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Anastomotic bilio-biliary stricture after adult liver transplantation: a retrospective study over 20 years in a single center

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Abbreviations:

LT: Liver Transplantation

ABS: anastomotic bilio-biliary stricture

ERCP: endoscopic retrograde cholangiopancreatography

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Jérôme Dumortier and Olivier Boillot had the idea of the project, participated in analysis and interpretation of data and wrote the manuscript.

Jérôme Dumortier and Christine Chambon-Augoyard collected the data.

Olivier Guillaud performed statistical analysis of data.

All authors were involved in the medical management of the patients reported here and approved the final version of the manuscript.

Abstract

Background: Biliary complications are the main surgical complication after liver transplantation (LT). The aims of the present retrospective single center study were to describe anastomotic bilio-biliary strictures (ABS) in a large cohort of liver transplant recipients with long follow-up.

Methods: All adult LT recipients who underwent a LT, with bilio-biliary anastomosis, between 1990 and 2010 in Edouard Herriot hospital, Lyon, France were included in the study.

Results: The study population consisted in 783 patients (70.0% males), median age 50.5 years; main indication was alcohol-related liver disease (46.8%). The median follow-up after LT was 11.9 years (range 0-27 years). The overall incidence of anastomotic biliary complications was 9.7%: 50 patients developed an ABS (6.6%), after a median delay of 4.4 months (range 0.1-245.2) after LT and 32 (4.1%) developed biliary leakage after a median delay of 25 days (range 1-179). The actuarial risk of developing an ABS was 1.6% at 1-month, 2.7% at 3-months, 4.1% at 6-months, and 5.1%, 6.0%, 6.4%, 6.6%, 7.3% at 1-, 2-, 5-, 10- and 15-years, respectively. Univariate analysis disclosed that post-reperfusion syndrome and liver graft steatosis ($\geq 30\%$) were significant risk factors for ABS. Multivariate analysis disclosed that graft steatosis (OR=6.262, 95%CI 1.936-20.257, $p=0.002$) and MELD score (OR=1.071, 95%CI 1.018-1.128, $p=0.008$) were significant risk factors for ABS. The first-line treatment of ABS consisted in endoscopic stenting for 44 patients (88.0%) and immediate success rate was 75.0%. Delayed recurrence of ABS occurred in 8/33 patients (24.0%).

Conclusion: Our results suggest that steatotic grafts should be used for recipients without severe liver failure to avoid ABS, and that endoscopic stenting of post-LT ABS leads to a high success rate, but is associated with a significant risk of recurrence.

Key words: liver transplantation; biliary complications; risk factors; treatment; outcome

INTRODUCTION

Biliary complications, and especially anastomotic biliary strictures, are the main surgical complication after liver transplantation (LT) (1). Since Thomas E. Starzl declared that biliary anastomosis is the Achilles' heel of LT, this issue has never been resolved (2). In a recent extensive systematic overview of 45 relevant published papers (period 2008-2013), including 14,411 patients, the reported incidence of biliary complications was 23.0%: biliary leakage occurred in 8.5%, biliary stricture in 14.7% (1). Identified risk factors deal with pre-operative recipient characteristics, surgical procedure, donor and liver graft characteristics, post-operative rejection, and arterial complications (1). The therapeutic management is based on surgery, interventional radiology and/or endoscopic retrograde cholangiopancreatography (ERCP) (1). Finally, biliary complications are associated with significant morbidity, but could also have an impact on graft and patients survival (3, 4).

The aims of the present retrospective single center study were to describe incidence, risk factors, treatment and outcome of anastomotic bilio-biliary strictures (ABS) in a large cohort of adult LT recipients from a single center, with long follow-up.

PATIENTS AND METHODS

Study design

The present retrospective study is based on the prospectively maintained database at Liver transplant unit, Edouard Herriot hospital, Lyon, France. The medical records of all adults (aged 18 years or older) who underwent LT, with initial bilio-biliary anastomosis, between October 1990 and September 2010 were reviewed, and patients with biliary complication were identified. Anastomotic biliary complications included biliary leak, anastomotic stricture (defined as stricture located within one centimeter of the anastomotic site), or both (non-anastomotic leaks and strictures were not included). Donor and recipient data on demographics, laboratory data, type of graft (whole or partial), operative parameters, postoperative course, and recipient overall survival and graft survival were collected. Data were reviewed for patients with biliary complication and compared with patients who underwent LT during the study period and did not develop biliary complication (controls). Treatment of ABS was reviewed and classified as either surgical (primary revision of biliary anastomosis or conversion to hepatico-jejunostomy) or nonsurgical (ERCP or percutaneous transhepatic biliary drainage); efficacy of treatment was evaluated.

