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Management and outcome of hepatic artery thrombosis after pediatric liver transplantation

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Abstract

Background: Pediatric LT are at particular risk of HAT, and its management still constitutes a matter of debate. Our purpose was to study predisposing factors and outcome of HAT post-LT, including the impact of surgical revisions on survival and biliary complications.

Methods: Among 882 primary pediatric LT performed between 1993 and 2015, 36 HAT were encountered (4.1%, 35 fully documented). Each HAT case was retrospectively paired with a LT recipient without HAT, according to diagnosis, age at LT, type of graft, and era.

Results: Five-year patient survivals were 77.0% versus 83.9% in HAT and non-HAT paired groups, respectively ($P = .321$). Corresponding graft survivals were 20.0% versus 80.5% ($P < .001$), and retransplantation rates 77.7% versus 10.7%, respectively ($P < .001$). One-year biliary complication-free survivals were 16.6% versus 83.8% in the HAT and non-HAT groups, respectively ($P < .001$). Regarding chronology of surgical re-exploration, only HAT cases that occurred within 14 days post-LT were re-operated, fourteen of them being explored within 7 days post-LT (revascularization rate: 6/14), versus two beyond 7 days (no revascularization). When revascularization was achieved, graft and biliary complication-free survival rates at 1 year were 33.3% and 22.2%, respectively, both rates being 0.0% in case of failure.

Conclusions: The pejorative prognosis associated with HAT in terms of graft survival is confirmed, whereas patient survival could be preserved through retransplantation. Results suggest that HAT should be re-operated if occurring within 7 days post-LT, but not beyond.

KEYWORDS

hepatic artery thrombosis, management, pediatric liver transplantation, surgical complication

Abbreviations: BA, biliary atresia; DD, deceased donor; HA, hepatic artery; HAT, hepatic artery thrombosis; IR, interventional radiology; LD, living donor; LT, liver transplantation; US, ultrasonography.

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1 | INTRODUCTION

Whereas the arterial flow only contributes for an average of 20% of the total hepatic blood flow, HAT constitutes a catastrophic event, particularly after LT.[1,2] In the peculiar context of LT in infants and small children, the technical challenge of performing a small size arterial anastomosis contributes to an increase in the risk of artery thrombosis, with HAT incidences greatly varying from center to center, between 1% and 26%.[3-5] The adverse consequences of HAT after LT range from acute graft necrosis and need for emergency retransplantation, to an asymptomatic course and satisfactory middle-term outcome.[6] Considering the prominent arterial vascularization of the allograft bile ducts, HAT may also result in extra- or intrahepatic bile duct necrosis leading to secondary biliary strictures, cholestasis, and sepsis.[7,8] Accordingly, the management of HAT occurring post-LT has depended on the individual center experience and may consist in either surgical or radiological attempt of arterial revascularization, or early retransplantation, or even conservative treatment, according to the variable impact of HAT on liver function.[9-12] However, the respective role of these therapeutic modalities still constitutes a matter of debate in the field of pediatric LT whether it be from DD or LD.

In this work, we hypothesized that (a) when compared to non-HAT cases, pediatric LT recipients with HAT are at risk of increased mortality, decreased graft survival, and increased retransplantation and biliary complication rates; (b) early HAT (occurring within 14 days post-LT) may be associated with a higher incidence of complications and worse outcome, when compared to late HAT (after 14 days post-LT); (c) the interval between LT and surgical attempt of arterial liver revascularization has an impact on the rate of successful HAT reversal, the earlier the surgical redo the higher the proportion of children with restoration of the graft arterial flow; and (d) when the arterial revascularization can be obtained at the time of surgical re-exploration, pediatric LT recipients present fewer late complications.

2 | PATIENTS AND METHODS

2.1 | Study population

The medical records of 1000 consecutive pediatric LT (recipients less than 20-year-old) transplanted between March 1, 1984, and March 18, 2015, at Cliniques universitaires Saint-Luc, Brussels, Belgium, were retrospectively reviewed. Among these transplants, the study particularly considered the 882 primary grafts (443 boys and 439 girls; median age: 1.9 years; range: 0.1-19.9 years), 118 retransplantation cases being excluded from the present analysis. Minimal post-LT follow-up was one year. Data collected retrospectively included demographic variables, surgical type of graft, and occurrence/chronology of HAT after LT among all 882 primary recipients. The hepatic transplantation was performed with a LD in 336 patients (38.1%), a DD whole-size liver graft in 243 patients (27.5%), a DD reduced-size liver graft in 236 patients (26.8%), and a DD split liver graft in 67 patients (7.6%). Pretransplant diagnoses were biliary atresia (BA, n = 542:61.5%), cholestatic diseases (n = 113:12.8%), metabolic diseases (n = 94:10.7%), liver malignancy (n = 51:5.8%), fulminant hepatitis (n = 36:4.0%), and other diagnoses in the remaining cases (n = 46:5.2%). As shown in Figure 1, more than half of the recipients (n = 458:51.9%) were under 2 years old at the time of transplantation.

