ORIGINAL ARTICLE

Pre-operative trans-catheter arterial chemo-embolization increases hepatic artery thrombosis after liver transplantation – a retrospective study

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SUMMARY

Little is known about nonsurgical risk factors for hepatic artery thrombosis (HAT) after liver transplantation (LT). We determined risk factors for HAT occurring within 90 days post-LT and analysed the effect of HAT on graft and patient survival. Donor and recipient demographics, surgery-related data and outcome in transplants complicated by thrombosis (HAT+) and their matched controls (HAT−) were compared. Risk factors were assessed by univariate logistic regression. Median (IQR) is given. A total of 25 HAT occurred among 1035 adult LT (1/1997–12/2014) and 50 controls were manually matched. Donor and recipient demographics were similar. Pre-LT trans-catheter arterial chemo-embolization (TACE) was more frequent in HAT+ (HAT+ 20% vs. HAT− 4%, $P = 0.037$). HAT+ had longer implantation [HAT+ 88 min (76–108) vs. HAT− 77 min (66–93), $P = 0.028$] and surgery times [HAT+ 6.25 h (5.18–7.47) vs. HAT− 5.25 h (4.33–6.5), $P = 0.001$]. Early graft dysfunction and sepsis were more frequent in HAT+ and hospitalization longer. TACE had the greatest odds ratio in unadjusted analysis (OR: 6, 95% CI: 1.07–33.53, $P = 0.03$). All but seven grafts were lost after HAT (HAT+ 72% vs. HAT− 36%, $P = 0.003$); however, patient survival was unaffected (HAT+ 79.8% vs. HAT− 76%, $P = 0.75$). LT candidates undergoing TACE are at risk of developing HAT early after transplant.

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Introduction

Hepatic artery thrombosis (HAT) is an infrequent but severe vascular complication after liver transplantation (LT), increasing both graft loss and recipient death [1]. The reported incidence ranges from 2% to 15% [2] and is significantly higher in paediatric (8.3%) than in adult LT (4.4%) [1,3]. The nonstandardized definition of early HAT, which has been described variably from within 1 month up to hundred days after transplantation, probably accounts for the wide range of reported incidences.

Early HAT is generally complicated by acute hepatocellular and bile duct necrosis (as the blood supply for

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the biliary tree relies mostly on the hepatic artery), often followed by sepsis, graft loss and – in the absence of retransplantation – recipient death [3,4].

Early HAT necessitates treatment which includes urgent thrombectomy and an attempt at revascularization. Minimal invasive treatment including percutaneous or pharmacological thrombolysis can be considered; however, suboptimal results and higher incidence of bleeding have been reported after intra-arterial thrombolysis [5].

Because presentation can be unremarkable and symptoms may be delayed, routine and frequent Doppler ultrasound evaluation of hepatic artery patency is necessary for early detection of HAT, prompting revascularization and increasing chances of graft survival [3,6,7]. Nevertheless, often retransplantation is the only option, and urgent allocation is generally granted to patients experiencing early HAT [8–10]. Indeed, graft survival 1 year after transplantation reaches a poor 50% when early HAT occurs, while patient survival ranges from 20% to 60% [3]. When HAT occurs at later stage, outcomes are less devastating. This is likely a consequence of newly formed vascular collaterals that minimize the harmful effect of thrombosis of the main hepatic artery [3].

Surgical risk factors of HAT have been identified (i.e. stenosis or kinking of the anastomosis, vascular graft interposition, multiple arteries), but several nonsurgical factors have also been explored. This comprised a hypercoagulable state, hemodynamic disturbances, immunologic factors, high donor/recipient weight ratio, extensive intra-operative blood transfusion and transcatheter arterial chemo-embolization (TACE) before transplantation have also been suggested [2,11]. The overall effect of nonsurgical factors on the risk of HAT remains unclear [12].

This study aimed to identify risk factors of HAT occurring ninety days after LT and to assess the impact of early HAT on graft and patient survival.

Materials and methods

Population and study design

A prospectively collected clinical database, including all adult solitary LT performed at our institution between 1 January 1997 and 31 December 2014, was reviewed and patients that developed early HAT were identified. Paediatric recipients, living-related transplantations and partial grafts were excluded from the analysis.

Early HAT was defined as any thrombosis of the hepatic artery suspected on Doppler ultrasound, and confirmed by computed tomography, angiography and surgical exploration occurring within 90 days after LT.

