Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

# Thrombotic and nonthrombotic hepatic artery complications in adults and children following primary liver transplantation with long-term follow-up in 1000 consecutive patients*

Ashokkumar Jain,[1,2] Guilherme Costa,[2] Wallis Marsh,[2] Paulo Fontes,[2] Michael Devera,[2] George Mazariegos,[2] Jorge Reyes,[3] Kusum Patel,[2] Ravi Mohanka,[1] Mary Gadomski,[2] John Fung[4] and Amadeo Marcos[2]

1 Department of Surgery, Division of Transplantation, University of Rochester Medical Centre, Rochester, NY, USA
2 Thomas E Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, PA, USA
3 Transplant Services, Children's Hospital and Regional Medical Centre, Seattle, WA, USA
4 Transplant Centre, Department of Surgery, The Cleveland Clinic Foundation, Cleveland, OH, USA

**Keywords**
early hepatic artery thrombosis, hepatic artery pseudo-aneurysm, hepatic artery stenosis, hepatic artery thrombosis, intermediate hepatic artery thrombosis, liver transplantation.

**Correspondence**
Ashokkumar Jain MD, Department of Surgery, Division of Transplantation, University of Rochester Medical Centre, Box SURG, 601 Elmwood Avenue, Rochester, NY 14642, USA. Tel.: (585) 275 2924; fax: (585) 506 0054; e-mail: ashok_jain@urmc.rochester.edu

*Data presented at the 25th Annual Scientific Meeting, The American Society of Transplant Surgeons (ASTS) May 1999, Chicago, IL, USA and Fifth Congress of the International Liver Transplantation Society, August 26–28, 1999, Pittsburgh, PA, USA.

Received: 5 July 2005
Revision requested: 12 August 2005
Accepted: 6 September 2005

doi:10.1111/j.1432-2277.2005.00224.x

## Summary

Arterial complications have a major impact on survival after liver transplantation (LTx). The aim of this study was to examine arterial complications in adults and children after LTx. A total of 1000 consecutive primary LTx patients [mean age 40.5 years: 600 males, 400 females, 834 adults; 166 children (age <18 years)] were studied. Forty-two patients (4.2%; 31 adults, 11 children) developed hepatic artery thrombosis (HAT). Thrombosis in children occurred significantly early (mean 5.4 days) compared with adults (mean 418.7 days, $P = 0.0001$). Nonthrombotic complications occurred in 30 patients (29 adults, one child). Overall, 13-year patient survival after HAT was 43.2% (72.7% children, 32.9% adults). For nonthrombotic complications, 54.3% of adults died and 69.4% grafts were lost. An overall incidence of 4.2% thrombotic and 3.2% nonthrombotic complications was observed. Rate of HAT was higher in children, but survival was better compared with adults.

## Introduction

Results of liver transplantation (LTx) have improved significantly in the last three decades [1]. Graft loss from acute or chronic rejection is rare [2–4] with currently available modern immunosuppressive agents. One of the commonest reasons of early graft loss is hepatic artery thrombosis (HAT). Risk factors for HAT that have been reported in the literature include anatomical variations, smaller hepatic artery diameter with reduced blood flow and hyper-coagulable states because of protein S, protein C, antithrombin-III deficiency or a rise in hematocrit because of dehydration [5–9]. However, there are very few studies that describe the variety of complications

related to hepatic artery that can be encountered after LTx over a long period of time in all age groups.

## Aim

To examine the rate of hepatic artery complications in adults and children after primary liver transplant from a single institution and their long-term outcomes.

## Patient and methods

One thousand consecutive patients who underwent primary LTx between August 1989 and December 1992 under tacrolimus-based immunosuppressive regimen were included in this study. There were 600 males and 400 females; 834 recipients were adults (age >18 years) and the remaining 166 were children (age ≤18 years). All patients were followed up, until August 2004. The mean follow-up period was 13.4 years (range 11.7–15). The immunosuppressive protocol used in this study population and their diagnosis has been previously reported [4,10]. Main hepatic artery with aortic cuff of the donor was anastomosed to the confluence of the main hepatic artery and gastro-duodenal artery in the recipient. Hepatic arterial anastomosis in children was performed using optical loupes of 3× or greater magnification. Usually, 7-0 or 8-0 prolene sutures were used in a running fashion. All children were commenced on anticoagulation during the first postoperative week when the international normalized ratio was ≤2.0. Anticoagulation was not used in adult population.

All patients underwent routine color duplex ultrasound examination not only during the first postoperative week, but also when abnormal liver function was clinically suspected and in febrile illness. Abnormal ultrasonic findings were evaluated by hepatic artery angiography.

Data were analyzed retrospectively after obtaining institutional review board exemption-approved protocol. A database was created after deleting patient-identifiable information by two independent brokers from an existing database. Based on the nature of the complication, patients were divided into two broad groups: thrombotic and nonthrombotic. Patients in the thrombotic group were further subdivided into early (<1 month), intermediate (1–6 months) and late (>6 months), depending on the period after LTx. Adults and children were separately examined for pattern of complications, rate of complications and survival outcomes.

### Statistical analysis

Results are described as mean ± SD. The difference in categorical values between adults and children were analyzed using the Pearson chi-square test. Differences between mean values were calculated using Student's *t*-test. Patient and graft survival were calculated and plotted for different groups and subgroups using Kaplan–Meier statistics. The survival differences between these groups were analyzed using the log-rank formula. $P < 0.05$ was considered significant. SPSS® version 13.0 for Windows® software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

## Results

Different types of arterial complications were observed and they were divided into two broad groups: thrombotic and nonthrombotic. The management strategy and survival outcomes were different in both groups.

### Thrombotic complications

Thrombosis was the most common among all arterial complications observed. It was also the most common cause of graft loss and death in the immediate postoperative period. Overall, 42 patients (4.2%) developed HAT, of which 11 were children (6.7%) and 31 adults (3.7%). The rate of HAT in children was almost double as compared to adults, but the difference was not statistically significant ($P = 0.088$) (Tables 1 and 2).

