Journal of Liver
ISSN: 2167-0889

Silva et al., J Liver 2018, 7:3
DOI: 10.4172/2167-0889.1000229

Research Article Open Access

Epidemiologic Study on the Incidence of Biliary Complications after Liver Transplantation

Ana Claudia De Souza Silva[1], Antônio Márcio De Faria Andrade[1], Quelson Coelho Lisboa[1], Cristiano Xavier de Lima[1], Juliana Papatella Araújo[1], Thaís Ribeiro Gambogi[1], Valdineria Oliveira Borges[1] and Idiberto José Zotarelli Filho[2]*

[1]Department of gastroenterology, Hepatology and Liver Transplantation - Felício Rocho Hospital, Belo Horizonte, MG, Brazil
[2]Post Graduate and Continuing Education (Unipos), Department of Scientific Production, Street Ipiranga, 3460, São José do Rio Preto SP, Brazil

Abstract

Introduction: Biliary complications after hepatic transplantation have a variable incidence of 10 to 25% among all complications after hepatic transplantation and mortality reported up to 10%, have an important impact on the patient's quality of life, since it implies the need for hospitalizations and multiple interventions for treatment. They are more frequent in the first year after transplantation, with progressive reduction of the frequency after 1 year. **Objective:** To evaluate the risk factors of greater impact in the development of bile duct stenosis in patients after liver transplantation.

Methods: One hundred and eighty-eight charts of liver transplant patients were retrospectively evaluated. Inclusion criteria: liver transplanted patients from 2011 to December 2017. Exclusion criteria: deaths that occurred between the first month after transplantation, incomplete medical records and most cases of retransplants, except for patients who retransplanted as a consequence of their own complication.

Results: Biliary complications were present in 14% (N=26) of the patients. Of these, 52% (N=21) presented stenosis of the biliary tract, followed by other complications such as cholangitis (20%), fistula calculation (10%), bilioma (3%). Among patients with bile duct stenosis, 19% (N=4) presented non-anastomotic stenosis and 81% (N=17) anastomotic stenosis. The cause of hepatopathy was in 42% of patients (N=9) ethanolic, followed by other causes such as: viral hepatitis, cryptogenic, autoimmune, fulminant hepatitis, NASH, CEP, glycogenosis and 1 case of secondary retransplantation to the bile complication itself.

Conclusion: The incidence of biliary complications is comparable with the incidence reported in other institutions. The low incidence of bile duct stenosis reduces the power of the study to identify the most impacting risk factors.

Keywords: Liver transplant; Biliary stenosis; Bile fistula; Biliary complications; Postoperative complications

Introduction

Biliary complications after hepatic transplantation have a variable incidence of 10 to 25% of all complications after hepatic transplantation and mortality reported in up to 10%, has an important impact on the quality of life of the patient [1], in the first year after transplantation, with progressive reduction of frequency after 1 year [1,2]. Complications can be early, those occurring in the first month or late when they occur after the first month. Among the possible bile complications, bile duct stenosis is the most common, representing 40% of all of them [2,3]. In Brazil, it occurred in São Paulo in 1985 and, currently, the country is third in the world in absolute number of transplants, after the United States and China [4-6].

In this scenario, bile reconstitution is one of the main challenges of liver transplantation, since biliary complications remain the most frequent postoperative technical complication [1,2,7]. Biliary complications have a high incidence, increase hospitalization time and hospital costs, as well as patient mortality [8]. In addition, they also compromise post-transplant quality of life, requiring treatments such as endoscopic, percutaneous and surgical procedures [9].

Thus, many scientist/researchers from different research area are working on this topic to reduce complications that occur after liver transplantation due to the vital importance of the surgery. For instance, software engineers have been developing several tools presenting information about volume of liver or location of liver boundaries or abnormal regions (such as cysts on the liver) to help medical doctors. In the literature, there are also many semi-/full-automated liver segmentation techniques [10-14], vessel segmentation [15,16], labeling of hepatic and portal vessels [17] based on MR/CT images for pre-evaluation of liver transplantation. These methods present quantitative information to doctors about liver (e.g., liver volume or size) and vascular structures to reduce complications after liver transplantation.