For each transplantation complicated by HAT, two controls were manually matched based on characteristics available in our clinical database, such as transplant era (±5 years), donor age (±5 years), donor type [Donation after Brain Death (DBD) or Donation after Circulatory Death (DCD)], donor quality [Extended Criteria Donor (ECD) or Standard Criteria Donor (SCD)], recipient age (±5 years), and lab Model for End-stage Liver Disease score (LabMELD) at the time of transplant (±3 points; Table S1). Patients' medical records were not consulted at the time of matching to reduce possible selection bias.

Donor demographics, cause of death, donor type, donor quality, Body Mass Index (BMI), positivity to cytomegalovirus and hepatitis C virus were considered and compared between transplants that developed early HAT (HAT+) and the matched controls that did not (HAT−). Recipients characteristics considered were age, gender, BMI, indication for LT, labMELD score at the time of transplantation, United Network for Organ Sharing status (UNOS), cytomegalovirus and hepatitis C virus positivity, history and number of TACE before transplantation, pretransplant portal vein thrombosis, gender mismatch, ABO mismatch and donor to recipient weight ratio. The incidence of multiple arterial anastomoses, vascular conduit interposition and anastomosis performed on the recipient aorta, the duration of surgery, cold ischaemia time (CIT), implantation time and the transfusion requirements during transplantation were also recorded and compared between groups.

Grafts were considered as ECD when one of the following criteria was met: age >65 years, permanence in intensive care unit >7 days, BMI >30, sodium >165 mM, last alanine transaminase (ALT) >105 IU/l, last aspartate transaminase (AST) >90 IU/l or last bilirubin >3 mg/dl. Donors without any of the aforementioned features were classified as SCD, as defined by Eurotransplant [13].

Cold ischaemia time was defined as the time between the start of cold flush during the donor procedure and the graft being taken out of the ice box for implantation. Implantation time in the recipient was defined as the time between the liver leaving the ice and vascular reperfusion (vena porta and hepatic artery).

Early allograft dysfunction (EAD) was defined as AST/ALT >2000 IU/l within the first-week post-LT, bilirubin >10 mg/dl on day 7th post-LT and/or international normalized ratio >1.6 on day 7th post-LT [14]. Other outcomes considered were the incidence of

biopsy proven acute rejection, infection, sepsis, biliary complications and the need for retransplantation. Graft loss was defined as retransplantation or death of the recipient of any cause.

Transplant procedure and postoperative care

All recipients underwent classical caval replacement with veno-venous bypass, in the majority of cases also with portal bypass. The portal vein is reconstructed in a standard end-to-end fashion. The preferred hepatic artery reconstruction consists on an end-to-end anastomosis on a Carrel-patch. When the recipient's hepatic artery is considered of poor quality, the dissection is extended proximally until a site suitable for anastomosis is found. Only after failure of this approach and in case of anatomical variation of donor and/or recipient hepatic artery we consider more complex arterial reconstruction, such as multiple arterial anastomoses, iliac allograft interposition or direct implantation of the donor artery on the recipient abdominal aorta.

Standard triple immunosuppression therapy including a calcineurin inhibitor, steroids and antimetabolite was started post-transplantation. Blood counts, biomarkers of inflammation, hepatic and renal function were assessed daily until normalization. Prophylaxis with low molecular weight heparin was administered in all patients to prevent deep venous thrombosis; none of the recipients received prophylactic antiplatelet medication in the first postoperative week. In cases where recipients were anticoagulated prior to LT (i.e. portal vein thrombosis), or in case the need for therapeutic anticoagulation was identified (i.e. Budd–Chiari), low molecular weight heparin was administered at therapeutic doses as soon as possible.

Doppler ultrasound was performed per protocol at least three times within the first 2 weeks after transplant: shortly after arrival of the patient in the intensive care unit, on first and on 14th postoperative day. Further imaging, such as additional Doppler ultrasound, computed tomography or magnetic resonance angiography, was performed during the first week post-LT based on clinical judgement (i.e. in case of abnormal liver test or graft dysfunction) or as a confirmation of a suspected HAT.

Statistical analyses

Continuous variables are expressed as median (IQR), and the difference between groups was evaluated with Student's test or Mann–Whitney *U* test according to data distribution. Categorical variables are expressed as percentages, and the difference in incidence was evaluated with the Pearson's chi-square or Fisher's exact test when appropriate. Logistic regression was used to identify risk factors of HAT. A bootstrap resampling was used to evaluate the stability of the obtained results (100 data sets). Survival analysis was performed with Kaplan–Meier curves, and the difference in survival was tested with the log-rank test. Additionally, univariate proportional hazard model was used to assess the relationship between HAT and graft loss.

