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OPEN

Biliary Strictures Are Associated With Both Early and Late Hepatic Artery Stenosis

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Background. Hepatic artery stenosis (HAS) following liver transplantation results in hypoperfusion and ischemic damage to the biliary tree. This study aimed to investigate how vascular intervention, liver function test derangement, and time point of HAS onset influence biliary complications. **Methods.** A single-center retrospective study of adult patients that underwent primary liver transplantation. Patients were grouped according to the presence or absence of HAS and then into early (≤90 d) or late (>90 d) subgroups. Biliary complications comprised anastomotic (AS) or non ASs (NASs). **Results.** Computed tomography angiography confirmed HAS was present in 39 of 1232 patients (3.2%). This occurred at ≤90 and >90 days in 20 (1.6%) and 19 (1.5%), respectively. The incidence of biliary strictures (BSs) in the group with HAS was higher than the group without (13/39; 33% versus 85/1193; 7.1%, $P = 0.01$). BS occurred in 8/20 (40.0%) and 5/19 (26.3%) of the early and late groups, respectively. The need for biliary intervention increased if any liver function test result was ≥3× upper limit of normal ($P = 0.019$). **Conclusions.** BS occurs at a significantly higher rate in the presence of HAS. Onset of HAS at ≤90 or ≥90 days can both be associated with morbidity. Significant liver function test derangement at HAS diagnosis indicates a higher likelihood of biliary intervention for strictures.

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INTRODUCTION

Vascular complications present a significant challenge following orthotopic liver transplant (LT) and can involve both inflow and outflow of the graft. Arterial complications can be thrombosis, stenosis, pseudoaneurysms, or vessel rupture.[1] A devastating event is hepatic artery thrombosis (HAT) as it can lead to graft loss in >50% of patients and is a significant cause of postoperative mortality.[2,3] HAT is reported to have an incidence of 2%–12% and presents most commonly in the early postoperative period.[4] A more subtle complication with significant impact on graft survival is in the form of hepatic artery stenosis (HAS). This problem develops in a more gradual manner and the median time until presentation is reported to be 100 days postoperatively.[4,5]

Clinical vigilance is required to detect HAS as it is reported that 65% of cases will progress to HAT within 6 months if left untreated.[6,7] The biliary epithelium receives their sole blood supply from the peribiliary capillary plexus, and the flow through this microvasculature is determined by supply from the hepatic artery.[4,8] Therefore, a stenosis at a proximal arterial position will precipitate ischemia of the bile duct epithelium and can lead to biliary stricture (BS) formation, graft dysfunction, bilomas, and bile leaks.[4,9,10] Duplex ultrasound (US) findings can be suggestive of HAS; however, a definitive map of the arterial tree requires computed tomography (CT) or digital subtraction angiography (DSA) which identify the stenosis location and severity.[10] Several hypotheses exist regarding the cause of HAS. Reasons such as surgical technique, vessel size mismatch, rejection, microvascular injury during cold ischemic time, vasa vasorum rupture, and hepatic disease recurrence are reported in the literature.[1,6] There is a lack of literature describing the biliary outcomes following HAS. In our anecdotal

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experience, the biliary complications relate to the timing of HAS onset and severity of liver function test derangement. A better understanding of this entity with uniform descriptions of severity is required to improve postoperative monitoring and to help guide the necessary therapeutic interventions.

The primary aim of this study was to determine if the incidence of BSs and requirement for surgical biliary reconstruction is greater if HAS develops within the first 90 postoperative days. Additional aims were to determine if endovascular intervention or surgical reconstruction of the stenotic arterial segment prevents the development of BSs, graft loss, or the need for subsequent biliary reconstruction. The impact of liver function test derangement, in association with HAS, was also assessed.

