

Research Article

Cheng Fang, Sheng Yan, Shusen Zheng*

Bile leakage after liver transplantation

<https://doi.org/10.1515/med-2017-0062>

received October 30, 2016; accepted October 18, 2017

Abstract: Objective: To evaluate the risk factors and outcome of bile leak after liver transplantation.

Methods: We undertook a retrospective study of patients who underwent liver transplantation in our institution between January 2010 and January 2014. The characteristics and survival rate of patients with or without bile leak were compared.

Results: Bile leak was observed in sixteen patients after liver transplantation (2.7% of the total number of patients transplanted). Total operating time and bile duct reconstruction technique (duct-to-duct anastomosis or Roux-en-Y cholangiojejunostomy) were found to differ significantly between patients with and without bile leak in univariate ($p = 0.001$ and 0.024 , respectively) and multivariate analyses ($p = 0.012$ and 0.026 , respectively). There was no difference in the one-year patient survival rate between the two groups. However, two-year patient survival rate was significantly lower in the bile leak group ($p = 0.003$). Both one-year and two-year graft survival rates were significantly lower in the bile leak group ($p = 0.049$ and <0.001 , respectively).

Conclusions: Cholangiojejunostomy and prolonged total operating time are risk factors for bile leak after deceased donor liver transplantation. Bile leak reduces graft and patient survival rates after deceased donor liver transplantation.

***Corresponding author: ShuSen Zheng**, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University School of Medicine. No.79 Qingchun Road, Hangzhou, Zhejiang Province, China, Tel: 86-571-87236570; Fax: 86-571-87236570; Email: shusenzheng@zju.edu.cn

Cheng Fang, Sheng Yan, Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, China

Authorship: Conceived and designed the research: Cheng Fang, Sheng Yan, Shusen Zheng. Performed the research: Cheng Fang, Sheng Yan, Shusen Zheng. Collected and analyzed the data: Cheng Fang. Wrote the paper: Cheng Fang, Shusen Zheng.

Keywords: Bile leak; Liver transplantation; Survival rate; Risk factors; Bile duct reconstruction; Operative time.

Abbreviations: LT, Liver transplantation; BL, Bile leakage; MELD, Model for end-stage liver disease; SD, standard deviation; BMI, Body mass index; OR, odds ratio; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; EST, endoscopic sphincterotomy; ENBD, endoscopic nasobiliary drainage.

1 Introduction

Biliary complications are common after liver transplantation; bile leak is reportedly among the most frequent, with an incidence of 2–25% [1]. Bile leak causes abdominal pain, fever and infection, and ultimately reduces graft and patient survival. It also prolongs hospital stay, increases medical costs and impairs quality of life after transplantation.

The need for multiple biliary reconstructions is reported to be a risk factor for bile leak in right-lobe living-donor transplant recipients, and is associated with lower patient and graft survival rates [2]. Bile leak is also common after hepatectomy. Total operating time, relaparotomy, bilioenteric anastomosis, elevated preoperative serum alanine transaminase concentration and laparoscopic surgery are considered to be risk factors for bile leak after hepatectomy [3-5]. The risk factors for bile leak after cadaveric liver transplantation, however, remain poorly understood.

Interventions such as percutaneous biliary drainage, endoscopic treatment and laparotomy may be needed to treat bile leak after transplantation, or a conservative management strategy may be adopted (prolonged abdominal drainage, antibiotic therapy and symptomatic treatment). As endoscopic techniques have developed and been refined, success rates have improved, and treatment by endoscopic retrograde cholangiopancreatography (ERCP) has become increasingly popular. Treatment by ERCP

mainly consists of endoscopic sphincterotomy (EST), endoscopic nasobiliary drainage (ENBD) and endoscopic stent placement. Dongwook and colleagues reported a clinical success rate of 77.3% using such a strategy to treat bile leak after liver transplantation [6].

We undertook a retrospective review of patients undergoing cadaveric liver transplantation to determine the risk factors for bile leak, evaluate treatment strategies and examine patient outcomes.