2.2 | Surgical techniques, immunosuppressive protocol, and post-transplant follow-up

The medical management and surgical techniques for LT were thoroughly described in previous publications from our center.[13-16] The immunosuppressive therapy varied along the eras, as similarly documented.[17,18] About the division into transplant eras, the following major events are to be retained: (a) The first era (1984-1988) corresponds to the period during which the reduced liver

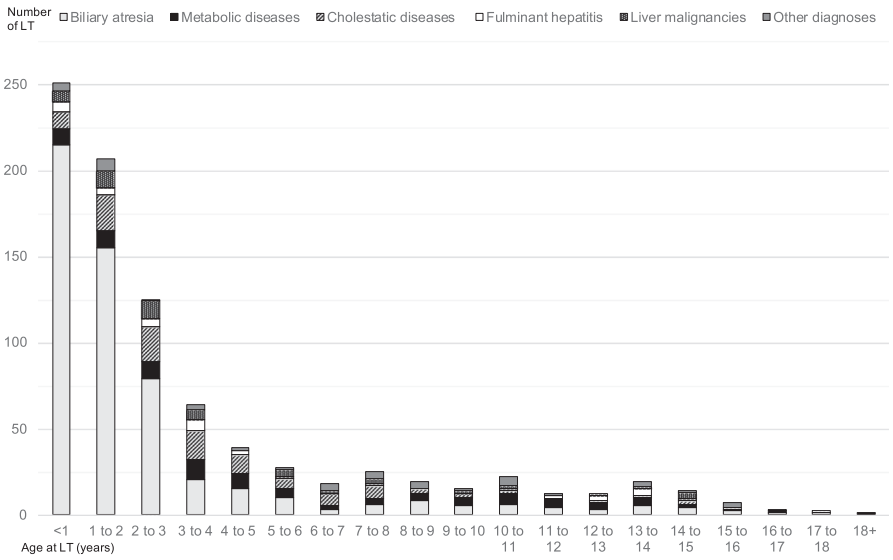


FIGURE 1 Histogram describing the number of liver transplantations (LT) and respective preoperative diagnoses according to age at transplant in the series of 882 pediatric patients who underwent primary LT at Cliniques universitaires Saint-Luc, Brussels, Belgium, between March 1, 1984, and March 18, 2015

and split liver techniques were gradually introduced; (b) during the second era (1989-1992), there were no major modifications; (c) in the third era (1993-1999), the year 1993 corresponds to the introduction of LD-LT in the pediatric LT program at Cliniques universitaires Saint-Luc, Brussels; (d) for the fourth era (2000-2006), the immunosuppressive therapy with tacrolimus steroid-free immunosuppression was introduced in 2000; (e) during the fifth era (2007-2010), new techniques for hepatic artery and portal vein reconstructions including portoplasty were developed; and (6) in the sixth era (2011-2015), the ABO incompatibility LT program was reactivate during pretransplant plasma exchange in the recipient. Regarding post-LT medical prophylaxis of vascular thrombosis, oral acetylsalicylic acid at a dosage of 3 mg/kg/day (Aspegic; Sanofi, Diegem, Belgium) was prescribed until week 6 post-LT, as soon as platelet count reached 100.000/microliter in the post-operative period, whereas intravenous/subcutaneous heparin therapy was not administered routinely. US Doppler controls of the transplant using a 7.5-MHz convex transducer were performed intraoperatively at LT, the next one within 6 hours following abdominal wall closure, then daily during the first 7 days after LT, twice a week from day 8 until patient discharge, thereafter bimonthly until month 3, and monthly until one year post-transplantation. The occurrence of HAT was defined as loss of intrahepatic arterial signal, as detected by US Doppler, whatever the clinical status of the child at the time of the diagnosis.[19,20] In this work, "early HAT" was defined as occlusion of the HA first diagnosed within 14 days after LT, and "late HAT" as that occurring beyond 14 days after LT. The timing of HAT was defined using the date of first signal loss. When early HAT occurred, and depending on the clinical status of the child, a surgical re-exploration was performed on the same day, consisting in intraoperative US Doppler to confirm HAT. If confirmed, excision of the thrombotic arterial anastomosis, injection of 5000 U Urokinase (Actosolv; Eumedica, Lörrach, Germany) into the distal arterial stump, and reconstruction of the arterial anastomosis using magnifying spectacles (x5.5), with interrupted non-absorbable 8/0 monofilament stitches using microsurgical technique were carried out by the transplant surgeon.[21] The arterial anastomosis was (a) a direct "end-to-end" anastomosis; or (b) indirect in cases where the recipient's HA was not recoverable, with the secondary interposition of an iliac arterial prosthesis of a post-mortem donor between the sub-renal aorta and the HA of the graft. A new intraoperative US Doppler control was performed to verify arterial patency, without doing an intraoperative arteriography. IR for arterial revascularization of the liver graft was not used in this series.