The time of diagnosis of HAT after LTx was different for children and adults. In children, HAT occurred within the first 2 weeks after LTx, while of 31 thrombosis in adults, 10 (32%) occurred in the first month post-LTx (mean 8.8 ± 6.8 days), eight (25.8%) occurred within 1–6 months post-LTx (mean 103.6 ± 45 days), and the remaining 13 (41.9%) occurred 6 months post-LTx (mean 922.9 ± 606.7 days). The difference was statistically significant ($P = 0.0001$).

### Nonthrombotic complications

Mean donor age was 41.5 ± 16.4 years for early, 32.9 ± 10.6 years for intermediate and 40.1 ± 15.8 years for late HAT ($P = 0.44$). The total ischemic time was 851.8 ± 134.0, 780.6 ± 122.6 and 918.9 ± 208.4 min for early, intermediate and late HAT, respectively ($P = 0.2$). The various types of nonthrombotic complications observed in this series consisted of arterial stenosis, redundant artery with kink, and hepatic artery pseudoaneurysm. Thirty patients (3.0%) were diagnosed with nonthrombotic complications, of which one was a child and the remaining 29 were adults. The difference in the incidence of nonthrombotic complications among adults and children was statistically significant ($P = 0.0001$).

In adults, stenosis was found at various anatomical regions on angiogram. The most common site of

**Table 1.** Incidence of hepatic artery complications.

| Complication | Children *n* (%) | Adults *n* (%) | Total *n* (%) |
|---|---|---|---|
| Thrombotic | 11 (6.6) | 31 (3.8) | 42 (4.2) |
| Nonthrombotic | 1 (0.6) | 29 (3.5) | 30 (3.0) |
| Anastomotic stenosis | 1 | 9 | 10 |
| Proximal main hepatic artery stenosis | 0 | 5 | 5 |
| Redundant hepatic artery with kink | 0 | 3 | 3 |
| Pseudo-aneurysm | 0 | 4 | 4 |
| Right hepatic artery stenosis | 0 | 2 | 2 |
| Left hepatic artery stenosis | 0 | 1 | 1 |
| Celiac axis stenosis | 0 | 1 | 1 |
| Infra-renal aortic graft stenosis | 0 | 1 | 1 |
| Redundant infra-renal aortic graft with kink | 0 | 1 | 1 |
| Anastomotic stenosis with celiac axis stenosis | 0 | 1 | 1 |
| Right and left hepatic artery stenosis | 0 | 1 | 1 |
| Total | 12 (1.2) | 60 (6.0) | 72 (7.2) |
| Mean time to thrombosis in days (mean ± SD) | 5.4 ± 4.5 | 418.7 ± 582.3 | 310.5 ± 531.0 |

stenosis was anastomosis of the hepatic artery ($n = 9$) or iliac graft ($n = 1$). This was followed by proximal hepatic artery postanastomotic stenosis ($n = 5$), redundant length with kink in hepatic artery ($n = 3$) or iliac graft ($n = 1$), isolated right ($n = 2$) and left ($n = 1$) hepatic artery stenosis, infra-renal aorto-iliac graft stenosis ($n = 1$), stenosis at the origin of native celiac axis ($n = 1$), combination of right and left hepatic artery stenosis ($n = 1$) and combination of celiac axis and anastomotic site stenosis ($n = 1$). In addition, four patients in the adult population developed pseudo-aneurysm of the hepatic artery at the site of anastomosis (Tables 1 and 3).

### Management of thrombotic complications and outcome

*Children*

Five children received re-transplantation (cases 31–36). One of them subsequently died (case 36) and four survived. In one, the artery was reconstructed surgically (case 41) and the child survived. One was treated with streptokinase and Fogarty embolectomy, but did not respond (case 38) and died before re-transplantation. In one child, only the right hepatic artery was thrombosed with some blood flow in the left hepatic artery with collateral formation and he survived (case 42). The other three children were kept under observation awaiting re-transplantation (cases 37, 39 and 40). Two of these three children survived and one died.

*Adult*

*Early thrombosis (within 1 month from LTx)*

In 31 cases of thrombosis, 10 patients had early thrombosis (cases 1–10), three of these patients (cases 2, 3 and 7) had aortic iliac graft thrombosis, one had a clotted right hepatic artery (case 10) and the remaining six had main HAT. Nine of 10 patients underwent re-transplantation and one patient (case 8) improved while waiting for re-transplantation, but he subsequently died from recurrent hepatitis C viral (HCV) infection. Five of nine re-transplanted patients died from aspergilliosis (0.5 month), sepsis (6.8 months), recurrent primary sclerosing cholangitis (34 months), multi-organ failure (4.5 months) and pancreatitis (5.0 months) (Table 2).

*Intermediate thrombosis (1–6 months from LTx)*

Of eight patients with intermediate thrombosis (cases 11–18), four patients underwent re-transplantation (cases 11, 12, 14 and 17), one of them with an infra-renal aorto-iliac graft (case 14) while four patients were under observation. Two among these four re-transplanted patients required a third transplantation 30 and 45 days later for thrombosis in the second allograft (cases 12 and 17, respectively). Both died at 9 and 21 months after second re-transplantation. The remaining two are alive at 116 and 109 months (Table 2).

All four patients who were under observation subsequently died of liver failure ($n = 1$), recurrent hepatocellular carcinoma ($n = 2$) and intrabdominal bleeding from pancreatic pseudocyst ($n = 1$).

