, and integrating biomarkers such as AFP into routine post-transplant surveillance.In the field of pediatric oncologic transplantation, we present the experience of the Pediatric Liver Transplant Center in Turin, which includes six transplants for hepatocellular carcinoma (HCC) in pediatric patients and twenty-one cases of hepatoblastoma.

PAEDIATRIC HCC

In the setting of pediatric liver transplantation for hepatocellular carcinoma (HCC), the Pediatric Liver Transplant Center in Turin has documented its experience with a cohort of six patients. The median age at diagnosis was 94 months, and the cohort included an equal number of male and female patients (three each), indicating no apparent gender predominance. All six patients had pre-existing underlying liver disease, which is a known risk factor for HCC in the pediatric population. At the time of diagnosis, tumor staging using the PRETEXT system revealed that five patients were classified as stage I, and one patient as stage II, suggesting that most tumors were localized without extensive intrahepatic spread.

Vascular involvement was limited in this series: portal vein invasion was observed in one case, while no patients demonstrated hepatic vein or inferior vena cava invasion. Importantly, none of the patients had pulmonary metastases at presentation, reflecting a potentially favorable disease profile. In terms of tumor burden, five patients had a solitary tumor focus, while one presented with three distinct foci. Tumor biopsy was performed in all cases prior to transplantation, and no cases of spontaneous or treatment-related tumor rupture were reported. Surgical resection margins were microscopically negative in all patients, indicating complete excision of the tumor tissue at the time of transplantation.

Neoadjuvant chemotherapy was not administered in any of the cases, nor was post-operative adjuvant chemotherapy employed. Additionally, none of the transplants were classified as "rescue" procedures following recurrence or incomplete resection. At the time of liver transplantation, histopathologic analysis revealed lymph node

involvement in one patient, while the remaining five had no lymph node metastases. Pulmonary metastases did not require surgical resection or clearance in any patient, either before or after the transplant procedure.
Post-transplant outcomes were notably positive. The average duration of follow-up was 101.5 months, equating to over eight years, allowing for a robust assessment of long-term outcomes. At the conclusion of the follow-up period, five out of the six patients were alive and free from disease recurrence, underscoring the potential effectiveness of liver transplantation as a curative strategy in selected pediatric patients with HCC. This series highlights the importance of careful patient selection, early-stage diagnosis, and complete tumor resection in achieving favorable long-term survival in this high-risk population.
Data from our experience on pediatric HCC are summarized in Table I.

HEPATOBLASTOMA

Among the pediatric liver transplant recipients managed at the Turin center, 21 patients underwent liver transplantation for hepatoblastoma. The mean age at transplantation was approximately 3 years, consistent with the typical presentation of this tumor in early childhood. Survival outcomes in this group were favorable, with 17 of 21 patients (81%) alive at the time of follow-up. Three patients were deceased, while survival data was unavailable for one case.
Regarding transplant procedures, graft type was recorded in nearly all cases, with the majority receiving split left lobe grafts (n = 10) or whole liver grafts (n = 7) (Fig. 1). One patient each received a living donor liver transplant (LDLT), a reduced-size graft, and a split right lobe graft.
Postoperative complications were relatively limited: acute rejection occurred in four patients, while no patients required surgical re-intervention (reoperation). However, two patients experienced an open abdomen in the postoperative course, likely due to abdominal compartment syndrome or technical factors.
Two transplants were performed as 'rescue' procedures following recurrence after previous hepatic resection.
Four patients developed pulmonary metastases after transplantation. Two underwent thoracic surgery, one received only adjuvant chemotherapy, while one young patient died with both pulmonary and hepatic recurrence
The average length of stay in the intensive care unit was approximately 3 days, and the overall average hospital stay was 11.25 days, reflecting a relatively rapid post-transplant recovery in most cases. These findings highlight not only the feasibility but also the favorable outcomes of liver transplantation for children with hepatoblastoma when performed in experienced centers. The low incidence of major complications and relatively short recovery times further reinforce the role of transplantation as a definitive and potentially curative treatment option for this pediatric malignancy.