MATERIALS AND METHODS

Study Design and Data Collection

All primary adult liver transplants with grafts from a deceased brain death donor performed between January 2007 and December 2017 at the Queen Elizabeth Hospital in Birmingham were included in this retrospective, observational cohort study. Retransplant procedures or recipients of a graft from a deceased circulatory death donor were excluded. This was to avoid the confounding effect of ischemic type biliary lesions in deceased circulatory death recipients and the higher rate of aortic conduits in retransplant procedures. The electronic medical records of all patients were traced through our electronic informatics system and patients that were diagnosed with HAS on CT angiography (CTA) identified. Routine CTA is not performed at our institution and indications for this investigation are either graft dysfunction or a duplex US suggestive of upstream stenosis (low resistive index). The patients with HAS identified on CTA were then divided into subgroups based on the time of diagnosis in relation to LT operation. These subgroups were HAS ≤90 days and HAS >90 days for the patients diagnosed within 90 days from transplant and after 90 days, respectively. Patients that did not develop HAS were used as a comparison group (no HAS group). Demographic, donor, and surgical characteristics were collated. Following LT, relevant radiology results, subsequent procedures (endoscopic, radiological, and surgical), need for retransplantation, and mortality were obtained. Data on biliary complications were identified in our database and were confirmed by review of imaging (US, magnetic resonance imaging/cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and percutaneus transhepatic cholangiogram) results by a senior author as appropriate. LFTs (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin) at the time of HAS diagnoses were collected and stratified as normal, elevated up to 3 times upper limit of normal (≤3× ULN) and elevated >3 times normal (≥3× ULN). The upper limit of normal was defined as 40 IU/L, 40 IU/L, 120 IU/L, and 20 mmol/L for aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin, respectively. The LFT with the highest level of elevation determined the group, and only 1 LFT parameter was required to be considered as elevated. This study was registered on our clinical audit registration management system (CARMS-16067 and CARMS-12214).

Statistical Analysis

Statistical analysis was performed using SPSS (Version 25.0.; IBM Corp, Armonk, NY). Baseline continuous variables were compared using independent samples t-tests and categorical variables were compared using the Fishers exact test. Two-sided tests of significance were utilized, and a P value ≤0.05 was considered statistically significant.

RESULTS

A total of 1232 primary transplants with brain death donor grafts were performed over the 10-year study period (January 2007 to December 2017). There was 39 (39/1232; 3.2%) cases of CTA-confirmed HAS in our study period; therefore, 1193 patients did not develop HAS (Figure 1). Demographic, donor, and surgical characteristics are displayed in Table 1. Biliary complications [anastomotic stricture (AS) and/or non-AS (NAS)] occurred at a rate of 13 of 39 (33%) and 85 of 1193 (7.1%) in the HAS and no HAS groups, respectively ($P \leq 0.01$). AS in the groups with and without HAS was 13 of 39 (33.0%) and 79 of 1193 (6.6%), respectively ($P = 0.01$). The incidence of NAS was 4 of 39 (10.2%) and 6 of 1193 (0.5%) in the group with HAS and non-HAS groups, respectively ($P = 0.001$); however, all NAS in the HAS group occurred in individuals who also had AS. Early HAS (HAS ≤ 90 d) occurred in 20 (20/1232, 1.6%) and late HAS (HAS ≥ 90 d) in 19 (19/1232, 1.5%) patients. In the HAS ≤90 days and HAS ≥90 days groups, 8 of 20 (40.0%) and 5 of 19 (26.3%) developed either AS or NAS ($P = 0.29$). The groups had similar baseline clinical and demographic characteristics (Table 2).

In the 39 patients with HAS, 13 underwent endovascular intervention and a single patient had a surgical reconstruction of the hepatic artery (14/39, 35.9%). Vascular intervention occurred in 6 of 20 and 9 of 19 patients diagnosed with HAS ≤90 and ≥90 days, respectively (Table 3). In the group of patients that underwent vascular intervention (14/39; 35.9%), 12 had vascular intervention performed before a BS was evident, and only 2 of 12 (16.7%) of these patients subsequently developed a BS. Vascular intervention was performed after a BS had developed in 2 patients, and the remaining 25 had conservative management; 11 of 27 of these patients developed BS (2/12, 16.7% versus 11/27, 40.7% $P = 0.134$).

In the HAS ≤90 days group, 14 of 20 did not receive vascular intervention, and 6 (6/14, 35.3%) of these patients later developed AS with or without NAS. In the HAS ≥90 days group, 10 of 19 did not receive vascular intervention, and 6 of 10 (60%) developed BSs. Overall, the rate of biliary complications with and without vascular intervention was 3 of 14 (21.4%) and 10 of 25 (40%) in patients with HAS ($P = 0.21$) (Table 3).