*Late thrombosis (>6 months from LTx)*

Of the 13 patients who presented with late thrombosis (cases 19–31), five had an infra-renal aorto-iliac graft. Eight of these 13 patients underwent re-transplantation and five were under observation. Two patients after re-transplantation, and two patients who did not receive

**Table 2.** Demographics and outcome of thrombotic complications.

| S no. | Age at LTx (years) | Gender | Primary diagnosis | Time to diagnosis (days from LTx) | | Anatomical site | Management | Outcome | Pt. survival (months) |
|---|---|---|---|---|---|---|---|---|---|
| Adults | | | | | | | | | |
| 1 | 19.1 | M | HBV | Early | 1 | Donor HA | ReTx | Alive | 96.1 |
| 2 | 50.8 | M | HCV | | 1 | Infra renal iliac graft | ReTx | Died of sepsis | 6.8 |
| 3 | 55.1 | M | HCV | | 2 | Infra renal iliac graft | ReTx | Alive | 52.9 |
| 4 | 33.4 | M | PSC | | 2 | Donor HA | ReTx | Died of hepatic failure | 34.0 |
| 5 | 44.3 | F | PBC | | 5 | Donor HA | ReTx | Alive | 168.2 |
| 6 | 65.3 | F | PBC | | 10 | Donor HA | ReTx | Alive | 167.0 |
| 7 | 35.7 | F | HCV | | 12 | Infra renal iliac graft | ReTx | Died of MOSF | 4.5 |
| 8 | 38.5 | F | HBV and HCC | | 16 | Donor HA | Observation | Died of reccurent HCC | 20.4 |
| 9 | 36.7 | M | ETOH and HCV | | 19 | Donor HA | ReTx | Died of aspergillosis | 0.5 |
| 10 | 52.1 | M | HCV | | 20 | Right HA | ReTx | Died of pancreatitis | 5.0 |
| 11 | 60 | M | A1A deficiency | Intermediate | 46 | Donor HA | ReTx | Alive | 158.1 |
| 12 | 34.4 | F | Auto-immune | | 49 | Donor HA | ReTx* | Died of hepatic failure | 21.9 |
| 13 | 60.6 | M | HBV | | 85 | Origin of celiac axis | Observation | Died of hepatic failure | 15.3 |
| 14 | 39.1 | M | HCV | | 114 | Infra renal iliac graft | ReTx | Alive | 149.1 |
| 15 | 60 | M | HCV and HCC | | 116 | Donor HA | Observation | Died of reccurent HCC | 9.1 |
| 16 | 66.6 | M | HCV | | 146 | Donor HA | Waitlisted for ReTx | Died of bleeding from pancreatic pseudocyst | 0.5 |
| 17 | 49.5 | F | BCS | | 162 | Donor HA | ReTx* | Died of hepatic failure | 11.8 |
| 18 | 55.3 | M | HBV | | 177 | Donor HA | Observation | Died of recurrent HCC | 0.7 |
| 19 | 38.7 | M | HBV | Late | 757 | Infra renal iliac graft | ReTx | Died of unknown cause | 75.5 |
| 20 | 28.9 | M | Caroli's disease | | 1184 | Donor HA | ReTx | Died of MOSF | 4.7 |
| 21 | 59.2 | M | HCV | | 366 | Infra renal iliac graft | ReTx | Died of recurrent HCV | 0.3 |
| 22 | 43.7 | M | HBV and ETOH | | 433 | Infra renal iliac graft | ReTx | Died of hepatic failure | 29.2 |
| 23 | 19.5 | M | Auto-immune and HCV | | 1360 | Right HA | ReTx | Alive | 120.4 |
| 24 | 45.6 | F | ETOH | | 1462 | Infra renal iliac graft | ReTx | Alive | 109.8 |
| 25 | 43.4 | M | ETOH | | 506 | Donor HA | ReTx | Died of MOSF | 27.5 |
| 26 | 59 | M | ETOH | | 2304 | Infra renal iliac graft | ReTx* | Died of unknown cause | 4.7 |
| 27 | 69.3 | F | HCV | | 260 | Donor HA | Waitlisted for ReTx | Died of MOSF | 0.5 |
| 28 | 49 | F | Cryptogenic | | 339 | Infra renal iliac graft | Observation | Alive | 128.6 |
| 29 | 38.4 | M | A1A deficiency | | 540 | Donor HA | Observation | Died of PTLD and hepatic failure | 84.2 |
| 30 | 51.3 | M | ETOH | | 1049 | Donor HA | Observation | Died of hepatic failure | 5.0 |
| 31 | 46.9 | M | PSC | | 1438 | Donor HA | Observation | Alive | 107.2 |
| Children | | | | | | | | | |
| 32 | 2.7 | M | Biliary atresia | | 13 | Donor HA | ReTx | Alive | 68.1 |
| 33 | 0.6 | F | Biliary atresia | | 1 | Donor HA | ReTx | Alive | 172.6 |
| 34 | 0.6 | F | Biliary atresia | | 10 | Donor HA | ReTx | Alive | 171.9 |
| 35 | 3.1 | M | Histiocytosis | | 2 | Donor HA | ReTx | Alive | 167.8 |
| 36 | 1.7 | F | Biliary atresia | | 5 | Donor HA | ReTx | Died of hepatic failure | 0.6 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 37 | 0.4 | F | Biliary atresia | 8 | Donor HA | Observation | Alive | 167.2 |
| 38 | 1 | M | Biliary atresia | 1 | Donor HA | Streptokinase embolectomy | Died of hepatic failure | 0.0 |
| 39 | 1.1 | M | Biliary atresia | 10 | Donor HA | Observation | Died of hepatic failure | 1.1 |
| 40 | 1.2 | M | Biliary atresia | 7 | Donor HA | Observation | Alive | 164.4 |
| 41 | 0.5 | M | Biliary atresia | 1 | Donor HA | Re-anastomosis | Alive | 165.5 |
| 42 | 1.5 | M | Giant cell hepatitis | 1 | Right HA | Observation† | Alive | 55.2 |

Pt., patient; LTx, liver transplant; ReTx, re-transplantation; HA, hepatic artery; HBV, hepatitis B viral disease; HCV, hepatitis C viral disease; ETOH, alcohol related disease; A1A, alpha 1 antitrypsin; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; BCS, budd chiari syndrome; PTLD, post-transplant lymphoproliferative disease; MOSF, multi-organ system failure.
*Underwent second ReTx.
†Split liver.

re-transplantation, are alive at 120, 110, 129 and 107 months respectively, after diagnosis of HAT. One patient required a third transplant after HAT of second graft (case 26).