2 Patients and methods

We undertook five hundred and eighty-five liver transplantations in our hospital between January 2010 and January 2014. Of these, sixteen cases (2.7%) were complicated by bile leak; eleven had undergone whole liver transplantation, three living donor liver transplantation, one split liver transplantation and one had undergone retransplantation.

Bile duct reconstruction in our hospital generally consists of duct-to-duct anastomosis and Roux-en-Y cholangiojejunostomy. Duct-to-duct anastomosis and cholangiojejunostomy were fashioned using a continuous suture in the posterior wall and interrupted sutures in the anterior wall using 6-0 polypropylene. Roux-en-Y reconstruction was mainly used in patients who had previously undergone cholangiojejunostomy. We performed modified piggyback liver transplantation in our hospital. The diagnosis of bile leak is mainly made if bile-like ascites is drained and is found to have an elevated bilirubin concentration (range 74–1,020 $\mu\text{mol/L}$). A bilirubin concentration in the drainage fluid three times that of the serum is diagnostic of bile leak [7].

Eleven patients who underwent whole liver transplantation and experienced bile leak were selected for comparison with a control group who underwent liver transplantation during the same period but in whom bile leak was not detected. Patients who received living donor or split liver transplantation, or who underwent retransplantation, and children under the age of eighteen years were excluded from the control group. As most bile leaks reportedly occur in the first thirty days after liver transplantation [1], those who died or required retransplantation in the first thirty days were also excluded. Patients included in the statistical analysis are shown in Figure 1.

Continuous variables were expressed by mean \pm SD, and compared by Student's *t* test or Mann-Whitney test, while categorical variables were compared by Chi-squared test or Fisher exact test. Variables considered with statis-

tical difference in univariate analysis were selected for logistic regression. Calculation were performed by the SPSS software (version 19, IBM, USA). Patient and graft survival curve were drawn by Graph pad Prism 5, using Log rank test. A *p* value less than 0.05 was considered statistically different. All transplantations were permitted by the ethical committee of the first affiliated hospital of Zhejiang University (Hangzhou, China).

Informed consent: Informed consent has been obtained from all individuals included in this study.

3 Results

The incidence of postoperative bile leak was 2.7%. The mean age of those patients who developed bile leak was forty-seven years (range 19–76 years); 75% were men (*n* = 12). Their primary diagnoses were liver cirrhosis (*n* = 8), hepatic carcinoma (*n* = 7) and graft failure (*n* = 1). The median interval between liver transplantation and bile leak was sixteen days (range 7–42 days). Ten patients presented with fever (range 37.7–39.5°C) or abdominal pain and distension, while six were asymptomatic. Bile leak sites were identified as the duct-to-duct anastomosis (*n* = 4), the cholangiojejunostomy anastomosis (*n* = 2) and the cut surface of the remnant liver (*n* = 1), but were not identified in nine patients who were managed conservatively or in whom ERCP examination did not reveal an obvious site of leakage.

Three patients received endoscopic treatment and ENBD, while seven were treated with continuous drainage alone; all recovered completely. Six patients ultimately required laparotomy; two underwent retransplantation due to massive necrosis of the common bile duct.

Univariate analysis showed that total operating time (*p* = 0.001) and bile duct reconstruction technique (*p* = 0.024) were significantly different between the bile leak and control groups, but there were no differences in terms of sex, age, Model For End-Stage Liver Disease (MELD) score, cold ischemia time, primary diagnosis, treatment with corticosteroids, blood-type incompatibility, anhepatic time or blood loss. Total operating time (*p* = 0.012) and bile duct reconstruction technique (*p* = 0.026) were found to be independent risk factors in the multivariate analysis. The results of univariate and multivariate analyses are shown in Tables 1 and 2, respectively. There was no significant difference in one-year patient survival rate between the groups (*p* = 0.18); however, two-year patient survival was significantly lower in the bile leak group (*p* =

0.003, Figure 2). One-year and two-year graft survival rates were also significantly lower in the bile leak group ($p = 0.049$ and <0.001 , respectively; Figure 3).