2.3 | Study design and pairing method

Univariate and multivariate analyses were conducted to investigate the relationship between HAT occurrence and age at LT, pretransplant diagnosis, surgical type of graft, and transplant era. Moreover, medical records were retrospectively analyzed for LT recipients with HAT ("HAT group"). In order to comparatively study the consequences of HAT on patient and graft survivals, retransplantation rates, and biliary complications, a paired control group was created ("non-HAT paired group"). For this purpose, any patient in "HAT group" was matched with one patient extracted from our whole series of 882 patients, according to the following pairing criteria: (a) LT performed within 2 years before and 2 years after the case patient, (b) same diagnostic category, (c) same type of graft (whole, reduced, split, and LD), and (d) the closest age at LT. Accordingly, all transplanted patients were included in one of the following diagnostic categories: (a) BA cirrhosis; (b) non-BA cirrhotic hepatopathy, including progressive familial intrahepatic cholestasis, Alagille's syndrome, Wilson's disease, and alpha-1 antitrypsin deficiency; and (c) non-cirrhotic liver diseases, including hepatoblastoma, fulminant hepatitis, hyperoxaluria, and glycogenoses.

In a second part of the study, patient and graft survival rates, and retransplantation and biliary complication rates were compared between early (within 14 days post-LT) and late (beyond 14 days post-LT) HAT cases. Comparative analyses were performed in the subgroup of patients with conservative management versus operative management, with or without HA revascularization after surgical re-exploration. Moreover, the impact of HAT timing on management was also studied.

2.4 | Statistical methods

Categorical variables were expressed as absolute number and percentage, and numeric variables as median and range. The chi-square or Fisher's exact test was used for comparing categorical variables and Mann-Whitney for numeric variables. Survival analysis (patients, grafts, biliary complication-free survival) was estimated using the Kaplan-Meier method and compared by the log-rank test. Retransplantation rate at one and five years post-LT was compared by Fisher's exact test. Risk factors for HAT were first investigated by univariate analysis. The risk factors with significant p-value at univariate analysis were tested by multivariate logistic regression analysis. A variable shown as non-significant at the present univariate analysis but previously described in the literature as an established risk factor for HAT was also forced into multivariate analysis ("forced variable").[22,23] A value of $P < .05$ was considered as significant. The analyses were performed using Prism 7 for Mac OS X, version 7.0a, April 2, 2016 (GraphPad Software, San Diego, CA, USA) and SPSS 24.0 for Mac (SPSS, Chicago, IL, USA) for multivariate analysis.

2.5 | Ethics committee

The research project was approved by the institutional review board of Cliniques universitaires Saint-Luc (Approval Number: 2016/15NOV/491).

3 | RESULTS

All 36 HAT cases observed among the 882 primary grafts occurred within the first year post-transplantation (median post-LT interval to HAT diagnosis: 4 days, range: 1-210 days post-LT), with accordingly an absolute HAT rate of 4.1% (36/882). The medical records of 35 children (17 boys and 18 girls) could be studied in detail in the present study, whereas the remaining patient transplanted in 1985 was lost of follow-up and excluded from the analysis. Median age at transplantation of HAT cases was 2.2 years (range: 0.4-11.2 years). The incidence of HAT varied along the eras from 12.1% (n = 14/116) in 1984-1988, to 1.1% (n = 1/91) in 2007-2010, and 0.0% (n = 0/131) in 2011-2015 (Figure 2). The incidence of HAT also varied with the type of graft: 20 HAT cases among 243 whole-size liver grafts (8.2%), 11 among 236 reduced-size liver grafts (4.7%), 2 among 67 split-liver grafts (3.0%), and 2 among 336 living donor origin grafts (0.6%) ($P < .001$).

3.1 | Predisposing factors for HAT

Table 1 compares four preoperative characteristics between pediatric liver recipients with HAT (n = 35) and the remaining pediatric liver recipients without HAT (n = 846), using univariate and multivariate analyses. At univariate analysis, age at LT ($P = .536$) and pretransplant diagnosis ($P = .432$) did not appear as predisposing factors for HAT, in contrast to the type of graft ($P < .001$) and transplantation era ($P < .001$) (Table 1). At multivariate analysis, the age at LT (forced variable: 1 year younger; 95% CI: 1.04-1.45, OR: 1.23, $P = .014$), the type of graft (DD whole-size liver graft compared with LD graft; 95% CI: 1.69-41.38, OR: 8.36, $P = .009$), and transplantation era (1984-1988 compared with 1989-1992; 95% CI: 1.28-9.09, OR: 3.44, $P = .014$) were found as predisposing factors for HAT.

