ORIGINAL ARTICLE

Late hepaticartery thrombosis after liver transplantation: which strategy? A single-center retrospective study

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SUMMARY

The management of late hepatic artery thrombosis (LHAT) after liver transplantation (LT) is not codified. The objective of this study was to retrospectively evaluate outcomes after LHAT. All patients with HAT diagnosed 3 months or later after LT on computed tomography between 1993 and 2017 were included. Our policy was to apply a conservative management for asymptomatic or mild symptomatic patients and reserve retransplantation to symptomatic patients with diffuse cholangitis or liver abscess. A total of 56 patients were analyzed. LHAT diagnosis was made after a median interval of 48 months from LT (ranging from 3 to 368.3). At diagnosis, 28 (50%) patients were asymptomatic, 10 (17.8%) had mild symptoms (transient acute cholangitis), and 18 (32.1%) had severe complications. Asymptomatic patients experienced a 5-year graft survival of 57% vs. 40% in those with mild symptoms and 11% in those with severe complications ($P < 0.001$). However, there was no difference in overall patient survival between groups. Our results suggest that conservative management of LHAT for asymptomatic patients or patients with mild complications is safe. Retransplantation should be reserved to patients with severe biliary complications.

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Introduction

Early arterial thrombosis (EAT) is a severe complication after liver transplantation (LT), leading to the loss of the graft in most of the cases [1]. In contrast, a few reports have shown that, when occurring at distance of the transplant, arterial thrombosis does not systematically compromise graft prognosis [2–4]. This difference in terms of clinical consequences leads to differentiate EAT from late hepatic artery thrombosis (LHAT).

Although EAT has been extensively studied [5], few series focusing specifically on LHAT have been published [6–8]. As a result, the prognosis and management of LHAT are not codified. The aim of this study was to retrospectively evaluate the results of our conservative strategy.

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Methods

Study population

This is a single-center retrospective study. In our cohort of adult LT recipients, we included all patients who developed LHAT at Paul Brousse Hospital, Villejuif, France, from January 1993 to December 2017. To identify these patients, we proceeded according to several steps:

Step 1: we made a research in our internal server using the key word "arterial thrombosis." This allows us to identify all reports (intraoperative, imaging, outpatient) that include the key word of interest.

Step 2: information (baseline characteristics, history, diagnosis circumstances, transplant procedures, and follow-up) of the selected patients was retrieved and collected.

Step 3: Our final study population was selected by using the definition of LHAT.

The design of this study and its objectives were discussed and approved during our research meeting.

Diagnosis of LHAT

There is no consensual definition of LHAT in the literature. Three weeks, and 1 month are usually used to define LHAT [6,9,10]. Since HAT occurring beyond 3 months from LT is thought to have different outcome and evolution [11], we used a cutoff of 3 months to define LHAT. The diagnosis was based on arterial phase computed tomography showing an absence of hepatic artery, regardless of resistive index on Doppler ultrasound.

Liver transplantation technique

Most of the LT were done with caval preservation. Replacement of vena cava was often preferred in case of large graft, circular dorsal sector, or retransplantation. Veno-venous bypass was used when total vascular exclusion was hemodynamically not well tolerated or in the presence of severe portal hypertension in patients with a history of complex abdominal surgery. Hepatic arterial anastomosis was usually done at the junction of the common hepatic artery and the gastroduodenal artery. The splenic artery or the aorta of the recipient was considered as the second and third options, respectively.

Split grafts were used when appropriate donors were available. Extended right grafts were transplanted in adults while the left lateral parts were transplanted in children.

Follow-up

After the discharge, follow-up includes physical examination, blood tests, and Doppler ultrasound every 15 days during the first 2 months after the transplantation and then every 3 months. Abnormalities in Doppler (no arterial signal or arterial index < 0.5) led to perform a CT scan and to check the patency of the graft artery. When arterial stenosis was diagnosed, radiologic treatment was preferred as previously reported [12]. A CT scan was performed at day 7, at 1 month and 3 months, and then every 6 months during the two first years in the absence of symptoms. Annual CT scan was routinely performed, except in patients with chronic renal insufficiency.

Management of LHAT

All hepatic artery abnormalities detected on CT scan were presented at our multidisciplinary meeting. The diagnosis of LHAT was confirmed and the management was discussed. MR cholangiography was done in the presence of symptoms. The global policy was to be conservative and avoid retransplantation, as long as it was clinically possible. Local biliary stenosis or mild cholangitis was managed by endoscopic stenting and antibiotics. Enlisting for retransplantation was considered in case of repeat episodes of cholangitis, in case of jaundice related to a diffuse ischemic cholangitis, or in case of multiple liver abscess.

