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Risk factors and management of hepatic artery stenosis post liver transplantation

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ABSTRACT

Background: Hepatic Artery Stenosis (HAS) after liver transplantation (LT), if untreated, can lead to hepatic artery thrombosis (HAT) that carries significant morbidity.
Aims: To identify risk factors associated with HAS and determine if endovascular therapy (EVT) reduces the occurrence of HAT.
Methods: This is a retrospective cohort study of adult LT patients between 2013 and 2018. The primary outcome was development of HAT, and secondary outcomes included graft failure and mortality. Logistic regression was used to ascertain the odds ratio of developing HAS. Outcomes between intervention types were compared with Fisher's-exact test.
Results: The odds of HAS doubled in DCD-donor recipients (OR=2.27; $P = 0.04$) and transplants requiring vascular reconstruction for donor arterial variation (OR=2.19, $P = 0.046$). Of the 63 identified HAS patients, 44 underwent EVT, 7 with angioplasty alone, 37 combined with stenting. HAT was not significantly different in those who underwent angioplasty with or without stenting than conservative treatment ($P = 0.71$). However, compared to patients without HAS, patients with HAS had higher odds of biliary stricture and decreased graft and overall patient survival (log-rank $P < 0.001$ & $P = 0.019$, respectively).
Conclusion: HAS is significantly higher in DCD-graft recipients. EVT was not associated with reduction in HAT progression. HAS has poor graft and overall survival.

1. Introduction

Hepatic artery stenosis (HAS) can be a significant finding after liver transplantation (LT), with a reported incidence in adult patients ranging from 3 to 15% [1–4]. HAS, if left untreated, may lead to graft dysfunction and progression to hepatic artery thrombosis (HAT) [5–8]. HAT has a 30–50% chance of graft failure and a 50% mortality [6,7].

The exact etiology of HAS is unclear. It has been postulated that the prolonged warm ischemic time during organ procurement in a donation after cardiac death (DCD) donor graft can be a risk factor for HAS. However, studies on this have shown mixed results. Hence, we aimed to investigate the risk factors, including the role of donor and recipient characteristics in the development of HAS, in addition to investigating the adverse outcomes associated with HAS in our study population.

The treatment for HAS ranges from conservative management with medications to endovascular treatment to invasive surgical revascularization [5]. Percutaneous revascularization of the hepatic artery with percutaneous balloon angioplasty or hepatic arterial stent placement by interventional radiology has emerged as the primary treatment for post-LT HAS [5,9–11]. However, the efficacy of these treatments to prevent HAT is unclear. Furthermore, there is also no precise data on the benefit of antiplatelet therapy in patients with HAS to prevent the occurrence of HAT. Therefore we also aimed to study the efficacy and safety profile of the two types of endovascular therapies, in addition to the role of antiplatelet therapy in HAS treatment. The primary outcome was development of HAT, and secondary outcomes included biliary stricture, graft failure, and mortality.

2. Materials and methods

We conducted a retrospective single-center cohort study of 337 adult patients who received orthotopic LT at our institution between 2013 and 2018. We collected pretransplant variables, includ-

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ing donor and recipient demographics, graft characteristics, perioperative variables, and recipient comorbidities. In addition, we also collected data on the post-LT course, including graft rejection, retransplantation, thrombosis, and biliary strictures.

Standard techniques were utilized for donor hepatectomy and recipient operation. End-to-end arterial anastomosis with a 6–0 Prolene suture in a routine manner was used for hepatic arterial anastomosis in the majority of the cases. Branch patch in donor and recipient hepatic artery was used for arterial anastomosis when the artery was appropriate. The level of arterial anastomosis was dependent on the donor and recipient arterial size and anatomy. Vascular reconstruction was performed if there was a donor hepatic arterial variant. The surgical technique-related variables, such as donor hepatic artery variants, the need for added vascular reconstruction, and the site of hepatic arterial anastomosis, were collected.

HAS was identified based on the following diagnostic criteria:

1. DUS findings of the main hepatic Resistive Index (RI) < 0.5, peak systolic velocity >200 cm/second, or presence of tardus parvus waveforms.

   (or)

2. 50% narrowing of the hepatic artery luminal diameter on a multidetector computed tomographic angiography (CTA).

This inclusive HAS diagnostic criterion using DUS results, in addition to standard CTA findings, was used in order to get a comprehensive assessment of all cases of HAS. In addition, the initial reason for suspicion of HAS and the type of imaging used to make HAS diagnosis were collected. Symptomatic HAS was defined as the presence of abnormal liver function test or concomitant biliary stricture at the time of HAS diagnosis.