### Management of nonthrombotic complications (stenosis, kink, pseudo-aneurysm)

*Anastomotic stenosis*

There were 11 anastomotic stenoses, one in a child (case 53) and 10 in adults (cases 43–52). The child underwent balloon angioplasty and he is alive for 13 years 9 months postangioplasty. Two adults were re-transplanted (cases 43 and 52), one of them had an infra-renal aorto-iliac graft. Two patients (cases 49 and 50) underwent balloon angioplasty and the other six patients were under observation. Four adult patients survived and six expired.

*Nonanastomotic stenoses*

Five adult patients (cases 54–58) had stenosis of the donor hepatic artery proximal to anastomosis. Three of these patients were treated with re-transplantation ($n = 2$) and angioplasty ($n = 1$). The remaining two patients were not suitable for any intervention and were under observation. One of them is currently alive. The remaining four patients died at 2.1, 2.3, 21.3 and 81.2 months after diagnosis of stenosis.

Four adult patients had a redundant length of artery resulting in a kink (cases 59–62). In three patients, the kink was in the hepatic artery and one patient had an infra-renal aorto-iliac graft kink (case 62). One patient was re-transplanted (case 59), two underwent balloon angioplasty (cases 60 and 62) and one patient was under observation. Two patients died at 22.3 and 79.4 months and the other two are currently alive.

Six adult patients (cases 63–68) had either an isolated stenosis in the right hepatic artery ($n = 2$, cases 66 and 68), in the recipient celiac artery at its origin (case 64), an anastomotic stenosis with celiac artery stenosis at its origin (case 63), a left hepatic artery stenosis (case 65) or stenosis of both the left and the right hepatic artery (case 67). Among these six patients two were re-transplanted (cases 64 and 67), one underwent balloon angioplasty (case 62), two were under observation (cases 65 and 66) and the remaining one died while awaiting re-transplantation (case 63).

Four adults (cases 69–72) were found to have hepatic artery pseudo-aneurysm at 1, 77, 139 and 482 days after LTx. One of them (case 72) underwent re-transplantation and is alive for 10 years and 5 months after LTx. The remaining three patients (cases 69–71) died at 2.5, 31.9 and 83.6 months after diagnosis of pseudo-aneurysm

**Table 3.** Demographics and outcome of nonthrombotic complications.

| No. | Age at LTx (years) | Gender | Primary diagnosis | Complication and anatomical site | Time to diagnosis (days from LTx) | Donor age (years) | Management | Outcome | Patient survival (months) |
|---|---|---|---|---|---|---|---|---|---|
| 43 | 32.8 | M | ETOH | Anastomotic stenosis | 21 | 39 | ReTx | Alive | 166.2 |
| 44 | 64.3 | M | HCV | Anastomotic stenosis | 150 | 51 | Observation | Alive | 42.6 |
| 45 | 73.6 | F | Cryptogenic | Anastomotic stenosis | 31 | 27 | Observation | Died of MOSF | 1.6 |
| 46 | 42 | F | HBV | Anastomotic stenosis | 41 | 19 | Observation | Died of MOSF | 2.6 |
| 47 | 43 | M | ETOH and HCV | Anastomotic stenosis | 53 | 17 | Observation | Died of pneumonia | 69.3 |
| 48 | 51.9 | M | HBV | Anastomotic stenosis | 87 | 28 | Observation | Died of PTLD | 153.0 |
| 49 | 51 | M | ETOH | Anastomotic stenosis | 10 | 14 | Balloon angioplasty | Died of recurrent HCC | 69.4 |
| 50 | 56.9 | M | HCV | Anastomotic stenosis | 148 | 39 | Balloon angioplasty | Alive | 24.8 |
| 51 | 42.9 | M | HCV and ETOH | Anastomotic stenosis | 16 | 42 | Observation | Alive | 79.0 |
| 52 | 31.8 | F | ETOH | Anastomotic stenosis of iliac graft | 101 | 49 | ReTx | Died of aspergillosis | 5.6 |
| 53 | 0.5 | M | Biliary atresia | Anastomotic stenosis | 268 | | Balloon angioplasty | Alive | 141.6 |
| 54 | 59.7 | F | PBC | Proximal HA stenosis | 54 | 24 | ReTx | Died of MOSF | 2.1 |
| 55 | 46.9 | M | ETOH | Proximal HA stenosis | 138 | 42 | ReTx | Died of broncho pneumonia | 21.2 |
| 56 | 62.9 | F | PBC | Proximal HA stenosis | 55 | 58 | Observation | Died of MOSF | 2.3 |
| 57 | 70.7 | M | ETOH | Proximal HA stenosis | 118 | 26 | Balloon angioplasty | Died of pneumonia | 80.9 |
| 58 | 65.4 | F | PBC | Proximal HA stenosis | 413 | 53 | Observation | Alive | 141.7 |
| 59 | 31.8 | M | HCV | Kink in HA | 87 | 33 | ReTx | Died of MOSF | 22.3 |
| 60 | 75 | F | ETOH | Kink in HA | 131 | 26 | Balloon angioplasty | Died of pneumonia | 146.5 |
| 61 | 43.9 | F | Tylenol toxicity | Kink in HA | 58 | 27 | Observation | Alive | 143.0 |
| 62 | 38.1 | M | A1A deficiency | Kink in iliac graft | 2501 | 16 | Balloon angioplasty | Alive | 179.3 |
| 63 | 57.7 | F | HBV | Anastomotic stenosis and celiac axis stenosis | 17 | 51 | Died on waiting list for ReTx | Died of hepatic failure | 0.9 |
| 64 | 53.1 | F | ETOH | Celiac axis stenosis | 3 | 45 | ReTx | Alive | 154.8 |
| 65 | 18.1 | M | Cryptogenic | Left HA stenosis | 2 | 53 | Observation | Alive | 141.1 |
| 66 | 64.5 | M | HCV | Right HA stenosis | 165 | 43 | Observation | Died of MOSF | 5.8 |
| 67 | 19.9 | F | Cystic fibrosis | Right and left HA stenosis | 81 | 56 | ReTx | Died of MOSF | 4.7 |
| 68 | 40.8 | F | ETOH and HCV | Right HA stenosis | 53 | 42 | Balloon angioplasty | Died of recurrent HCV | 10.5 |
| 69 | 65.8 | F | HCV | Pseudo-aneurysm | 77 | 59 | Resection of aneurysm and reconstruction | Died of recurrent HCV | 31.9 |
| 70 | 48.8 | M | PNC non-A non-B | Pseudo-aneurysm | 1 | 27 | Observation | Died of MOSF | 2.5 |
| 71 | 40.9 | F | HCV | Pseudo-aneurysm | 139 | 25 | Percutaneous embolization | Died of recurrent HCV | 83.6 |
| 72 | 58.4 | F | Cryptogenic | Pseudo-aneurysm | 482 | 60 | Failed recostruction, ligation, ReTx | Alive | 141.0 |