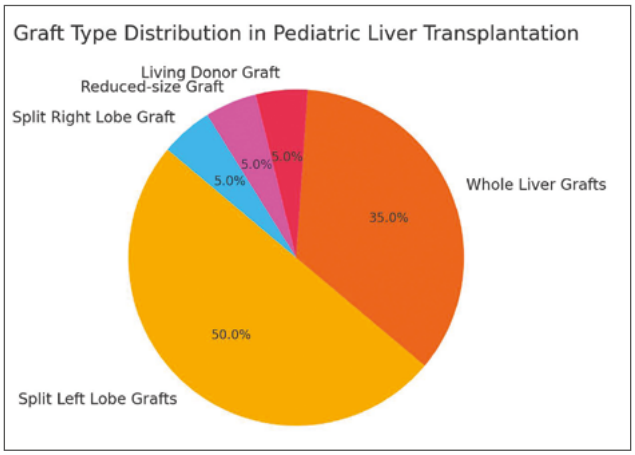


Figure 1. Graft type distribution in paediatric liver transplantation for hepatoblastoma.

RARE ONCOLOGICAL DISEASE AND PAEDIATRIC LIVER TRANSPLANTATION

In addition to the classical indications for pediatric liver transplantation in oncologic diseases – such as hepatocellular carcinoma and, more commonly, hepatoblastoma – the literature describes a limited number of case series and case reports documenting transplants performed for rare oncologic conditions. These cases may involve indications that are more typical in adults but are exceptionally rare in children, such as cholangiocarcinoma or giant hemangioma, as well as entities that are uncommon even in adult populations, such as inflammatory myofibroblastic tumors. The rarity of these indications significantly complicates the diagnostic and therapeutic pathway in pediatric patients, as they often fall outside standardized protocols and established clinical guidelines, posing a considerable challenge for specialists working in this field.
In an interesting study, Kaliciński et al. emphasize the role of liver transplantation as a vital therapeutic option for children with unresectable hepatic tumors, including rare cases of benign giant hemangiomas. These vascular tumors, when involving the entire liver and accompanied by massive arteriovenous shunting, can rapidly lead to circulatory collapse and multiorgan failure in neonates and infants. The authors describe three such critically ill infants who failed to respond to conventional treatments – such as corticosteroids, cyclophosphamide, transarterial embolization, and hepatic artery ligation – and subsequently underwent urgent liver

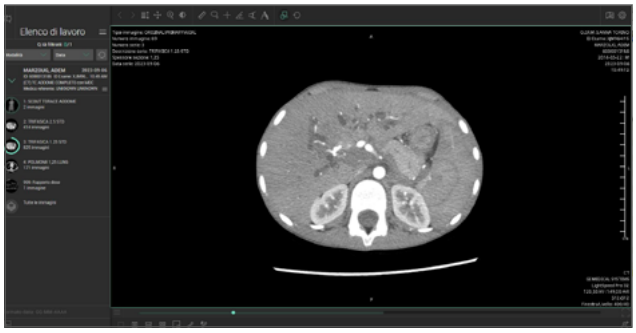


Figure 2. CT scan at diagnosis.



Figure 3. Percutaneous cholangiography demonstrates separation of the biliary systems.

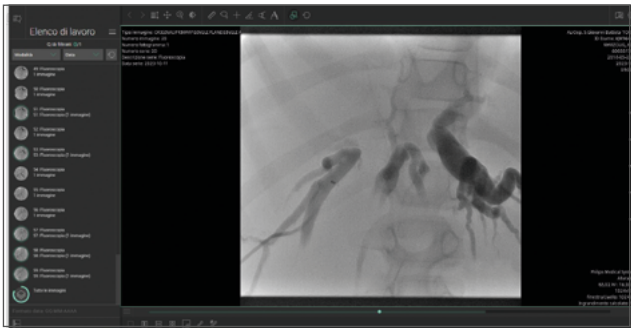


Figure 4. embolization of the branch of the hepatic artery feeding the tumor.

transplantation. All three survived and remained clinically stable, supporting the notion that transplantation can be life-saving when other therapies are insufficient. Literature reports indicate high mortality among similar patients without access to transplant intervention, making this approach particularly valuable in such extreme presentations [13-15]. The authors also note that, in their broader clinical experience, almost 30 infants with clinically significant hepatic hemangiomas were managed successfully, with transplantation reserved for only the most severe cases [16]. These findings argue for a broadened consideration of liver transplantation even in benign tumors, when aggressive vascular features cause systemic decompensation unresponsive to standard medical or interventional therapy [17,18].

