Hepatic Artery Thrombosis–Related Risk Factors After Living Donor Liver Transplantation: Single-Center Experience From Turkey

B. Unal, F. Gonultas, C. Aydin, E. Otan, C. Kayaalp, and S. Yilmaz

ABSTRACT

Aim.   The purpose of this retrospective study is to evaluate the risk factors hepatic artery thrombosis (HAT) after orthotopic liver transplantation (OLT) in a consecutive series from a single center.

Materials and Methods.   Between January 2010 and May 2012, we performed 278 living donor liver transplantations, including 189 males and 89 females. We compared the risk factors between HAT and non-HAT groups according to the following variables: age, gender, body mass index (BMI), graft weight, use of graft, Child-Pugh and model for end stage liver disease score, level of hemoglobin, blood pressure, operation time, blood transfusion, presence of ascites, international normalized ratio (INR) level, and etiology.

Results.   Eighteen patients, including 15 males and 3 female, had HAT after the operation (mean age, 45.1 years; age range, 22–60 years). There were no pediatric patients in the HAT group. HAT rate was 6.5% in our series. Graft loss and retransplantation due to HAT was 38.7% in a 2-year period. Biliary leakage was observed in 72 (25.8%) living donor liver transplantations; this rate was higher in patients with HAT (n = 8; 44.4%). The infection rate was 50% (n = 9) in the HAT group and was 32.7% (n = 91) in the non-HAT group. Mean INR value was 2.15 in the HAT group and 1.72 in the non-HAT group. When we compared the groups according to use of graft for anastomosis, biliary lekage, infection, and INR value, the differences were statistically significant ($P < .05$).

Conclusion.   Although the results of OLT have improved over the past years, HAT is still associated with substantial morbidity, high incidence of graft failure, and high mortality rates. The most important findings associated with HAT in our series were found as INR levels, bile leakage, and resistant infections. Use of vascular graft for hepatic artery anastomosis was found to increase HAT risk.

VASCULAR complications after orthotopic liver transplantation (OLT) are one of the most frightening problems that frequently result in graft and patient loss. Arterial complications in liver transplantation are the most frequent cause of vascular complications and are present in 3% to 12% of all transplantation.[1,2] Hepatic artery thrombosis (HAT) is a serious complication in patients undergoing OLT. In general, HAT is divided into 2 categories: early HAT and late HAT.[2–4] Early HAT is a major complication following liver transplantation and it is an important cause of graft loss and mortality.[5–8] The cornerstone of this therapy has been urgent retransplantation that is limited by organ availability.[3] In this study, we retrospectively analyzed the risk factors for the development of HAT after living donor liver transplantation.

MATERIALS AND METHODS

This is a single-center study and data was derived from a prospectively collected data base from January 2010 to May 2012. In terms of risk factors that may be associated with early ($\leq$30 day) and late ($\geq$30 day) HAT, 278 living donor liver transplantation patients were evaluated. There were 189 males and 89 females (mean age, 41.6 years; age range, 4 months–72 years). The mean model for end-stage liver disease score before transplantation was 16.3 ± 2.

Routine Doppler screening was performed peroperatively and on the first day after surgery. Diagnoses of arterial complications were performed based on clinical and biological findings. Multislice computed tomography (CT) and arteriography were performed when the doppler showed pathological findings or when the clinical and laboratory profile suggested thrombosis. Anticoagulant therapy was not routinely administered. Hepatic artery anastomosis was performed using interrupted 8-0, 9-0, 10-0 (in some pediatric cases) polypropylene sutures under the vision of surgical loupes (8×) by the same surgeon.

Statistical analyses were performed using SPSS Advanced Statistics 16.0 software package (SSPS Inc, Chicago, Ill, United States).

RESULTS

In this series with 278 OLT, HAT rate was 6.5% (n = 18). According to the time of diagnosis, the rate of early HAT was 17/18 and late HAT was 1/18. Eighteen patients, including 15 males and 3 females, had HAT after the operation (mean age, 45.1 years; age range, 22–60 years). Graft loss and retransplantation due to HAT was 38.7% in the 2-year period. There were 10 pediatric patients (age range, 4–60 months). There was no pediatric patients in the HAT group.

Etiologic factors associated with chronic liver disease are shown in Table 1 The indications for OLT in those recipients subsequently developing HAT were as follows: 9 (50%) had a history of hepatitis B virus (HBV)-related liver cirrhosis, 3 (16.6%) had HBV + hepatitis D virus (HDV), 2 (11.1%) had HBV + hepatocellular carcinoma (HCC). Two patients (2/18) had HCV, 1 case (1/18) had Wilson's disease, and another case (1/18) had cryptogenic liver disease.