Liver graft procurement and surgical biliary reconstruction during liver transplantation

Liver procurement was performed according to the Starzl's rapid technique with exclusive aortic cannulation (5). In the majority of cases, LTs were done using piggyback technique with side-to-side cavo-caval anastomosis. Two experienced surgeons (OB, MA) performed all LT during the study period. Biliary anastomosis was typically fashioned between the donor and recipient bile ducts in an end-to-end (duct-to-duct) fashion using interrupted absorbable (6-0 polydioxanone) sutures following re-cutting of the two donor and recipient biliary extremities in well vascularized tissue. Caution was taken not to do electrocoagulation for hemostasis at the bile duct extremities. Since 1992, choledocho-choledochostomy without T-tube was the standard technique; T-tube was used in selected cases of donor-recipient duct size mismatch. In living donor LT a trans-anastomotic cystic-type drain was systematically inserted. First intent Roux-en-Y hepaticojejunostomy was reserved for recipients with PSC, small-sized ducts, poor-quality bile ducts, and significant donor-recipient duct size mismatch.

Diagnosis and treatment of anastomotic biliary strictures

Anastomotic biliary strictures were typically diagnosed on workup of symptoms (cholangitis), and/or elevated liver enzymes with ultrasonography, CT scan, magnetic resonance imaging cholangiopancreatography, ERCP, and/or percutaneous transhepatic cholangiography and biliary drainage. On first intent, ABS were predominantly managed with sequential dilation and stenting during ERCP and/or percutaneous transhepatic biliary drainage, with surgical revision reserved for refractory cases. There could have been overlap between the various available diagnostic and therapeutic modalities.

Statistical analyses

Categorical variables were expressed as percentages and compared with the Chi-squared or Fischer's exact tests. Continuous variables were expressed as mean \pm SD and compared using the Student's t test or the Mann-Whitney's test in case of non-Gaussian distributions. All significant variables in the univariate analysis with a level set at $p < 0.12$ were incorporated into the multivariate model. Patient survival was calculated from the date of LT to that of death or the final clinical visit. Graft survival was calculated from the date of LT to that of retransplantation, death or last visit if there was no retransplantation. Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test. A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 13.0 (IBM, Armonk, NY, US).

RESULTS

Study population

The study population consisted in 783 adult patients (70.0% males), with a median age of 50.5 years at the time of LT; main indication was alcohol-related liver disease, with or without hepatocellular carcinoma (46.9%). The median follow-up after LT was 11.9 years (range 0-27 years).

Diagnosis of biliary complications

The overall incidence of anastomotic biliary complications was 9.7% (76 patients). From the entire cohort, 50 developed an ABS (6.6%), after a median delay of 4.4 months (range 0.1-245.2) after LT and 32 (4.1%) developed biliary leakage after a median delay of 25 days (range 1-179).

The actuarial risk of developing an anastomotic biliary complication was 3.7% at 1-month, 5.5% at 3-months, 7.6% at 6-months, and 8.6%, 9.5%, 9.9%, 10.1%, 10.8% at 1-, 2-, 5-, 10- and 15-years, respectively (Figure 1A). The actuarial risk of developing an ABS was 1.6% at 1-month, 2.7% at 3-months, 4.1% at 6-months, and 5.1%, 6.0%, 6.4%, 6.6%, 7.3% at 1-, 2-, 5-, 10- and 15-years, respectively (Figure 1B). The diagnosis of ABS was made because of biochemical cholestasis (n=48, 96.0%), imaging (n=17, 34.0%), or biliary sepsis (n=3, 6.0%).

Risk factors for anastomotic biliary stricture

Univariate analysis disclosed that post-reperfusion syndrome (defined as a decrease in mean arterial pressure greater than 30% below the baseline value, lasting for at least 1 min, occurring during the first 5 min after reperfusion of the liver graft (unclamping of hepatic hilum and inferior vena cava)(6)) and graft steatosis ($\geq 30\%$) were significant risk factors for ABS (Table 1). Recipient age and gender, initial liver disease, MELD score, donor age and gender, donor cardiac arrest, type of graft (whole *vs.* partial), retransplantation, preservation solution (UW *vs.* IGL1), use of T-tube, cold and warm ischemia times, vascular complications (arterial or venous, thrombosis or stenosis), rejection were not significantly associated with ABS (Table 1).

