Open Peer Review on Qeios

Biliary Complications Following Liver Transplantation: The First Single-Center Tunisian Experience

Wael Ferjaoui

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Biliary complications remain a major source of morbidity and mortality in liver transplant recipients. In Tunisia, liver transplantation has been performed for twenty years but no study was interested in reviewing the biliary complications occurring after liver transplantation.

In this study, we seek to report our experience with the biliary complications after liver transplantation and to identify the risk factors.

We conducted a single center retrospective review of 49 liver transplantations performed in 47 patients between 1999 and 2020. The evaluated factors were early and late biliary complications and their predictive factors.

The overall biliary complications rate was 38%. The early biliary complications rate was 21% with a bile leakage rate of 13% and a stricture rate of 9%. By means of univariate analysis, the risk factors were umbilical vein repermeabilization (p=0.029), grade 3 esophageal varices (p=0.029), jaundice (p=0.006), hemoglobin level < 10 g/dl (p=0.012), and hepaticojejunostomy (p=0.042). the late biliary complications rate was 41% with a leakage rate of 10%, stricture rate of 38% and lithiasis rate of 7%. By means of univariate analysis, the risk factors were collateral venous circulation (p=0.023) and cold ischemic time > 8 hours (p=0.022). multivariate analysis did not identify any independent predictors.

The biliary complications rate found in our study was superior to the ones reported un literature. The risk factors had significant impact only in univariate analysis. Future studies with a larger population and more sophisticated methodology might accord more credits to our conclusions.

Sahir omrani[1], **Fatma Medhioub**[1], **Firas Ayadi**[1], **Nizar Cherni**[2], **Ferjaoui Wael**[1,*], **Mestiri Hafedh**[1], **Rached Bayar**[1]

[1] *Department of General surgery, Mongi Slim University Hospital, Faculty of medicine of Tunis, University of Tunis El Manar*

[2] *Department of Urology, Military Hospital, Faculty of medicine of Tunis, University of Tunis El Manar*

[*]Corresponding Author.

Tel: +216 52430099

E mail: farjaouiwael4@gmail.com

ORCID iD: 0000-0002-4279-9370

Introduction

In Tunisia, the first liver transplantation was performed in 1998 in Sahloul hospital in Sousse. Since December 1999, Mongi Slim hospital took over and performed 56 transplantation until February 2020.

Despite advances in surgical techniques, organ preservation and immunosuppression protocols, several serious complications still endanger successful short and long term outcome. Biliary complications appear to be one of the most common issues during follow up. For that reason, biliary reconstruction is considered to be the Achilles's heel of the liver transplantation. Biliary complications are a considerable burden on the health care system as they increase hospital stay, cost and operative mortality.

The objective of the present study was to evaluate the incidence and the risk factors of biliary complications.

Methods

Study design, duration and settings

This study isretrospective, descriptive and analytic. It has compiled patients who underwent a liver transplantation at the department of general surgery at Mongi Slim hospital (La Marsa, Tunisia) from December 1999 to February 2020.

Patients screening

Inclusion criteria were hepatic transplanted patients from December 1999 to February 2020. Exclusion criteria were incomplete records and deaths that occurred peroperatively or because of primary graft non-function.

Risk factors associated with the recipient were collected, such as sex, age, laboratory tests, blood type and transplantation motif. Factors associated with the donor as type of graft, age, ABO mismatch with the recipient and time of cold and warm ischemia. And factors post transplantation that include arterial and portal stenosis/thrombosis, exposure to cytomegalovirus, small for size syndrom, acute and chronic graft rejection and recurrence of the initial disease.

Study endpoints

Onset of early and late biliary complications is defined as primary study endpoint. They include strictures, leaks and stones or debris. They are classified in two categories: early biliary complications which present within 30 days of the transplantation and late biliary complications which present beyond this time.

