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RETROSPECTIVE STUDY

Risk factors associated with early and late HAT after adult liver transplantation

Yi Yang, Ji-Chun Zhao, Lu-Nan Yan, Yu-Kui Ma, Bin Huang, Ding Yuan, Bo Li, Tian-Fu Wen, Wen-Tao Wang, Ming-Qing Xu, Jia-Yin Yang

Yi Yang, Ji-Chun Zhao, Yu-Kui Ma, Bin Huang, Ding Yuan, Department of Vascular Surgery, Liver Transplantation Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
Lu-Nan Yan, Bo Li, Tian-Fu Wen, Wen-Tao Wang, Ming-Qing Xu, Jia-Yin Yang, Liver Transplantation Center, Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
Author contributions: Yan LN and Zhao JC contributed equally to this work; Yan LN, Zhao JC and Yang Y designed the research; Zhao JC, Ma YK, Huang B, Yuan D and Yang Y contributed to the reconstruction of the hepatic artery; Li B, Wen TF, Wang WT, Xu MQ and Yang JY contributed to the clinical LT work; Yang Y wrote the manuscript; Zhao JC and Yan LN reviewed the manuscript.
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Correspondence to: Ji-Chun Zhao, MD, PhD, Department of Vascular Surgery, Liver Transplantation Center, West China Hospital, Sichuan University, Guoxue Alley 37, Chengdu 610041, Sichuan Province, China. zhao_jc120@126.com
Telephone: +86-28-85422473 Fax: +86-28-85422473
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Abstract

AIM: To identify risk factors that might contribute to hepatic artery thrombosis (HAT) after liver transplantation (LT).

METHODS: The perioperative and follow-up data of a total of 744 liver transplants, performed from February 1999 to July 2010, were retrospectively reviewed. HAT developed in 20 patients (2.7%). HAT was classified as early (occurring in fewer than 30 d post LT) or late (occurring more than 30 d post LT). Early HAT developed in 14 patients (1.9%). Late HAT developed in 6 patients (0.8%). Risk factors associated with HAT were analysed using the χ^2 test for univariate analysis and logistic regression for multivariate analysis.

RESULTS: Lack of ABO compatibility, recipient/donor weight ratio $\geqslant$ 1.15, complex arterial reconstruction, duration time of hepatic artery anastomosis > 80 min, duration time of operation > 10 h, dual grafts, number of units of blood received intraoperatively $\geqslant$ 7, number of units of fresh frozen plasma (FFP) received intraoperatively $\geqslant$ 6, postoperative blood transfusion and postoperative FFP use were significantly associated with early HAT in the univariate analysis ($P < 0.1$). After logistic regression, independent risk factors associated with early HAT were recipient/donor weight ratio $\geqslant$ 1.15 (OR = 4.499), duration of hepatic artery anastomosis > 80 min (OR = 5.429), number of units of blood received intraoperatively $\geqslant$ 7 (OR = 4.059) and postoperative blood transfusion (OR = 6.898). Graft type (whole/living-donor/split), duration of operation > 10 h, retransplantation, rejection reaction, recipients with diabetes preoperatively and recipients with a high level of blood glucose or diabetes postoperatively were significantly associated with late HAT in the univariate analysis ($P < 0.1$). After logistic regression, the independent risk factors associated with early HAT were duration of operation > 10 h (OR = 6.394), retransplantation (OR = 21.793) and rejection reactions (OR = 16.936).

CONCLUSION: Early detection of these risk factors, strict surveillance protocols by Doppler ultrasound and prophylactic anticoagulation for recipients at risk might be determined prospectively.

Key words: Liver transplantation; Hepatic artery throm-

bosis; Risk factors; Complication; Blood transfusion

Core tip: By analysing in detail the risk factors associated with early and late hepatic artery thrombosis (HAT) after adult liver transplantation (LT), we found factors that increased the risk for early and late HAT after LT, as well as some independent predictors of early and late HAT, particularly the postoperative use of blood transfusion which has not been mentioned in previous publications. For patients at increased risk for early and late HAT as described above, prophylactic anticoagulant treatment or daily surveillance by Doppler ultrasound could be considered for the possible prevention or early detection of HAT after LT.