One of the most challenging areas in pediatric transplantation for oncologic disease is undoubtedly represented by the rare cases of cholangiocarcinoma.

Although cholangiocarcinoma remains a rare indication for liver transplantation in pediatric patients, recent findings underscore the need for early recognition and timely intervention in children with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD). In the cohort analyzed by Kaj-Carbaidwala et al., 21 pediatric-onset PSC-IBD patients developed cholangiocarcinoma, with nearly 40% of cases emerging within just two years of the second diagnosis-either PSC or IBD-and 50% occurring during the critical transition from pediatric to adult care, between ages 14 and 25. This narrow window not only highlights the aggressive nature of the disease in this subset but also stresses the importance of establishing effective surveillance protocols that extend beyond childhood and into early adulthood. While transplantation was not directly addressed in this study, the short latency period and young age at diagnosis in many cases support the rationale for considering liver transplantation early in the disease course, particularly when curative resection is not feasible. Given the high mortality associated with cholangiocarcinoma and the challenges in managing it once advanced, the integration of liver transplantation as a therapeutic strategy for select pediatric PSC-IBD patients with localized cholangiocarcinoma may be

Table I. HCC patients in Torino.

Patient No	Age (mo)	Gender	Liver disease	Pretext	PV Inv.	HV/IVC Inv.	Pulm. Mets	Umor Foci	Rup
1.0	100	F	1	I	0	0	0	1	
2.0	12	F	1	I	0	0	0	1	
3.0	156	M	1	I	0	0	0	1	
4.0	82	F	1	I	0	0	0	1	
5.0	120	M	1	II	1	0	0	3	
6.0	94	M	1	I	0	0	0	1	

warranted and should be explored further in prospective trials [19-21]. Moreover, these findings emphasize the need for consistent multidisciplinary surveillance in pediatric patients with PSC-IBD, particularly during the transitional care phase, to enable timely detection and referral for potentially curative treatments, including transplantation [22-24].

Finally, an exceptionally rare but particularly challenging condition to manage is represented by inflammatory myofibroblastic tumors, which exhibit a highly peculiar biological behavior.

Although inflammatory myofibroblastic tumor (IMT) is a rare pediatric soft tissue neoplasm, hepatic presentations in infants represent an especially challenging subgroup due to diagnostic complexity and treatment considerations. In the systematic review by Raitio and Losty, abdominal and pelvic IMTs accounted for the majority of cases (58%), and among these, hepatic involvement – while not always explicitly isolated – emerges as a clinically relevant site due to the tumor's potential for local invasion and recurrence [25]. Infantile IMTs, particularly those involving the liver, demand a tailored approach, as surgical resection may be technically difficult and carries increased risk in this age group [26]. Nevertheless, complete surgical resection (R0) remains the cornerstone of treatment, with positive margins being strongly associated with recurrence and mortality ($p < 0.0001$) [25]. Despite IMT's often indolent behavior, approximately 6% of patients in the review died of disease, reinforcing the potential severity of hepatic and abdominal presentations in early life [25,27]. Moreover, the literature indicates that even in cases where systemic therapy is required, ALK-targeted treatments may offer benefit in ALK-positive tumors [28], although ALK status was not consistently predictive of outcome in this cohort [25]. Case reports have also described rare hepatic IMTs with ETV6::NTRK3 fusions, expanding the potential for molecularly guided therapy in difficult cases [29]. Given the potential for recurrence and the need for reoperation in up to 20% of patients, close postoperative surveillance is particularly warranted in infants with hepatic IMT [25,30]. These findings underscore the necessity for early, aggressive – but balanced – intervention in infantile hepatic IMT, ideally managed within experienced multidisciplinary centers.

A PROOF OF CONCEPT: PEDIATRIC TRANSPLANTATION FOR ONCOLOGIC DISEASES AS A DISTINCT ENTITY WITHIN THE FIELD OF TRANSPLANT MEDICINE

As widely recognized in the field of transplantation, pediatric liver transplantation is fundamentally distinct from adult transplantation. Each pediatric patient presents with unique clinical characteristics, and the indications for transplant in children differ markedly from those in adult transplant protocols. Furthermore, pediatric transplantation may involve exceptional and rare clinical scenarios not commonly encountered in larger adult cohorts described in the literature – as demonstrated in the case presented below.