HAS was managed either conservatively or by endovascular therapy (EVT). Conservative management consisted of no EVT, with or without the use of antiplatelet or anticoagulant therapy. EVT was performed by the interventional and vascular radiologists at our institution. A stent was the first choice for intervention unless the anatomy was inappropriate for stent placement. Angioplasty alone, was preferred in very tortuous vessels that precluded stent placement or if HAS was located at the origins of the left and right hepatic artery. Stents were classified into uncovered body stents, covered body stents, cardiac stents, and neurointerventional stents. A covered stent was most commonly used. Following the procedure, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel was used. Post-intervention, serial monthly follow up with DUS were performed.

Outcomes were evaluated by studying the development of HAT, which was identified by lack of blood flow and thrombosis of donor hepatic artery on DUS or CT. In addition, other outcomes, including post-EVT complications, restenosis, biliary stricture identified on endoscopic retrograde cholangiopancreatography, graft failure, and death, were collected. The median follow-up duration of the study was 18 months. The study was conducted in accordance with the approval of the institutional review board. Informed consent was waived due to the study's retrospective nature with minimal risk to the participants

3. Data analysis

All data were described using descriptive statistics. Continuous variables were reported as medians and interquartile ranges (IQR), and categorical variables were reported as counts and percentages. When appropriate, all categorical variables were compared using the Fisher exact or $\chi 2$ test, and continuous variables were compared using the Wilcoxon Rank Sum test. Univariable and multivariable logistic regression analysis was used to identify the patient variables associated with the development of HAS. Nagelkerke R^2 was used to determine the proportion of variance of the dependent variable explained by the set of independent variables in the model. Outcomes between interventions-types were compared with Fisher's-exact test. P-values less than 0.05 were considered significant. Data were analyzed using STATA 17, College Station, TX.

4. Results

4.1. Patient characteristics

After excluding four patients who underwent prior-LT, our final cohort included a total of 337 adult liver transplanted patients between 2013 and 2018. Of them, 63 patients were identified with HAS, with a median age of 59 years (IQR 50, 63), and 73.4% were males Tables 1 and 2 describe their clinical characteristics. The median time to diagnose HAS after LT was 68 days (IQR 28 - 228). In addition, 44 patients with HAS (69.8%) were diagnosed within six months from the date of LT. HAS was diagnosed based on DUS criteria in 11 (17.5%), and CTA in 52 (82.5%) patients (Fig. 1). Initial HAS evaluation was prompted by a new biliary stricture diagnosis or abnormal liver function test in 37 patients (58.7%). Abnormal hepatic artery findings on CT or ultrasound performed for other reasons prompted HAS workup in the remainder.

4.2. Donor hepatic artery characteristics

Among the 63 patients with HAS, 15 (23.8%) had donor hepatic arterial variations that needed arterial reconstruction, and included a replaced right hepatic artery constructed to the gastroduodenal artery GDA ($n = 7$), replaced left hepatic artery ($n = 2$) combined replaced left and right hepatic artery ($n = 1$), accessory left and replaced right hepatic artery ($n = 1$), three separate hepatic arteries with a replaced right, left, and central hepatic artery ($n = 3$), replaced common hepatic artery from the superior mesenteric artery (SMA) ($n = 1$), with varied reconstructions. Recipient hepatic artery variations were seen in 3 patients. Of them, one patient with poor flow in the recipient hepatic artery (most likely due to an arcuate ligament) required aortohepatic artery bypass with donor iliac graft.

In the remaining 45 patients without donor arterial anatomic variations, an end-to-end arterial reconstruction was performed between the common hepatic artery of the donor and the common hepatic artery of the recipient at the level of bifurcation of gastroduodenal artery (GDA) ($n = 14$); donor celiac to recipient celiac artery anastomosis ($n = 15$); and hepatic artery recipient to celiac artery donor ($n = 13$). A branch patch between donor splenic artery branch patch and recipient GDA branch was performed in 3 patients.

Among the patients without HAS, donor hepatic artery variations were seen in 44 of the 274 patients, of which 32 (11.7%) needed arterial reconstruction. An end-to-end arterial anastomosis was performed in 261 patients, and branch patch anastomosis was performed in 13.

4.3. Adverse effects associated with HAS

Patients with HAS had a lower probability of both graft survival (log-rank $P < 0.001$) and overall survival than patients who did not have HAS (log-rank $P = 0.019$) (Supplementary Fig. 1). Patients with HAS also had 5.3 times higher odds of biliary strictures compared to patients without HAS (OR=5.31 (2.71, 10.4); $P < 0.001$) (Table 5).

4.4. Factors associated with HAS

The donor graft characteristics and perioperative variables in LT patients with and without HAS are compared in Table 1. We

Table 1
Graft characteristics.