Statistical analyses were performed using SPSS (version 20; SPSS Inc. Chicago, IL, USA), and SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Early HAT is infrequent

Between 1 January 1997, and 31 December 2014, 1035 solitary adults LT were performed at our institution. Twenty-five recipients developed HAT within 90 days after transplantation, counting for an overall incidence of 2.4%. HAT was diagnosed 15 days [2–20] after LT.

Urgent relaparotomy for revascularization was performed in six (24%) patients that were transplanted for liver failure ($n = 1$), postethyl cirrhosis ($n = 1$), autoimmune hepatitis ($n = 1$) and hepatocellular carcinoma (HCC; $n = 3$). All the HCC patients requiring revascularization received TACE before transplantation. In patients that underwent urgent relaparotomy, HAT was diagnosed shortly after reperfusion of the graft: intraoperatively in one case due to sudden disappearance of artery pulsatility; by routine doppler ultrasound at the admission in the dedicated ICU in three patients, and at postoperative day 1 and 2 by routine Doppler ultrasound and based on investigation following clinical suspicion in the two remaining recipients. Effective revascularization was achieved in all six patients, with direct redo anastomosis in four cases (after rinse of the graft with heparin via the re-opened stump of the hepatic artery in two patients) and with Fogarty catheter embolectomy through a collateral branch in the remaining two recipients. In all six cases, retransplantation of the graft was avoided. One patient developed intrahepatic biliary strictures 5 months after HAT occurrence (effectively treated with endoscopic procedures) and two recipients died after cardiogenic shock and chronic rejection/bile duct vanishing syndrome, respectively. Conservative management resulted successful in just one additional patient in which a percutaneous

angiography 39 days after transplantation showed HAT with collaterals effectively revascularizing the graft.

The remaining 18 recipients underwent retransplantation. The median time between diagnosis of HAT and ReLT was 12.5 days (3–106); 61% of HAT+ recipients were retransplanted within the first postoperative week (3 days [1–3]).

Risk factors for HAT

As expected after case matching, donor and recipient demographics were equally distributed (Table 1; Table S1). The most frequent indication for LT was postethyl cirrhosis ($n = 18$) and HCC ($n = 16$), and six of the transplants considered (three in each group) were a retransplant. The labMELD score at the time of transplantation (HAT+ 12 [8–17] vs HAT− 12 [9–19], $P = 0.66$) and the UNOS status did not differ. The frequency of gender, ABO mismatch and donor to recipient weight ratio was similar between groups. Five of seven patients pretreated with TACE developed thrombosis (HAT+ 20% vs HAT− 4%, $P = 0.037$). No difference in the incidence of right or left TACE was observed, and all patients underwent more than one session. Similarly, the incidence of patients pretreated with radio-frequency ablation or transplanted without down-staging did not differ. Finally, the rate of incidental diagnosis of previously missed HCC and tumour outside Milan criteria at pathology was similar (Table 1).

Cold ischaemia time was similar but HAT+ had a significant longer implantation time and transplant procedures (Table 2). However, the incidence of multiple arterial anastomoses (HAT+ 16% vs HAT− 30%, $P = 0.26$), direct anastomosis on recipient aorta (HAT+ 4% vs HAT− 0%, $P = 0.33$) or conduit interposition (HAT+ 4% vs HAT− 0%, $P = 0.33$) did not differ between groups (Table 2).

In recipients experiencing HAT, the postoperative course was complicated by higher incidence of EAD (HAT+ 60% vs HAT− 26%, $P = 0.006$) and sepsis (HAT+ 16% vs HAT− 0%, $P = 0.01$). Patients required a longer intensive care unit stay (HAT+ 5.5 day [3–26] vs HAT− 2.5 day [2–7], $P = 0.006$). No difference in the incidence of biliary complications, such as leakage and strictures, was observed between groups. Nevertheless, interventions to treat biliary strictures were more frequently performed in recipients that developed HAT (three patients underwent endoscopic dilatation and stenting, and three recipients needed ReLT) while a conservative approach was more often used in controls that experienced biliary complications (HAT+ 0% vs HAT− 12%, $P = 0.04$; Table 3).

The duration of both transplantation and implantation time was significantly associated with an increased probability to develop HAT in univariate logistic regression. However, pretransplant TACE resulted the predictor with the strongest impact, increasing the probability to develop HAT by sixfold (OR: 6.00, 95% CI: 1.07–33.53; $P = 0.03$). After bootstrap analysis TACE remained a significant predictor in univariate regression in 85% of the resampling (Table 4).