Thus, several risk factors are related to the appearance of biliary complications [6]. These include hepatic artery thrombosis, acute cell rejection, time of cold ischemia of the transplanted organ, and advanced age of donor and recipient. There are few studies that relate these and other risk factors with results of liver transplantation services in Brazil [6].

Therefore, the present study had as objective to evaluate the risk factors of greater impact in the development of bile duct stenosis in patients after hepatic transplantation.

***Corresponding author:** Prof. Dr. Idiberto José Zotarelli Filho, Unipos - Post Graduate And Continuing Education, Street Ipiranga, 3460, São José do Rio Preto SP, Brazil 15020-040, Tel: +55(17) 98166-6537; E-mail: scientificresearch@unipos.com.br; m.zotarelli@gmail.com

Received August 01, 2018; **Accepted** August 13, 2018; **Published** August 18, 2018

Citation: Silva ACDS, Andrade AMDF, Lisboa QC, Lima CXD, Araújo JP, et al. (2018) Epidemiologic Study on the Incidence of Biliary Complications after Liver Transplantation. J Liver 7: 229. doi: 10.4172/2167-0889.1000229

Methods

Participants

A total of 188 participants were submitted to eligibility analysis, followed by the rules STROBE (Strengthening the Reporting of Observational studies in Epidemiology), https://www.strobe-statement.org/index.php?id=strobe-home

Study design

The present study followed a retrospective longitudinal and observational model on the analysis of the profile of patients who underwent liver transplant at Brazil. The descriptors were: Liver transplant, Liver disease, Biliary complications, Postoperative complications.

Patients screening

One hundred and eighty-eight charts of liver transplant patients were retrospectively evaluated. Inclusion criteria were hepatic transplanted patients from 2011 to December 2017. Exclusion criteria were deaths that occurred between the first month after transplantation, incomplete records and most cases of retransplants, except for patients who retransplanted as a consequence of the biliary complication itself. For all patients included in the study, risk factors associated with the recipient were collected, such as sex, transplantation motif, presence or absence of hepatocellular carcinoma, and age. Factors associated with the donor as age and serum sodium level, associated with the graft, as the size and time of cold ischemia. And lastly factors post transplantation that includes arterial and portal stenosis/thrombosis, ischemia and reperfusion injury and exposure to citalomegalovirus. For statistical analysis the data were tested for Normality through the Kolmogorov-Smirnof test, which indicated normality present for the variables "donor age and donor sodium", therefore, the parametric test class was used. For the other variables, the non-parametric test class was used, since the data did not present a normal distribution (Figure 1).

Results

Biliary complications were present in 14% (N=26) of the patients, of which 52% (N=21) had stenosis of the biliary tract, followed by other complications such as cholangitis (20%), fistula 10%), bilioma (3%). Among patients with bile duct stenosis, 19% (N=4) presented non-anastomotic stenosis and 81% (N=17) anastomotic stenosis.

The cause of hepatopathy was in 42% of patients (N=9) ethanolic, followed by other causes such as: viral hepatitis, cryptogenic, autoimmune, fulminant hepatitis, non-alcoholic steatohepatitis (NASH), congenital erythropoietic porphyria glycogenosis and 1 case of retransplantation secondary to the bile complication itself (Tables 1 and 2).

Median age, cold graft ischemia time, and the highest value of

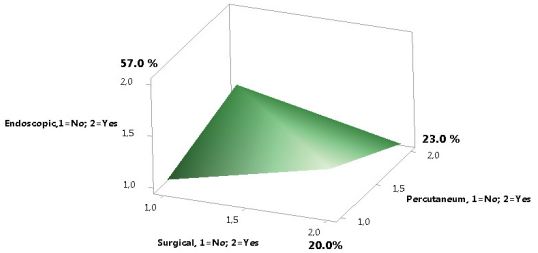

Figure 1: 3D chart showing the percentages of the main treatment used.