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INTRODUCTION

Liver transplantation (LT) has become the most effective therapy for many patients with acute and chronic end-stage liver disease[1]. Hepatic artery thrombosis (HAT), which is the most common and dreaded vascular complication after LT with a high mortality rate, can lead to graft loss associated with septic hepatic infarction and bile duct ischemia[2]. HAT is usually divided into two categories: early (occurring in less than 1 mo or 4 wk post LT) and late (occurring more than 1 mo or 4 wk post-LT)[3-5]. Compared to the relatively high incidence reported in the first decade of LT[6], the present incidence of HAT after LT varies widely, with a reported frequency of 2.5%-15.0%[7,8]. HAT has generally been more frequent after pediatric LT[2,8].

Compared to the relatively mild course of late HAT, early HAT is associated with an aggressive course, a higher rate of graft loss and increased recipient mortality[9]. With improvements in perioperative care and postoperative surveillance, the present incidence of early HAT has decreased. In a systematic review by Bekker *et al*[5], the incidence of early HAT was 2.9% in adults and 8.3% in children. Late HAT has a prevalence of 2%-20%[5]. The diagnosis of HAT is often suggested by Doppler ultrasonography (DUS) and is confirmed by selective coeliac angiography, computed tomographic arteriography (CTA), exploratory laparotomy, or autopsy[2,5,10]. Retransplantation used to be the only possible therapy for HAT, with a mortality rate approaching 50%[2,4,11]. In the face of a shortage of organs, urgent surgical revascularization has become an effective option for graft salvage in cases of early detection, and can be used to temporarily avoid the need for retransplantation[3-5,8-12]. In recipients with mild symptoms, endovascular management such as intra-arterial thrombolysis, percutaneous transluminal angioplasty, and stent placement have also been attempted in recent years as less invasive alternatives to surgical intervention[13]. Despite these treatments, the overall mortality rate in early HAT was 33.3%, and it was significantly higher in adults than in children (34.3% *vs* 25%, $P < 0.03$)[5].

The real etiology of HAT remains a matter of debate and is in most cases, unidentifiable. It was traditionally proposed that surgical technique was the most important risk factor for HAT[14]. However, other risk factors such as graft preservation, ischemia-reperfusion injury, immunological factors, coagulation abnormalities, infections, donors being elderly, rejection episodes, retransplantation, arterial conduits, prolonged operation time, low recipient weight, and genetic factors have also been implicated[5,15,16].

The identification of risk factors could result in the prompt diagnosis of HAT by concentrating on those patients at risk and could allow for appropriate prophylactic treatment. Therefore, this study employed univariate and multivariate analyses of early and late HAT to identify the independent risk factors contributing to HAT after adult LT in a single institution.

MATERIALS AND METHODS

Patients

Data were derived from a prospectively collected database of all LTs conducted at the West China Hospital of Sichuan University from February 2002 to July 2010. A total of 744 consecutive LTs, including deceased donor liver transplantations (DDLTs) and living donor liver transplantations (LDLTs), were performed at our centre in 726 adult patients suffering from end-stage liver disease. The recipients were 610 men and 116 women, with an age range of 18-69 years (mean age, 44.90 ± 9.98 years). The patients were monitored until December 2012 or their death, and their medical records were retrospectively reviewed. All of the liver grafts were from brain dead donors or living donors. Living and deceased donations were voluntary and altruistic in all cases and were approved by the West China Hospital Ethics Committee. All donations were obtained in accordance with the ethical guidelines of the Declaration of Helsinki. HAT is divided into two categories: early (occurring within less than 1 mo post LT) and late (occurring later than 1 mo post LT).