HAT impacts on graft but not patient survival

The rate of retransplantation was significantly higher in LT complicated by HAT (HAT+ 72% vs HAT− 2%, $P < 0.0001$; Table 3). The overall mean survival of the graft was considerably shorter after development of hepatic artery thrombosis [HAT+ 3.1 year (95% CI 1.29–4.91) vs HAT− 9.12 year (95% CI 7.61–10.62), $P < 0.0001$], reaching a poor 39.3% already 1 year after transplantation (HAT+ 39.3% vs HAT− 82%, $P < 0.0001$; Fig. 1). A univariate Cox regression confirmed that the occurrence of HAT is associated with a nearly fourfold increase in the risk of graft loss (HR: 3.89, 95% CI: 1.95–7.76, $P = 0.0001$). Nevertheless, the survival of patients one and 5 year after transplantation was not reduced by the occurrence of HAT (HAT+ 84% vs HAT− 84%, $P = 0.99$; and HAT+ 79.8% vs HAT− 76%, $P = 0.75$, respectively; Fig. 2).

Discussion

This study, covering more than fifteen years of transplantation, shows a low incidence of HAT occurring within 90 days post-LT (2.4%), in line with the incidence reported in a recent systematic review (2.9%) [3]. A considerable reduction of graft survival 1 year after transplantation was observed and the unadjusted analysis confirmed a nearly fourfold increase in the risk of graft loss in transplant complicated by HAT.

Surgery-related factors were considered of paramount importance in the development of HAT [15]. Despite we did not observe increased risk of HAT in transplants in which multiple arterial anastomoses, vascular conduit interposition or anastomosis on recipient aorta were performed, a ‘complex operation’ might have contributed to the risk of HAT. In our series, a difficult isolation of the vascular elements was described only in five cases, due to the presence of intimal dissection in a recipients pretreated with TACE ($n = 1$) or intense inflammation of the pedicle

and peri-arterial tissues ($n = 4$). Considered the scarcity of such cases, the logistic regression could not provide any valuable estimation of the effect of a 'complex procedure'.

Recent advances in transplant surgery and diligent surgical technique might have downsized this additional risk [6,12]. Nevertheless, the duration of both surgery and

Table 1. Overview of donors and recipients demographics.

	HAT− ($n = 50$)	HAT+ ($n = 25$)	*P*-value
Donor			
Age (year)	52.5 (39.5–61)	52 (37.5–64.5)	0.91
Gender (male), *n* (%)	30 (60%)	9 (36%)	0.09
BMI (kg/m²)	24,69 (23.12–26.12)	24.69 (22.27–27.55)	0.36
Cause of death, *n* (%)			
Trauma	21 (42%)	10 (40%)	0.25
Cerebrovascular accident	27 (54%)	12 (48%)	
Anoxia	0 (0%)	2 (8%)	
Other	2 (4%)	1 (4%)	
CMV positive, *n* (%)	16 (32%)	9 (36%)	0.8
HCV positive, *n* (%)	2 (4%)	0 (0%)	1
DCD donor type, *n* (%)	4 (8%)	3 (12%)	0.68
ECD, *n* (%)	20 (40%)	7 (28%)	0.44
Recipient			
Age (year)	54.1 (45.73–62.51)	56.09 (44.64–60.48)	0.95
Gender (male), *n* (%)	28 (56%)	11 (44%)	0.34
BMI (kg/m²)	24.12 (21.55–28.81)	26.54 (20.57–30.83)	0.6
MELD score	12 (8.5–18.7)	11.7 (7.6–17.4)	0.66
Retransplantation, *n* (%)	3 (6%)	3 (12%)	0.39
CMV positive, *n* (%)	27 (54%)	11 (44%)	0.47
HCV positive, *n* (%)	8 (16%)	1 (4%)	0.26
UNOS score, *n* (%)			
UNOS 1	5 (10%)	3 (12%)	0.53
UNOS 2	4 (8%)	4 (16%)	
UNOS 3	41 (82%)	18 (72%)	
Indication, *n* (%)			
Acute liver failure	4 (8%)	3 (12%)	0.68
Metabolic liver disease	9 (18%)	2 (8%)	0.32
Polycystic liver disease	5 (10%)	1 (4%)	0.66
Postethyl cirrhosis	13 (26%)	5 (20%)	0.78
Post-HCV cirrhosis	8 (16%)	1 (4%)	0.26
Post-HBV cirrhosis	0 (0%)	3 (12%)	0.03
Cholestatic liver disease	6 (12%)	2 (8%)	0.71
Other	5 (10%)	5 (20%)	0.29
HCC	9 (18%)	7 (24%)	0.38
HCC incidental diagnosis at pathology	7 (14.3%)	2 (8%)	0.71
HCC outside Milan criteria at pathology	4 (8%)	2 (8%)	1
TACE pre-LT, *n* (%)	2 (4%)	5 (20%)	0.037
Number of TACE session, *n*	4 (4–4)	2 (2–3)	0.1
Time between last TACE and LT (day)	57 (57–243)	90 (80–137)	1
Type of TACE, *n* (%)			
Right	1 (50%)	1 (20%)	0.53
Left	0 (0%)	2 (40%)	
Bi-lobar	1 (50%)	2 (40%)	
Radio-frequency ablation, *n* (%)	6 (12%)	1 (4%)	0.41
No down-staging, *n* (%)	2 (4%)	1 (4%)	1
Portal vein thrombosis, *n* (%)	4 (8%)	3 (12%)	0.58
Gender mismatch, *n* (%)	22 (44%)	15 (60%)	0.23
Recipient/Donor weight ratio	0.97 (0.82–1.24)	1.05 (0.84–1.29)	0.6