Reason for Transplantation	Number of Patients
Ethanolic liver cirrhosis	59
Viral hepatic cirrhosis	34
Cryptogenic hepatic cirrhosis	23
Cryptogenic hepatic cirrhosis + EHE	11
Acute Fulminant Hepatitis	10
Autoimmune hepatitis	10
Ethanolic + viral hepatic cirrhosis	9
NASH	7
CEP	5
CBP	5
Hepatorenal Polycystic Disease	3
Alpha 1 antitrypsin deficiency	2
Glycogenose	2
Sd. Budd - Chiari	2
Hemangioendothelioma Ep. Non-returnable	2
Hereditary hemochromatosis	2
Primary hyperoxaluria	2

Table 1: Demographic data.

Variables	Stenosis								p-value
	No				Yes				
	N	Mean	Standard deviation	Median	N	Mean	Standard deviation	Median	
Age	167	54.7	11.8	58	21	51.1	11.3	56	0.086*
TIF	167	6.7	2.3	6.3	21	6.1	1.8	6	0.277*
BT	167	5.7	5.4	3.8	21	7	6.1	4.3	0.416*
RNI	167	3.7	20.7	1.8	21	2.1	0.6	2	0.610*
SGOT	167	1766.5	2996.3	757	21	2543.8	3584.8	784	0.644*
Donor age	167	35.8	13.7	36	21	33.1	12.6	33	0.407**
Sodium donor	167	150.2	9.6	150	21	152.1	8.6	152	0.379**

*TesteMann-Whitney
** Teste T de Student

Table 2: General data of descriptive statistics of patients with and without stenosis.

bacterial translocation (BT), reactive nitrogen intermediate (RNI) and Serum glutamic oxalacetic transaminase (SGOT) in the first week among patients with biliary bile duct stenosis, were respectively 56 years, 6 hours, 4.3, 2.0, 784, while in the group without stenosis were 58 years, 6.3 hours, 3.8, 8.8, 787. Mean age of the donor and the donor sodium value of patients with stenosis were respectively 33.1 years and 152.1 years, versus 35.8 years and 150.2 years for patients without stenosis. In relation to sex, 23.8% (N=5) of the patients with biliary stenosis were female and 76.2% (N=16) were male. Hepatocellular carcinoma (HCC) was present in 14.3% (N=3) and portal vein thrombosis/stenosis occurred in 4.8% (N=1) of patients with stenosis (Tables 3 and 4).

Treatment of citalomegalovirus (CMV) was instituted in 33.3% (N=7), of these 42.8% (N=3) treated infection prior to the development of the complication, the others presented with early biliary complication and then CMV infection did not have a risk factor. 9.5% (N=2) of patients with stenosis received a large graft. In all of these analyzes, a $p>0.05$ was found, indicating that there was no statistically significant difference in the group with or without the complication (Table 5).

Finally, hepatic artery thrombosis/stenosis was present in 19% (N=4) of patients with biliary stenosis after hepatic transplantation. For this analysis a $p<0.05$ was found, proving that there was a statistically significant difference of stenosis / hepatic artery thrombosis in the group with biliary stenosis. Endoscopic treatment was instituted in 57.0% of the patients, 23.0% percutaneous treatment and 20.0% surgical treatment (Tables 6-8).

			Stenosis		Total
			No	Yes	
Sex	Female	Number	41	5	46
		% Stenosis	24.60%	23.80%	24.50%
	Male	Number	126	16	142
		% Stenosis	75.40%	76.20%	75.50%
Total		Number	167	21	188
		% Stenosis	100%	100%	100%
p-value			p>0.05	p>0.05	

Table 3: Percentage of females and males is similar in patients with and without stenosis, with p>0.05.

			Stenosis		Total
			No	Yes	
HCC	No	Number	115	18	133
		% Stenosis	68.90%	85.70%	70.70%
	Yes	Number	52	3	55
		% Stenosis	31.10%	14.3%	29.30%
Total		Number	167	21	188
		% Stenosis	100%	100%	100%
p-value			p>0.05	p>0.05	

Table 4: Similar percentage of HCC in patients with and without stenosis, with p>0.05.