We performed 2 retransplantations as a result of recurrence of liver disease during this study period. The factors evaluated for patients with HAT are shown in Table 2. The HAT rate was 27.3% (3/11) in the vascular graft group and 5.6% (15/267) in the without vascular graft group (P < .05). Double-hepatic artery anastomosis was the preferred technique for 12 patients of the 278 patients. There was no HAT

Table 1. Etiologic Factors Associated With Chronic Liver Disease

HBV	137 (49.2)
HBV + HCC	17 (6.1)
HCC	5 (1.7)
HCV	15 (5.3)
Ethanol	4 (1.4)
Autoimmune	3 (1.07)
Biliary atresia	1 (0.3)
Echinococcus alveolaris	2 (0.7)
Budd-Chiari	7 (2.5)
Fulminant hepatitis	25 (8.9)
Cryptogenic	46 (16.5)
Primary biliary cirhosis	3 (1.07)
Other	13 (4.6)

Abbreviations: HBV, hepatitis B Virus; HCV, hepatitis C Virus; HCC, hepatocelluler carcinoma.

in the double-hepatic artery anastomosis group. Three saphenous vein grafts, 3 cadaveric arterial grafts were used and 4 splenic artery interpositions, 1 gastric artery interposition were performed due to intimal dissection in the artery or peroperative thrombosis during the initial surgery. Among these patients, there was 1 HAT in a saphenous vein graft, 1 in a splenic artery interposition group, and 1 in a left gastric artery group.

As a treatment, we performed end-to-end anastomosis of the graft artery and recipient splenic artery with interposition in 2 HAT patients, end-to-side anastomosis between the graft hepatic artery and the recipient aorta with synthetic graft in 1 HAT patient's end-to-end anastomosis of the graft artery, and recipient hepatic artery with cadaveric arterial and saphenous vein grafts in 2 HAT patients (Fig 1). We gained hepatic inflow with embolectomy in 3 patients and with end-to-end hepatic artery re- anastomosis in the remaining patients.

Mean international normalized rate (INR) value was 2.15 in the HAT group and 1.72 in the non-HAT group. Biliary leakage was seen in 72 (25.8%) living donor liver transplantations; this rate was higher in patients with HAT (n = 8; 44.4%). The infection rate was 50% (n = 9) in the HAT group and was 32.7% (n = 91) in the non-HAT group. When we compared the groups according to biliary leakage, infection, and INR, the differences were statistically significant (P < .05). The mortality due to sepsis, multiple-organ failure, and graft dysfunction was 38.9% (n = 7) of the patients with HAT and 20.1% (n = 52) of the non-HAT patient group (P < .05).

DISCUSSION

HAT after liver transplantation is a severe complication that may lead to graft infarction and subsequent graft loss. HAT when it occurs early post OLT may present with acute graft failure, sepsis, or liver abscess, and bile duct complications such as biliary leak or stricturing.[5] The incidence of HAT was reported as 3%–12% of adult liver transplantations and subsequently resulted in retransplantation in 50%–75% of these patients in the literature.[2] The HAT rate was 6.5% in our series and the graft loss due to HAT was 38.7% in a 2-year period. Several series reported HAT in <10% of recipients, with higher rates for children.[6] The number of pediatric patients was 10 (age range, 4–60 months) in our series. There were no pediatric patients in the HAT group.
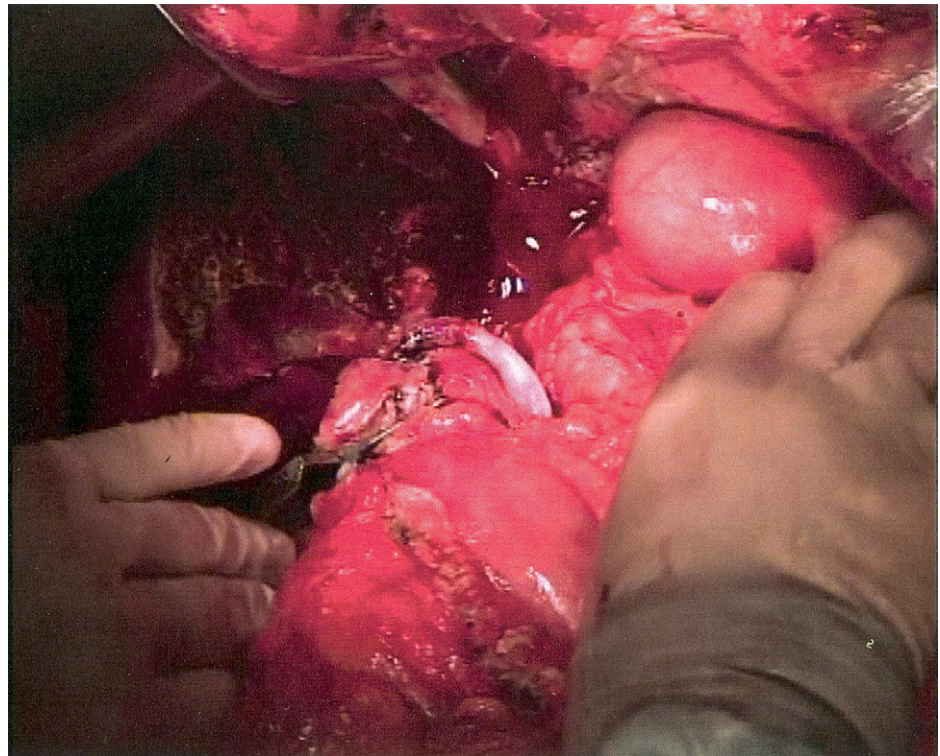
The symptoms, signs, and abnormal laboratory values are mostly absent in early HAT because its presentation is mostly acute; screening by routine doppler ultrasound is very important. In addition to doppler ultrasound, multislice CT and digital angiography technologies have provided an accurate and rapid method for detecting HAT before ischemic damage of the allograft.[7,8] We systematically use routine doppler screening at our institution first intraoperatively after the anastomosis and daily during the first week.