LTx, liver transplant; ReTx, re-transplantation; HA, hepatic artery; HBV, hepatitis B viral disease; HCV, hepatitis C viral disease; ETOH, alcohol related disease; A1A, alpha 1 antitrypsin; PBC, primary biliary cirrhosis; PTLD, post-transplant lymphoproliferative disease; MOSF, multiorgan system failure.

because of multi-organ failure or recurrent HCV and hepatic failure (Table 3).

### Survival outcome

*Patient survival*

Overall 13-year patient survival after HAT was 43.2%. It was 72.7% for children and 32.9% for adults. This difference was not statistically significant ($P = 0.088$) (Fig. 1a and b). Among adults with thrombosis, the 13-year patient survival was 40%, 29.2% and 30.8% when they developed early, intermediate and late thrombosis, respectively, after LTx ($P = 0.995$) (Fig. 1b). In adult patients who developed nonthrombotic complications the 13 year survival was 45.7% (Fig. 2b). Causes of death with thrombotic and nonthrombotic complications

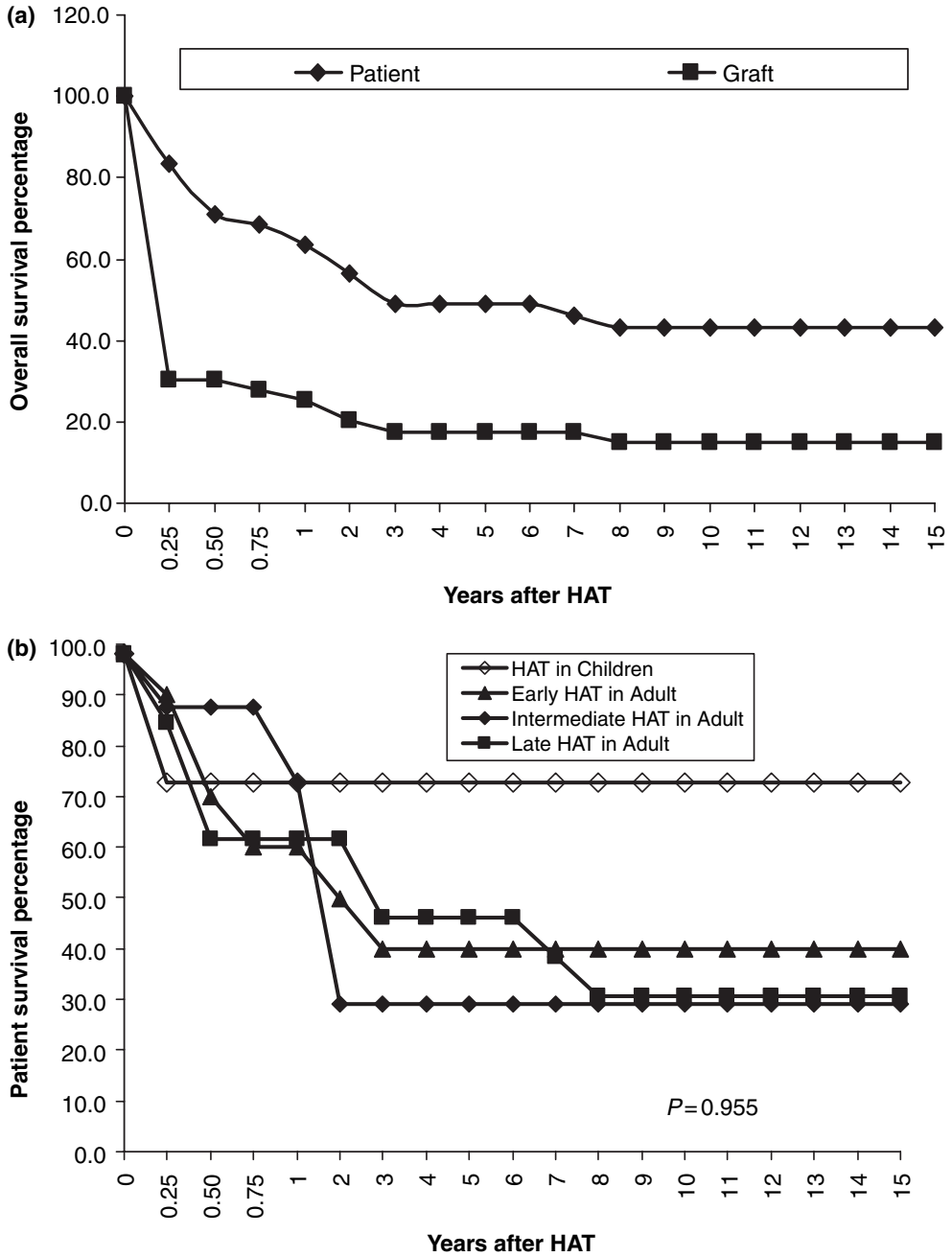


**Figure 1** Patient and graft survival. (a) Overall patient and graft survival. (b) Patient survival in children and adults with early, intermediate and late hepatic artery thrombosis.

with and without re-transplantation are summarized in Table 4.

*Graft Survival*

Overall 13-year graft survival after diagnosis of thrombosis was 15.1% (Fig. 1a). It was 36.4% in children and 7.0% in adults. This difference was not statistically significant ($P = 0.155$) (Fig. 2a). Among adults with thrombosis, the 13-year graft survival values were 0%, 0% and 15% when they developed early, intermediate and late thrombosis, respectively, after LTx ($P = 0.029$) (Fig. 2a). The 13-year graft survival for nonthrombotic complications was 30.4% in adults (Fig. 2b) and 100% in children.