3.2 | Case-control study

The comparability between HAT and non-HAT paired groups is described in Table 2. As shown in Figure 3, 3-month, 1-year, and 5-year patient survival rates were 82.8% (n = 29 at risk), 80.0% (n = 28), and 77.0% (n = 26) in the HAT group, respectively, versus 93.7% (n = 30), 90.5% (n = 28), and 83.9% (n = 25) in the non-HAT paired group, respectively ($P = .321$). Similarly, 3-month, 1-year, and 5-year graft survival rates were 25.7% (n = 9), 25.7% (n = 9), and 20.0% (n = 8) in the HAT group, respectively, versus 90.6% (n = 29), 87.4% (n = 27), and 80.5% (n = 24) in the non-HAT paired group, respectively ($P < .001$). Five-year retransplantation rates were 77.7% (26 retransplantations) in the HAT group versus 10.7% (3 retransplantations) in the non-HAT paired group ($P < .001$). In the HAT group, 24 children were retransplanted before 3 months post-LT and 2 children after 3 months post-LT, whereas in the non-HAT paired group, the corresponding figures were 2 cases and 1 case, respectively. One-year biliary complication-free survival rates were 16.6% (n = 5 at risk) versus 83.8% (n = 25) in the HAT and the non-HAT paired groups, respectively ($P < .001$). The median interval between LT and the diagnosis of biliary complication was 16 days (range: 2-7693 days) in the HAT group, versus 2680 days (range: 6-11 084 days) in the non-HAT paired group. In the HAT group, 25.0% (n = 6) of biliary complications were anastomotic strictures, the remaining 75.0% (n = 18) being intrahepatic biliary strictures, combined with an anastomotic stricture in 9 instances. The corresponding figures in the non-HAT paired group were 5/7 anastomotic strictures and 2/7 intrahepatic strictures, combined with an anastomotic stricture in both latter cases.

3.3 | Early HAT and late HAT cases

Among the 35 cases studied, 28 HAT cases (80.0%) occurred between day 1 and day 14 post-LT (early HAT subgroup) versus 7 cases

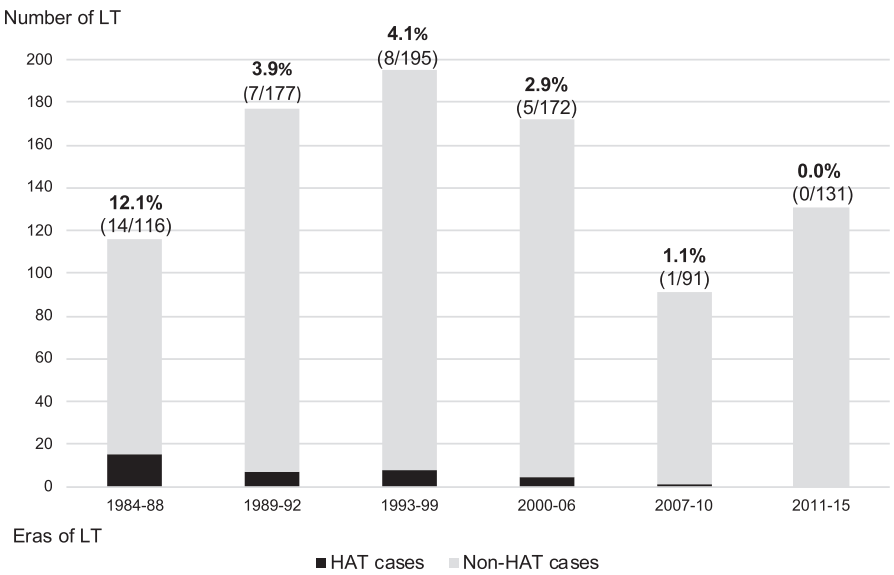


FIGURE 2 Rate of hepatic artery thrombosis (HAT), according to transplantation eras in the series of 882 pediatric patients who underwent primary liver transplantation (LT) at Cliniques universitaires Saint-Luc, Brussels, Belgium, between March 1, 1984, and March 18, 2015

TABLE 1 Results of univariate and multivariate analyses studying putative predisposing factors for hepatic artery thrombosis (HAT), comparing 35 recipients with HAT (excluding one HAT case lost of follow-up) to 846 recipients without HAT, in a total series of 882 primary pediatric liver transplantation (LT) performed at Cliniques universitaires Saint-Luc, Brussels, Belgium, between March 1, 1984, and March 18, 2015