The predominant biliary complication in the HAS and no HAS groups were ASs. In the patients who developed HAS ≤90 days and an AS (n = 8), 4 patients were successfully managed endoscopically, and 4 (50%) required a biliary reconstruction. In the group that developed HAS ≥90 days and an AS (n = 5), 3 patients had successful endoscopic management. One patient underwent an unsuccessful attempt at endoscopic intervention but subsequently received conservative management; another had repeated endoscopic interventions but subsequently required biliary reconstruction. Therefore, the rate of biliary reconstruction in the HAS ≤90 days and HAS ≥90 days was 4 of 20 (20%) and 1 of 19 (5.3%), respectively ($P = 0.342$). A time-to-event analysis did not identify a statistically significant difference between groups (Figure 2, $P = 0.159$).

The LFT results for the HAS ≤90 days and HAS ≥90 days subgroups are shown in Table 2. The LFTs of the HAS group at the time of diagnosis were normal in 9, elevated up to 3× ULN

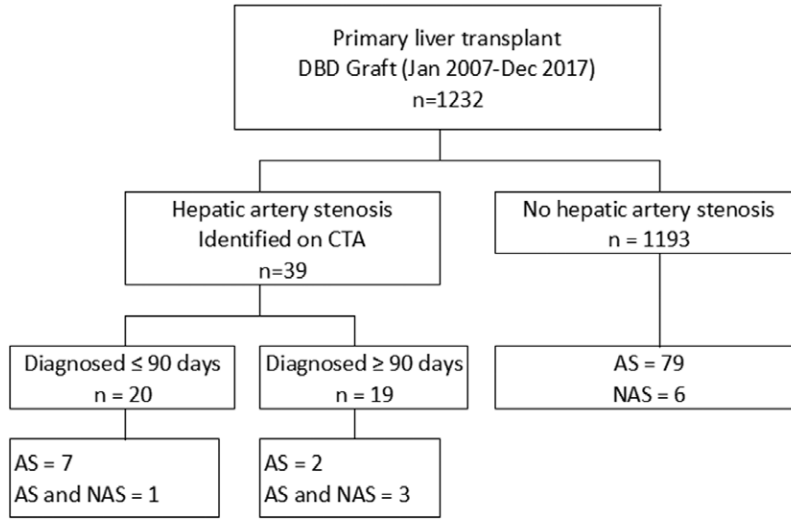

FIGURE 1. Study flow diagram. Flow diagram demonstrating the number of patients with HAS, time of diagnosis and biliary complications. AS, anastomotic stricture; CTA, computed tomography angiography; HAS, hepatic artery stenosis; NAS, nonanastomotic stricture.

in 13 and >3× the ULN in 17 patients. Overall, the requirement for biliary intervention increased as the LFTs progressed from normal (0/9; 0%) to ≤3× ULN (4/13; 31%) and then ≥3× ULN (9/17; 53%), and this was statistically significant (P = 0.019). The effect of LFT derangement was not apparent in the HAS ≤90 days (P = 0.351) and HAS ≥90 days (P = 0.124) subgroups (Table 1). Patients with normal LFTs in both the HAS ≤90 days and HAS ≥90 days that underwent vascular intervention did not subsequently develop any BSs.

The progression of HAS to HAT occurred in 3 patients (3/39, 7.7%), with one of these in the HAS ≤90 days group and 2 in the HAS ≥90 days group. The patient from the HAS ≤90 days who progressed to HAT required urgent surgical vascular reconstruction but subsequently died before being retransplanted. One of the patients from the HAS ≥90 days who progressed to HAT was retransplanted, and the other died from recurrent biliary sepsis. Vascular intervention was not performed in any of these 3 patients before progression to HAT.

TABLE 1.