Table 1. Continued.

	HAT− (*n* = 50)	HAT+ (*n* = 25)	*P*-value
Blood group, *n* (%)			
Match	48 (96%)	23 (92%)	0.6
Compatible	2 (4%)	2 (8%)	

BMI, body mass index; CMV, cytomegalovirus; DCD, donation after circulatory death donors, ECD, extended criteria donors; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, model for end-stage liver disease; TACE, trans-catheter arterial chemo-embolization; UNOS, united network for organ sharing score.

ECD have been defined, according to Eurotransplant definition, when one of the following criteria was met: age >65 years, permanence in intensive care unit >7 days, Body Mass Index (BMI) >30, sodium >165 mM, last alanine transaminase (ALT) >105 IU/l, last aspartate transaminase (AST) >90 IU/l or last bilirubin >3 mg/dl [31].

Data are expressed as median (IQR) when not differently indicated.

$P < 0.05$ was considered significant.

Table 2. Surgery-related variables.

	HAT− (*n* = 50)	HAT+ (*n* = 25)	*P*-value
Length of surgery (h)	5.25 (4.33–6.5)	6.25 (5.18–7.47)	0.001
Cold ischaemia time (h)	8.27 (6.37–9.42)	7.63 (6.58–9.74)	0.6
Implantation time (min)	77 (66–93)	88 (76–108)	0.03
Duration of hepatic artery anastomosis (min)	29.5 (23–39)	33 (26.5–49)	0.11
Duration of vena porta anastomosis (min)	44 (38–58.5)	54 (40–58)	0.27
PRBC (U)	2 (0–5)	2 (0–6)	0.99
FFP (U)	2 (0–4)	4 (0–6)	0.18
PLTS (U)	0 (0–1)	1 (0–2)	0.13
Conduit interposition, *n* (%)	0 (0%)	1 (4%)	0.33
Anastomosis on aorta, *n* (%)	0 (0%)	1 (4%)	0.33
Multiple artery anastomoses, *n* (%)	15 (30%)	4 (16%)	0.26

FFP, fresh frozen plasma; PLTS, platelets; PRBC, packed red blood cell.

Data are expressed as median (IQR) when not differently indicated.

$P < 0.05$ was considered significant.

implantation time reflecting at least partially the complexity of LT associated with the risk of HAT at univariate analysis.

In the present study, a history of pretransplant TACE was associated with sixfold increase of the probability to develop HAT early after LT (OR: 6, 95% CI: 1.07–33.53).

Trans-catheter arterial chemo-embolization is the current foundation treatment for nonresectable, intermediate stage, hepatocellular carcinoma [16], and it is extensively used as a bridge to transplant in HCC candidates to prevent drop-out from the waiting list due to neoplastic progression [17], or to downstage patients initially outside Milan criteria [18].

The cannulation of the hepatic artery induces traumatic injuries of the endothelium [19], and the antitumoural drugs most commonly injected (doxorubicin hydrochloride and mitomycin C) have a direct cytotoxic effect on endothelial cells, promoting intimal hyperplasia, fibrin thrombus formation and local arteritis [20,21]. Drug-eluting bead TACE seems to reduce the incidence of these dose-dependent side effects by a controlled release of the antitumoural drugs [22]. In our series however, only two patients were treated with this type of chemoembolization and they both developed HAT after transplant (cases number 17 and 24 in Table S1).