Preoperative characteristics	HAT recipients (n = 35)	Non-HAT recipients (n = 846)	Univariate analysis (*P-value*)	Multivariate analysis (*P-value*)
Age at LT (days)[a]	748 (162-4076)	698 (34-7282)	*P* = .536[b]	*P* = .014
Pretransplant diagnosis				
Biliary atresia	n = 23 (65.7%)	n = 518 (61.2%)	*P* = .432[c]	
Metabolic diseases	n = 5 (14.3%)	n = 89 (10.5%)		
Cholestatic diseases	n = 5 (14.3%)	n = 108 (12.8%)		
Fulminant hepatitis	n = 2 (5.7%)	n = 34 (4.0%)		
Liver malignancies	n = 0 (0.0%)	n = 51(6.0%)		
Other diagnoses	n = 0 (0.0%)	n = 46 (5.4%)		
Type of graft				
Whole-size liver	n = 20 (57.1%)	n = 222 (26.2%)	*P* < .001[c]	*P* = .009
Reduced-size liver	n = 11 (31.4%)	n = 225 (26.6%)		
Split liver	n = 2 (5.7%)	n = 65 (7.7%)		
Living donor graft	n = 2 (5.7%)	n = 334 (39.5%)		
Transplant eras				
1984-1988	n = 14 (40.0%)	n = 101 (11.9%)	*P* < .001[c]	*P* = .014
1989-1992	n = 7 (20.0%)	n = 170 (20.1%)		
1993-1999	n = 8 (22.9%)	n = 187 (22.1%)		
2000-2006	n = 5 (14.3%)	n = 167 (19.7%)		
2007-2010	n = 1 (2.9%)	n = 90 (10.6%)		
2011-2015	n = 0 (0.0%)	n = 131 (15.5%)		

[a]Median and range.
[b]Mann-Whitney test.
[c]Chi-square test.

(20.0%) beyond day 14 post-LT (late HAT subgroup). One-year patient survival rates in early and late HAT subgroups were 78.6% (n = 22/28 at risk) versus 85.7% (n = 6/7), respectively (*P* = .963). In contrast, the corresponding 1-year graft survival rates were 17.8% (n = 5/28 at risk) versus 57.1% (n = 4/7), respectively (*P* = .025). One-year retransplantation rates were 75.0% (n = 21/28 at risk) and 42.8% (n = 3/7) for early and late HAT subgroups, respectively (*P* = .171). Similarly, 1-year biliary complication-free survival rates were 15.0% (n = 1) and 14.3% (n = 2) in the early and late HAT subgroups, respectively (*P* = .334).

3.4 | Management of HAT

In presence of HAT, two therapeutic options were considered: (a) surgical management aiming at arterial revascularization; (b) conservative management (prophylactic anticoagulation with low molecular weight heparin and regular US Doppler follow-up). When surgery was attempted, hepatic artery flow could have been restored ("effective surgery") or not ("ineffective surgery"). With respect to these two therapeutic options, patient, graft, and biliary complication-free survival rates and retransplantation rates at 1-year post-LT are presented in Figure 4. In brief, among the 16 children managed surgically, arterial revascularization could be obtained in 6 (37.5%) of them, which resulted at one year in 100% (n = 6) patient survival, 33.3% (n = 2) graft survival, and 22.2% (n = 2) biliary complication-free survival, the corresponding figures being 60.0%, 0%, and 0% in the 10 remaining children where arterial revascularization could not be obtained at surgical revision. Considering the particular group of late HAT cases beyond the 14th day post-LT (7 cases), the outcomes were as follows: HAT case on day 15 post-LT (retransplantation at day 17 for infected hepatic necrosis, died 10 years later); HAT case on day 39 (partial necrosis of the liver graft with partial hepatectomy on day 48, alive on follow-up); HAT case on day 40 (biliary redos on days 147 and 201, alive on follow-up); HAT case on day 49 (retransplantation at day 50 for hepatic necrosis, died on day 71); HAT case on day 54 (retransplantation at day 77 for infected hepatic necrosis, alive on follow-up); HAT case on day 210 (no complications, alive on follow-up); and HAT case on day 1391 (retransplantation at day 1450 for progressive secondary biliary cirrhosis, alive on follow-up).