Demographic, donor, and surgical details of study patients

	Total sample		Patients with HAS	
	HAS	No HAS	HAS ≤ 90 d	HAS ≥ 90 d
No. patients	39	1193	20	19
Female	10 (26.3%)	480 (40.2%)	3 (15%)	7 (36.8%)
Age, y	49.5 (28–70)	52 (16–75)	48 (31–58)	54 (29–70)
UKELD score[a]	55 (44–72	55 (17–80)	55 (46–70)	53 (44–72)
Indication for transplant (%)				
Alcoholic liver disease	9 (23.1)	269 (22.5)	3 (15)	1 (5)
Hepatitic C cirrhosis	6 (15.4)	161 (13.5)	2 (10)	4 (20)
Primary sclerosing cholangitis	6 (15.4)	130 (10.9)	5 (25)	1 (5)
Hepatitis B cirrhosis	2 (5.1)	26 (2.2)	1 (5)	2 (10)
Primary biliary cirrhosis	4 (10.3)	107 (9.0)	2 (10)	2 (10)
NAFLD cirrhosis	2 (5.1)	99 (8.3)	1 (5)	1 (5)
Seronegative hepatitis	4 (10.2)	73 (6.1)	2 (10)	1 (5)
Drug-induced liver failure	2 (5.1)	49 (4.1)	–	–
Cryptogenic cirrhosis	2 (5.1)	31 (2.6)	1 (5)	1 (5)
Polycystic liver disease	–	36 (3.0)	–	2 (10)
Other	2 (5.1)	212 (17.8)	3 (15)	4 (25)
Donor age, y	44 (14–77)	45 (7–84)	44.5 (14–68)	43 (22–77)
Surgical variables (%)				
CIT (min)	515 (123–805)	469 (60–1205)	551 (123–765)	510 (127–372)
Split graft	5 (12.8)	141 (11.8)	3 (15)	2 (10.5)
Multiple arterial anastamoses	6 (15.4)	149 (12.5)	2 (10)	4 (21.1)
Duct-to-bowel anastomoses	8 (20.5)	159 (13)	4 (20)	4 (20.1)
T-tube	2 (5.1)	83 (7)	0 (0)	2 (10.5)

Demographic, donor and surgical details for patients with and without HAS.

CIT, cold ischemic time; HAS, hepatic artery stenosis; NAFLD, nonalcoholic fatty liver disease; UKELD, United Kingdom model for end-stage liver disease.

[a]UKELD at time of transplant. Available for 81% of subjects.

TABLE 2.

HAS severity, complications, and interventions

Time of HAS onset	Liver function tests		Vascular intervention	Type	Biliary complication	AS and/or NAS	Intervention
HAS diagnosed ≤ 90 d (n = 20)	Normal	2	2	An, St, and Em	0		
	Elevated ≤ 3× ULN	7	1	Su	2	NAS and AS, AS	ERCP, ERCP
	Elevated ≥ 3× ULN	11	2	An, An	6	AS, AS, AS, AS, AS, AS	BR[a], BR, ERCP, ERCP, BR[b], BR[b]
HAS diagnosed > 90 d (n = 19)	Normal	7	4	Em, An, An, St	0		
	Elevated ≤ 3× ULN	6	2	An, Emb	2	AS and NAS, AS and NAS	ERCP, ERCP[c]
	Elevated ≥ 3× ULN	6	3	An, St and Emb	3	AS, AS, AS and NAS	BR[a], ERCP, ERCP

Patients with HAS grouped based on timing, liver function tests, complications, and interventions.
[a]Biliary reconstruction following multiple ERCPs.
[b]Biliary reconstruction following failed ERCP.
[c]ERCP attempted twice but unsuccessful, decision made for conservative management.
An, angioplasty; AS, anastomotic stricture; BR, biliary reconstruction (hepaticojejunostomy); Em, embolization of splenic artery ± gastroduodenal artery; ERCP, endoscopic retrograde cholangiopancreatography; NAS, nonanastomtic stricture; St, hepatic artery stent; Su, surgical reconstruction; ULN, upper limit of normal.

TABLE 3.