At the best of our knowledge, the present study is the first to clearly document high probability to develop HAT after transplant in patients previously treated with TACE. Our results differ from reports in both deceased- and living-related LT [2,23–26]. As outlined in Table 5, previous clinical studies were single-centre retrospective analyses comparing recipients that received TACE with those that did not, and the majority of them considered

Table 3. Short term postoperative outcomes.

	HAT− (n = 50)	HAT+ (n = 25)	P-value
Intensive care unit stay (days)	2.5 (2–7)	5.5 (3–26.25)	0.006
Length of hospital stay (days)	20 (13.75–30)	28.5 (15.25–64.25)	0.08
EAD, n (%)	13 (26%)	15 (60%)	0.006
Acute rejection, n (%)	25 (50%)	9 (36%)	0.37
Infection, n (%)	10 (20%)	9 (36%)	0.16
Sepsis, n (%)	0 (0%)	4 (16%)	0.01
Retransplantation, n (%)	1 (2%)	17 (72%)	<0.0001
Biliary leak, n (%)	2 (4%)	4 (16%)	0.91
Non-anastomotic strictures, n (%)	9 (18%)	5 (20%)	1
Anastomotic strictures, n (%)	7 (14%)	3 (12%)	1
Treatment for biliary strictures, n (%)			
Conservative	6 (12%)	0 (0%)	0.04
ERCP	5 (10%)	3 (12%)	
Retransplantation	0 (0%)	3 (12%)	
Hepaticojejunostomy	2 (4%)	0 (0%)	

EAD, early allograft dysfunction; ERCP, endoscopic retrograde cholangiopancreatography.

EAD was defined when AST/ALT>2000 IU/l in the first week post-transplant and/or bilirubin>10 mg/dl in day 7th after transplantation and/or international normalized ratio>1.6 in day 7th after transplantation [14].

Data are expressed as median (IQR) when not differently indicated.

$P < 0.05$ was considered significant.

Table 4. Summary of univariate analysis of predictors associated with HAT occurrence. In 85% of the bootstrap resampling (100 data sets) pretransplant TACE was a significant predictor of HAT.

	Unadjusted analysis		
	OR	95% CI	P-value
Duration of surgery (min)	1.71	1.2–2.4	0.003
Implantation time (min)	1.03	1.001–1.06	0.04
TACE pre-LT (yes)	6.00	1.07–33.53	0.03

LT, liver transplantation; TACE, trans-catheter arterial chemoembolization.

$P < 0.05$ was considered significant.

the incidence of vascular complications including hepatic artery stenosis, pseudoaneurysm and thrombosis rather than HAT only, failing largely on identifying TACE as a risk factor [23,24,26]. Although pseudoaneurysm, stenosis and thrombosis might present as an evolving complication in a clinical scenario, the underlying pathogenic mechanisms might be different and analyses including these three entities in a single endpoint might not be the most adequate to identify risk factors unequivocally. Indeed, in the work of Li *et al.* [26] the incidence of HAT after transplantation was significantly greater at univariate analysis in patients treated with chemoembolization (TACE 6.23% vs non-TACE 2.03%, $P = 0.004$), despite no association with vascular complications was observed at multivariate regression. Panaro *et al.* [11] focused on explant pathology of the hepatic artery of recipients that received TACE or not. They observed a significant higher incidence of fibrosis and thrombosis at both intrahepatic level (distant from the tumour localization) and main trunk of the hepatic artery in recipients previously treated with chemoembolization (Table 5). In contrast to the aforementioned clinical studies, the explant pathology showed that severe histological injuries of the hepatic artery are present at the time of transplantation in recipients pretreated with TACE. In line with this result, Sueyoshi *et al.* [27] showed that TACE can induce nonreversible occlusion of the hepatic artery already at the time of the radiological procedure, especially in cirrhotic patients. In the present study and in contrast to those summarized in Table 5, we investigated risk factors of HAT considering patients that developed only this complication. Among the possible risk factors explored, pretransplant TACE was associated with the probability to develop HAT. Despite the small number of events limits the estimation of the independent effect of TACE, we found pre-LT chemoembolization persistently associated to HAT in 85% of the bootstrap resampling procedure. Therefore, we believe that our findings provide for the first time a relevant