## Discussion

Hepatic artery complications after LTx are well known and well documented [11,12]. It is one of the most common complications after LTx and has significant impact on graft and patient survival. The present report describes

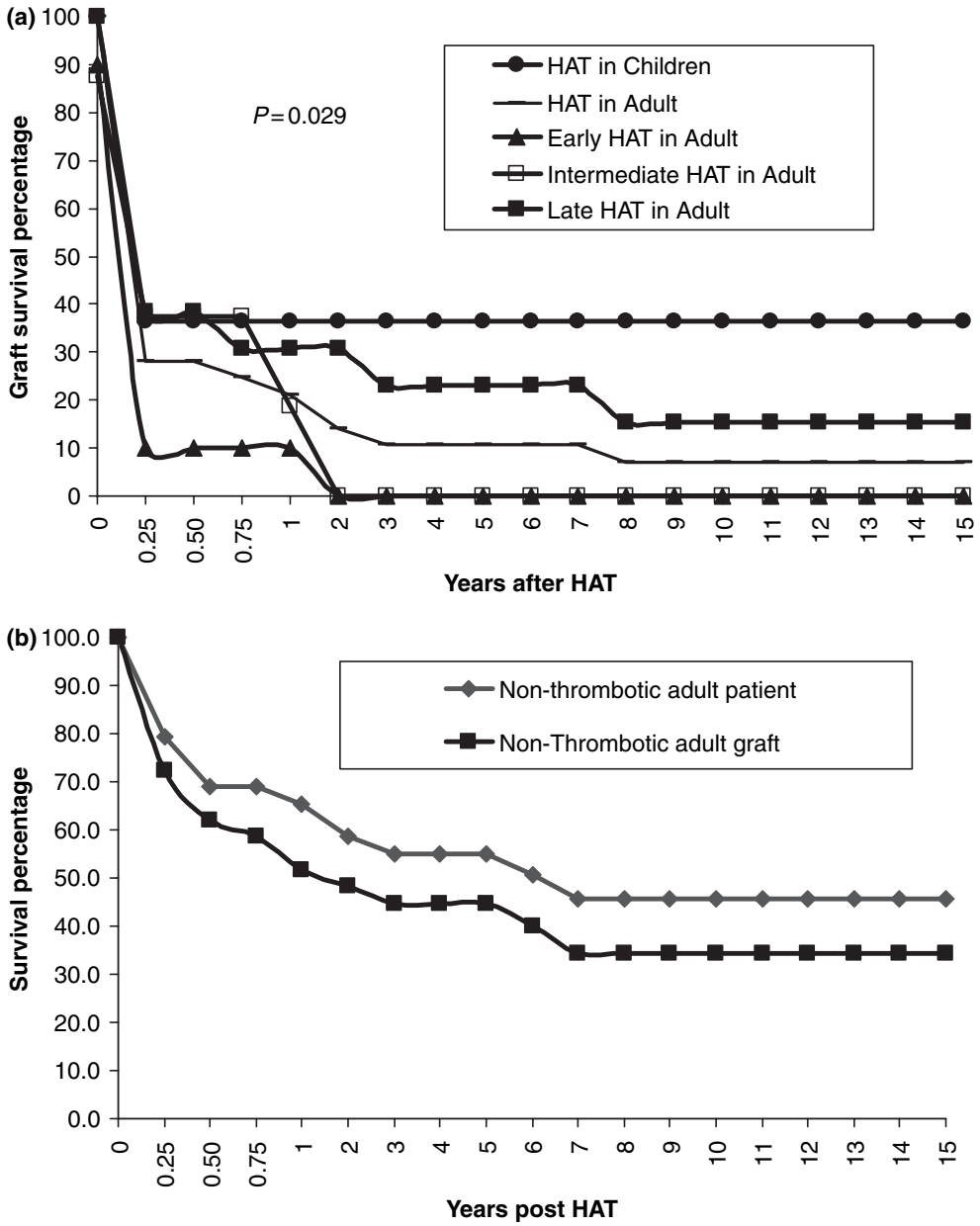


**Figure 2** Patient and graft survival. (a) Graft survival in children and adults with early, intermediate and late hepatic artery thrombosis. (b) Patient and graft survival in adult patients with nonthrombotic complications.

**Table 4.** Causes of death.

| | Without Re-Tx | With Re-Tx | Total |
|---|---|---|---|
| Hepatic artery thrombosis | | | |
| Sepsis | 0 | 1 | 1 |
| Graft failure | 4 | 5 | 9 |
| MOSF | 1 | 3 | 4 |
| Recurrent HCC | 3 | 0 | 3 |
| Aspergilliosis | 0 | 1 | 1 |
| Pancreatitits | 0 | 1 | 1 |
| Bleeding | 1 | 0 | 1 |
| Recurrent HCV | 0 | 1 | 1 |
| PTLD | 1 | 0 | 1 |
| Unknown cause | 0 | 2 | 2 |
| Total | 10 | 14 | 24 |
| Nonthrombotic | | | |
| MOSF | 5 | 3 | 8 |
| Graft failure | 1 | 0 | 1 |
| Pneumonia | 3 | 1 | 4 |
| PTLD | 1 | 0 | 1 |
| Recurrent HCC | 1 | 0 | 1 |
| Recurrent HCV | 3 | 0 | 3 |
| Aspergilliosis | 0 | 1 | 1 |
| Subtotal | 14 | 5 | 19 |

Re-Tx, re-transplant; MOSF, multiorgan failure; HCV, hepatitis C viral infection; PTLD, post-transplant lympho-proliferative disease; HCC, hepatocellular carcinoma.

the impact of various types of arterial complications after LTx and its long-term impact on patient and graft survival. A striking difference in adult and pediatric populations in terms of rate of complications, types of complications, timing of complications and survival outcomes after LTx is apparent in the present report.