Perioperative prophylaxis and surveillance protocol for HAT

The detailed surgical techniques for the donors' and recipients' operations were previously reported[17,18]. All of the allografts were preserved in the University of Wisconsin (UW) solution at 4 ℃. Hepatic arterial reconstruction was performed using microvascular techniques after the adoption of systemic anticoagulation (heparin, 62.5 U/kg, intravenous, 5 min before anastomosis). Administration of alprostadil (20 μg) to maintain artery patency

Table 1 Indications for liver transplantation in those developing early and late hepatic artery thrombosis

Indication for LT	HAT	% HAT for indication	Early HAT	Late HAT
Malignancy	10	3.1% (10/327)	6	4
Hepatitis B cirrhosis	6	2.3% (6/265)	5	1
Acute liver failure	3	5% (3/60)	2	1
Hepatic echinococcosis	1	14.3% (1/7)	1	0

HAT: Hepatic artery thrombosis; LT: Liver transplantation.

was used in all of the cases after the completion of hepatic arterial reconstruction. The patency of the arterial anastomosis was evaluated by intraoperative Doppler ultrasonography.

Postoperative prophylaxis and surveillance protocol for HAT

Maintenance immunosuppression, which was previously reported, consisted of a triple-drug regimen that included tacrolimus or cyclosporine, mycophenolate and prednisone[19]. All of the recipients received low-molecular-weight heparin (LMWH) subcutaneously (nadroparin, 0.1 mL/10 kg, every 12 h) and alprostadil (20 μg/d) intravenously as thrombosis prophylaxis for the first 7 post-LT days, as soon as the prothrombin time was less than 20 s, the activated partial thromboplastin time was less than 50 s, the platelet count was more than 30×10^9 cells/L, and no evidence of hemorrhagic complications or bleeding tendency was found. All of the patients underwent DUS every 12 h during the first postoperative week and daily during the second postoperative week to confirm hepatic artery patency. The diagnosis of HAT after LT was based on clinical presentations, color DUS findings, and hepatic artery arteriography. If elevated hepatic enzymes, cholestasis, bile leakage, or a high fever in the absence of acute rejection was detected, color DUS, CTA, or selective hepatic artery angiography was performed to establish the diagnosis. If hepatic arterial inflow was not observed by color DUS, contrast-enhanced ultrasound examination was performed in LDLT cases beginning in January 2005[20]. Recipient hepatic arterial inflow was followed regularly with a color DUS scan 3 or 6 mo after discharge.

Analysis of risk factors

Donor-related, recipient-related, intraoperative and postoperative factors were compared between the patients with and without early or late HAT, respectively. The donor factors that were considered were gender, age (≤ 60 *vs* > 60 years), recipient/donor body weight ratio and blood group. The recipient factors were gender, age (≤ 60 years *vs* > 60 years), aetiology (benign *vs* malignant liver disease), pretransplantation Child-Pugh class, MELD score, blood group, pretransplantation abdominal operative history, transcatheter arterial chemoembolization (TACE) prior to LT and diabetes status. The intraoperative factors were type of allograft (deceased donor whole liver, living-donor or split liver graft), number of grafts (dual or single graft), complex hepatic arterial reconstruction, method of biliary reconstruction, cold ischemia time (CIT), warm ischemia time (WIT), hepatic artery anastomosis time, duration of LT, and transfusion of blood, cryoprecipitate, fresh frozen plasma (FFP) and platelets. The postoperative factors were posttransplantation rejection episodes, transfusion of blood, cryoprecipitate, FFP and platelets (present, absent), bile leakage, portal vein thrombosis (PVT), infection (including pulmonary, biliary, abdominal or other infection), posttransplantation hyperglycemia/diabetes status and retransplantation. For our study, a "complex hepatic arterial reconstruction" was defined as the presence of bench arterial reconstruction, multiple numbers of anastomoses, or bypass for hepatic arterial reconstruction.