TABLE 2 Comparability of 35 recipients with hepatic artery thrombosis (HAT), versus 35 paired non-HAT recipients, among 882 primary pediatric liver transplantation (LT) performed at Cliniques universitaires Saint-Luc, Brussels, Belgium, between March 1, 1984, and March 18, 2015

Comparability variables	HAT group (n = 35)	Non-HAT paired group (n = 35)	Univariate (*P-value*)
Pretransplant diagnosis			
BA cirrhosis	n = 23	n = 23	$P > .999$[b]
Non-BA hepatopathy	n = 8	n = 8	
Non-cirrhotic liver disease	n = 4	n = 4	
Type of graft			
Whole-size liver	n = 20	n = 19	$P = .913$[b]
Reduced-size liver	n = 11	n = 13	
Split liver	n = 2	n = 1	
Living donor graft	n = 2	n = 2	
Recipient age[a]	2.2 years (0.4 - 11.2)	2.4 years (0.6 - 14.5)	$P = .530$[c]
Male/female ratio	17/18	23/12	$P = .227$[d]
ABO Compatibility			
Identical	n = 28	n = 32	$P = .322$[b]
Compatible	n = 6	n = 3	
Incompatible	n = 1	n = 0	

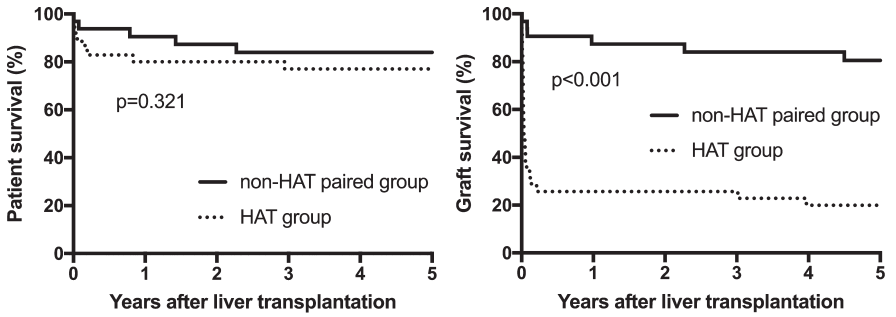
[a]Median and range.
[b]Chi-square test.
[c]Mann-Whitney test.
[d]Fisher's exact test.

3.5 | Impact of HAT timing on management

In case of early occurrence (1-14 days post-LT) of HAT (n = 28/35), the management was surgical in 57.2% of patients (n = 16/28). In case of late HAT (beyond 14 days post-LT), the management was conservative in all instances (n = 7/7). In order to further explore a possible threshold for post-LT interval to achieve an arterial revascularization at surgical re-exploration, the 16 revision surgeries were analyzed in more details. When the surgical revision of HAT took place during the first 7 days post-LT (n = 14/16), the arterial flow could be restored in 6 of them (42.8%). In contrast, when revision surgery was performed beyond day 7 post-LT (n = 2/16), arterial liver revascularization could never be obtained in the present series.

4 | DISCUSSION

Children constitute a population of LT recipients at higher risk of HAT, the incidence being almost four times more frequent when compared to adults.[24,25] Accordingly, Werner et al reported in 2020



No. Patients at risk						
Years post-LT	0	1	2	3	4	5
non-HAT paired group	35	28	27	26	25	25
HAT group	35	28	28	27	26	26

No. Grafts at risk						
Years post-LT	0	1	2	3	4	5
non-HAT paired group	35	27	27	26	25	24
HAT group	35	9	9	9	8	8

FIGURE 3 Kaplan-Meier patient and graft survival curves of 35 recipients with hepatic artery thrombosis (HAT group), compared to a paired group of 35 recipients without HAT (non-HAT paired group), among 882 primary pediatric liver transplantation (LT) performed at Cliniques universitaires Saint-Luc, Brussels, Belgium, between March 1, 1984, and March 18, 2015