Silva et al reported that bile leak was associated with 12 of the 61 patients who developed HAT, as compared to 39

Fig 1. End-to-end anastomosis of the graft artery and recipient hepatic artery with saphenous vein graft.

of the 1196 recipients who did not develop HAT (P = .001) in their 10-year period.[8] When we compared the biliary leakage rates between the HAT and non-HAT groups, we also found statistically significant difference (P < .05) between the 2 groups.

Treatment modalities for HAT include thrombectomy alone, intrahepatic arterial thrombolysis with thrombolytic agents, creation of a new anastomosis between a more proximal part of the recipient artery and a more distal part of the donor hepatic artery, and introduction of an interposition graft or retransplantation. Early diagnosis is a prerequisite for these revascularization strategies. Early HAT presents mostly with acute fulminant hepatic failure and these conditions require retransplantation. Retransplantation is limited by both organ availability and the patient's clinical condition. Urgent revascularization with thrombectomy and a combination of thrombectomy with revision of anastomosis has been successful in some patients with an early diagnosis. Treatment modality depends on the time of diagnosis.[2,9] The rate of early HAT was 17/18 and late HAT was 1/18 in patients with HAT in our series. Because of the rate of early HAT, an early aggressive treatment procedure was selected and embolectomy and reanastomosis with/without graft was performed in 11 patients. The retransplantation rate was 38.9%. According to the current literature almost 50% of HAT patients died without retransplantation.[9,10] Those who did survive in patients with HAT suffered significant morbidity, related to problems of hepatic sepsis and biliary tree complications.[9]

Although retransplantation has been credited with reducing the mortality of HAT, the inadequate supply of donor organs has limited this option in our country. Therefore, we are supposed to diagnose this condition early and apply embolectomy and reanastomosis techniques to preserve the transplanted liver. The feasibility of using immediate revascularization to avoid the need for retransplantation has been reported in the literature. The use of the splenic artery for the arterial inflow in HAT has been previously described and there have been several reports of transplant arterial reconstruction using some interposition grafts.[11–15] We preferred following procedures for hepatic inflow in patients with HAT: end-to-end anastomosis of the graft artery and recipient splenic artery with interpositions, end-to-side anastomosis between the graft hepatic artery and recipient aorta with synthetic graft, end-to-end anastomosis of the graft artery and recipient hepatic artery with cadaveric arterial and saphenous graft, embolectomy, and end-to-end hepatic artery re- anastomosis.

Urgent revascularization with the reuse of recipient hepatic artery may carry the risk for inadequate flow or other problems in this vessel, which may contribute to re-HAT.[8,9] But we suggest a revascularization procedure if the presence of back-bleeding from the graft hepatic artery is present with normal-appearing liver.