The overall rate of HAT in children was almost twice that of the rate in the adult population. However, this difference was not statistically significant. Moreover, while all HAT in children occurred within the first 2 weeks, in adults, only one third of HAT was noticed in the first month post-LTx. At 14 years after HAT, 72% of children were alive compared with 32.9% of the adult population, which also did not reach statistical significance. Settmacher *et al.* [13] described a rate of 2.7% for HAT and 3.22% for stenosis in 1000 LTx patients, which is comparable with our findings. However, higher rates of HAT have been reported by Mas *et al.* [14] (7%) and Parera *et al.* [15] (8.8%). Mas *et al.* [14] also found prothrombin G20210A polymorphism in two of 14 hepatic allograft DNA. Fifty percent of children and 67.74% of adults underwent re-transplantation. For the adult population, this was 90% with early thrombosis, 50% with intermediate and 61.6% with late thrombosis.

Patient survival at 1, 5 and 10 years after re-transplantation in adults was 57.1%, 42.9%, 37.5% and that in children was 80%, 80%, and 80%. Survival in children after HAT is better than in adults as children are more resilient and bounce back quickly. Moreover, some adults have associated age-related co-morbid conditions, which adds to the overall mortality, not to mention the recurrence of viral, auto-immune, recurrent or *de novo* malignancy [1,4]. Postma *et al.* [16] recently reported better survival after re-transplantation because of HAT compared with re-transplantation due to other causes.

In the adult population, graft survival was 0% by the end of 2 years for early and intermediate thrombosis, while this was 30.8% at 2 years and 11.4% by 11 years for late thrombosis. This was mainly due to the development of collateral circulation and re-canalization as seen by Tian *et al.* [17]. Valente *et al.* [18] have described a relatively benign course of late HAT.

Nonthrombotic complication among children was surprisingly found in only one child (0.6%) who was treated successfully by balloon angioplasty. In adults, a variety of nonthrombotic complications were encountered like anastomotic stenosis, postanastomotic proximal hepatic artery stenosis, redundant arterial length with kink, stenosis at the origin of celiac axis, pseudo-aneurysm at the anastomotic site and various combinations of these. They were managed by re-transplantation in 26.67% patients, angioplasty in 24.2%, and the remaining patients were under observation. While the only child who suffered this complication survived, the patient and graft survival for adult population was disappointingly low at 45.7% and 34.4%, respectively, at 13 years.

In the adult population, infra-renal aorto-iliac graft was either thrombosed or stenosed in eight patients accounting for 13.2% of all arterial complications, most of them occurring as a late complication. Unfortunately the exact number of patients who received infra-renal aorto-iliac graft is not known in this retrospective study. Stange *et al.* [19] have reported a HAT rate of 2.17% in the adult population of 1192 LTx that increased to 5.76 fold when interposition graft to supraceliac aorta was used. Muralidharan *et al.* [20] have reported a 1–5 year patency rate of 88.5–80.8% when arterial conduits were used for hepatic artery revascularization in adult LTx. Muiesan *et al.* [21] have suggested interpositional arterial graft from the cadaveric superior mesenteric artery with higher success rate. This type of reconstruction was not performed in this population. Arterial anatomical variations have also been described as a risk factor [5,6]. In the present retrospective analysis, this information was also not available.

The incidence is higher in smaller children where the lumen is smaller and with even a small degree of hypotension due to any cause can lead to HAT. Hepatic artery with small diameter and lower blood flow are very well described risk factors for thrombosis. Mazzaferro *et al.* [8] described a hepatic artery diameter of <3 mm as a

risk factor. Lin *et al.* [7] have observed that arterial flow lower than 200 ml/min increased the rate of HAT by a factor 5. This has been the main reason why the rate of HAT in children was almost twice as much compared with adults. Interestingly nine of the 11 children who developed HAT were <2 years and the other two were 2.7 and 3.1 years of age. HAT was not observed in children who were >3.1 years of age. Rela *et al.* [22] described a higher rate of HAT in children <5 years of age and prolonged cold ischemic time as a risk factor, which also support our findings. However, using higher magnification either with the optical loupe or microscope, the rate has now decreased in pediatric population. Recently, Guarrera *et al.* [23] published excellent reports in 28 cases of segmental pediatric LTx using operative microscope with 12–16·magnification ($n = 14$) and loupe optics with 6× magnification without any incidence of HAT .

Various studies [5–9] have described hypercoagulable state as an independent risk factor. However, this was not worked up in these patients. In the present series, anticoagulation therapy in the first week was used routinely in children as suggested by Heffron *et al.* [24] and Abou Ella *et al.* [25]. In the past, we have described the use of hyperbaric oxygen therapy for HAT in children [26]. However, in the present series none of the children received this treatment. All HAT in children occurred in the early postoperative period while in the adult population it appears to occur early as well as late after LTx. Late HAT adults may be related to donor or recipient age. Often there is a history of hypertension or diabetes either in the donor and/or recipient, which is known to affect the intima of the artery and wall thickness. This may be the reason why late hepatic arterial complications and postanastomotic strictures are seen in children. This aspect in transplant population has not been examined. Moreover, the hypercoagulable state is not routinely worked up in transplant population. We feel that the hypercoagulable state in the adult population should be investigated more routinely to prevent late HAT.

Moreover, redundancy of hepatic artery resulting in kinking has been observed in this report. We suggest that when there is a redundancy, instead of entire length of donor hepatic artery with aortic cuff, a shorter length with patch at the level of splenic artery branch may be a better option. Also a small piece of omentum in continuity to prevent kink behind the anastomosis may be useful.

Postanastomotic stenosis is most likely from the clamp used on donor hepatic artery which may be causing some intimal damage resulting in stenosis at a later date. It may be possible that the rate of such stenosis may be even higher than reported here as routine surveillance ultrasound examination was not performed in this population. It is now routine to have duplex color ultrasound at 1 year in all adult patients at this institution. Outcome of such practice is awaited with great anticipation.

## Conclusion

In the present series with long-term follow-up, 4.2% of patients with thrombotic and 3.2% with nonthrombotic complications were under observation. The incidence of HAT was higher in children than in adults and occurred significantly earlier. Survival outcome was better in children than in adults. Nonthrombotic complications were significantly higher in adults than in children and had a significant impact in terms of graft and patient survival. It may be preventable in some cases by reducing the redundancy in the donor hepatic artery with careful clamping and handling. Routine workup of hypercoagulable state in adults, surveillance duplex ultrasound, and use of higher magnification for arterial reconstruction in smaller children and anticoagulation therapy may reduce the overall incidence of HAT.