Statistical analysis

SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, United States) was used to analyse the relevant data. All of the numerical data are presented as mean ± SD or as median. For univariate analysis, categorical variables were compared using χ^2 test for associations and the Mann Whitney *U* test was used for nonparametric data analysis. For univariate analysis, $P \leqslant 0.05$ was considered significant. Variables with $P < 0.05$ in the univariate analysis were entered into a forward stepwise logistic regression analysis to estimate the OR of each HAT (dependent variables) and the presence or absence of potential prognostic factors (independent variables). The OR was defined as the exp (β-coefficient) with its 95%CI.

RESULTS

The characteristics of the patients included in the study are shown in Tables 1 and 2. In this series of 744 adult LTs, 20 episodes of HAT were observed, for an overall incidence of 2.7%. Early HAT occurred in 14 (1.9%) recipients and late HAT in 6 (0.8%). The median time until HAT was detected was 3 (range: 1-20) d in the early group and 52 (range: 30-70) d in the late group. All of the HAT cases (Table 1) were identified by Doppler ultrasound and were confirmed or diagnosed by hepatic artery angiography and surgical exploration.

Early HAT

Table 2 shows the donor and recipient characteristics associated with early HAT. In univariate analysis, recipients of ABO-incompatible grafts showed a significantly greater incidence of HAT (16.7%), compared with those who secured ABO-identical (1.8%) or compatible (1.1%) grafts ($P = 0.025$). Body weight ratio (recipient/donor) greater than 1.15 ($n = 112$) was associated with an incidence of early HAT of 5.4% compared to 1.3% of the 632 cases with a ratio < 1.15 ($P = 0.003$). There were no significant differences in the incidences of early HAT between the recipients' groups by age, gender, aetiology, Child-Pugh class, MELD scores, recipients' pretrans-

Table 2 Univariate analysis for recipient and donor factors associated with early hepatic artery thrombosis *n* (%)

Variable	Patients	Early HAT	*P* value
Number of LTs	744	14 (1.9)	-
Recipient gender			
Male	627 (84.3)	13 (2.1)	
Female	117 (15.7)	1 (0.9)	0.370
Recipient age (yr)			
> 60	63 (8.5)	2 (3.2)	
≤ 60	681 (91.5)	12 (1.8)	0.460
Aetiology			
Malignancy	327 (44)	6 (1.8)	
Benign	417 (56)	8 (1.9)	0.930
Child-Pugh class			
A	233 (31.3)	3 (1.3)	
B	291 (39.1)	5 (1.7)	
C	220 (29.6)	6 (2.7)	0.510
MELD score	14 (6-59)	12.5 (6-36)	0.538
Pre-LT abdominal operation			
Yes	222 (29.8)	2 (0.9)	
No	522 (70.2)	12 (2.3)	0.199
TACE history			
Yes	67 (9.0)	2 (3.0)	
No	677 (91.0)	12 (1.2)	0.490
Diabetes			
Yes	40 (5.4)	1 (2.5)	
No	744 (94.6)	13 (1.8)	0.770
Blood group			
Match	649 (87.2)	12 (1.8)	
Compatible	89 (12.0)	1 (1.1)	
Incompatible	6 (0.8)	1 (16.7)	0.025
Recipient/donor wt. ratio			
≥ 1.15	112 (15.1)	6 (5.4)	
< 1.15	632 (84.9)	8 (1.3)	0.003
Donor gender			
Female	113 (15.0)	3 (2.7)	
Male	641 (85.0)	11 (1.7)	0.495
Donor age (yr)			
≥ 60	4 (0.5)	0	
< 60	750 (99.5)	14 (1.9)	0.780

LT: Liver transplantation; wt: Weight; TACE: Transcatheter arterial chemoembolization.