			Stenosis		Total
			No	Yes	
thrombosis/Stenosis Arterial	No	Number	164	17	181
		% Stenosis	98.20%	81.00%	96.30%
	Yes	Number	3	4	7
		% Stenosis	1.80%	19.00%	3.70%
Total		Number	167	21	188
		% Stenosis	100%	100%	100%
p-value			p<0.05	p<0.05	

Table 5: Percent thrombosis/arterial stenosis was significantly higher in patients with stenosis, with p<0.05.

			Stenosis		Total
			No	Yes	
thrombosis/stenosis portal	No	Number	162	20	182
		% Stenosis	97.00%	95.20%	96.80%
	Yes	Number	5	1	6
		% Stenosis	3.00%	4.80%	3.20%
Total		Number	167	21	188
		% Stenosis	100%	100%	100%
p-value			p>0.05	p>0.05	

Table 6: Percent thrombosis/stenosis and portal vein was similar in the group with or without stenosis, with p>0.05.

			Stenosis		Total
			No	Yes	
Treatment CMV	No	Number	123	14	137
		% Stenosis	73.70%	66.70%	72.90%
	Yes	Number	44	7	51
		% Stenosis	26.30%	33.30%	27.10%
Total		Number	167	21	188
		% Stenosis	100%	100%	100%
p-value			p>0.05	p>0.05	

Table 7: CMV percentage was similar in the group with or without stenosis, with p>0.05. 3 pctes - CMV as FR; 4 pctes - CMV post stenosis (early stenosis - mean 16 days).

			Stenosis		Total
			No	Yes	
Big Graft	No	Number	161	19	180
		% Stenosis	96.40%	90.50%	95.70%
	Yes	Number	6	2	8
		% Stenosis	3.60%	9.50%	4.30%
Total		Number	167	21	188
		% Stenosis	100%	100%	100%
p-value			p>0.05	p>0.05	

Table 8: Porcentagem semelhante de enxerto grande em pacientes com e sem estenose, com p>0.05.

Discussion

The present study showed that half of the patients had biliary stenosis up to 137 days after liver transplantation. All patients received graft from deceased donors after brain death, with ABO compatibility; biliary reconstruction in the majority of the patients was choledochrocoledocian type; the rate of biliary complication: 26 patients (14.0%); bile duct stenosis: 21 patients (52.0%).

In this context, according to the work of Coelho et al. [2], 153 (84.1%) deceased donors and 29 (15.9%) live donor transplants were performed. Biliary complications occurred in 49 patients (26.9%): 28 stenoses (15.4%), 14 leaks (7.7%) and seven leaks followed by stenoses (3.85%). Hepatic artery thrombosis was present in 10 patients with biliary complications (20.4%; p=0.003). Percutaneous and endoscopic interventional procedures were the treatment of choice for bile complications. Success was achieved in 45.0% of patients undergoing endoscopic or percutaneous procedures and in 61.9% of those who underwent surgery. Therefore, biliary complications are frequent events after hepatic transplantation and require new interventions [2].

In addition, one study showed an important scientific finding showing that IL6 on reperfusion is a valid biomarker for predicting long-term survival. In addition, it assists in the interpretation of cytolysis in the prediction of early vascular complications [1].

Published papers confirm that biliary complications after hepatic transplantation present a high incidence due to ischemia of the bile ducts [1-7]. After transplantation, its vascularization is exclusively supplied by vessels derived from the hepatic artery itself, due to the sectioning of the collateral vessels of the liver ligaments during liver withdrawal for transplantation [8,18,19].

Other factors associated with biliary complications are acute graft rejection, immunosuppression, ABO incompatibility, cytomegalovirus infection, and technical factors [20-22]. Acute rejection causes reduced blood flow and increased hepatic volume, leading to predisposition to thrombosis. Immunosuppression impairs the inflammatory response necessary for healing and formation of firm and mature fibrotic tissue [23]. Furthermore, cytomegalovirus infection is believed to produce vasculitis, impairing liver circulation [24,25].