Incidence of biliary complications in study groups

	All cohort	HAS	No HAS	HAS ≤ 90 d	HAS ≥ 90 d	HAS with VI	HAS without VI
n	1232	39	1193	20	19	14	25
AS	92 (7.5%)	13 (33.0%)	77 (6.5%)	8 (40.0%)	5 (26.3%)	3 (21.4%)	10 (40.0%)
NAS	10 (0.8%)	4 (10.2%)	6 (0.5%)	1 (5.0%)	3 (15.8%)	1 (7.1%)	3 (12.0%)
Subjects with biliary strictures	98 (8.0%)	13 (33.0%)[a]	83 (7.0%)[a]	8 (40%)	5 (26.3%)	3 (21.4%)	10 (40.0%)

Rates of biliary complications in different study groups.
[a]$P = 0.01$.
AS, anastomotic stricture; HAS, hepatic artery stenosis; NAS, nonanastomtic stricture; VI, vascular intervention.

The graft loss and mortality of each group is displayed in Table 4. A single patient with HAS underwent retransplantation for recurrent biliary sepsis during the follow-up period, and this patient experienced HAS ≥90 days and did not undergo vascular intervention. In the group of patients with HAS, 6 of 39 (15.4%) died during the follow-up period, and 3 of these were unrelated to vascular or biliary complications (hepatitis C virus recurrence, hepatocellular carcinoma recurrence, and pulmonary complication). Two patients in the HAS ≤90 days died as a result of vascular or biliary complications; one patient progressed to early HAT and died before retransplantation, and another experienced recurrent biliary sepsis and declined retransplantation. A patient in the HAS ≥90 days experienced recurrent biliary sepsis and was listed for retransplantation but died before receiving a graft.

DISCUSSION

Arterial hypoperfusion of a liver graft and the subsequent development of strictures are well described in the literature.[1,11] Both HAS and HAT can result in premature graft loss and patient death if not managed in an appropriate manner. In addition to interventions aimed at optimizing arterial inflow, management of BSs may also be required if this complication is already established. Endovascular interventions have now become the established first-line treatment option for HAS, and this may involve angioplasty, stenting, or embolization of arterial branches that are contributing to a steal syndrome. Magand et al[6] reported hepatic artery patency rates without HAT or restenosis at 12 months to be 73.3% for angioplasty and 93.8% for stenting. Intervention is not without risks as the complication rate was 2.9% and 12.5% for angioplasty and stenting, respectively, and included 2 iatrogenic HATs. A universal definition of HAS does not exist, and terms used to describe HAS in clinical practice and the literature are short, long, focal, >50% or >70%.[6,10-12]

The rate of HAS in our patient cohort (3.6%) is comparable to the rate of 3.5%–11% reported in the existing literature.[1,6] A comparable number of patients (20/1232, 1.6% versus 19/1232, 1.5%) presented with HAS in our predefined early (≤90 d) and late (≥90 d) groups, this is not unsurprising as previous authors have found the median time of diagnosis is 100 days postoperatively.[5] The incidence of biliary complications (AS and NAS) in the group of patients with HAS was higher than the group of patients without HAS. This therefore supports the belief that the stenosis induced hypoperfusion of the biliary epithelium leads to ischemic injury and subsequent stricturing. Our findings are consistent with a previous study by Dacha et al[7] that demonstrated a higher BS rate (AS and NAS) in patients with HAS in comparison to without HAS (60% versus 9.7%). Kaldas et al[13] also demonstrated that HAS was a strong risk factor for AS with an odds ratio 3.81 (95% confidence interval [CI], 1.30-11.17; $P = 0.02$). The outcome in relation to the timing of onset was not reported in either of these studies. In our study, the incidence of AS was similar in the groups of patients that presented early and late (8/20, 40% and 5/19, 26.5%) demonstrating both time points can be associated with morbidity. Despite statistical insignificance, biliary reconstruction was performed more often in the HAS ≤90 days as opposed to HAS ≥90 days (5/8 versus 1/5) suggesting a more severe biliary injury in those who experience early HAS. A proposed explanation for the observation in early HAS is that there has been inadequate time for the establishment of arterial collaterals, this neovascularization takes time to develop and lessens the ischemic insult. Our finding is consistent with previous authors who found arterial collaterals