Statistical analysis

The SPSS statistics software version 25 was used to perform statistical analysis. Qualitative variables were expressed as percentages. Quantitative variables were expressed as means and medians. The data was evaluated by the Mann-Whitney test and Fisher's exact test. All variables which were significant in univariable binary logisticregression analysis were considered for the multivariable binary regression model. For all statistical tests a P-value < 0.05 was defined as significant.

Results

Of a total of 49 liver transplantations performed in 47 patients. Cadaveric liver transplantation was done in 37 patients (79%) and living donor liver transplantation in 10 (21%).

Eighteen patients (38%) had biliary complications. They were early in 10 patients and late in 11 patients.

Types of biliary complications

Bile leakage occurred in 9 patients (50%) on postoperative days 2 to 45. It was early in 6 patients and late in 3. They were treated with one or more of the following procedures: conservative treatment (n=1), surgery with peritoneal cleansing and drainage (n=5), percutaneous drainage of biloma (n=3).

Biliary stricture occurred in 13 patients (72%) on postoperative days 3 to 1440. It was the most common biliary complication. It was early in 4 patients and late in 9 patients. The stenosis was anastomotic in 11 patients and non-anastomotic in 2 patients. Both of them were due to a thrombosis of the hepatic artery causing the death of the patients. Anastomotic strictures were treated with one or more of the following procedures: conservative treatment (n=1), Ganciclovir for a cytomegalovirus infection (n=1), endoscopic dilatation (n=1), endoscopic stenting (n=7), surgery for revision of choledococholedocostomy (n=1) or conversion of choledococholedocostomy to hepaticojejunostomy (n=7). Five patients had bile leakage and subsequent anastomotic stricture.

Biliary lithiasis was diagnosed in 2 patients on postoperative days 300 to 6120. were treated with one or more of the following procedures: endoscopic biliary stenting with sphincterotomy (n=1) and surgery for hepaticojejunostomy (n=1). One patient had anastomotic stricture and subsequent lithiasis.

Patient characteristics

Pre-operative data

A total of 12 patients (67%) were male and 6 females (33%). The age of recipients varied from 9 to 62 years with an average of 41 years. The average body mass index was 24 kg/m^2. Jaundice was present in 13 patients (72%).

The indications of liver transplantation were decompensated cirrhosis in 17 patients (94%) and progressive intrahepatic familial cholestasis in 1 patient (6%). The median MELD score was 17. Most patients had a score between 10 and 20.The most common causes of cirrhosis were virus B hepatitis and primary sclerosing cholangitis followed by virus C hepatitis, primary biliary cholangitis and auto-immune hepatitis.

Cadaveric liver transplantation was done in 14 patients (78%) and living donor liver transplantation in 4 (22%). The mean age of the donors was 30 years ranging from 15 to 52 years. Two recipients (1%) didn't have the same ABO blood group as the donors.

Per-operative data

The mean cold ischemia time was 8 hours and 20 minutes. The mean warm ischemia time was 1 hour. Biliary reconstruction was a choledococholedocostomy in 16 patients and a choledochojejunostomy in 2 patients. Bile duct drainage was employed in all the patients with choledococholedocostomy.

Postoperative data

Small for size syndrom was found in one patient. A stenosis of the hepatic artery was found in one patient. A thrombosis of the hepatic artery was found in 6 patients, it was early in 5 and late in 1. A chronic rejection was found in 2 patients. A portal vein stenosis was found in 1 patient. The early mortality rate was 17% (3 patients). The average time was 12 days. The late mortality rate was 22%. The average time was 38 months.

Risk factors of the development of BCs

Univariate analysis indicated that significant predictors of early biliary complications were umbilical vein repermeabilization (p=0.029), grade 3 esophageal varices (p=0.029), jaundice (p=0.006), hemoglobin level < 10 g/dl (p=0.012), and hepaticojejunostomy (p=0.042). Predictors of late biliary complications were collateral venous circulation (p=0.023) and cold ischemic time > 8 hours (p=0.022).