We report the case of a 9-year-old child who presented to our Emergency Department after having been diagnosed in a non-European country of origin with a centrohepatic liver lesion detected on abdominal ultrasound, performed in the setting of jaundice.

Upon arrival, the patient was in poor general condition, asthenic, and had reduced oral intake. A repeat abdominal ultrasound confirmed the presence of the hepatic mass, which was further evaluated by a CT scan (Fig. 2) showing a lesion approximately 3 × 3 cm in size, with infiltration of the portal vein, presence of a portal cavernoma, and significant collateral circulation.

A biopsy of the lesion was performed, which revealed an **inflammatory myofibroblastic tumor** (IMT).

To palliate obstructive jaundice, the patient underwent a percutaneous cholangiography with placement of three internal-external biliary drains, due to the complete separation of the biliary systems (Fig. 3).

Once serum bilirubin levels decreased to 4 mg/dL, systemic chemotherapy with **vinblastine and methotrexate** was initiated following a multidisciplinary team discussion. After four cycles, a re-staging CT scan showed substantial disease stability. A new collegial discussion recommended continuing chemotherapy for an additional four cycles, with a subsequent re-staging. In the event of further

ture	Biopsy	Margins resection	LN + at LT	Rescue LT	NeoCHT	AdjCHT	Alive	Disease-free	Follow-up (mo)
0	1	1	0	0	0	0	1	1.0	24
0	1	1	0	0	0	0	1	1.0	58
0	1	1	0	0	0	0	1	1.0	276
0	1	1	0	0	0	0	1	1.0	23
0	1	1	1	0	0	0	0	nan	120
0	1	1	0	0	0	0	1	1.0	108

stability or partial response, the patient would be eligible for listing for liver transplantation.
However, after only two additional cycles, the patient returned to the Emergency Department due to **haemobilia and hematemesis**. An urgent CT scan showed no evidence of active bleeding and confirmed stable disease. The patient was admitted for observation. In the following hours, bleeding recurred with hemodynamic compromise, requiring an **arteriographic embolization** of the branch of the hepatic artery feeding the tumor (Fig. 4).
The patient was therefore listed in the national pediatric liver transplant program with **Status 1B**.
Approximately 72 hours after listing, a whole liver from a 40-year-old donor became available, and liver transplantation was successfully performed.
The **postoperative course was uneventful**. At the time of writing, follow-up is approximately 18 months: the child is alive and **disease-free**. In agreement with the oncology team, **no adjuvant chemotherapy** was administered post-transplant, and the patient remains under active surveillance. **Immunosuppression is currently managed with tacrolimus**, which is being gradually minimized.