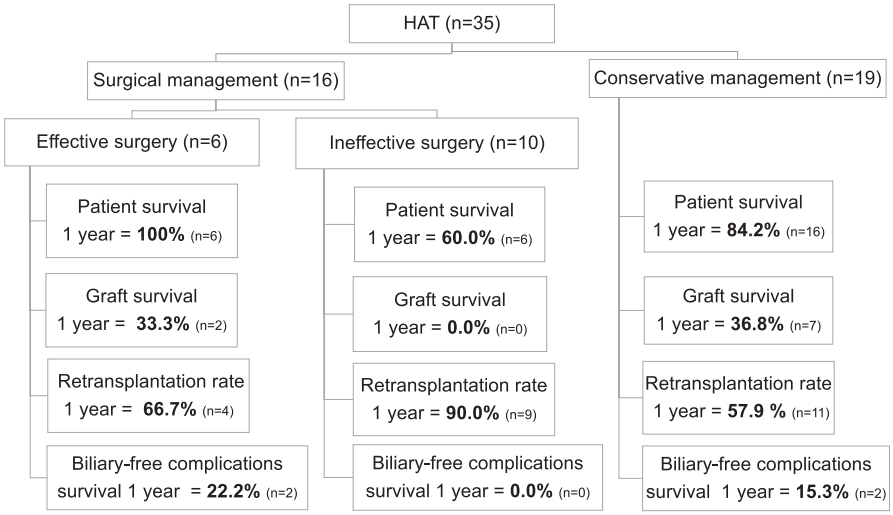


FIGURE 4 Outcomes of 35 recipients with hepatic artery thrombosis (HAT) according to type of HAT management (surgical or conservative) and their results, in the series of 882 pediatric patients who underwent primary liver transplantation (LT) at Cliniques universitaires Saint-Luc, Brussels, Belgium, between March 1, 1984, and March 18, 2015

a variable HAT incidence after pediatric LT, ranging from 5% to 18%.[25] Besides the small size of the recipient hepatic artery particularly in non-cirrhotic patients, several factors might be involved to account for such difference, including discrepancy between donor and recipient arterial stumps, the use of full-size pediatric DD liver grafts with small donor vascular pedicles, and the existence of portal overflow leading to a buffered, low arterial flow particularly in patients with an established cirrhosis.[26] The overall incidence of HAT was 4.1% (n = 36/882) in the present cohort of children transplanted over a 31-year period, a rate comparable with other reports in the literature.[3,25] Nevertheless, univariate and multivariate analyses of the data given in this work suggest that HAT rate seemed to decrease along the learning curve of our LT program. To partly explain such decrement, it may be hypothesized that the implementation of our LD pediatric LT program from 1993, including the introduction of microsurgical principles for arterial anastomosis, contributed to progressive technical improvements of the arterial reconstruction of liver transplants.[21] Accordingly, the type of graft was also shown to play a significant role with 8.2% (n = 20/243) HAT incidence after whole-size LT from pediatric DD, as compared to 0.6% (n = 2/336) after LT with a LD. Such differences are in line with the results observed by Li-Hong Gu et al in their 330 cases series which showed HAT rate significantly higher in full-size LT when compared to LD.[27] However, in contrast with the latter work and when considering post-HAT outcome, the present series did not confirm a higher rate of mortality after HAT, as post-HAT *patient* survival was not significantly reduced ($P = .321$), at the cost, however, of a liberal retransplantation policy at our center. In the present series, post-HAT *graft* survival was shown to be drastically reduced ($P < .001$) with a corresponding increase in retransplantation rate ($P < .001$). These results are partly consistent with those of Neto et al who found patient and graft survival rates significantly worse in the aftermath of arterial occlusion of the liver graft.[3]

As documented in the liver transplant literature, the present data confirmed that biliary complication incidence after HAT was high, with rates at 50.0% and 80.0% at 1 month and 1 year after LT, respectively.[19,28] The negative impact of HAT on bile ducts can be explained by the almost exclusive arterial origin of bile duct vascularization.[29-31] Moreover, in the transplant setting, capsular arterial vessels that might also contribute to supply intrahepatic biliary tract are obviously disrupted at the time of LT.[27] Accordingly, most of the biliary complications secondary to HAT were diffuse and extended in the intrahepatic biliary tract. The HAT had been previously described as an independent risk factor for non-anastomotic biliary strictures by a multivariate analysis in a North American study including 749 adults transplanted.[32] Such diffuse lesions are usually inaccessible for surgical or radiological interventions, leading to worsening cholestasis and recurrent biliary sepsis, and finally the need for liver retransplantation.[7]

At our center, current preventive strategies for HAT include the following intraoperative and post-operative measures: (a) no touch technique when dissecting the native and donor hepatic arterial tracts; (b) intraoperative graft US Doppler to be carried out at the completion of vascular anastomoses and immediately before abdominal closure; (c) splenic artery ligation when arterial resistivity index at intraoperative US Doppler is measured above 1, suggesting a portal overflow; (d) avoidance of recipient hematocrit level above 30% during the peri-operative period.[33] As mentioned above, there was no contribution of a separate microsurgical team and no use of surgical microscope in this experience. At our program, transplant surgeons have followed a particular microsurgical training and they use microsurgical techniques including the use of x5.5 magnifying spectacles, microinstruments, and 8/0 stitches for HA anastomosis. In accordance with the results of this work, early diagnosis of HAT as allowed by daily post-LT US Doppler follow-up constituted an opportunity for early vascular rescue with 42.8% (n = 6/14) of arterial revascularization achieved when HAT was diagnosed within 7 days post-LT versus 0.0% (n = 0/2) beyond 7 days post-LT. In this very limited series, such revascularization was also shown to modestly alleviate the rate of late biliary complications (Figure 4).[9] When the absence of hepatic arterial flow is discovered at US Doppler post-operatively, the main question is indeed to decide whether either to re-operate, aiming at early revascularization, or to opt for conservative management. The latter includes intravenous heparin