Donor and peri–operative Characteristics	No HAS $n = 274$	Yes HAS $n = 63$	*P*-value
Donor Age (median, IQR)	40.5 (28, 54)	46 (34, 55)	0.13
Gender (male,%)	173 (63.37)	32 (50.79)	0.06
Donor Risk, No.(%)			0.03
SCD	213 (77.7)	40 (63.5)	
ECD	17 (6.20)	4 (6.25)	
DCD	43 (15.7)	19 (30.2)	
DLT	1 (0.36)	0 (0.00)	
PHS High, No. (%)	74 (27)	12 (19)	0.19
Hepatitis serology (Positive,%)			
HBcAB	19 (6.9)	1 (1.6)	0.14
HBsAg	0 (0.0)	0 (0.0)	N/A
HCV Ab	31 (11.2)	5 (7.8)	0.38
Peri-operative times, Min (median, IQR)			
Total OR Time	256 (226, 304)	246 (216, 287)	0.08
Cold Ischemic Time	220 (175.2, 297)	210 (160.2, 271.2)	0.26
Warm Ischemic Time	30 (25.2, 35)	29 (25, 34)	0.44
Donor hepatic arterial variation needing reconstruction, No. (%)	32 (11.7)	15 (23.8)	0.01

SCD: standard criteria donor; ECD: Extended criteria Donor; DCD: donation after cardiac death; DLT: Domino liver transplant; PHS: public health service; OR: operative time.

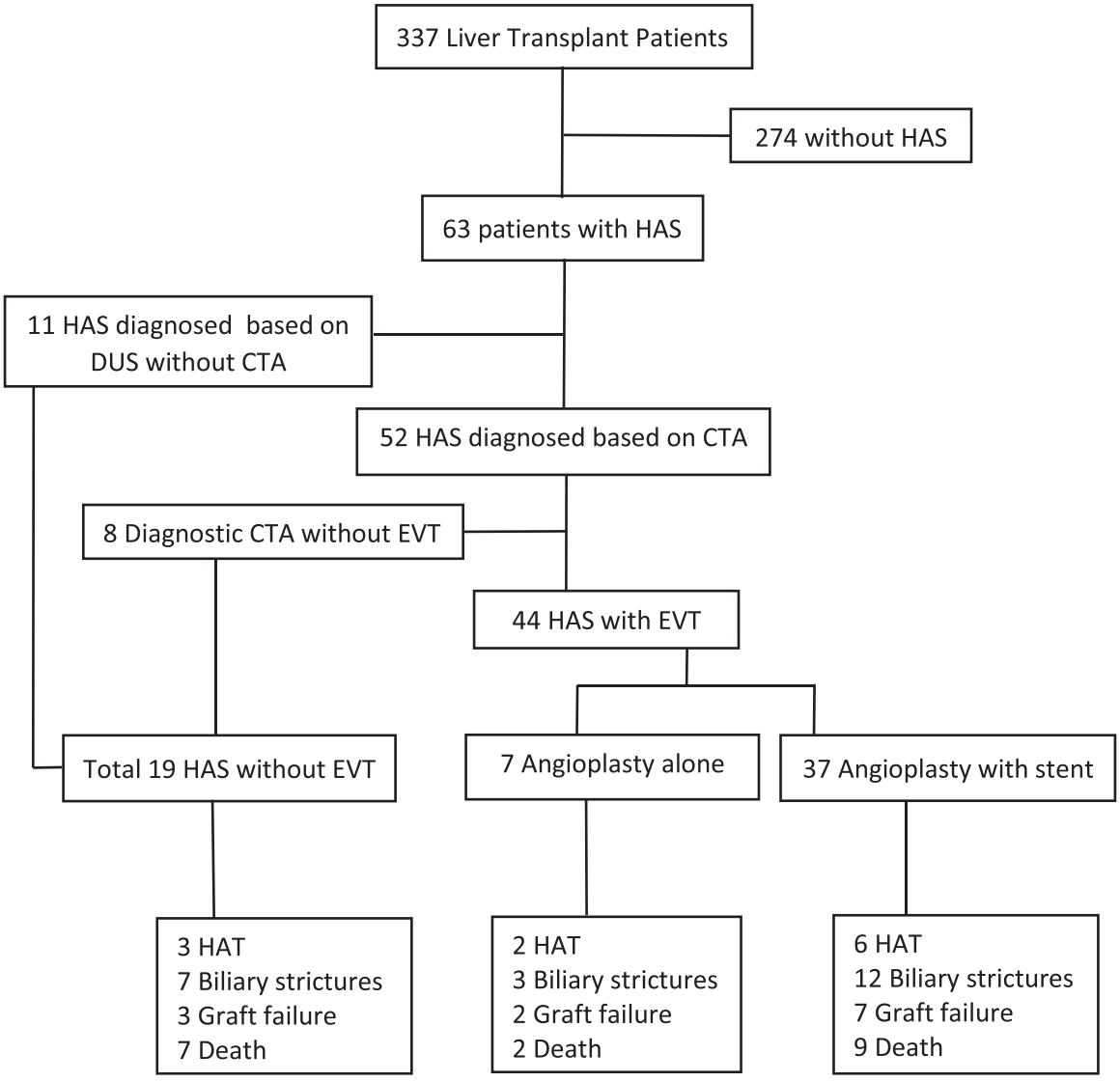

Fig. 1. HAS distribution, management, and outcomes.