## Acknowledgements

We acknowledge the help of Dr Manoj Purohit in finalizing the manuscript.

This study was supported by internal funding only.

## Conflicts of interest

There are no conflicts of interest associated with this study.

## References

1. Jain A, Reyes J, Kashyap R, *et al.* Long-term survival after liver transplantation in 4000 consecutive patients at a single center. *Ann Surg* 2000; **232**: 490.
2. Jain A, Demetris AJ, Kashyap R, *et al.* Does tacrolimus offer virtual freedom from chronic rejection after primary liver transplantation? Risk and prognostic factors in 1048 liver transplantations with a mean follow-up of 6 years. *Liver Transpl* 2001; **7**: 623.
3. Jain A, Mazariegos G, Pokharna R, *et al.* The absence of chronic rejection in pediatric primary liver transplant patients who are maintained on tacrolimus-based immunosuppression: a long-term analysis. *Transplantation* 2003; **75**: 1020.
4. Jain A, Reyes J, Kashyap R, *et al.* What have we learned about primary liver transplantation under tacrolimus immunosuppression? Long-term follow-up of the first 1000 patients. *Ann Surg* 1999; **230**: 441.

5. Hardy KJ, Jones RM. Hepatic artery anatomy in relation to reconstruction in liver transplantation: some unusual variations. *Aust N Z J Surg* 1994; **64**: 437.
6. Ishigami K, Zhang Y, Rayhill S, Katz D, Stolpen A. Does variant hepatic artery anatomy in a liver transplant recipient increase the risk of hepatic artery complications after transplantation? *AJR Am J Roentgenol* 2004; **183**: 1577.
7. Lin M, Crawford M, Fisher J, Hitos K, Verran D. Hepatic artery thrombosis and intraoperative hepatic artery flow rates in adult orthotopic liver transplantation. *ANZ J Surg* 2002; **72**: 798.
8. Mazzaferro V, Esquivel CO, Makowka L, *et al.* Hepatic artery thrombosis after pediatric liver transplantation – a medical or surgical event? *Transplantation* 1989; **47**: 971.
9. Tisone G, Gunson BK, Buckels JA, McMaster P. Raised hematocrit – a contributing factor to hepatic artery thrombosis following liver transplantation. *Transplantation* 1988; **46**: 162.
10. Jain AB, Fung JJ, Todo S, *et al.* One thousand consecutive primary orthotopic liver transplants under FK 506: survival and adverse events. *Transplant Proc* 1995; **27**: 1099.
11. Todo S, Makowka L, Tzakis AG, *et al.* Hepatic artery in liver transplantation. *Transplant Proc* 1987; **19** (1 Pt 3): 2406.
12. Tzakis AG, Gordon RD, Shaw BW Jr, Iwatsuki S, Starzl TE. Clinical presentation of hepatic artery thrombosis after liver transplantation in the cyclosporine era. *Transplantation* 1985; **40**: 667.
13. Settmacher U, Stange B, Haase R, *et al.* Arterial complications after liver transplantation. *Transpl Int* 2000; **13**: 372.
14. Mas VR, Fisher RA, Maluf DG, Wilkinson DS, Garrett CT, Ferreira-Gonzalez A. Hepatic artery thrombosis after liver transplantation and genetic factors: prothrombin G20210A polymorphism. *Transplantation* 2003; **76**: 247.
15. Parera A, Salcedo M, Vaquero J, *et al.* Arterial complications after liver transplantation: early and late forms. *Gastroenterol Hepatol* 1999; **22**: 381.
16. Postma R, Haagsma EB, Peeters PM, van den Berg AP, Slooff MJ. Retransplantation of the liver in adults: outcome and predictive factors for survival. *Transpl Int* 2004; **17**: 234.
17. Tian MG, Tso WK, Lo CM, Liu CL, Fan ST. Treatment of hepatic artery thrombosis after orthotopic liver transplantation. *Asian J Surg* 2004; **27**: 213.
18. Valente JF, Alonso MH, Weber FL, Hanto DW. Late hepatic artery thrombosis in liver allograft recipients is associated with intrahepatic biliary necrosis. *Transplantation* 1996; **61**: 61.
19. Stange BJ, Glanemann M, Nuessler NC, Settmacher U, Steinmuller T, Neuhaus P. Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl* 2003; **9**: 612.
20. Muralidharan V, Imber C, Leelaudomlipi S, *et al.* Arterial conduits for hepatic artery revascularisation in adult liver transplantation. *Transpl Int* 2004; **17**: 163.
21. Muiesan P, Rela M, Heaton ND. Use of cadaveric superior mesenteric artery as interpositional vascular graft in orthotopic liver transplantation. *Br J Surg* 2001; **88**: 70.
22. Rela M, Muiesan P, Bhatnagar V, *et al.* Hepatic artery thrombosis after liver transplantation in children under 5 years of age. *Transplantation* 1996; **61**: 1355.
23. Guarrera JV, Sinha P, Lobritto SJ, Brown RS Jr, Kinkhabwala M, Emond JC. Microvascular hepatic artery anastomosis in pediatric segmental liver transplantation: microscope vs loupe. *Transpl Int* 2004; **17**: 585.
24. Heffron TG, Pillen T, Welch D, Smallwood GA, Redd D, Romero R. Hepatic artery thrombosis in pediatric liver transplantation. *Transplant Proc* 2003; **35**: 1447.
25. Abou Ella KA, Al Sebayel MI, Ramirez CB, Rabea HM. Hepatic artery thrombosis after orthotopic liver transplantation. *Saudi Med J* 2001; **22**: 211.
26. Mazariegos GV, O'Toole K, Mieles LA, *et al.* Hyperbaric oxygen therapy for hepatic artery thrombosis after liver transplantation in children. *Liver Transpl Surg* 1999; **5**: 429.