In a recent systematic review by Nemes et al. [8], there were reports of significant biliary complications, increased preoperative plasma sodium levels, presence of hepatocellular carcinoma, and advanced age of the donor (>60 years), long aneuploid phase time, long cold ischemia time (>12 h), and length of hospital stay in intensive care. The presence of rejection, presence of malignancy, recurrence of viral disease, age of the transplanted patient over 60 years and presence of hepatic artery thrombosis [8] were also analyzed in the literature. Of these, only the presence of hepatic artery thrombosis was statistically significant for the increased incidence of biliary complications [8].

This, together with the relatively low number of analyzed cases of each factor, can contribute to the statistical significance obtained. The incidence of hepatic artery thrombosis in this study was 9.34%. Of these, 58.82% evolved to bile complications and 62.5% to retransplants [8]. The proportion of hepatic artery thrombosis reported in international studies varies between 2.5 and 6.8%. The rate of bile complications was 26.92% in the present study. In cadaveric donor transplants it was found in 24.1%, while in intervivium occurred in 41.38%. These rates are similar to those found in other published studies [8].

In addition, Axelrod et al. [3] found a 75% variation between the observed and expected incidence of biliary complications in American hospitals, after statistical correction of the individual risk factors. Possible explanations for variation include lower transplant volume and lower split liver rates. The most frequent biliary complication was stenosis followed by biliary fistula. Some bile stenoses may have originated in the healing process of fistulas.

Literary work has shown that most stenoses were treated primarily with dilatation of the balloon bile duct, both endoscopically and percutaneously [26-28]. Fistulas had a higher proportion of primary surgical treatment (17.6%); however, the main form of management was still the endoscopic or percutaneous placement of intra-bile prostheses and drains. Reanastomosis was reserved for treatment failure and retransplantation for hepatic artery thrombosis. Endoscopic or percutaneous procedures had resolution in 45% of patients with biliary complications [26-28]. The resolution of the biliary complication by hepatic retransplantation was 25.0%. His mortality was 62.5%, with all deaths occurring up to the eighth postoperative month, which is above the literature average [28].

Conclusion

The incidence of biliary complications is comparable with the incidence reported in other institutions. The low incidence of bile duct stenosis reduces the power of the study to identify the most impacting risk factors. However, a statistically significant difference was identified in the occurrence of hepatic artery thrombosis/stenosis as a risk factor for the development of bile duct stenosis after transplantation. Endoscopic management is preferred over other therapeutic modalities. Other prospective studies with larger series of patients are needed to identify other factors associated with the development of the complication.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Faitot F, Besch C, Lebas B, Addeo P, Ellero B, et al. (2018) Interleukin

6 at reperfusion: a potent predictor of hepatic and extrahepatic early complicationsafter liver transplantation. Clin Transplant 25: e13357.