Multivariate analysis disclosed that graft steatosis ($\geq 30\%$) (OR=6.262, 95%CI [1.936-20.257], $p=0.002$) and MELD score (OR=1.071, 95%CI [1.018-1.128], $p=0.008$) were significant risk factors for ABS (Table 2).

Treatment of biliary stricture and outcome

The first-line treatment of ABS consisted in ERCP and endoscopic stenting for 44 patients (88.0%) (plastic stents, 39/44, or metal stents, 5/44), surgery for 5 patients (10.0%) (*i.e.* biliary anastomosis surgical revision $n=4$, bilio-digestive anastomosis, $n=1$), or percutaneous drainage in 1 patient (2%). Success rate was 75.0% for endoscopic treatment ($n=33/44$), 0% for percutaneous treatment (0/1) and 80.0% for surgery (4/5, one failure of anastomosis revision). Second-line treatment after failure of endoscopic treatment consisted in surgery in 8 patients or percutaneous drainage in one (two patients died and had no second-line treatment). Recurrence of ABS after a first successful endoscopic treatment occurred in 8/33 patients (24.0%), after a median delay of 6.5 months (range 3.8-112.4) (Figure 2). All patients were treated with a second course of endoscopic stenting.

Survival

Patients and grafts survivals were not affected by the occurrence of biliary complication. Patients survival was 87.8%, 76.7%, 67.2% and 57.9% at 1-, 5-, 10- and 15-years, respectively, for patients without biliary complication, and 93.4%, 84.2%, 73.3% and 63.0% at 1-, 5-, 10- and 15-years, respectively, for patients with biliary complication. Graft survival was 87.1%, 76.5%, 66.6% and 57.6% at 1-, 5-, 10- and 15-years, respectively, for patients without biliary complication, and 93.4%, 82.9%, 73.2% and 62.8% at 1-, 5-, 10- and 15-years, respectively, for patients with biliary complication.

DISCUSSION

Biliary complications after LT represent a wide spectrum including anastomotic strictures, which by definition are strictures located within one centimeter of the anastomotic site, non-anastomotic bile duct strictures which are strictures or irregularities in the biliary tree, not including the anastomosis, and biliary leaks (anastomotic or from liver cut surface in cases of LT with partial graft). We focused the present study on anastomotic bilio-biliary complications, especially ABS.

We confirm here, from one of the largest reported cohort, that ABS usually occur in the first months (median delay 4.4 months), but can develop as late as 20 years after LT! We report a low incidence of biliary stricture (6.6%); possible explanations for this are multiple, and related to well known risk factors. First of all, all LT were performed by only two experienced surgeons. Recently, Rammohan and coll. analyzed biliary complications in 640 LT recipients from both living (n = 481) and deceased donors (n = 159), strongly recalling our population, and operated between 2009 and 2016 (7). The overall incidence of biliary complications was 13.7%. It reduced from 23% to 5% over a 6-year period. Risk factors for biliary complications included living donor liver transplantation, prolonged time to re-arterialization, recipient age above 16 years, prolonged cold ischemia time after deceased donor liver transplantation, but also biliary reconstruction performed by anyone but the senior surgeon. In addition, our population included a vast majority of LT with whole liver graft (84.7%) and it has been largely demonstrated that use of partial grafts (especially from living donor) are associated with an increased risk to develop ABS (1). This could be due to inherent size-mismatch between donor and recipient bile ducts and also to more extensive hilar dissection which may lead to impaired vascularization of the bile duct. In our experience, the risk of ABS was lower (but not statistically significant) when a partial graft was used; this is probably related to a selection of optimal donor and graft. Recipient and donor advanced ages, and female donor are reported risk factors for ABS (8-10) but it was not in our series, probably because of relatively young ages of both donors and recipients. Similarly, were not risk factors of ABS in our experience, whereas they had previously been reported: warm ischemia time (10), cold ischemia time (7), UW preservation solution (10), and intraoperative blood transfusion (11). The impact of internal stenting or T-tubes on ABS occurrence has been a matter of debate for more than 2 decades. A recent meta-analysis reviewed a

collection of 15 studies (six randomized control trials and nine comparative studies) to compare biliary complications after biliary tract reconstruction with or without T-tube (12). The analysis disclosed that the biliary tract reconstruction with T-tube and without T-tube had equivalent outcomes for overall biliary complications. Nevertheless, in the group with T-tube there were better outcomes for biliary strictures. Therefore, it has been proposed to use T-tube for recipients who possibly have high risks of biliary stricture. This was our strategy.