Table 3 Univariate analysis for potential intraoperative factors associated with early hepatic artery thrombosis *n* (%)

Variable	Patients	Early HAT	*P* value
Type of allograft			
Whole size	544	10	
LDLT	196	4	
Split	4	0	0.948
Dual grafts			
Yes	10 (1.3)	1 (10.0)	
No	734 (98.7)	13 (1.8)	0.057
Complex arterial reconstruction			
Yes	30 (4.0)	3 (10.0)	
No	714 (96.0)	11 (1.5)	0.001
HA anastomosis time (min)			
> 80	153 (20.6)	8 (5.2)	
≤ 80	591 (79.4)	6 (1.0)	0.001
Biliary reconstruction			
R-D	74 (9.9)	1 (1.4)	
D-D	670 (90.1)	13 (1.9)	0.723
Operation time (h)			
> 10	208 (28.0)	9 (4.3)	
≤ 10	536 (72.0)	5 (0.9)	0.002
Blood (U)			
≥ 7	383 (51.5)	12 (3.1)	
< 7	361 (48.5)	2 (0.6)	0.010
FFP (U)			
≥ 6	295 (39.7)	10 (3.4)	
< 6	449 (60.3)	4 (0.9)	0.014
Platelets			
Yes	223 (29.9)	2 (0.9)	
No	521 (70.1)	12 (2.3)	0.199
WIT (min)	51 (36-105)	54 (38-82)	> 0.1
CIT (min)	359 (109-782)	341 (134-542)	> 0.1

LT: Liver transplantation; LDLT: Living donor liver transplantation; R-D: Roux-en-Y choledochojejunostomy biliary reconstruction; D-D: End to end choledochocholedochostomy; FFP: Fresh frozen plasma; WIT: Warm ischemia time; HAT: Hepatic artery (HA) thrombosis; CIT: Cold ischemia time.

plant history of laparotomy or TACE or diabetes status or the age or gender of the donor.

Early HAT was shown to be associated primarily with intraoperative factors as observed in Table 3. The incidence of early HAT in patients transplanted with dual grafts (n = 10) was 10%, compared to 1.8% occurring in recipients transplanted with a single graft (n = 734), but without reaching statistical significance (P = 0.057). There was a significant difference in the rate of early HAT in cases involving complex hepatic arterial reconstruction (10% of 30 recipients), compared to hepatic artery anastomosis without complex reconstruction (1.5% of 714 recipients, P = 0.001). The incidence of early HAT among recipients with time to hepatic artery anastomosis longer than 80 min (5.2% of 153 cases) was significantly greater than that for those recipients with durations ≤ 80 min (1.0% of 591 cases). Early HAT occurred more frequently in recipients with longer total operative times of more than 10 h, compared with those with operative times within 10 h (4.3% of 208 cases *vs* 0.9% of 536 cases, P = 0.002). The incidence of HAT reached statistical significance when intra-operative whole blood transfusions of 7 or more units were included (P = 0.01). The infusion of 6 or more units of FFP intraoperatively increased the incidence of early HAT significantly (P = 0.014). Neither the number of units of platelets transfused nor the number of units of cryoprecipitate transfused had any significant impact on the incidence of early HAT. There was no significant difference in the rate of early HAT between recipient groups by type of allograft, methods of biliary reconstruction, CIT, or WIT.

Postoperative factors were also analysed, as shown in Table 4. The incidence of early HAT was significantly greater in patients who required blood transfusions than in those without transfusion requirements of blood (3.7% of 244 cases *vs* 1.0% of 500 cases, P = 0.011). The transfusion requirement for FFP was significantly associated with early HAT in univariate analysis (P = 0.044), but no association was reported with transfusion requirement for platelets. Postoperative factors, such as posttransplantation rejection episodes, bile leakage, PVT, infection (including pulmonary, biliary, abdominal or other

Table 4 Univariate analysis for potential postoperative factors associated with early hepatic artery thrombosis *n* (%)