Table 2
Recipient characteristics.

Recipients Characteristics	No HAS $n = 274$	Yes HAS $n = 63$	*P*-value
Age at Transplant (median, IQR)	58 (58, 62)	59 (50, 63.0)	0.83
Gender (male,%)	183 (66.1)	47 (73.4)	0.36
Race, No. (%)			0.59
Caucasian	155 (56.6)	33 (52.4)	
Hispanic	74 (27.0)	16 (25.4)	
Native American	24 (8.7)	6 (9.5)	
Asian	9 (3.3)	2 (3.2)	
Black	10 (3.6)	4 (6.3)	
Multiracial	2 (0.7)	2 (3.2)	
Blood Type, No. (%)			0.26
A	92 (33.6)	23 (36.5)	
B	39 (14.2)	4 (6.3)	
O	131 (47.8)	35 (55.6)	
AB	12 (4.4)	1 (1.6)	
BMI (median, IQR)			
BMI at Listing, kg/m^2	27.8 (24.5, 31.4)	27.8 (25.3, 30.8)	0.44
BMI at Transplant, kg/m^2	27.5 (24.9, 31.3)	28.0 (25.8, 32.1)	0.25
MELD (median, IQR)			
MELD at Listing	19 (11, 32)	17 (9, 35)	0.76
MELD at Transplant	26 (13, 40)	23 (10, 37)	0.17
Blood transfusion during LT (median, IQR)			
Units of PRBC	6 (2, 8)	5 (2, 8)	0.82
Units of PLT	2 (1, 3)	2 (0.5, 3)	0.09
Units of FFP	5 (2, 10)	5 (2, 8)	0.23
Estimated Liters of blood Loss	2 (1.2, 4)	2 (1.5, 3.5)	0.67
Co-morbidities, No. (%)			
Hypertension (HTN)	58 (21.2)	11 (17.7)	0.51
Diabetes Mellitus (DM-2)	80 (29.2)	16 (25.4)	0.55
End stage renal disease (ESRD)	17 (6.2)	2 (3.17)	0.54
Coronary artery disease (CAD)	33(12.04)	6 (9.52)	0.57
History of malignancy	16 (5.8)	1 (1.6)	0.21
Hyperlipidemia	23 (8.4)	1 (1.6)	0.06
Pulmonary hypertension	8 (2.9)	2 (3.2)	1.00
Depression	35 (12.8)	10 (15.9)	0.42
Pancreatitis	11(4.0)	2 (3.2)	1.00
Liver disease causes, No. (%)			
Alcohol related liver disease	106 (38.7)	22 (34.9)	0.58
Hepatitis C	113 (41.2)	33 (52.3)	0.11
Hepatitis B	47 (17.1)	10 (15.9)	0.81
Non-alcoholic steatohepatitis (NASH)	47 (17.15)	10 (15.8)	
Primary biliary cholangitis (PBC)	6 (2.2)	0 (0.0)	0.59
Primary sclerosing cholangitis (PSC)	8 (2.9)	0 (0.0)	0.36
Autoimmune hepatitis (AIH)	11 (4.0)	1 (1.6)	0.70
Hepatocellular carcinoma (HCC)	114 (41.6)	33 (52.3)	0.12
Drug induced liver injury (DILI) /others	25 (9.1)	4 (6.3)	0.62
Prior TIPS, No (%)	39 (14.2)	9 (14.2)	0.99
Complications of liver disease, No (%)			
Hepatic encephalopathy (HE)	124 (45.3)	29 (46)	0.91
Ascites	134 (48.9)	26 (41.3)	0.27
Portal Vein thrombosis (PVT)	23 (8.4)	8 (12.7)	0.29
Hepatorenal syndrome (HRS)	64 (23.6)	11 (17.5)	0.31
Esophageal varices	116 (42.3)	30 (47.6)	0.44
Portopulmonary hypertension (POPH)	5 (1.8)	0 (0.0)	0.58
Post-LT factors, No (%)			
Cellular graft rejection	40 (14.6)	11 (17.5)	0.57
Re-transplantation	6 (2.2)	2 (3.2)	0.64
Post-LT Deep vein thrombosis	22 (8)	10 (15.9)	0.055