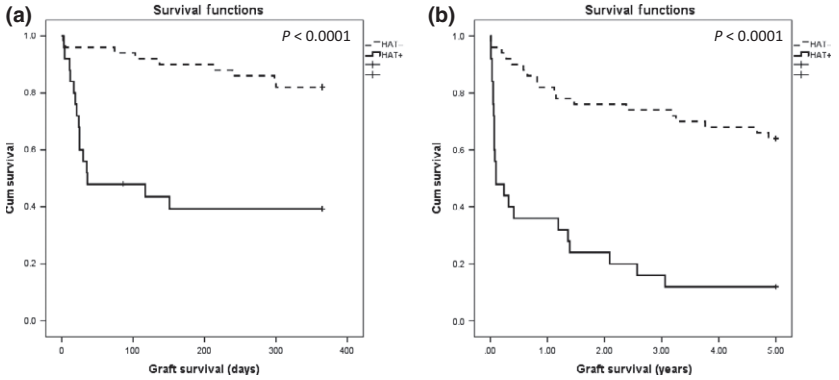

Figure 1 Univariate graft survival in transplantation complicated by HAT vs controls. (a) survival 1 year after transplantation; (b) survival 5 years after transplantation.

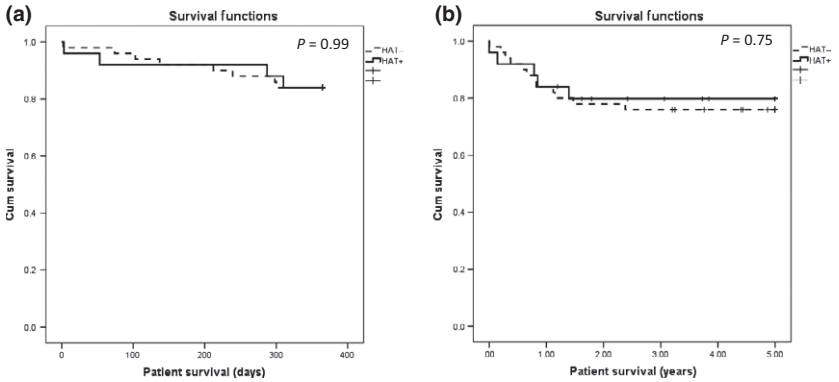

Figure 2 Univariate patient survival in transplantation complicated by HAT vs controls. (a) survival 1 year after transplantation; (b) survival 5 years after transplantation.

clinical insight to a concept long theorized by transplant surgeon. Despite Yang *et al.* [2] used an approach similar to ours, it is important to note that the number of events considered was smaller compared with our study (14 LT vs 25 LT; Table 5) and might partly explained their different results.

It may be argued that the HCC *per se* rather than the pretreatment with TACE might increase the risk of HAT. However, we did not observe any association between HCC and HAT at univariate analysis, not even when incidental diagnosis of previously missed tumours or hepatocellular carcinoma outside Milan criteria at explant pathology was considered.

Transplant surgeons may share the feeling that candidates pretreated with chemoembolization present a more inflamed pedicle and in particular a more fragile hepatic artery at the time of transplant. However, we believe that limiting the use of TACE to reduce the risk of hepatic artery thrombosis after LT is not justified, as the advantages of chemoembolization in HCC patients waiting for LT are undoubtable and the incidence of HAT remains low.

Nevertheless, recipients previously treated with TACE should be considered at risk, and precautions should be taken to prevent and detect earlier the occurrence of thrombosis. Although we did not observe any difference in the time between the last TACE and LT, it might be considered to perform a transplant only after a period of at least 3 months from the last chemoembolization, as the endothelium of the hepatic artery is thrombogenic up to ninety days after TACE [28,29]. At the time of transplantation, it might be considered to extend the dissection of the hepatic artery proximally, closer to the coeliac trunk, which usually appears suitable for anastomosis even after TACE. Additionally, intra-operative flow measurement might help identifying cases with inadequate flow or 'stealing syndrome', thereby reducing the risk of HAT. In the postoperative phase, Doppler velocimetry allowed in our experience the diagnosis of HAT within the first-day post-LT in three recipients transplanted after TACE, and urgent revascularization avoided ReLT in all cases. Finally, early pre-emptive administration of antiplatelet medications might be beneficial. Vivarelli *et al.* [30] observed indeed a reduction of late HAT in

Table 5. Overview of previously published studies investigating hepatic artery complications after trans-catheter arterial chemo-embolization.