Variable	Patients	Early HAT	*P* value
Episode of rejection			
Yes	42 (5.6)	1 (2.4)	
No	702 (94.4)	13 (1.9)	0.806
Retransplantation			
Yes	18 (2.4)	0	
No	726 (97.6)	14 (1.9)	0.708
Infection			
Yes	126 (16.9)	3 (2.4)	
No	618 (83.1)	11 (1.8)	0.651
Blood			
Yes	244 (32.8)	9 (3.7)	
No	500 (67.2)	5 (1.0)	0.011
FFP			
Yes	240 (32.3)	8 (3.3)	
No	504 (67.7)	6 (1.2)	0.044
Platelets			
Yes	60 (8.1)	1 (1.7)	
No	684 (91.9)	13 (1.9)	0.898
Hyperglycemia/diabetes			
Yes	268 (36.0)	5 (1.9)	
No	476 (64.0)	9 (1.9)	0.981
PVT			
Yes	9 (1.2)	0 (11.1)	
No	735 (98.8)	14 (1.9)	0.679
Bile leak			
Yes	17 (2.3)	0	
No	727 (97.7)	14 (1.9)	0.721

FFP: Fresh frozen plasma; PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis

Table 5 Independent predictors of early hepatic artery thrombosis after liver transplantation

Variable	*P* value	OR	95%CI
Recipient/donor wt. ratio ⩾ 1.15	0.008	4.499	1.487-13.608
HA anastomosis time > 80 min	0.004	5.429	1.725-17.086
Intraoperative blood transfusion ⩾ 7 U	0.017	4.059	1.290-12.770
Postoperative blood transfusion	0.015	6.898	1.463-32.526

HA: Hepatic artery; wt: Weight.

infections), posttransplantation hyperglycemia/diabetes status and retransplantation had no significant impact on the incidence of early HAT.

The factors independently predictive of early HAT are listed in Table 5. After logistic regression, independent risk factors associated with early HAT included recipient/donor weight ratio ⩾ 1.15 (OR = 4.499), duration of hepatic artery anastomosis > 80 min (OR = 5.429), the number of units of blood received intraoperatively ⩾ 7 (OR = 4.059), and the receiving of blood transfusions postoperatively (OR = 6.898).

Late HAT

In univariate analysis, donor and recipient characteristics and their intraoperative or postoperative associations with the development of late HAT are shown in Table 6. Diabetes was diagnosed preoperatively in 2 of the 40 recipients who developed late HAT, with 4 cases of diabetes diagnosed in the 704 without HAT ($P = 0.037$). The incidences of late HAT in patients with reduced liver grafts (LDLT and split) were 0.5% and 25%, respectively, reaching statistical significance ($P < 0.001$). Surgical durations longer than 10 h increased the incidence of late HAT significantly (1.7% of 208 cases, $P = 0.034$). In total there were 18 regrafts in the 744 transplants in this series. Late HAT occurred in one of these retransplantations (1/18). Retransplantation was found to be a risk factor for late HAT in this study ($P = 0.023$). The incidence of late HAT among recipients with an episode of rejection (4.2% of 48 cases) was significantly greater than that for those without rejection (0.2% of 696 cases, $P = 0.05$), and recipients with diabetes preoperatively and those with a high level of blood glucose or diabetes postoperatively ($P = 0.025$) were also associated with late HAT in univariate analyses. There were no significant differences in the incidences of late HAT between patients grouped by age, gender, aetiology, Child-Pugh class, MELD score, recipient pretransplant history of laparotomy or TACE, age or gender of donor, ABO or Rh blood type and matching, body weight ratio (recipient/donor), duration of arterial reconstruction, method for arterial reconstruction, or type of graft. Intraoperative elements were evaluated for their potential associations with the development of late HAT. Neither the duration of arterial anastomosis nor complex arterial reconstruction increased the incidence of late HAT significantly.