BMI: body mass index; MELD: model for end-stage liver disease; PRBC: packed red blood cells; FFP: fresh frozen plasma.

did find a significant association between HAS and DCD graft type (OR = 2.27; $P = 0.04$) and HAS with donor hepatic artery anatomical variation needing vascular reconstruction (OR=2.19, $p = 0.046$). The effects remained significant after adjusting for various factors such as recipient and donor age, F-M gender mismatch, perioperative variables including total operative times, cold ischemic and warm ischemic times, the severity of liver disease, retransplant status, presence of post-LT biliary stricture, and cellular graft rejection, on multivariable regression analyses (Table 5). No significant association between donor age and HAS was found. Similarly, the association between HAS and female donor-to-male recipient (F-M) mismatch was insignificant ($P = 0.17$). We analyzed the recipient characteristics between HAS and no HAS (Table 2). No significant differences between recipient age, gender, comorbidities, liver disease, and complications were noted.

4.5. HAS management

19 (30.1%) of the 63 HAS patients did not undergo EVT (Fig. 1). In 11 patients diagnosed based on DUS criteria, without subsequent CT angiogram, treatment with antiplatelet/anticoagulant therapy ($n = 6$) and serial DUS monitoring was performed. Reasons for non-intervention included incidental and asymptomatic HAS, ongoing treatment with full anticoagulation for existing thrombosis in another location, and contrast allergy. The remaining eight had HAS diagnosed by CT angiograms. EVT was not performed in

Table 3
Characteristics in HAS with and without EVT.

Characteristic	HAS with EVT $n = 44$	HAS without EVT $n = 19$	*P*-Value
Age, years (median, IQR)	59.4 (51–63)	56.4 (48.3–62.5)	0.55
Gender female, No. (%)	16 (36.3)	2 (10.5)	0.04
Race/ethnicity, No. (%)			
Non-Hispanic white	24 (54.5)	9 (47.4)	0.81
Hispanic	10 (22.7)	6 (31.6)	
Black	3 (6.8)	1 (5.3)	
Native Americans	5 (11.4)	1 (5.3)	
Others	2 (4.5)	2 (10.5)	
BMI at listing kg/m2, (median, IQR)	28.2 (25.6–30.8)	27.5 (24.4–30.8)	0.78
BMI at transplant kg/m2, (median, IQR)	28.6 (25.2–32)	27.8 (26.6–32.4)	0.88
MELD at listing, (median, IQR)	14 (11–31)	19 (8–39)	0.65
MELD at transplant, (median, IQR)	23 (11–35)	20 (9–40)	
Donor type No. (%)			0.64
DCD	14 (31.8)	5 (26.3)	
ECD	2 (4.5)	2 (10.5)	
SCD	28 (63.6)	12(63.2)	
Primary liver disease No. (%)			
Hepatocellular carcinoma	22 (50.0)	11 (57.9)	0.56
Alcohol liver disease	17 (38.6)	5 (26.3)	0.35
NASH	7 (15.9)	3 (15.8)	0.99
Hepatitis C	22 (50)	11 (57.9)	0.56
Autoimmune hepatitis	1 (2.3)	0 (0)	0.51
Drug induced liver injury /others	3 (6.82)	1 (5.26)	0.82
Comorbidities, No. (%)			
Diabetes Mellitus	16 (36.4)	0 (0)	0.002
Hypertension	8 (18.1)	3 (15.8)	>0.99
Atrial fibrillation	7 (15.9)	1 (5.3)	0.42
End Stage Renal Disease	2 (4.6)	0 (0)	>0.99
Coronary artery disease	5 (11.4)	1 (5.3)	0.66
Complications of liver disease No. (%)			
Hepatic encephalopathy	19 (43.2)	10 (56.2)	0.49
Ascites	20 (45.5)	6 (31.6)	0.31
Hepatorenal syndrome	6 (13.6)	5 (26.3)	0.22
Portal Vein thrombosis (PVT)	8 (18.8)	0 (0)	0.05
Hepatopulmonary syndrome	1 (2.3)	0 (0)	0.51
Hospital length of stay (median, IQR)	7 (5–14)	8 (5–17)	0.62
ICU length of stay (median, IQR)	3 (1–4.5)	2 (1–5)	0.94
Graft rejection No. (%)	8 (18.8)	3 (15.8)	0.82
HAS parameters			
Duration between LT and HAS diagnosis, days (median, IQR)	68.5 (30–182)	140 (26–229)	0.85
Duration between HAS diagnosis to HAT occurrence (median, IQR)	221 (53.5–447)	113 (14–118)	0.31
Symptomatic HAS No. (%)	27 (61.4)	10 (52.6)	0.52
Antiplatelet, anticoagulant therapy (No.%)	42 (95.5)	11 (57.9)	0.00
Aspirin	6 (13.6)	9(47.4)	
Clopidogrel	10 (22.7)	0 (0)	
DAPT	21 (47.7)	1 (5.3)	
Coumadin	3 (6.8)	1 (5.3)	
Rivaroxaban	2 (4.5)	0 (0)	
None	2 (4.5)	8 (42.1)	
Tortuosity (No.%)	9 (20.5)	1 (5.3)	0.13
Ultrasound features (No.%)	34 (77.3)	17 (89.5)	0.32
RI <0.5 (No.%) mean	18 (52.9), 0.425	9 (52.9), 0.392	0.69
TP (No.%)	18 (52.9)	3 (18.7)	0.02
PSV >200 cm/s (No.%) mean	11 (32.3), 369.4	6 (37.5), 349.7	0.48