We therefore divided our study population into three groups according to the severity of LHAT at diagnosis. Asymptomatic group included patients without symptoms and normal or slight abnormalities in liver test (normal bilirubin level, cholestasis, or cytolysis lower than three times the upper limit of normal). The group with mild symptoms refers to patients with acute cholangitis, controlled by short course of antibiotics, with preserved biliary tree. Local biliary stenosis or intrahepatic stones could be observed. Severe symptoms were defined by intractable chronicle sepsis, or liver abscess or diffuse destruction of biliary tree on imaging.

Statistical analysis

Continuous variables and categorical variables were expressed as median (range) and percentage, respectively. Comparisons were done by using Chi-squared test, or Fisher test or Wilcoxon test, as appropriate. Survival curves were plotted by using the Kaplan–Meier method. Survival probabilities were compared with the

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log rank test. Calculations were done with R3.3.3 software and the *ggplot2* package.

Results

Of the 2687 adult LT performed over the study period, LHAT was observed in 56 patients (2.1%), after a median time from LT of 48 months (range, 3–368 months). The median age of recipients was 47 years (range, 15–73 years). Full graft was used in most of the cases ($N = 48$; 85.7%), after a median cold ischemia time of 502 min (range, 160–900 min).

Circumstances of LHAT diagnosis

The synopsis of the study population and the evolution are summarized in Fig. 1. At the time of diagnosis, 28 patients (50%) were asymptomatic. Mild presentations (hepatic stones, localized biliary stenosis, and acute cholangitis) were present in 10 patients whereas the other 18 patients exhibited diffuse cholangitis, and/or multiple liver abscess with chronic sepsis (severe presentations). An example of each situations is given in Fig. 2.

Comparisons of asymptomatic versus mild or severe presentations at diagnosis

Demographic, clinical, technical characteristics were compared according to the presence of symptoms at the time of LHAT diagnosis (no symptom vs. mild or severe presentation). Briefly, baseline characteristics and technical aspects were similar. However, symptomatic presentations occurred much later than asymptomatic ones (median interval of 111 vs. 20.7 months; $P < 0.001$). Results are provided by Table 1.

Doppler arterial index

At the time of LHAT diagnosis, of the 49 patients with available arterial index on Doppler, no arterial signal, abnormal index, and normal arterial index were observed in 15, 18, and 16 patients, respectively.

The absence of any detectable arterial signal on Doppler was more often observed in patients with severe presentation compared to those with no symptoms or mild presentation (5/8 (62.5%) vs. 10/41 (24.4%), $P = 0.046$). We did not find any association between index and graft survival among patients with no symptoms or mild presentation.

Conservative management of LHAT with asymptomatic presentation

Of the 28 (50%) asymptomatic patients at diagnosis, nine (32%) were finally retransplanted after a median time of 44.7 months (range, 7–101 months) after developing severe complications.