administration and US Doppler follow-up to monitor possible reappearance of intrahepatic arterial flow and, on the other side, development of biliary duct complications. The results of the present study suggest that the surgical revision strategy may be valid when HAT is diagnosed within 7 days post-LT, whereas, in our limited number of patients, surgical re-exploration seemed futile beyond 7 days. It should be mentioned that US Doppler was only performed twice a week from day 8 post-LT, and this potentially resulted in delayed HAT diagnosis. This is obviously a limitation in our study because the role of urgent revascularization following HAT had already been mentioned in the 1990s and delayed HAT diagnosis could cause lower outcomes.[34] Extending the daily monitoring by US Doppler until day 14 could perhaps be considered to better identify the time limit in which to propose surgical re-exploration of HAT. Moreover, the 1-year biliary complication-free survival rate was slightly, although not significantly, better after revascularization, 22.2% versus 10.1% without revascularization ($P = .910$). Our results contrast with those of Ackermann et al in their series of 590 LT with 44 HAT cases occurring within 15 days, with successful urgent surgical revascularization in 19 cases compared with the 25 cases who either did not undergo urgent surgical revascularization or those for whom arterial revascularization failed. Indeed, Ackerman et al, in accordance with the present series, reported a slightly better patient survival rates after HAT surgical revascularization, whereas these authors showed a significant increase in graft survival rate after successful urgent surgical revascularization (77% versus 24%, $P = .0007$).[35]

In the present work, HAT diagnosed beyond 14 days after LT was only managed conservatively, taking into account that any attempt of late revascularization was considered as futile and also possibly deleterious considering that surgical mobilization of the liver graft would have destroyed peri-hepatic adhesions and the accompanying putative arterial collateralization. Such hypothesis was also suggested by Stringer et al who reported the formation of collateral circulation as soon as 3 weeks after LT, originating from an arterial neo-vascularization through the liver graft capsule.[36] More recently in 2017, Li-Hong et al found that collateral intrahepatic arterial flow might develop within 2 weeks after HAT.[27]

IR techniques were not used at our pediatric LT program in the context of HAT, which represents a limitation in the interpretation of the present work. However in 2018, Sanada et al described promising results with a HAT cure rate of 100% using IR, in their series of 283 pediatric LD-LT.[37] But IR was performed as first treatment option for only 7 patients (46.7% of HAT cases). It is likely that the risk of vascular injury (rupture, dissection, or hemorrhage) and uncertainty regarding long-term outcomes remains a barrier to the use of this technique in pediatrics.[37-39] Kodama et al proposed that IR should be used more than one week after LT to minimize the risk of procedural complications but the "safe time period" to perform IR remains unknown.[40] This period may vary, taking into account the evolution of endovascular material, and the evolution of IR toward less invasive procedures.[37,41] One interesting study to mention is Gastaca et al who presented in 2020 promising results after endovascular therapy of arterial complications within one week post-LT, without major complication in 7 adult LT.[42] Unfortunately, the extrapolation from adult to child remains difficult and pediatric data are scarce at the present day.[43] Currently, we may suggest that IR could be considered for the HAT occurring in the particular gray interval between day 8 and day 14 post-LT. Appropriate studies comparing surgical revision and IR in a pediatric population are still lacking. These would provide additional information regarding the clinical decision-making algorithm to be applied in case of HAT after pediatric LT.

In conclusion, the present work studied the burden of HAT in a large, single-center pediatric liver transplantation program. Despite the learning curve with respect to its rate, HAT still represents a significant threat for children undergoing LT, with considerable morbidity and often the need to use a second liver graft when a retransplantation is finally required. According to the data analyzed, this work proposed a detection scheme of HAT in the early post-LT period, as well as surgical or conservative management options depending on chronology of the event before or after the 7th day post-transplant. Delimitation of the respective role of surgery versus IR in HAT will require additional research.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

AUTHORS' CONTRIBUTIONS

Dr A. Channaoui contributed to the conception of the study, data collection and interpretation, performed univariate statistical analysis and prepared the first draft of the manuscript. Dr R. Tambucci made substantial contributions to the study and contributed to data collection and interpretation. Prof C. de Magnée contributed to data collection and interpretation. Dr A. Pire, Prof E. Sokal, Prof F. Smets, Prof X. Stephenne, and Prof I. Scheers contributed to the interpretation of data. Prof R. Reding conceived the study, and contributed to the interpretation of data and revision of further drafts of the manuscript, before the final version. All authors contributed to the critical revision of the manuscript, approved the final version of the manuscript and the authorship list, and take full responsibility for the manuscript.

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