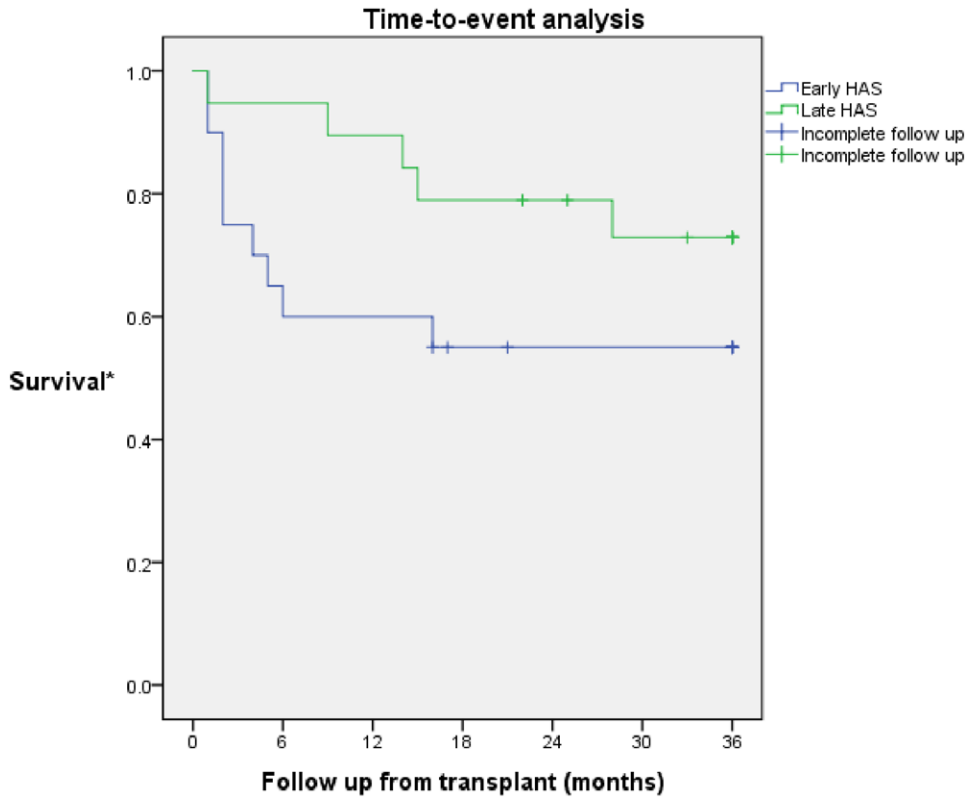

FIGURE 2. Time-to-event analysis for subjects with HAS. Kaplan–Meier survival curves for the early and late HAS groups. The x-axis represents time from transplantation. Several subjects did not achieve 36-mo follow-up. *P = 0.159 (log-rank). Event-free survival. Event defined as development of biliary stricture, death, or retransplant due to graft failure. HAS, hepatic artery stenosis.

to be protective against biliary complications as they provide perfusion to the biliary tree.[10] The milder clinical presentation associated with late HAT is attributed to the same process.[14]

The incidence of AS following liver transplantation ranges from 4% to 9% and reported risk factors include a postoperative bile leak, use of a T-Tube and arterial complications.[15,16] Sequential dilation and stenting via endoscopic retrograde cholangiopancreatography is the accepted first-line approach in the setting of a duct-to-duct anastomoses.[17,18] The average number of times the procedure needs repeating is four and a successful outcome is achieved in 46%–90% of cases.[19,20] In situations where endoscopic access via the ampulla no longer exists, such as duct-to-bowel anastomoses, dilation and stenting can be performed percutaneously. Five patients in our study required biliary reconstruction due to unsuccessful endoscopic or percutaneous intervention. These patients all had significantly elevated LFTs and would have likely experienced significant morbidity, graft loss, or death if they did not undergo biliary reconstruction. Impaired arterial perfusion has previously been suggested to result in ASs more refractory to endoscopic therapy, and our findings are consistent with this concept.[21] The effect seems more pronounced in those that develop HAS in the first 90 postoperative days, and this likely relates to the lack of arterial collaterals at this point.

TABLE 4.