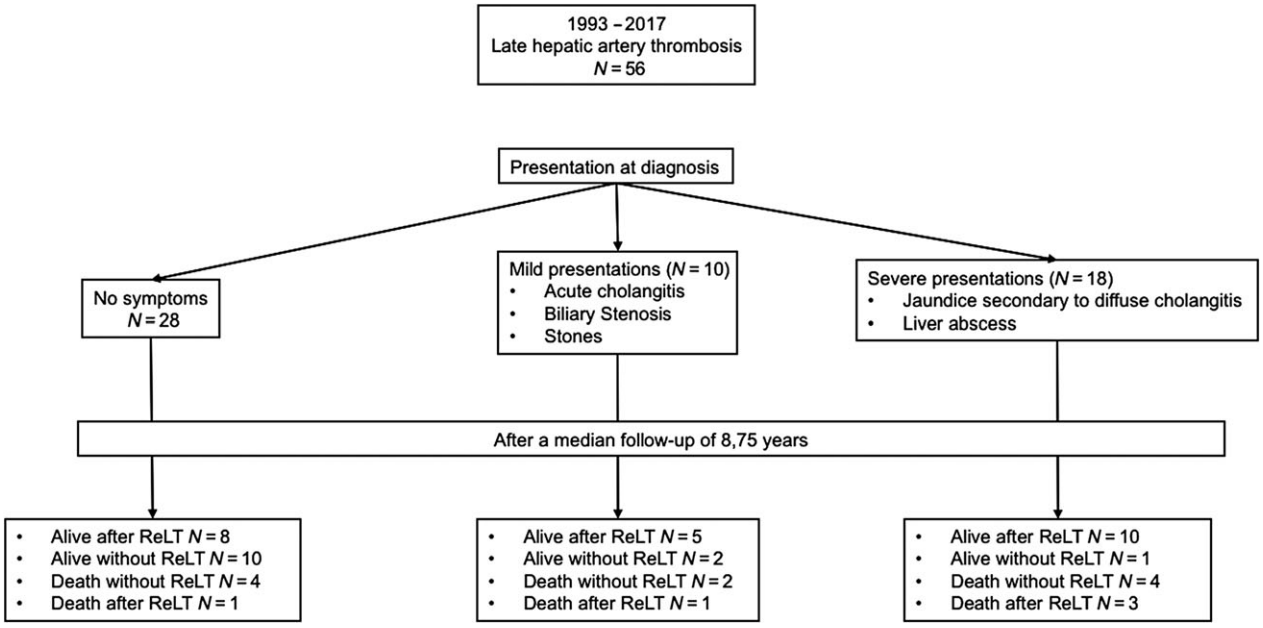

Figure 1 Synopsis of the study population.

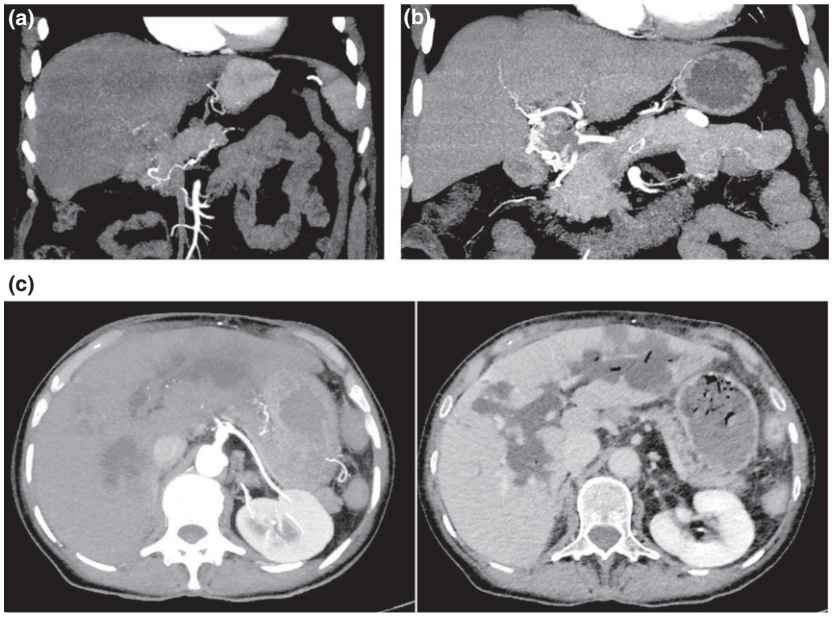

Figure 2 (a) Asymptomatic presentation: A 56-year-old female who developed a LHAT 8 months after LT for cirrhosis and hepatocellular carcinoma. She had no symptoms at diagnosis and still remains asymptomatic after a 4-year follow-up. (b) Mild presentation: LHAT in a 54-year-old patient, 20 years after LT for idiopathic cirrhosis, revealed by acute cholangitis and intrahepatic stones. CT scan showed arterial cavernoma. He underwent a clearance of biliary tree and hepatico-jejunostomy. He is symptom-free since 10 years. (c) Severe presentation: A 67-year-old female, hospitalized for sepsis and multiple liver abscesses secondary to LHAT 31 years after LT for primary sclerosing cholangitis. She was enlisted after prioritization and was successfully retransplanted 1 month after LHAT diagnosis.

Table 1. Comparisons of characteristics according to the presence of symptoms at diagnosis.