Study	Year	Type of study	Population	Endpoint	TACE as a risk factor	Other findings
Richard *et al.* [19]	2000	Retrospective, single centre	1201 DDLT TACE vs non-TACE	Hepatic artery complications	No	–
Lin *et al.* [25]	2009	Retrospective, single centre	54 LDLT TACE vs non-TACE	Intimal dissection	Yes	–
Goel *et al.* [23]	2014	Retrospective, multicentre	456 DDLT TACE vs non-TACE	Hepatic artery complications, Biliary complications	No	Higher incidence of hepatic artery stenosis after TACE
Panaro *et al.* [11]	2014	Retrospective, single centre	67 DDLT TACE vs non-TACE	Hepatic artery complications	Yes	Higher incidence of histological injuries of recipient's hepatic artery after TACE
Yang *et al.* [2]	2014	Retrospective, single centre	744 DDLT HAT+ vs HAT–	Early hepatic artery thrombosis	No	Recipient/donor weigh ratio ≥1.15, Artery anastomosis time >80 min, Intra-operative blood transfusion ≥7 U, Postoperative blood transfusion.
Baccarani *et al.* [24]	2015	Retrospective, single centre	266 DDLT TACE vs non-TACE	Hepatic artery complications	No	–
Li *et al.* [26]	2015	Retrospective, single centre	450 DDLT TACE vs non-TACE	Hepatic artery complications	No	Higher incidence of HAT after TACE

DDLT, deceased donor liver transplantation; HAT, hepatic artery thrombosis; LDLT, living donor liver transplantation; LT, liver transplantation; TACE, trans-catheter arterial chemo-embolization.

recipients treated with aspirin in a retrospective analysis, although we are not able to comment this hypothesis because none of our recipients received aspirin prophylaxis within the first week after LT.

The occurrence of HAT did not reduce patient survival in our series and only two recipients died due to the consequences of hepatic artery thrombosis shortly after the diagnosis. The 8% mortality we observed is lower than the 50% reported by others [2], and it might be partially explained by our low threshold for treatment of confirmed HAT, without waiting for signs of decompensation or infection. We usually attempt urgent revascularization when the thrombosis of the hepatic artery is diagnosed in the very first day after LT. When HAT occurs afterwards, we proceed with relisting the recipient: 61% of the ReLT in this series were performed within the 7th postoperative day. The considerable impact observed on graft survival might have been partially biased by the policy adopted in our centre.

Some limitation should be considered: this is a single-centre retrospective analysis considering LT performed over a significant long period and with a relatively small sample size. Nevertheless, matching the characteristics of donors (age, type and quality) and recipients (age, labMELD score and year of transplantation) enabled us to compare patients with similar basal risk at the time of LT and ensures that the results observed are representative of actual differences in risk factors for HAT. Additionally, the adjusted effect of TACE on the probability to develop HAT could not be estimated due to the small number of events we observed; however, we believe that the strength of the observed unadjusted association between TACE and HAT at our analysis is clinically relevant and unravels the need of efforts shared by a large number of centres to collect evidences prospectively and to tackle a doubt burdening the transplant community since the introduction of TACE. Moreover, we did not adjust our analysis for the use of anticoagulation therapy. However, we did not observe any difference in the incidence of conditions that require such therapy (i.e. pre-LT portal vein thrombosis and Budd Chiari syndrome) and the influence of this additional anticoagulation was likely minimal in our series. Finally, histological examination of the recipient hepatic artery at the time of transplantation was not performed, as the sampling of the recipient hepatic artery at different levels of its extrahepatic course is not routinely performed in our centre. Nevertheless, a pathological confirmation was provided already by Panaro *et al.* [11] who have clearly

proved that chemoembolization significantly increases the incidence of a variety of injuries of the artery wall, from oedema to necrosis and thrombosis, thereby supporting our clinical observation.

In conclusion, HAT occurring early after LT increases the risk of graft loss greatly despite its very low incidence. LT candidates suffering from HCC and treated with TACE should be considered at higher risk of developing HAT. A large multicentre prospective observational study is desired to confirm our results. Early diagnosis of thrombosis is of paramount importance because it can allow prompt revascularization of the hepatic artery, rescuing the graft. In our experience, retransplantation performed in due time before the occurrence of decompensation or infection seemed effective on reducing mortality after HAT.

Authorship

NG, LVP and JP conceived the study; NG and LVP collected, analysed data, performed statistical analyses and drafted the manuscript; CV, GM, WL, SVDM, DV, FN, DM and IJ gave important intellectual contribution and critically revised the manuscript.

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Conflict of interest

The authors declare that there are no conflicts of interest to declare with regard to the conduction and reporting of the data of the clinical trial presented in this manuscript, in line with the editorial policy of Transplant International.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Overview of the study population after matching donor and recipient characteristics.

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