2. Coelho JCU, Leite LO, Molena A, Freitas ACT, Matias JEF (2017) Biliary complications after liver transplantation. Arq Bras Cir Dig 30: 127-131.
3. Axelrod DA, Dzebisashvili N, Lentine KL, Xiao H, Schnitzler M, et al. (2015) Variation in biliary complication rates following liver transplantation: Implications for cost and outcome. Am J Transplant 15: 170-179.
4. Bittencourt PL, Farias AQ, Couto CA (2016) Liver Transplantation in Brazil. Liver Transpl Surg 22: 1254-1258.
5. Kadaba R, Bowers K, Khorsandi S, Hutchins R, Abraham A, et al. (2016) Complications of biliary-enteric anastomoses. Ann R Coll Surg Engl 23: 1-6.
6. Meirelles Júnior RF, Salvalaggio P, Rezende MB De, Evangelista AS, Guardia B Della, et al. (2015) Liver transplantation: history, outcomes and perspectives. Einstein (Sao Paulo) 13: 149-152.
7. Nacif LS, Ducatti L, Andraus W, Albuquerque LCD (2015) Hepatic Artery Thrombosis after Orthotopic Liver Transplantation. Adv Res Gastroenterol Hepatol 1: 2-5.
8. Nemes B, Gámán G, Doros A (2015) Biliary complications after liver transplantation. Expert Rev Gastroenterol Hepatol 9: 447-466.
9. Ribeiro-Jr MA, Medrado MB, Rosa OM, Silva AJ, Fontana MP, et al. (2015) Liver transplantation after severe hepatic trauma: current indications and results. Arq Bras Cir Dig 28: 286-289.
10. Goçery E (2016) Fully automated liver segmentation using Sobolev gradient-based level set evolution. Int J Numer Method Biomed Eng.
11. Dura E, Domingo J, Ayala G, Marti-Bonmati L, Goceri E (2017) Probabilistic liver atlas construction. Biomed Eng Online 16: 15.
12. Goçery, Unlu MZ, Dicle O (2015) A Comparative Performance Evaluation of Various Approaches for Liver Segmentation from SPIR Images. Turk J Elec Eng Comp Sci 23: 741-768.
13. Göçeri E, Gürcan MN, Dicle O (2014) Fully automated liver segmentation from SPIR image series. Comput Biol Med 53: 265-278.
14. Domingo R, Dura E, Göçeri E (2016) Iteratively Learning a Liver Segmentation Using Probabilistic Atlases: Preliminary Results. 15th IEEE Int Conference on Machine Learning and Applications (ICMLA'16), California, USA.
15. Zeng YZ, Zhao YQ, Liao SH, Liao M, Chen Y, et al. (2018) Liver vessel segmentation based on centerline constraint and intensity model. Biomed Signal Proces Cont 45: 192-201.
16. Goceri E, Shah ZK, Gurcan MN (2017) Vessel segmentation from abdominal magnetic resonance images: adaptive and reconstructive approach. Int J Numer Method Biomed Eng 33: e2811.
17. Goceri E (2016) Automatic labeling of portal and hepatic veins from MR images prior to liver transplantion. Int J Comput Assist Radiol Surg 11: 2153-2161.
18. Zanchet MV, Silva LL, Matias JE, Coelho JC (2016) Post-reperfusion liver biopsy and its value in predicting mortality and graft dysfunction after liver transplantation. Arq Bras Cir Dig 29: 189-193.
19. No authors listed (2016) EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 64: 433-485.
20. Fernández-Simon A, Díaz-Gonzalez A, Thuluvath PJ, Cárdenas A (2014) Endoscopic Retrograde Cholangiography for Biliary Anastomotic Strictures After Liver Transplantation. Clin Liver Dis 18: 913-926.
21. Ostroff JW (2010) Management of Biliary Complications in the Liver Transplant Patient. Gastroenterol Hepatol (N Y) 6: 264-272.
22. Zepeda-Gómez S, Baron TH (2011) Benign biliary strictures: current endoscopic management. Nat Rev Gastroenterol Hepatol 8: 573-581.
23. Koksal AS, Eminler AT, Parlak E, Gurakar A (2017) Management of biliary anastomotic strictures after liver transplantation. Transplant Rev 31: 207-217.
24. Kienlein S, Schoening W, Andert A, Kroy D, Neumann UP, et al. (2015) Biliary complications in liver transplantation: Impact of anastomotic technique and ischemic time on short- and long-term outcome. World J Transplant 5: 300-309.
25. Kochhar G, Parungao JM, Hanouneh IA, Parsi MA (2013) Biliary complications following liver transplantation. World J Gastroenterol 19: 2841-2846.
26. Atwal T, Pastrana M, Sandhu B (2012) Post-liver Transplant Biliary Complications. J Clin Exp Hepatol 2: 81-85.
27. Gámán G, Gelley F, Doros A, Zádori G, Görög D, et al. (2013) Biliary complications after orthotopic liver transplantation: the Hungarian experience. Transplant Proc 45: 3695-3697.
28. Sibulesky L, Nguyen JH (2011) Update on biliary strictures in liver transplants. Transplant Proc 43: 1760.