BMI: body mass index; MELD: model for end-stage liver disease; DCD: donation after cardiac death; ECD: Extended criteria Donor; SCD: standard criteria donor; NASH: Non-alcoholic steatohepatitis; ICU: intensive care unit; RI: resistive index; TP: transperineal; PSV: peak systolic velocity.

them due to the presence of arterial collaterals, long stenotic segment, HAT at the time of angiogram, and tortuous hepatic artery anatomy; of these, more than half ($n = 5$) were treated with antiplatelet therapy.

44 (69.8%) patients with HAS underwent EVT. The median duration between the diagnosis of HAS and EVT was eight days (IQR 1–46), with 68.1% undergoing intervention within three weeks. Seven had angioplasty alone, of which 71.4% were placed on subsequent antiplatelet or anticoagulant therapy. Thirty-seven underwent stent placement along with angioplasty, of which 100% were on antiplatelet or anticoagulant therapy.

4.6. Factors associated with EVT

Although the combined HAS cohort had fewer females in proportion as described above, they were more likely to undergo EVT than males (88.2% vs. 68.2%; $P = 0.04$). All 16 HAS patients with diabetes mellitus ($P = 0.002$) and all eight HAS with pre-transplant portal vein thrombosis (PVT) ($P = 0.047$) underwent EVT (Table 3). Antiplatelet agents and anticoagulants (warfarin and rivaroxaban) were more commonly used in patients with HAS who underwent EVT (95.5% vs. 57.9%) than HAS without intervention; ($P < 0.001$). DUS findings showed more tardus parvus waveforms in the EVT group (52.9% vs. 18.7%; $P = 0.02$), without significant differences in the mean resistive index and peak systolic velocities.

4.7. Outcomes of HAS therapy

Graft failure ($P = 0.76$) and mortality ($P = 0.62$) were not significantly different among the HAS patients who were managed conservatively compared to those who underwent EVT. 11 out of 63

Table 4
Comparison of HAS outcomes with types of treatment.

Outcomes	No EVT $n = 19$	Angioplasty only $n = 7$	Stent and angioplasty $n = 37$	*P*-value
Hepatic artery thrombosis (HAT) (Yes,%)	3 (15.8)	2 (28.6)	6 (16.2)	0.71
Restenosis (Yes,%)	0 (0)	4 (57.1)	3 (8.1)	0.001
Biliary stricture (Yes,%)	7 (36.8)	3 (42.8)	12 (32.4)	0.85
Complications after EVT (Yes,%)	0 (4.76)	2 (28.6)	6 (16.2)	0.09
Graft failure (Yes,%)	3 (15.8)	2 (28.6)	7 (18.9)	0.76
Mortality (Yes,%)	7 (36.8)	2 (28.6)	9 (24.3)	0.62

EVT: Endovascular therapy.

Table 5
Univariable and multivariable logistic regression model for identifying factors associated with the development of HAS.

Donor and recipient characteristics	Univariable			Multivariable		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age at Transplant	0.99	0.97–1.02	0.99	–		
Donor age	1.02	0.99–1.04	0.09	–		
F-M gender mismatch	1.51	0.83–2.74	0.17	–		
Donor risk DCD (Compared to SCD)	2.35	1.24–4.45	0.01	2.27	1.05–4.90	0.04
Donor risk ECD (Compared to SCD)	1.25	0.4–3.9	0.69	–		
MELD at transplant	0.98	0.97–1.0	0.26	–		
Total OR Time	0.99	0.99–1.0	0.09	–		
Cold Ischemic Time	1	0.99–1.0	0.88	–		
Warm Ischemic Time	0.99	0.96–1.02	0.72	–		
Donor hepatic artery variation with reconstruction	2.36	1.18–4.69	0.01	2.19	1.01–4.72	0.046
Re-transplantation	1.46	0.28–7.43	0.65	–		
Graft acute cellular rejection	1.23	0.59–2.57	0.57	–		
Biliary stricture	5.71	3.05–10.7	< 0.01	5.31	2.71–10.4	< 0.01