Variables	Asymptomatic presentation *N* = 28 No. (%)/range	Mild/severe presentation *N* = 28 No. (%)/range	*P*
Demographic			
Male	18 (64.3%)	17 (60.7%)	>0.99
Median age, yrs	46.5 (15.3–73.3)	48.2 (18.4–69.7)	0.743
Time from LT to LHAT diagnosis, mo	20.7 (4.10–210)	111 (3.08–368)	0.001
Underlying disease			0.323
Autoimmune	5 (17.9%)	4 (14.3%)	
Hepatocellular carcinoma	3 (10.7%)	1 (3.6%)	
Cholangitis	6 (21.4%)	2 (7.1%)	
Fulminant hepatitis	1 (3.6%)	6 (21.4%)	
Idiopathic cirrhosis	1 (3.6%)	1 (3.6%)	
Alcohol	1 (3.6%)	2 (7.1%)	
Others	6 (21.4%)	4 (14.3%)	
Hepatitis B	4 (14.3%)	4 (14.3%)	
Hepatitis C	1 (3.57%)	4 (14.3%)	
Graft characteristics			
Median donor age, yrs	52 (17–83)	41 (15–61)	0.050
Split graft	3 (10.7%)	5 (17.9%)	0.705
Median cold ischemia time, min	513 (220–900)	500 (160–887)	0.705
Technical aspects			
First LT	14 (50.0%)	8 (28.6%)	0.171
Single arterial anastomosis	15 (62.5%)	13 (52.0%)	0.650
Hepatico-jejunostomy anastomosis	10 (41.7%)	11 (42.3%)	>0.99

Conservative management of LHAT with mild presentation

No revascularization procedures were attempted in patients with LHAT. The different options included medical treatment (antiplatelets and/or antibiotics) and biliary drainage (transhepatic or endoscopic). At last follow-up, six (60%) patients underwent retransplantation.

Management of patients with LHAT and severe presentation

Of the 18 patients, three (16.6%) died of sepsis from hepatic origin before retransplantation could be attempted. Two patients with liver abscess recovered after drainage and antibiotics and were finally not retransplanted. The remaining 13 patients underwent retransplantation after a median time of 3.6 months.

Long-term outcomes

The median follow-up from the date of LHAT diagnosis was 8.7 years.

Since our management of LHAT was based on the presence and the type of symptoms at diagnosis, outcomes are presented according to the three groups of patients: no symptom, mild symptoms, and severe symptoms.

At last follow-up, 28 (50%) patients were finally retransplanted. The 90-day and 1-year mortality rates after retransplantation were 0% and 8%, respectively.

As expected, graft survival was significantly different between the three groups ($P < 0.001$). The median graft survival time in patients without symptoms was 8.4 years vs. 2.4 years in patients with mild presentation. In patients with severe presentation, the median graft survival was 3.5 months. Kaplan–Meier graft survival curves and 5-year graft survival rates are presented in Fig. 3a.

The 5-year OS rates after LHAT diagnosis were of 88%, 79%, and 69% for the asymptomatic group, mild presentation group, and severe presentation group, respectively ($P = 0.28$; Fig. 2b).

Outcomes of patients with asymptomatic or mild presentation

Of the 38 patients without severe symptoms, the probability of remaining alive and retransplant-free was 52% and 41% at 5 and 10 years, respectively. Median graft survival was of 5.9 years. Of note, six patients died without being retransplanted. Cause of death included cancer ($N = 2$), liver failure ($N = 1$), cardiac failure ($N = 1$), and unknown origin ($n = 2$).

Discussion

Our study showed that LHAT is a rare event after LT (2.1%), that can occur unpredictably, even many years after transplantation. In half of cases, the diagnosis was made by CT scan during post-transplant follow-up in asymptomatic patients. In the other half of patients, LHAT was revealed by various types of symptoms with