Discussion

Biliary complicationsonce considered as the technical "Achilles heel" of liver transplantation, still remain a common source of morbidity and mortality. Despite all the progress insurgical techniques, they are still frequent. The incidence reported in recent studies varies between 23% to 28% [1][2]. In our study, biliary complications were found in 38% of our patients.

To date, tremendous efforts have been made to determine the risk factors for the development if biliary complications. These complications have been reported to be related to many conditions, notably prolonged cold ischemia time, hepatic artery thrombosis, ABO blood type incompatibility, cytomegalovirus infection, recurrence of primary disease, the method of biliary reconstruction and acute rejection [3][4][5][6][7][8][9][10][11][12][13].

In addition, we identified preoperative signs of portal hypertension as a risk factors for biliary complications. The hypothesis is that patients with important portal hypertension have poor liver function and complete hemostasis is difficult to achieve and may require mobilization of the graft for exposure and may lead to disruption of the biliary anastomosis[14]. Also, a number of previous studies had found that the preoperative serum bilirubin level number was an important determinant of liver transplantation outcome. It was shown to be an independent predictor of biliary complications though the mechanism remains unexplained[14].

Anemia is highly prevalent in patients with severe chronic liver disease. It has been reported in previous studies that preoperative hemoglobin level below 10 g/dl is associated with poorer short-term outcomes after liver transplantation [15]. However, its impact on the biliary anastomosis has not been investigated. To the best of our knowledge, this was the first study to show anemia as a risk factor of biliary complications after liver transplantation.

Currently, the two opinions in performing a biliary reconstruction in liver transplant recipients are the choledocho-choledocostomy or duct-to-duct technique, and the Roux-en-Y hepaticojejunostomy or choledochojejunostomy [16]. The choice is likely influenced by multiple factors, such as underlying liver disease, graft type, size of donor and prior transplant or other biliary surgery [17]. Currently, the choledococholedocostomy is the preferred technique in adults. It is easier to perform, has low incidence of enteric reflux and allows easy endoscopic assessment in the case of complications[14]. According to some early studies, biliary complications are more frequent after CJ reconstruction than after DDreconstruction. In the presented study, a DD reconstruction was the procedure of choice. We concluded that the hepaticojejunostomy was associated with more biliary complication. However, this type of anastomosis was only performed in patients with PSC, which could also be a risk factor for biliary complications.

Even though the presence of HAT was not significantly associated with biliary complications, we noticed that the incidence of BCs was affected by the presence of HAT. In fact, among the 10 patients with HAT, five presented with a biliary complication. This is related to the biliary tract vascularization that is exclusively supplied by vessels originated from the hepatic artery [3].

Conclusion

The onset of post-transplant biliary complications endanger patients as well as graft survival even in the long run[18]. This has serious implications for healthcare economy[18]. That is why such complications should be avoided and efforts must be made to reduce the biliary complications rate. This study is limited by its single enter design and its retrospective character. Also, the limited number of patients and the long observation period may be other sources of bias. Further larger-scale prospective randomized studies are required to confirm our results and conform to patient-tailored treatment regimens for better outcomes.