4 Discussion

Bile leak is reported to occur in 2–25% of patients after liver transplantation [1]. The incidence of bile leak in our hospital was 2.7% during the study period, lying at the

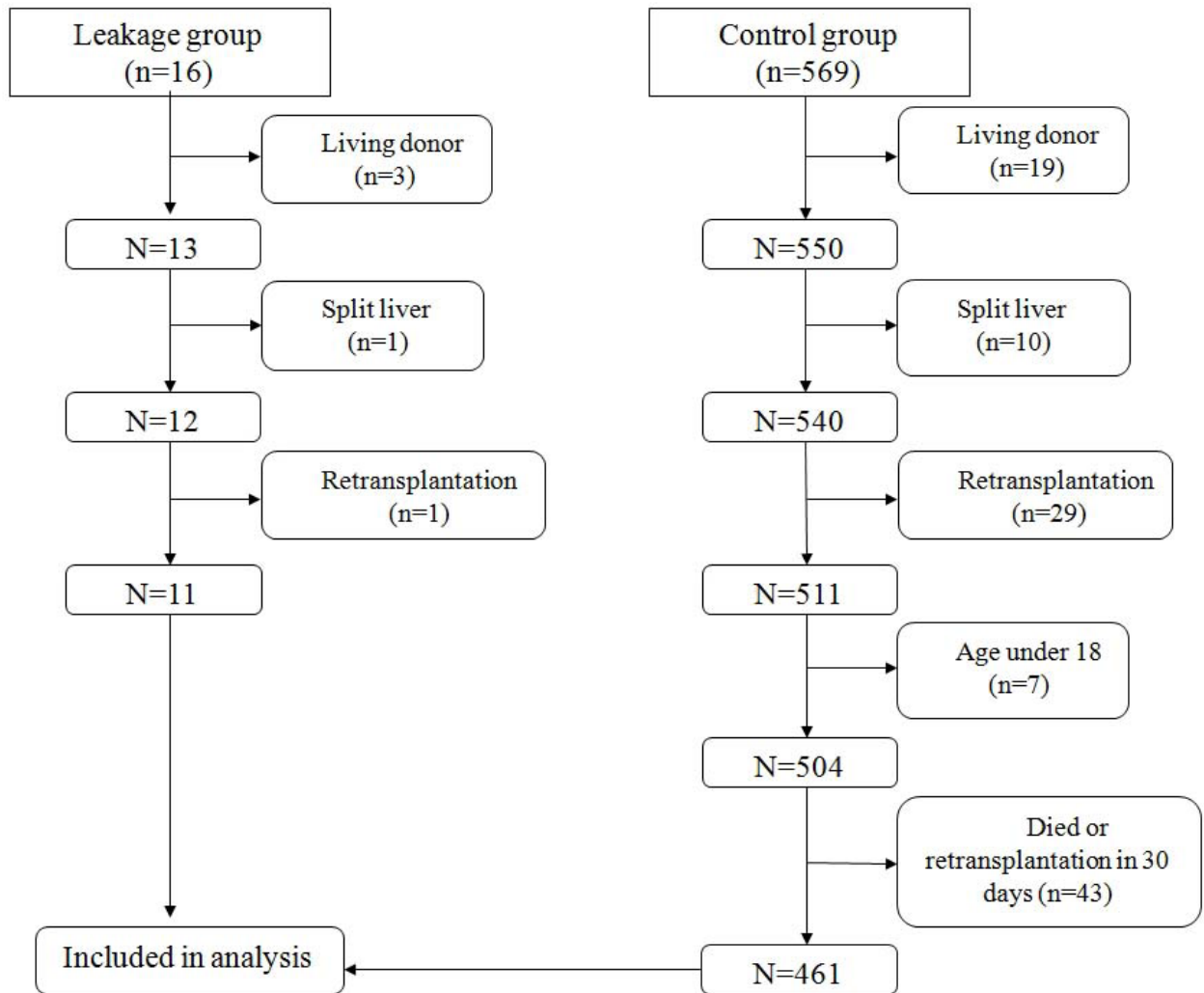


Figure 1: Patients included in statistical analysis.