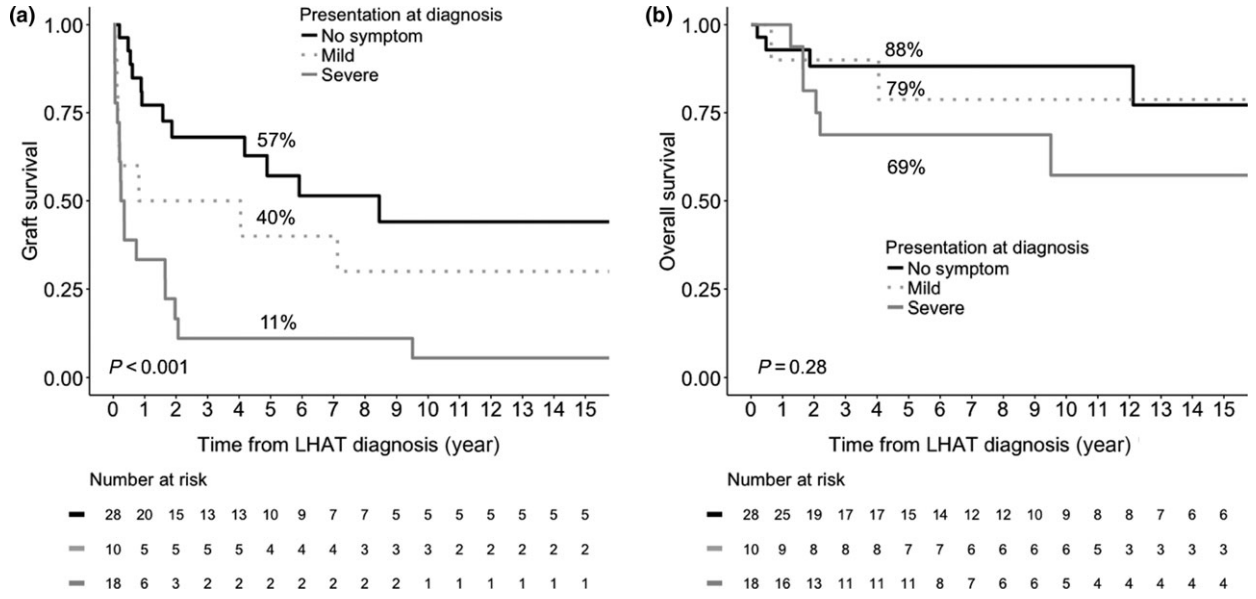

Figure 3 Kaplan–Meier graft survival (a) and overall survival (b) curves after LHA diagnosis.

different degree of severity. Of note, there were no cases of acute liver necrosis and all symptoms were directly related to ischemic damage of the biliary tract. These findings are in accordance with previous series in the literature summarized in Table 2. The reasons why symptomatic LHAT were detected later than asymptomatic LHAT are unclear. It might result from the lower frequency of follow-up CT scan at distance from LT, or a frequent use of ultrasound in the early post-transplant period, thus decreasing the probability of finding a fortuitous LHAT.

The management of LHAT is still a matter of debate. Some groups consider retransplantation as the treatment choice in selected patients [13], whereas others have reported "non-retransplant" procedures with good results [14]. Here, we observed that follow-up of asymptomatic form, and conservative treatment of patients with mild presentation is associated with an overall survival similar to that of patients quickly retransplanted. This attitude makes possible for half of patients to remain "retransplant-free" after a median follow-up of 8.7 years from LHAT diagnosis. These results suggest that the "wait and see" strategy in asymptomatic patients and the conservative management of mild forms are acceptable alternatives compared to upfront retransplantation.

The favorable outcome of LHAT compared to EAT is allowed by the development of arterial collaterals, that can arise from superior mesenteric artery, splenic artery, inferior phrenic artery, left gastric artery, and arteries from the omentum, providing arterial blood supply via the hilar plate [15,16]. This could explain the persistence of resistive index in patients with no more patent hepatic artery. Although it cannot be demonstrated here, it is likely that a pre-existing arterial stenosis with prolonged ischemia might favor the development of efficient arterial supply, in contrast with acute deprivation of arterial flow. Although absence of arterial signal was more often diagnosed in patients with severe symptoms, we did not find a prognostic value of index among asymptomatic patients or patients with mild presentation. This suggests that decision and management should be based on symptoms.

Keeping retransplantation as the last option is justified by the feasibility of conservative management of LHAT, current organ shortage and inherent morbidity and mortality of a second transplantation. Survival of retransplantated patients in this study was comparable to that of larger series of retransplantation [17–19]. However, it should be mentioned that the existence of LHAT might increase the degree of technical difficulty, compared to retransplantation in others indications. Indeed, the existence of liver abscess with sepsis might impair the hemodynamic tolerance of the total hepatectomy. Moreover, the resaturation of satisfactory arterial flow is more challenging, forcing to find another site of arterial anastomosis. Celiac trunk or splenic artery has

Table 2. Overview of the literature.