In the present study, we identified two significant risk factors for ABS, one related to the recipient (MELD score), and one related to the liver graft (steatosis $\geq 30\%$). The impact of recipient's liver failure, estimated from bilirubin level, prothrombin time/INR or MELD score has been previously reported (10, 11, 13). We hypothesize that the most severely ill patients could have more intra-operative hemodynamic instability, leading to possible ischemic biliary damage (14). Finally, the risk of ABS was significantly increased by using steatotic liver graft, as reported previously (15, 16). We believe that graft steatosis is associated in some other relevant risk factors, such as post-reperfusion syndrome (from our univariate analysis) or post-operative peak values of liver enzymes and bilirubin (17). Baccarani and coll. reported in a small series of 117 LT, a 36.8% incidence of biliary complications (including 30.8% of ABS), in which multivariate analysis indicated that macrovacuolar steatosis of the graft ($>25\%$) was a significant predictors of biliary complications (OR = 5.21, $p=0.002$) (15). Similarly, Lattanzi and coll. from 177 patients, reported a 23% incidence of ABS and that graft macrovesicular steatosis $>25\%$ (OR 3.38, $p=0.05$) was an independent risk factor for ABS (15, 16). Several mechanisms have been proposed for explaining the correlation between ABS and steatosis: steatosis might reduce the hepatic blood flow because of the distortion of microvascular system by fat-filled hepatocytes, leading to a lower tolerance of the liver graft against ischemia–reperfusion injury (18, 19). In addition, the post-reperfusion release of inflammatory factors, such as TNF- α , IL-6, IL-12, and INF- γ , could directly impair bile duct endothelial cells and contribute to biliary strictures (20).

Therapeutic options for ABS consist of ERCP, percutaneous transhepatic drainage and surgery, including re-transplantation. Our results strongly confirm that ERCP and biliary stenting is a successful treatment in the majority of patients, and is considered to be more safe compared to both percutaneous and surgical treatment. Nevertheless, there are some procedure failures and also some contra-indications, such as a

minimal time (2 weeks?) between surgery and endoscopic procedure. The spectrum of endoscopic therapies includes biliary sphincterotomy, balloon dilation of strictures, basket and balloon extraction of stones, and the placement of one or multiple, side-by-side, biliary plastic or metal stents (21). Endoscopic therapy of ABS usually requires biliary sphincterotomy, balloon dilatation and stent placement. The use of balloon dilatation alone in early onset anastomotic strictures (the first 2 months following LT) may be effective, but it leads to a high rate of recurrent stricture formation (22, 23). Multiple 10-Fr plastic stents are usually maintained until stricture resolution or for a minimum of 12 months, with stent exchange scheduled every 3-4 months to reduce the chance of stent blockage and cholangitis; this was our main strategy. In a recent systematic review that included 446 LT-related ABS treated with multiple simultaneous plastic stents, the mean success resolution rate was approximately 85% for early as well as late ABS (24). Higher resolution rates (97% vs. 78%) and lower stricture recurrence rates (1.5% vs. 14%) have been reported with stenting durations >12 months vs. 12 months. As reported herein, most cases of ABS recurrence were successfully managed with repeat plastic stenting. A recent alternative to multiple plastic stents is the use of covered self-expandable metal stents (this concerned only 5 of our patients, in the most recent period). In the systematic review cited above (24), covered metal stents had a much higher stent migration rate (16%) compared with simultaneous multiple plastic stenting, and a risk of tissue ingrowth and stent impaction. The stricture resolution rates with metal stents were high when stent duration was 3 months or longer (80%-95%) compared with a duration less than 3 months (53%-88%). Similarly, a very recent study showed that the use of fully covered self-expandable metallic stents with anti-migration system significantly decreased the risk of stent migration, improved stricture resolution at the time of stent removal, and reduced the rate of stricture recurrence during follow-up (25). Therefore, current evidence does not suggest a clear advantage of metallic stents use over multiple simultaneous plastic stenting for the management of LT-related ABS. This will probably be investigated more largely in the near future.

In conclusion, we report here a very low rate of ABS after LT. The only significant risk factors identified were liver graft steatosis and higher recipient MELD score, and this suggests that steatotic grafts should be used for recipients without severe liver failure. In our experience, endoscopic treatment of post-LT biliary

stricture was the first therapy, leading to a high success rate, but was associated with a significant risk of recurrence.