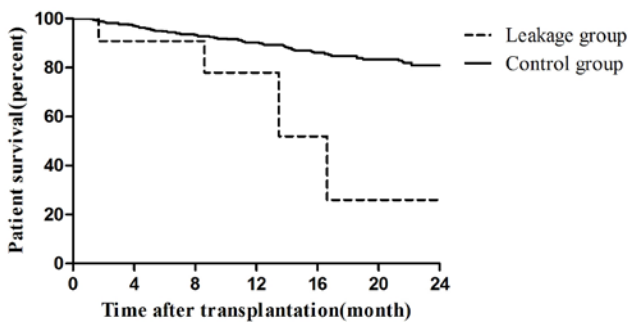


Figure 2: Patient survival curve of the two groups.

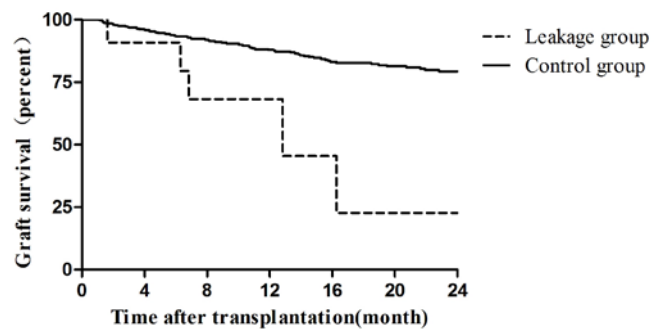


Figure 3: Graft survival curve of the two groups.

Table 1: Comparison of the characteristics of the leakage and control groups

	Leakage group (n=11)	Control group (n=461)	P value
Gender			
Male	9	391	0.68
Female	2	70	0.68
Age	50.27±12.17	47.47±9.81	0.60
BMI index	23.23±2.78	22.51±2.86	0.51
Child-Pugh score	8.36±1.75	8.59±2.63	0.86
MELD score	14.64±6.14	18.07±9.93	0.40
Total operation time (min)	382.64±51.30	316.15±73.54	0.001
Anhepatic time (min)	64.55±17.12	68.81±21.21	0.54
Blood loss (ml)	2927.27±1601.31	2258.66±1900.81	0.06
Cold ischemia time (min)	654±195.66	612.86±174.02	0.44
Bile duct reconstruction			
Duct to duct	9	452	0.024
Cholangiojejunostomy	2	9	0.024
Primary diagnosis			
Cirrhosis with hepatitis B	3	144	1
Alcoholic cirrhosis	0	22	1
Biliary cirrhosis	1	17	0.35
Acute liver failure	0	29	1
Hepatic carcinoma	7	228	0.38
Others	0	21	1
Steroid use	8	288	0.75
Blood type incompatible	2	61	0.64

Table 2: Multivariate analysis for the risk factors of bile leakage

Variable	OR	95% CI	P value
Total operation time	1.01	1.002-1.017	0.012
Cholangiojejunostomy	7.12	1.261-40.161	0.026

low end of this range. Bile leak may cause abdominal pain, fever, peritonitis, sepsis or even death. It prolongs hospital stays, elevates medical costs and ultimately impairs graft survival. Gondolesi and colleagues reported that patients who developed bile leak are at greater risk of graft failure and death [2]. We also found that one- and two-year graft survival and two-year patient survival were significantly lower in patients who developed a bile leak. Bile leak has also been reported to be an independent risk

factor for the development of biliary stricture, possibly as a result of free peritoneal bile provoking intra-abdominal inflammation and subsequently peribiliary fibrosis [8,9].

Kazuhiko and colleagues reported that complex hepatectomy and operating time were independent risk factors for bile leak after hepatectomy [4]. Gondolesi and colleagues found that the requirement for multiple biliary reconstructions was a risk factor for bile leak in a study of 96 consecutive patients undergoing right lobe living donor liver transplant. We found that total operating time and cholangiojejunostomy were independent risk factors for bile leak after deceased donor liver transplantation. The reason may be that in patients that received cholangiojejunostomy, the tissue and cellular characteristics of the jejunum and bile duct are substantially different, which may impair healing compared with duct-to-duct anastomosis. Cholangiojejunostomy may also provoke a stronger immune response after liver transplantation, as a

result of genetic and cellular heterogeneity. Further study will be needed to illuminate the potential pathophysiologic mechanisms responsible for our findings.