Surgical technique is probably not a major risk factor at our high-volume transplantation center. Some studies demonstrated that the HAT rate was higher in case of multiple hepatic artery anastomoses. When we compared the num-

Table 2. Factors Evaluated for Patients With HAT

	HAT Group (n = 18)	Non-HAT Group (n = 260)
Female/male	3/15	86/174
Age	45.1 (22–60 y)	41.6 (4 mo–72y)
BMI	24.4 kg/m^2	24.7 kg/m^2
Mean CHILD score	9	8
Mean MELD score	18	17
Mean graft weight	726.4 g	759.6 g
Hemoglobin level	11.7 g/dL	11.8 g/dL
Blood transfusion	800 mL	800 mL
INR	2.15	1.72
Presence of ascite	13 (72.2%)	182 (70%)
Biliary leakage	8 (44.4%)	72 (25.8%)
Infection rate	9 (50%)	91 (32.7%)
Pediatric patients	0	10 (10.8%)
Retransplantation	0	2 (0.76%)
2 arterial anastomosis	0	12 (4.6%)
Use of vascular graft	3 (27.3%)	15 (5.6%)

Abbreviations: BMI, body mass index; CHILD, Child-Pugh Score; MELD, Model For End Stage Liver Disease; INR, international normalized ratio.

ber of arterial anastomoses for reconstruction, we observed that there was no HAT when double hepatic artery anastomoses were performed in our series.

Bile leak and infection (cholangitis and so on) were also found to be common in patients with HAT. It is unclear whether these biliary complications were the cause of or a consequence of HAT. INR values in our study were also found to be significantly different in the HAT group, although other series found it was not significantly associated with increased risk for HAT.[9,16]

In conclusion, the HAT rate was 6.5% in our series and HAT has a significant impact on survival, with a 38.9% mortality rate in those with the complication in the 2-year period. Revascularization procedures are the most important approaches regarding the patient's life because of the inadequate supply of donor organs. Early diagnosis is a prerequisite for revascularization strategies. The most important findings associated with HAT are bile leakage and presence of resistant infections. Use of vascular grafts increases risk for HAT.

REFERENCES

1. Stange BJ, Glanemann M, Nuessler NC, et al. Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl*. 2003;9:612–620.

2. Pinna AD, Smith CV, Furukawa H, et al. Urgent revascularization of liver allografts after early hepatic artery thrombosis. *Transplantation*. 1996;62:1584–1587.

3. Langnas AN, Marujo W, Stratta RJ, et al. Hepatic allograft rescue following arterial thrombosis. Role of urgent revascularization. *Transplantation*. 1991;51:86–90.

4. Wozney P, Zajko AB, Bron KM, et al. Vascular complications after liver transplantation: a 5-year experience. *AJR Am J Roentgenol*. 1986;147:657–663.

5. Bhattacharjya S, Gunson BK, Mirza DF, et al. Delayed hepatic artery thrombosis in adult orthotopic liver transplantation-a 12-year experience. *Transplantation*. 2001;71:1592–1596.

6. Mali VP, AW M, Quak SH, et al. Vascular complications in pediatric liver transplantation; single-center experience from Singapore. *Transplant Proc*. 2012;44:1373–1378.

7. Nishida S, Kato T, Levi D, et al. Effect of protocol Doppler ultrasonography and urgent revascularization on early hepatic artery thrombosis after pediatric liver transplantation. *Arch Surg*. 2002;137:1279–1283.

8. Silva MA, Jambulingam PS, Gunson BK, et al. Hepatic artery thrombosis following orthotopic liver transplantation: a 10-year experience from a single centre in the United Kingdom. *Liver Transpl*. 2006;12:146–151.

9. Bekker J, Ploem S, de Jonga KP, et al. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplant*. 2009;9:746–757.

10. Tzakis AG. The dearterialized liver graft. *Semin Liver Dis*. 1985;5:375–376.

11. Katz E, Fukuzawa K, Schwartz M, et al. The splenic artery as the inflow in arterial revascularization of the liver graft in clinical liver transplantation. *Transplantation*. 1982;53:1373–1374.

12. Cherqui D, Riff Y, Rotman N, et al. The recipient splenic artery for arterialization in orthotopic liver transplantation. *Am J Surg*. 1994;167:327–330.

13. Figueras J, Pares D, Aranda H, et al. Results of using the recipient's recipient splenic artery for arterial reconstruction in liver transplantation in 23 patients. *Transplantation*. 1997;64:655–658.

14. Garcia-Valdecasas JC, Grande L, Rimola A, et al. The use of the saphenous vein for arterial reconstruction in orthotopic liver transplant. *Transplant Proc*. 1990;22:2376–2377.

15. Asakura T, Ohkohchi N, Orii T, et al. Arterial reconstruction using vein graft from the common iliac artery after hepatic artery thrombosis in living-related liver transplantation. *Transplant Proc*. 2000;32:2250–2251.

16. Oh CK, Pelletier SJ, Sawyer RG, et al. Uni- and multivariate analysis of risk factors for early and late hepatic artery thrombosis after liver transplantation. *Transplantation*. 2001;71:767–772.