Table 6 Univariate analysis for risk factors associated with early hepatic artery thrombosis *n* (%)

Variable	Patients	Late HAT	*P* value
Diabetes pre-LT			
Yes	40 (5.4)	2 (5.0)	
No	704 (94.6)	4 (0.6)	0.037
Type of LT			
Whole size	544 (73.1)	4 (0.7)	
LDLT	196 (26.3)	1 (0.5)	
Split	4 (0.5)	1 (25)	< 0.001
Operation time			
> 10 h	208 (28.0)	4 (1.7)	
⩽ 10 h	536 (72.0)	2 (0.4)	0.034
Retransplantation			
Yes	18	1	
No	726	5	0.023
Hyperglycemia/post-LT diabetes			
Yes	268 (36.0)	5 (1.9)	
No	476 (64.0)	1 (0.2)	0.025
Episode of rejection			
Yes	48 (6.5)	2 (4.2)	
No	696 (93.5)	4 (0.6)	0.050

LT: Liver transplantation; LDLT: Living donor liver transplantation.

As shown in Table 7, after logistic regression, the independent risk factors associated with late HAT were duration of surgery > 10 h (OR = 6.394), retransplantation (OR = 21.793), and rejection reactions (OR = 16.936).

Table 7 Independent predictors of late hepatic artery thrombosis after liver transplantation

Variable	*P* value	OR	95%CI
Operation time > 10 h	0.050	6.394	0.998-40.977
Episode of rejection	0.004	16.936	2.424-118.317
Retransplantation	0.001	21.793	3.302-143.836

DISCUSSION

HAT after LT is a common critical vascular complication. It occurs infrequently, but is a potentially devastating complication. In our series of 744 consecutive LTs, the incidence of early HAT was 1.9%, similar to the published experiences[5], while late HAT occurred in 0.8% of patients, which was superior to the reported result[3]. As risk factors, the clinical presentations and treatment of early HAT were widely different from those of late HAT. This variation was associated with the time at which HAT developed.

In early reports, early HAT was largely correlated with surgical technique[14]. Owing to advances in surgical techniques for LT, surgical technique is most likely not a major risk factor at some LT centres[4,7]. Warner *et al*[10] reported that every additional 10 min of reperfusion time (interval between portal vein reperfusion and restoration of arterial flow) was associated with a 27% increase in risk. Prolonged hepatic artery anastomosis time (> 80 min) increased the risk of early HAT significantly, similar to the Warner's finding, and it was also an independent risk for early HAT in multivariate analysis in our series (OR = 5.429, $P = 0.004$). The majority of the recipients who needed prolonged artery anastomosis time required complex artery reconstruction, in cases of recipients requiring dual-graft LT, arterial conduit or bench arterial reconstruction. Prolonged artery anastomosis duration could increase the risk of arterial intimal injury, which has been associated with HAT after LT. In a previous report[4], the incidence of early HAT was significantly greater in recipients receiving Roux-en-Y biliary reconstruction, which was not found to be a risk factor for early or late HAT in our series.

Oh *et al*[3] found that a recipient/donor weight ratio greater than 1.25 increased the risk of early HAT after LT. Similar to their finding, our study also showed that a recipient/donor weight ratio ⩾ 1.15 significantly increased the risk of early HAT in both univariable and multivariable analyses. Other donor factors included a low donor/recipient age ratio, which was previously described as a risk factor. Donor age older than 50 years has also been identified as an independent risk factor for HAT[21]. Although our data did not identify this association, other studies have found increased donor age to be a risk factor for HAT[22]. Transplantation across ABO blood groups was found to be aetiologically linked to HAT[16]. In our analysis, the lack of ABO compatibility increased the risk of early HAT in the univariable analysis significantly but not independently in the multivariate analysis. This complication could potentially be prevented by careful selection of donors during the pre-transplant decision-making process.

Living and deceased donor left lateral segment grafts were associated with an increased rate of HAT in a previous study, compared with whole liver grafts[23]. Other published studies have not shown an increased risk of HAT in recipients of these grafts[4,24]. In our series, there was no statistically significant increase in the risk of HAT in recipients of whole or living donor liver grafts. Split liver graft was found to be significant in the univariable analysis but not in the multivariable analysis, possibly because of the small number of these grafts. Previous upper abdominal surgery could cause increased adhesions and prolonged operative time, and operative time was significantly associated with HAT[4]. Previous upper abdominal surgery was not a risk factor for HAT in our study. Similar to these studies[4,21], retransplantation was identified as an independent risk for late HAT in our series (OR = 21.793).