CONCLUSIONS

Pediatric liver transplantation for the treatment of childhood oncologic diseases is now a well-established indication, with solid outcomes in terms of both survival and post-transplant quality of life**.**
The case report presented here serves as an example of how unusual and complex scenarios may arise in the clinical practice of pediatric transplant surgeons, highlighting the essential role of a multidisciplinary approach in ensuring the best possible outcomes for these patientsRecent literature suggests that liver transplantation (LT) may be a viable and effective treatment option for hilar inflammatory myofibroblastic tumors (IMTs) when complete surgical resection is unfeasible due to local invasion of critical vascular and biliary structures. In their report, Costa et al. presented the case of a 3-year-old boy with a large hilar IMT invading both the portal vein and the inferior vena cava (IVC), who successfully underwent living donor liver transplantation (LDLT) with vascular reconstruction using cadaveric iliac vein grafts for both vessels. The procedure was technically complex, yet resulted in complete tumor resection with free margins and an uneventful long-term follow-up at three years, without recurrence or graft-related complications [31].
This case is particularly relevant because it represents the **first reported pediatric LDLT** for a hilar IMT with IVC replacement using a deceased donor venous graft, a strategy previously described only in the context of advanced hepatoblastoma [32,33]. In the broader review of pediatric cases, only 11 instances of hilar IMT have been documented, and among these, just two involved IVC invasion [14]. Notably, 42% of transplant cases reported for hepatic IMT were performed as **rescue transplantations** following failed resections or postoperative complications, further emphasizing the importance of LT as both a primary and salvage option in selected patients [34].
Given the uncertain response of IMTs to chemotherapy and the absence of standardized treatment guidelines, surgical resection remains the mainstay of curative intent therapy when feasible [35]. However, in cases involving complex vascular invasion or anatomically critical locations such as the hepatic hilum, transplantation – particularly LDLT when deceased donor options are limited – should be considered as a definitive approach, provided that complete resection can be achieved [36].
As for the classical transplant indications for hepatocellular carcinoma and hepatoblastoma, the existing literature consistently confirms excellent outcomes in terms of both survival and post-transplant quality of life. However, the management of immunosuppression remains a critical issue, particularly in light of its potential oncologic risks.
A recent single-center retrospective study evaluated the safety and efficacy of converting from tacrolimus (TAC) to sirolimus (SRL) in pediatric liver transplant recipients who had undergone transplantation for unresectable hepatoblastoma (HB) after cisplatin-based chemotherapy. The authors observed that early conversion (within the first year post-transplant) to SRL led to a statistically significant improvement in measured glomerular filtration rate (mGFR) in 5 of 6 patients, without any notable adverse effects or HB recurrences during a follow-up of up to 6 years (37). While half of the patients experienced biopsy-proven acute rejection (BPAR), all episodes responded effectively to steroid therapy. These results were comparable to a control group of non-HB pediatric liver transplant recipients maintained on TAC, suggesting no increased rejection risk due to SRL [38]. The potential nephroprotective and antiproliferative effects of SRL make it a promising alternative in this setting, particularly for patients at risk of renal dysfunction from TAC and prior chemotherapy exposure [39]. Moreover, no cases of dyslipidemia, infections, or other SRL-related adverse effects were reported, reinforcing the safety profile observed in previous pediatric transplant experiences with mTOR inhibitors [40]. Although limited by its small cohort and retrospective design, this study adds to the emerging evidence supporting SRL conversion as a viable immunosuppressive strategy in selected pediatric liver transplant populations [41].
Finally, an additional topic that has recently gained attention in the literature is that of infectious complications in pediatric patients undergoing liver transplantation for oncologic diseases.

The SIOPEL group investigated infectious complications following liver transplantation (LT) in a multicenter cohort of pediatric patients with hepatoblastoma (HB), analyzing data from 102 transplanted children. The study found that **47% of patients experienced at least one infectious episode** within the first year post-transplant, with bacterial infections being the most frequent (37%), followed by viral (16%) and fungal (3%) infections [23]. Bloodstream infections and surgical site infections were the most common bacterial presentations. Importantly, the presence of infection did not significantly impact overall survival, which remained high at 84% at 5 years, consistent with outcomes reported in broader LT series for HB [42].

The analysis also highlighted several risk factors for infection, including **extended perioperative antibiotic use,** need for **reoperation**, and prolonged hospital stay. Interestingly, patients transplanted earlier (within 4 weeks of completing chemotherapy) did not have a higher infection risk, suggesting that prompt transplantation – even with recent chemotherapy – is not contraindicated [43]. These findings support the feasibility and safety of performing LT soon after neoadjuvant treatment, when tumor control is optimal, without significantly increasing the burden of infectious complications [44].

This study represents one of the largest dedicated analyses of infectious risks in pediatric HB transplant recipients and reinforces the need for optimized perioperative protocols and early recognition strategies to minimize morbidity while maintaining excellent oncologic outcomes [44].

Pediatric liver transplantation for oncologic indications is now a well-established therapeutic option, with satisfactory survival outcomes. However, the extreme variability in the clinical presentation of pediatric oncologic diseases, combined with the technical complexity of transplantation and the subsequent management of immunological complications and immunosuppressive therapy, continues to represent one of the greatest challenges in this field.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

DC, RR: conceptualization and programming of the study, data collection, and manuscript preparation.

All other authors: critical revision of the manuscript and contribution to the literature review.

Ethical consideration

The research was conducted ethically, with all study pro- cedures being performed in accordance with the require- ments of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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