Details of patients who experienced graft loss or mortality

Time of HAS onset	Liver function tests		Developed HAT	Graft loss	Death
HAS diagnosed ≤ 90 d (n = 20)	Normal	2			
	Elevated ≤ 3× ULN	7	X		XO
	Elevated ≥ 3× ULN	11			⌓
HAS diagnosed ≥ 90 d (n = 19)	Normal	7	◊	◊	☐
	Elevated ≤ 3× ULN	6			
	Elevated ≥ 3× ULN	6	Δ		Δ●

X Developed early HAT and underwent vascular reconstruction. Died before retransplantation.
O Developed refractory biliary sepsis. Declined retransplantation.
⌓ Died of respiratory complications.
◊ Developed late HAT and underwent retransplantation.
☐ Died of HCV recurrence.
Δ Developed late HAT and died of recurrent biliary sepsis.
● Died of HCC recurrence.
HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ULN, upper limit of normal.

The clinical decision to treat the culprit lesion causing HAS is frequently influenced by the patients liver function tests. In the absence of routine CTA, the true incidence of HAS is unclear because it may not result in graft dysfunction and therefore, may not prompt investigation. Previous authors have reported that approximately 20% of HAS are subclinical.[22] LFT derangement in the setting of HAS may provide evidence that an ischemic injury is occurring to the graft, or it may be secondary to established strictures, bilomas, or cholangitis. Previous authors have advocated that vascular intervention should take place before significant biliary ischemia and strictures develop.[7] In our study, no patient with normal LFTs who underwent vascular intervention subsequently developed BSs. It is not possible to conclusively state that intervening in these cases had a preventative effect as 3 patients with normal LFTs did not undergo vascular intervention and did not develop BSs either. Previous authors have also demonstrated that patients with HAS and normal LFTs have a low risk of developing BSs.[11] Vascular intervention for HAS before the

onset of biliary complications, results in a lower rate of BS development (2/12, 16.7% versus 11/27, 40.7% $P = 0.134$). The effect that vascular intervention has on the progression of established biliary complications is less clear. In our study, the majority of patients diagnosed with HAS did not undergo any therapeutic vascular intervention (25/39, 64.1%). In a retrospective propensity matched cohort study, Pulitano et al[11] demonstrated that endovascular treatment in patients who develop HAS within 6 months of LT have improved BS free survival. Benefit of endovascular intervention in patients diagnosed >6 months from transplant was minimal, and these authors suggested conservative management in this scenario.[11] Our study was not designed to assess the benefits of intervention, but we have demonstrated that despite a late onset of HAS with adequate time for neovascularization to occur, both AS and NAS can subsequently develop and can be refractory to first-line treatment.

Our institution performs investigative imaging when clinically indicated, rather than as routine surveillance. Therefore, it is possible that subjects with HAS and/or BS without clinical manifestations may have been classified as not having HAS or BS. Furthermore, it is possible that patients diagnosed with HAT may have had a period of preceding HAS that was clinically silent and the vascular complication only diagnosed once it had progressed to HAT. Both these factors may have resulted in our underestimation of HAS and the rate of progression to HAT.

Despite 25 patients undergoing conservative management for HAS, the progression from HAS to HAT occurred in only 3 (3/25, 12.0%), which is much lower than the 65% progression rate reported by other authors.[6] Our findings demonstrate that the prognosis of HAS is variable, and basing management decisions purely on the presence or absence of HAS would be erroneous. This study was not designed to assess the optimal timing intervention to manage HAS; the only means of achieving this aim would be a randomized trial. The limitations of our study are its retrospective nature and the small number of patients with HAS with an associated risk of type II error. The number of patients who underwent arterial intervention was small, which limits the power to determine the benefit. In addition, the rationale for choosing certain management options is difficult to accurately ascertain in retrospect.

The findings of this study demonstrate that HAS is associated with a higher rate of BSs, which is consistent with previous reports. HAS can occur in either the early or late postoperative period, and both are associated with increased morbidity from AS or NAS. The need for biliary intervention, in the form of endoscopy or surgery, increases as the LFTs become progressively more deranged, and these individuals need close surveillance. Our results suggest biliary reconstruction appears to be required more frequently if HAS onset is within 90 days and if LFTs are ≥3× ULN.

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