References

1. ^Kim T-S, Ahn KS, Kim YH, Kim HT, Kang KJ. THE FATE OF BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION: SINGLE-CENTER EXPERIENCE. Transplantation 2020;104.
2. ^Senter-Zapata M, Khan AS, Subramanian T, Vachharajani N, Dageforde LA, Wellen JR, et al. Patient and Graft Survival: Biliary Complications after Liver Transplantation. J Am Coll Surg2018;226:484–94. https://doi.org/10.1016/j.jamcollsurg.2017.12.039.
3. a, bCoelho JCU, Leite L de O, Molena A, Freitas ACT de, Matias JEF. BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION. ABCD Arq Bras CirDig São Paulo 2017;30:127–31. https://doi.org/10.1590/0102-6720201700020011.
4. ^De Souza Silva AC, De Faria Andrade AM, Coelho Lisboa Q, Xavier de Lima C, Papatella Araujo J, Ribeiro Gambogi T, et al. Epidemiologic Study on the Incidence of Biliary Complications after Liver Transplantation. J Liver 2018;07. https://doi.org/10.4172/2167-0889.1000229.
5. ^Nemes B, Gámán G, Doros A. Biliary complications after liver transplantation n.d.:20.
6. ^Sanchez-Urdazpal L, Batts KP, Gores GJ, Moore SB, Sterioff S, Wiesner RH, et al. Increased bile duct complications in liver transplantation across the ABO barrier. Ann Surg1993;218:152–8. https://doi.org/10.1097/00000658-199308000-00006.
7. ^Sanchez-Urdazpal L, Gores GJ, Ward EM, Maus TP, Wahlstrom HE, Moore SB, et al. Ischemic-type biliary complications after orthotopic liver transplantation. Hepatology 1992;16:49–53. https://doi.org/10.1002/hep.1840160110.
8. ^Colonna JO 2nd, Shaked A, Gomes AS, Colquhoun SD, Jurim O, McDiarmid SV, et al. Biliary strictures complicating liver transplantation. Incidence, pathogenesis, management, and outcome. Ann Surg1992;216:344–52. https://doi.org/10.1097/00000658-199209000-00014.
9. ^Pascher A, Neuhaus P. Biliary complications after deceased-donor orthotopic liver transplantation. J Hepatobiliary PancreatSurg2006;13:487–96. https://doi.org/10.1007/s00534-005-1083-z.
10. ^Dacha S, Barad A, Martin J, Levitsky J. Association of hepatic artery stenosis and biliary strictures in liver transplant recipients. Liver Transpl2011;17:849–54. https://doi.org/10.1002/lt.22298.
11. ^Gotthardt DN, Senft J, Sauer P, Weiss KH, Flechtenmacher C, Eckerle I, et al. Occult cytomegalovirus cholangitis as a potential cause of cholestatic complications after orthotopic liver transplantation? A study of cytomegalovirus DNA in bile. Liver Transpl2013;19:1142–50. https://doi.org/10.1002/lt.23713.
12. ^Kowdley KV, Fawaz KA, Kaplan MM. Extrahepatic biliary stricture associated with cytomegalovirus in a liver transplant recipient. TransplInt1996;9:161–3. https://doi.org/10.1111/j.1432-2277.1996.tb00872.x.
13. ^Halme L, Hockerstedt K, Lautenschlager I. Cytomegalovirus infection and development of biliary complications after liver transplantation1. Transplantation 2003;75.
14. a, b, cQian YB, Liu CL, Lo CM, Fan ST. Risk Factors for Biliary Complications After Liver Transplantation. ARCH SURG 2004;139:5.
15. ^Badawy A, Kaido T, Hammad A, Yagi S, Kamo N, Yoshizawa A, et al. The Impact of Preoperative Hemoglobin Level on the Short-Term Outcomes After Living Donor Liver Transplantation. World J Surg2018;42:4081–9. https://doi.org/10.1007/s00268-018-4696-5.

16. ^ *Verdonk RC, Buis CI, Porte RJ, Haagsma EB. Biliary complications after liver transplantation: A review. Scand J Gastroenterol 2006;41:89–101. https://doi.org/10.1080/00365520600664375.*

17. ^ *Akamatsu N, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome: Biliary reconstruction. TransplInt2011;24:379–92. https://doi.org/10.1111/j.1432-2277.2010.01202.x.*

18. a, b *Kaltenborn A, Gutcke A, Gwiasda J, Klempnauer J, Schrem H. Biliary complications following liver transplantation: Single-center experience over three decades and recent risk factors. World J Hepatol2017;9:147. https://doi.org/10.4254/wjh.v9.i3.147.*