Endoscopic treatment is a safe and effective means of treating post-transplant biliary complications [10], with a reported success rate of 70% to 80% in patients with bile leak [11-17]. Nevertheless, ERCP also has complications, such as acute pancreatitis, intestinal perforation and bleeding. Patients in whom biliary stents have been deployed are also at increased risk of biliary infection and recurrent fever, which ultimately may necessitate removal of the stent. Plastic stents must be replaced when expired, which also adds to the risks and discomfort experienced by patients.

Furthermore, ERCP intervention has a higher failure rate in recipients of living donor liver transplants, as a more complex bile duct reconstruction may be needed than in a cadaveric transplant.

It's hard to perform ERCP in patients with cholangiojejunostomy for anatomical reasons. For these patients, ultrasound guided percutaneous drainage is often used for conservative treatment. The head of the drainage tube should be placed adjacent to the anastomosis. However, in patients with intrahepatic bile duct dilation, percutaneous transhepatic cholangial drainage (PTCD) combined with percutaneous drainage can be taken into consideration. In patients with percutaneous drainage, ultrasound examination was first performed to find the best puncture site. Then the drainage tube was placed into the peritoneal cavity under the guidance of ultrasound. The head of the drainage tube should be placed adjacent to the leakage site suspected or at the center of the peritoneal fluid collection. More than one tube can be placed to ensure adequate drainage.

Three of our patients who developed bile leak were treated by ERCP, and seven by continuous drainage. Our success rate for non-surgical treatment for bile leak was 62%. In our experience, patients with a small leak in a small volume of ascites and without any symptoms or discomfort can be treated by continuous drainage. In cases where there is repeated fever and abdominal pain, or large fluid volumes are drained from the abdominal cavity, we follow an endoscopic strategy. Patients treated by ERCP in our center underwent EST and ENBD to drain the bile and prevent leakage into the abdominal cavity. We undertake surgical intervention if there is severe abdominal infection or unstable vital signs, if conservative or endoscopic treatment has failed, or if it is judged that there is a high risk of septicemia. The size of a leak can be determined by taking into account the volume of ascites drained each day alongside a patient's symptoms and the results of imaging

investigations. In our cohort, all patients treated with continuous drainage drained less than 300 mL a day. The healing of bile leakage was mainly judged according to the amount and color of the drainage fluid and image examination. In our cases, the drainage tube was removed after the color of drainage fluid turned normal, almost no fluid drained out and examination showed no obvious liquid accumulation. The concentration of bilirubin detected in the drainage fluid was lower than that in blood. In patients without cholangiojejunostomy, ERCP can also be applied to evaluate the healing of biliary anastomosis.

To prevent postoperative bile leak, care should be taken when suturing the bile duct anastomosis, while ensuring that the bile duct has an adequate blood supply. Surgeons should strive to improve their operating skills to reduce operating time as much as possible. Postoperatively, we recommend that symptoms and physical signs are observed daily, with particular attention to the volume and color of drain fluid. Close attention should be paid to the patient's nutritional status. The concentration of bilirubin in ascitic fluid should be measured, and ultrasound examination should be undertaken to detect intra-abdominal fluid collection, twice a week. Contrast-enhanced computed tomography examination of the abdomen may be required if necessary.

Bile leak is common after liver transplantation. It severely impairs quality of life, prolongs hospital stays and leads to lower graft and patient survival. Understanding the risk factors for bile leak will help clinicians choose the optimal treatment strategies for patients, so as to reduce the morbidity and mortality caused by bile leak and achieve better patient outcomes.

Acknowledgement: This work was supported by the Public Welfare Technology Application Research Plan of Zhejiang (no. 2015C33117), National S&T Major Project (No. 2016ZX10002020) and Foundation for Innovative Research Groups of the National Natural Science Foundation of China (No. 81421062).