Author	Year	LT No.	LHAT cases No.	Diagnosis of LHAT	% asymptomatic presentation (%)	ReLT at last follow-up (%)
Valente *et al* [22]	1996	140	4 (2.8%)	>6 months	0	50
Bhattacharjya *et al* [23]	2001	1097	31 (2.8%)	>30 days	51.6	51.2
Gunsar *et al* [6]	2003	634	11 (1.7%)	>30 days	0	63.3
Stange *et al* [9]	2003	1992	16 (0.8%)	>30 days	6.2	56.2
Leonardi *et al* [8]	2004	178	9 (5.1%)	>30 days	22.2	0
Vivarelli *et al* [24]	2004	747	13 (1.7%)	>30 days	NA	76.9
Silva *et al* [10]	2006	1257	39 (3.1%)	>30 days	NA	28
Duffy *et al* [1]	2009	4234	70 (1.6%)	>30 days	NA	51.4
Pareja *et al* [25]	2010	1674	16 (0.9%)	>30 days	12.5	75
Scarinci *et al* [26]	2010	739	6 (0.8%)	>30 days	16.7	83.3
Panaro *et al* [15]	2011	407	17 (4.2%)	>30 days	58.8	29.4
Leithead *et al* [7]	2012	2047	78 (3.8%)	>30 days	NA	62.8
Mourad *et al* [16]	2014	1507	71 (4.7%)	>21 days	4	40.8
Yang *et al* [27]	2014	744	6 (0.8%)	>30 days	NA	NA
Frongilio *et al* [28]	2015	421	7 (1.6%)	>30 days	43	14.3
Reigada *et al* [29]	2017	263	6 (2.2%)	>30 days	0	16.7
Bastante *et al* [30]	2018	334	17 (5.1%)	>30 days	NA	0
Present study	2018	2687	56 (2.1%)	>3 months	50	50

LT, Liver transplantation, LHAT, Late hepatic artery thrombosis; NA, not available.

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proved to be good options [20], whereas implantation on aorta, that requires in most of the cases an interposed graft is at higher risk of thrombosis [21]. Among the 28 retransplantations, native splenic artery ($N = 10$) and common hepatic artery ($N = 9$) were more preferentially used for arterial re-anastomosis. Celiac trunk ($N = 3$), aorta ($N = 3$), and gastroduodenal artery alone ($N = 1$) were more seldomly chosen. The preference for hepatic artery or splenic artery is explained by better accessibility and easiness of anastomosis without the need for vascular grafts, a potential risk factor for subsequent thrombosis.

The good results after retransplantation of our series might be related to the short waiting time. It has been shown that intercurrent infection is the critical determinant of outcome in patients listed and retransplanted for LHAT [7]. Fast access to retransplantation was made possible, thanks to specific prioritization (exception to MELD score), thus shortening the waiting period.

In patients with LHAT, timing for retransplantation is a question of major interest. However, the present series makes it impossible to clearly address this issue. Only one patient among the 38 patients without severe symptoms subsequently died of sudden acute liver failure. At admission, his condition was too poor (multiple organ failure) to consider for retransplantation. The median graft survival in this group was 5.9 years. On the contrary, in the presence of severe symptoms at diagnosis, our attitude was to enlist for quick retransplantation, considering that chances for recovery were very limited. Symptomatic treatment of liver abscess was undertaken during the waiting period. In such cases, a prioritization was specifically asked to our national organ sharing organization, in order to obtain a new graft in short delay. Despite this strategy, three patients died of sepsis and multiple organ failure before retransplantation. The retrospective analysis of our policy (conservative management for asymptomatic or mild presentation and early retransplantation for severe presentation) showed that conservative management is not a loss of chance in the majority of patients without severe symptoms. For patients with severe symptoms, conservative attitude cannot be properly assessed because most of them were enlisted for retransplantation.

This study is limited by its retrospective nature and the small size of the study population. In addition, since CT scan and prospective collection of the "LHAT" event has been done over time, identification biases cannot be excluded. However, our strategy remained constant over time, making it possible a retrospective evaluation. We acknowledge that graft survival observed according to the type of presentation directly results from our management. However, it gives information about the results of conservative strategy in patients without severe symptoms at LHAT diagnosis.

In conclusion, the "wait and see" strategy for asymptomatic patients and conservative management in mild forms are feasible without increased mortality. Retransplantation should be indicated for patients with intractable biliary lesions, knowing that success requires short waiting time after enlisting.

Authorship

RC, MAA, and RA: Conception & Design. RC, MAA, DCh, and RA: Writing. RC, MAA, OC, and NG: Data collection. RC, MAA, RA, and DCh: Analysis & interpretation. ASC, EV, OC, GP, NG, and DCa: Review & corrections.

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Conflict of interest

The authors declare no conflict of interest.

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