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Table 1. Univariate analysis for post-transplant anastomotic bilio-biliary stricture

Variables	post-transplant anastomotic biliary stricture		p
	Yes (n=50)	No (n=733)	
Recipient-related			
Recipient age at the time of LT	50.2±11.5	50.6±10.0	0.833
Recipient gender: male	37 (74.0%)	511 (69.7%)	0.633
Initial liver disease etiology: alcohol	24 (48.0%)	343 (46.8%)	0.885
MELD score	21.5±13.5	14.8±9.2	0.063
Donor- and LT-related			
Donor age	39.7±17.1	38.6±15.9	
Donor gender: male	30 (60.0%)	491 (67.4%)	0.282
Cardiac arrest before procurement	3 (6.5%)	82 (12.5%)	0.347
Use of IGL1 solution (vs. UW)	18 (36.0%)	280 (38.5%)	0.766
Duration of cold ischemia	576.8±187.9	580.1±223.4	0.906
Duration of warm ischemia	45.1±12.3	41.8±9.9	0.505
Graft steatosis ≥30%	13 (26.0%)	89 (12.1%)	0.009
Graft steatosis ≥50%	5 (10.0%)	33 (4.5%)	0.087
Retransplantation	2 (4.0%)	15 (2.0%)	0.297
Surgeon: O Boillot	43 (86.0%)	557 (76.3%)	0.163
Post-reperfusion syndrome	15 (30.0%)	120 (16.6%)	0.021
Use of T-tube	7 (14.0%)	161 (22.1%)	0.215
Partial graft (split or living donor)	4 (8.0%)	124 (16.9%)	0.115
Vascular complication (arterial or venous)	8 (16.0%)	71 (9.7%)	0.148
Episode of acute rejection	26 (52.0%)	282 (38.5%)	0.072

Table 2. Multivariate analysis for post-transplant anastomotic bilio-biliary stricture

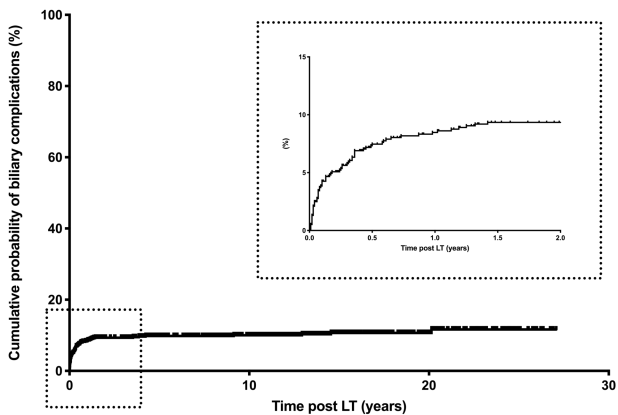
Variables	risk of post-transplant anastomotic biliary stricture		
	OR	95 % CI	p
Recipient-related			
MELD score*	1.071	1.018-1.128	0.008
Donor- and LT-related			
Graft steatosis $\geq 30\%$	6.262	1.936-20.257	0.002
Post-reperfusion syndrome	2.207	0.677-7.188	0.189
Partial graft (split or living donor)	0.308	0.034-2.785	0.295
Episode of acute rejection	1.723	0.522-5.686	0.371

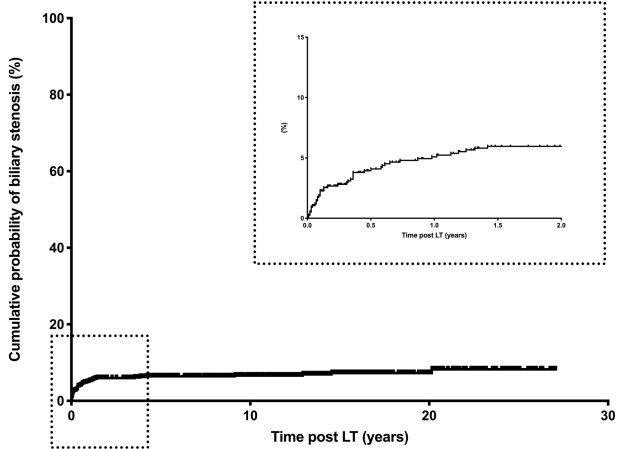
* per point

Legends for figures

Figure 1: Cumulative probability of a biliary complication (A) or anastomotic bilio-biliary stricture (B) after liver transplantation.

Figure 2: Flow chart of the patients included in the study.





Adult LT with bilio-biliary anastomosis (1990-2010) n= 783



Anastomotic stricture n= 50 (6.6%)



**Endoscopic
biliary stenting
n= 44 (88%)**

**Success rate
75%**

**Recurrence
24%**



**Surgery
n= 5 (10%)**
biliary anastomosis
revision n= 4,
bilio-digestive
anastomosis, n=1

**Success rate
80%**



**Percutaneous
biliary drainage
n= 1 (2%)**

**Success rate
0%**