Increased operation time and prolonged cold ischemia and warm ischemia times have been found to increase the risk of early HAT in previous studies[4,7,15]. Prolonged CIT and WIT were not found to increase the risk of HAT in our series. Prolonged operative time (⩾ 10 h) increased the risk of early and late HAT, which was an independent risk factor (OR = 6.394) for late HAT in multivariable analysis in our series. The intraoperative use of 7 or more units of transfused blood and 6 or more units of FFP and the postoperative use of transfused blood or FFP increased the risk of early HAT. These associations have also been previously reported[4,7,15]. Due to ischemia/reperfusion damage to liver grafts, haemostasis tends to rapidly normalize after LT[25]. Furthermore, delayed recovery of plasma levels of antithrombin Ⅲ and protein C after LT induced a hypercoagulable status[26]. This status could be further exacerbated by the transfusion of blood or FFP. The possible mechanisms leading to late HAT were not clear, but they might involve immunosuppressants, hypertension, hypercholesterolemia, and diabetes mellitus[27]. Furthermore, although the occurrence of CMV infection could activate the endothelium, resulting in a prothrombotic state[25], which has been demonstrated in previous publications[3,4], monitoring the CMV status of donors and recipients is not routine at our center.

Although a number of centers use prophylactic heparin post LT[3,4,10], a randomized controlled trial needs to be undertaken to analyze the risks and benefits of such a method. Low-dose LMWH is used in patients at high risk for HAT in our center. In contrast, the administration of antiplatelet medication has been described as an attractive choice. Vivarelli *et al*[28] reported a reduction in late HAT and cardiovascular events with long term aspirin in a single-center, retrospective study. Prospective, randomized studies on aspirin prophylaxis need to be performed to analyze the safety and efficacy of such an approach.

In conclusion, for patients at increased risk for early and late HAT, as shown above, prophylactic anticoagulant treatment and daily Doppler ultrasound screening should be considered for the possible prevention or early detection of HAT after LT. Multicentre studies or randomized prospective controlled studies should be performed to assess this high-risk group.

COMMENTS

Background

Liver transplantation (LT) has become the most effective therapy for many patients with acute and chronic end-stage liver disease. Hepatic artery thrombosis (HAT) is the most common and dreaded vascular complication after LT, with a high mortality rate. The identification of risk factors could improve prompt diagnosis of HAT by concentrating on those patients at risk and allowing for appropriate prophylactic treatment.

Research frontiers

The real etiology of HAT remains a matter of debate and, in most cases, is unidentifiable. It was traditionally proposed that surgical technique was the most important risk factor for HAT. However, other risk factors such as graft preservation, ischemia reperfusion injury, immunological factors, coagulation abnormalities, infections, donor's age, rejection episodes, retransplantation, arterial conduits, prolonged operative time, low recipient weight, and genetic factors have also been implicated.

Innovations and breakthroughs

This study was a retrospective analysis of a large case series. Several independent risk factors for early HAT were identified, including a recipient/donor weight ratio $\geqslant$ 1.15, duration of hepatic artery anastomosis > 80 min, number of units of blood received intraoperatively $\geqslant$ 7 and the receiving of blood postoperatively. Additionally, duration of surgery > 10 h, retransplantation and rejection reactions were found to be independent risk factors for late HAT. These findings include important information for transplant surgeons.

Applications

For patients at increased risk for early and late HAT as shown above, prophylactic anticoagulant treatment and daily Doppler ultrasound screening should be considered for the possible prevention or early detection of HAT after LT.

Peer review

The article by Yi *et al* "Risk factors associated with early and late HAT after adult liver transplant" is overall well-written and provides a contemporary analysis of a long-standing problem in liver transplantation. The article's strengths are particularly related to the operative/perioperative phase with regard to the effects of complicated transplants and requirement of blood products in a contemporary era where blood products are overall reduced across the field.

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