DCD: donation after cardiac death; OR: operative time; SCD: standard criteria donor; ECD: extended criteria donor.
Dash (-) indicates that the variable was included in the multivariable model but was not statistically significant.
Nagelkerke R^2 =0.198.

patients with HAS developed HAT with a median duration of 118 days (IQR 23–317) from the time of HAS diagnosis. There was no significant difference in the occurrence of HAT ($P = 0.79$) between the three treatment groups - no EVT, angioplasty with and without stent combination (Table 4). We also compared the HAT rates between the three HAS groups classified based on EVT timing relative to the diagnosis of HAS. They were not significantly different. Furthermore, the rate of biliary stricture ($P = 0.98$) did not significantly differ between the three intervention groups.

4.8. Post-EVT restenosis and complications

After 46 EVT, there were seven with restenosis (15.2%), and all of them underwent re-intervention. Restenosis was significantly more common in angioplasty alone than those treated with a stent combination (57.1% vs. 8.1%, $P < 0.001$).

Eight complications were noted among the total attempted interventions. They included four hepatic artery dissections (2 treated with stent repair, 1 underwent exploratory laparotomy with hepatic artery bypass, 1 with no intervention due to distal location and improving flow in delayed images); two intraprocedural HAT (treated successfully with thrombectomy and thrombolysis); one stent erosion and extravasation (treated with a covered stent); and one pseudoaneurysm (treated with stent placement). In addition, the complications after EVT were significantly associated with the occurrence of HAT ($P = 0.003$) in a subset analysis of HAT. Interestingly, in this analysis, the use of antiplatelet therapy also did not significantly reduce HAT.

5. Discussion

In this single-center experience of hepatic arterial complications in LT recipients, we found an 18.7% ($n = 63$) incidence of HAS, using our inclusive diagnostic criteria that incorporate DUS findings alone. The odds of developing HAS doubled in DCD donor recipients and transplants requiring vascular reconstruction of the donor hepatic arterial variants. Among the patients with HAS, factors such as female sex, presence of diabetes mellitus, and pre-LT PVT were associated with treatment by EVT. Treatment of HAS with EVT was not associated with a reduction in the occurrence of HAT when compared to noninvasive therapy, although there was a trend to prolong the median duration between HAS to HAT (221 in the EVT group vs. 113 in the non-intervention group; $P = 0.32$). Despite the mortality rate being numerically lower in the EVT group relative to the non-EVT group (24.3% vs. 36.8%, $P = 0.62$), EVT was not significantly associated with a decrease in the graft failure or mortality and even biliary strictures, the odds of developing which were 5.3 times higher in patients with HAS. In addition, the timing of EVT, before and after 21 days of HAS diagnosis did not alter the rate of occurrence of HAT and other outcomes.

The pathogenesis of HAS in a DCD setting may include arterial intimal injury and higher warm ischemic times during organ procurement, microthrombi in liver circulation during graft preservation or following re-perfusion, and other unknown mechanisms [12–15]. While studies have shown more complicated management of HAS in DCD grafts, without significant differences in hepatic arterial complications between DCD and DBD grafts [16], other studies have shown greater HAS with DCD compared with DBD grafts [15,17]. Our study supports that DCD impacts the development of HAS. In addition, the benefits of new preservation technology using normothermic preservation could impact the development of HAS [18,19].

Hepatic artery anatomical variants are not uncommon, with a reported prevalence rate of 30% [20]. However, their relationship with the occurrence of HAS is not clearly defined. A tendency for prolonged cold ischemic times and bleeding during the arterial reconstruction and the frequent presence of poor primary organ function together with complex arterial reconstructions, which can, in turn, lead to impaired intrahepatic blood flow, might be some of the factors associated with the development of HAT [21,22]. It is

also speculated that the total number of arterial variants needing reconstructions and the number of arterial anastomoses performed are proportional to the chances of developing vascular complications [21]. Some studies have shown that hepatic artery variants needing vascular reconstruction are not significantly associated with arterial complications [22,23]. In contrast, others have shown that complex donor hepatic artery and need for back-table reconstruction were associated with increased HAS and HAT, respectively [16,24]. Our findings of greater odds of HAS in donor hepatic arterial variants needing reconstruction supports the latter.