Conflict of interest statement: The authors have no conflicts of interest to disclose.

References

- [1] Kochhar G, Parungao JM, Hanouneh IA, Parsi MA. Biliary complications following liver transplantation. *World J Gastroenterol.* 2013;19(19):2841-6. PMID: 3660810
- [2] Gondolesi GE, Varotti G, Florman SS, Munoz L, Fishbein TM, Emre SH, et al. Biliary complications in 96 consecutive right

- lobe living donor transplant recipients. *Transplantation*. 2004;77(12):1842-1848
- [3] Hoekstra LT, van Gulik TM, Gouma DJ, Busch OR. Posthepatectomy bile leakage: how to manage. *Dig Surg*. 2012;29(1):48-53
- [4] Sakamoto K, Tamesa T, Yukio T, Tokuhisa Y, Maeda Y, Oka M. Risk Factors and Managements of Bile Leakage After Hepatectomy. *World J Surg*. 2016;40(1):182-9. PMID: 4695499
- [5] Zheng SM, Li H, Li GC, Yu DS, Ying DJ, Zhang B, et al. Risk factors, treatment and impact on outcomes of bile leakage after hemihepatectomy. *ANZ J Surg*. 2015
- [6] Oh DW, Lee SK, Song TJ, Park do H, Lee SS, Seo DW, et al. Endoscopic management of bile leakage after liver transplantation. *Gut Liver*. 2015;9(3):417-23. PMID: 4413977
- [7] Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery*. 2011;149(5):680-688
- [8] Verdonk RC, Buis CI, Porte RJ, van der Jagt EJ, Limburg AJ, van den Berg AP, et al. Anastomotic biliary strictures after liver transplantation: causes and consequences. *Liver Transpl*. 2006;12(5):726-735
- [9] Welling TH, Heidt DG, Englesbe MJ, Magee JC, Sung RS, Campbell DA, et al. Biliary complications following liver transplantation in the model for end-stage liver disease era: effect of donor, recipient, and technical factors. *Liver Transpl*. 2008;14(1):73-80
- [10] Dechene A, Kodde C, Kathemann S, Treckmann J, Lainka E, Paul A, et al. Endoscopic treatment of pediatric post-transplant biliary complications is safe and effective. *Dig Endosc*. 2015;27(4):505-511
- [11] Tarantino I, Barresi L, Petridis I, Volpes R, Traina M, Gridelli B. Endoscopic treatment of biliary complications after liver transplantation. *World J Gastroenterol*. 2008;14(26):4185-9. PMID: 2725380
- [12] Morelli J, Mulcahy HE, Willner IR, Baliga P, Chavin KD, Patel R, et al. Endoscopic treatment of post-liver transplantation biliary leaks with stent placement across the leak site. *Gastrointest Endosc*. 2001;54(4):471-475
- [13] Polese L, Cillo U, Brolese A, Boccagni P, Neri D, Bassi D, et al. Endoscopic treatment of bile duct complications after orthotopic liver transplantation. *Transplant Proc*. 2007;39(6):1942-1944
- [14] Liao JZ, Zhao Q, Qin H, Li RX, Hou W, Li PY, et al. Endoscopic diagnosis and treatment of biliary leak in patients following liver transplantation: a prospective clinical study. *Hepato-biliary Pancreat Dis Int*. 2007;6(1):29-33
- [15] Park JS, Kim MH, Lee SK, Seo DW, Lee SS, Han J, et al. Efficacy of endoscopic and percutaneous treatments for biliary complications after cadaveric and living donor liver transplantation. *Gastrointest Endosc*. 2003;57(1):78-85
- [16] Chahal P, Baron TH, Poterucha JJ, Rosen CB. Endoscopic retrograde cholangiography in post-orthotopic liver transplant population with Roux-en-Y biliary reconstruction. *Liver Transpl*. 2007;13(8):1168-1173
- [17] Tsujino T, Isayama H, Sugawara Y, Sasaki T, Kogure H, Nakai Y, et al. Endoscopic management of biliary complications after adult living donor liver transplantation. *Am J Gastroenterol*. 2006;101(10):2230-2236