Several patient characteristics, including female gender, pre-transplant portal vein thrombosis, and the presence of diabetes, were associated with treatment for HAS in our study. Factors such as estrogen and underlying hypercoagulability effects on vascular patency [25,26] and small vessel arteriolosclerosis (with histological features of hyaline thickening of hepatic arteriolar walls), which is widely prevalent in diabetics and females [27], could have influenced the development and severity of HAS and led to the decision to pursue EVT. However, whether these factors were involved and whether they influence the outcome of different therapies for HAS is an area for future investigation.

We found a high incidence of HAS (18.7%) in our study compared to prior work. However, we employed inclusive diagnostic criteria, incorporating standard DUS findings alone, as sufficient to make the diagnosis in order to capture all potential cases. If we confined the diagnosis of HAS to include only those with diagnostic criteria on CTA, the rate was lower (15.4%). If we further limited our diagnosis to those who underwent intervention, rates declined further to a level more aligned with prior studies (13%). Interestingly, of the 11 patients in whom HAS was diagnosed by DUS alone, one developed HAT, four developed biliary strictures, and four died. These findings suggest that detecting HAS by DUS alone may have clinical significance.

Prior studies on HAS management after LT have yielded varied results. A study of 30 patients with HAS, treated with primary stent placement, found no HAT occurrence at a median follow-up of 41 months [11]. Other studies show varied HAT rates ranging from 6.3%, at a median follow-up of 22 months post EVT, to 7.1%, at a median follow-up of 12 months, to 19% in those who underwent EVT with angioplasty alone [5,28,29]. The HAT rates in patients with HAS managed conservatively without EVT also varied. Pulitano et al. ($n = 54$ patients with HAS) found a 4.3% HAT rate in the 23 patients treated conservatively [1]. Untreated HAS had a much higher HAT rate of 65% in the Saad study [28], in contrast to the 15.8% HAT rate in patients with HAS who did not undergo EVT in our study. The presence of collaterals and relatively lower severity are putative explanations for these findings in our study. Regarding medical therapy, prophylactic, low-dose aspirin in post-LT patients has been shown to reduce late HAT [29,30]. In contrast, low-dose aspirin did not prevent HAT in those with HAS in a study by Wolf et al [31]. Our findings, where antiplatelet and anticoagulant therapy were used more commonly in those with HAS who underwent EVT, did not detect a significant change in HAT incidence.

While it is postulated that untreated HAS progresses to HAT due to slow blood flow leading to stagnation [10], our finding that HAS may progress to HAT despite successful EVT in combination with antiplatelet therapy suggests a more complex pathogenesis. The association between HAS and biliary strictures has been postulated to be secondary to ischemic injury and damage to the integrity of the biliary epithelium from the compromised blood flow in HAS, as the hepatic artery is the only source of blood supply to the graft biliary system [8,32]. Although previous studies have suggested that EVT should be considered in ischemic biliary strictures to reduce further graft damage, the benefit of EVT for HAS in preventing new biliary strictures is not clear based on our results. In prior studies, EVT complications after HAS therapy ranged from 0 to 23% [5]. We found complications in 12.6%. In addition, despite successful treatment, those with complications after EVT were significantly associated with the occurrence of HAT, similar to the study findings by Goldsmith et al [5]. Hence, more data and careful patient selection for EVT is essential in the setting of HAS.

There are several limitations in this study owing to its single-center and retrospective nature. First, the population is small. Second, diagnostic evaluation was not the same for all patients, as we included DUS alone to assess severity in a subset, although CT angiography was not and could have provided important additional information on severity to inform therapy. Third, there was heterogeneity between our treatment groups, with the EVT group having significantly more diabetes, pre-transplant PVT, and females. However, because of the small sample size, we could not adjust for these factors as well as HAS severity, hepatic artery anatomy, and collateralization, all of which may have influenced outcomes. Fourth, our EVT protocol was not standardized, and there was variability in use and types of stents and anticoagulation. Despite these limitations in our analysis, we did not find a difference in HAS outcome in those undergoing EVT therapy.

In conclusion, donor and graft hepatic arterial anatomy-related factors significantly influence the occurrence of HAS, emphasizing the importance of donor selection and surveillance in DCD grafts and in transplants with complex donor arterial reconstruction. HAS has inferior outcomes with increased biliary stricture, poor graft, and overall patient survival compared to patients without HAS. Our results indicate that no particular type of therapy (invasive management of HAS by EVT with angioplasty alone or combination with stents, and noninvasive therapy with or without antiplatelet therapy) was clearly beneficial relative to the others in reducing complications. However, these results are not necessarily generalizable, given our small sample size and heterogeneity among treatment groups. Rapid advances and changes in stents and technology are likely influencing results. Multicenter studies with large numbers and standardized protocols are needed to guide the optimal management of HAS after LT.

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Conflict of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.02.012.

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