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Predictors of Treatment Outcomes in The Management of Biliary Complications Post Living Donor Liver Transplantation

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Abstract

Background: Liver transplantation (LT) is the optimal treatment for many patients with advanced liver disease, including decompensated cirrhosis, hepatocellular carcinoma and acute liver failure

Aim and objectives: To identify predictors of treatment outcomes in the management of biliary complications post living donor liver transplantation.

Patients and methods: This open labeled prospective study conducted on 200 patients who perform living donor liver transplantation (LDLT) and a retrospective analysis for patients transplanted with living donor liver transplantation during last 10 years. They divided into two groups: **Group (1):** Patients who underwent LDLT, and developed biliary complications and **Group (2):** Patients who underwent LDLT, and did not develop any biliary complications. This study conducted in Faculty of Medicine, Cairo University from February 2012 to February 2021.

Results: Liver enzymes as well as bilirubin level improved significantly 12 months after treatment in patients who had biliary complications. Elevated bilirubin had more sensitivity and accuracy (98.6%, 73.5%, respectively) followed by ALT, AST, MELD score, alkaline phosphatase, then GGT and age. Biliary stricture (anastomotic) was the most prominent complication found in 46 patients (95.8%), while only 2 patients (4.17%) had biliary leak.

Conclusion: Higher MELD score, prolonged ischemia time and multiplicity of bile duct anastomoses could be risk factors for development of biliary strictures in our series. Thesis complications can be successfully managed by non-operative treatment in most of patients. Overall success rate is high (92%). Overall survival is improved after successful management of biliary complications.

Key words: LT, LDLT, Liver enzymes, Biliary Complications

Introduction

Liver transplantation (LT) is the optimal treatment for many patients with advanced liver disease, including decompensated cirrhosis, hepatocellular carcinoma and acute liver failure. The vast majority of LT involves the use of organs from deceased donors but despite strategies to increase the supply of deceased donors, organ shortage continues to be the main determinant of death on the waiting list (1).

The morbidity and mortality rates for liver graft donors have been reported to be about 21% and 0.2% to 0.5%, respectively. The most frequent donor complications following living donor liver transplantation (LDLT) are biliary complications. Studies have reported that 6% to 9% of donor's experience biliary complications following LDLT and that these complications are more common in right lobe than in left lobe donors (2).

The incidence of biliary complications after orthotopic liver transplantation varies between 11%-35% (3), with a decreasing trend in recent years. These include strictures, leaks, casts, sludge, stones and Sphincter of Oddi dysfunction of which strictures, bile leaks and cast formation are the commonest, affecting patient and graft survival as well as re transplantation rates. Biliary complications occur because of several anatomical and technical reasons and the management depends on a multi-disciplinary approach involving surgery, hepatology and radiology (4).

Although most biliary complications are minor or transient and improve with conservative care, some require endoscopic, percutaneous, or surgical treatment and even long-term hospitalization. To date, however, few reports have assessed biliary complications experienced by right lobe donors after partial liver resection (5).

The aim of this study was to identify predictors of treatment outcomes in the management of biliary complications post living donor liver transplantation.

Patients and methods

This open labeled prospective study conducted on 200 patients who perform living donor liver transplantation (LDLT) and a retrospective analysis for patients transplanted with living donor liver transplantation during last 10 years. Patients were divided into two groups: **Group (1):** included patients who underwent LDLT, and developed biliary complications and **Group (2):** included patients who underwent LDLT, and did not develop any biliary complications. One hundred and thirty (130) patients recruited from El-Manial Specialized Hospital and the other seventy (70) patients from National Hepatology and Tropical Medicine Research Institute. The study was performed in Faculty of Medicine, Cairo University from February 2012 to February 2021.

Inclusion criteria: Adult patients more than or equal to 18 years old, underwent LDLT, diagnosed biliary obstruction post LDLT, no previous biliary intervention done, both sexes included and able to perform a confirmed consent.

Exclusion criteria: Deceased donor liver transplantation (DDLT), patients with previous biliary intervention with ERCP or PTD, patients with previous surgical biliary reconstruction, patients with autoimmune diseases such as Behcet disease, systemic lupus erythematosus, or sarcoidosis and patients who refuse to participate in the study.

Ethical considerations: The study was conducted after approval of the protocol by the Local Research Committee & the Studies Committee as well as the Research Ethics Committee. An informed written consent was obtained from all patients

Methods

Patients in whom liver transplantation was done and developed obstructive jaundice were subjected to: Full history taking, general examination and laboratory investigation for both groups included blood testing and imaging studies

Abdominal ultrasonography (US):

Abdominal ultrasonography was performed to confirm biliary obstruction with a real-time sector scanner using 3.0- or 5.0-MHz transducers. To obtain an accurate ultra-sonographic evaluation of gallbladder and biliary ducts, the patient needs to lie in supine position, or, occasionally, to rest on the right side. Oblique and longitudinal scans were obtained below the costal margin along the right hypochondrium, while axial scans were acquired at the epigastric level. Sometimes, intercostal scans through right intercostal gaps may be necessary. 4–6-h fasting is necessary to allow visualization of a distended organ. Biliary system US study requires a systematic approach thorough the examination of the right upper quadrant viscera including liver, bile ducts, gallbladder, pancreas and portal vein. However, the entire abdomen and pelvis should be scanned.

Hepatic Vascular Doppler: Toshiba Xario Ultrasound system, Aplio 300 (Global Medical Imaging Company, Rampart St., Charlotte, NC 28203) with PVT-375BT Curved Array Transducer. The system was equipped with automated velocity tracing of spectral waveforms to measure and compute maximum peak velocity and resistive index in order to reduce inter-operator variability. Doppler angle of insonation was maintained at less than 60° to ensure accuracy.

Magnetic resonance cholangiopancreatography (MRCP): Magnetic resonance examinations were performed on the 1.5 T General Electric magnet (GE, Boston, MA). This consisted of the following: axial T2 single shot fast spin echo with fat saturation, 8 mm thickness/1 mm gap; repetition time (TR), 550-635; echo time (TE), 88; axial single shot fast spin echo without fat saturation, 8 mm thickness/1 mm gap; TR, 550-635; TE, 88; coronal T2 single shot fast spin echo with fat saturation, 4 mm thickness/0 mm gap; TR, 850-113; TE, 201; and coronal 3D respiratory triggered fast spin echo, 1.4 mm thickness/0 mm gap reconstructed with 50% overlap; TR, 3750; TE, 505-515 (6).

Percutaneous liver biopsy when indicated: It involved inserting a thin needle through the skin into the liver and removing a small piece of tissue. The skin over the liver region was then cleaned and prepared by applying antiseptic. Some local anesthetic was then injected into a small area of skin and tissues just over a part of the liver (usually between two lower ribs on the right-hand side) to make the skin in this area numb. A special hollow needle was inserted through your skin into the liver. The clinician asked the patient to breathe in and then out and then hold breath while the needle was inserted into the liver. The needle removed a small sample of liver tissue for further examination. The clinician obtaining the biopsy may be guided by an ultrasound scanner or CT scan for greater accuracy (7).

Follow-up: The patients were followed-up every two weeks in the first month, and then every three months for one year after the procedure.

Management Algorithm for Treatment:

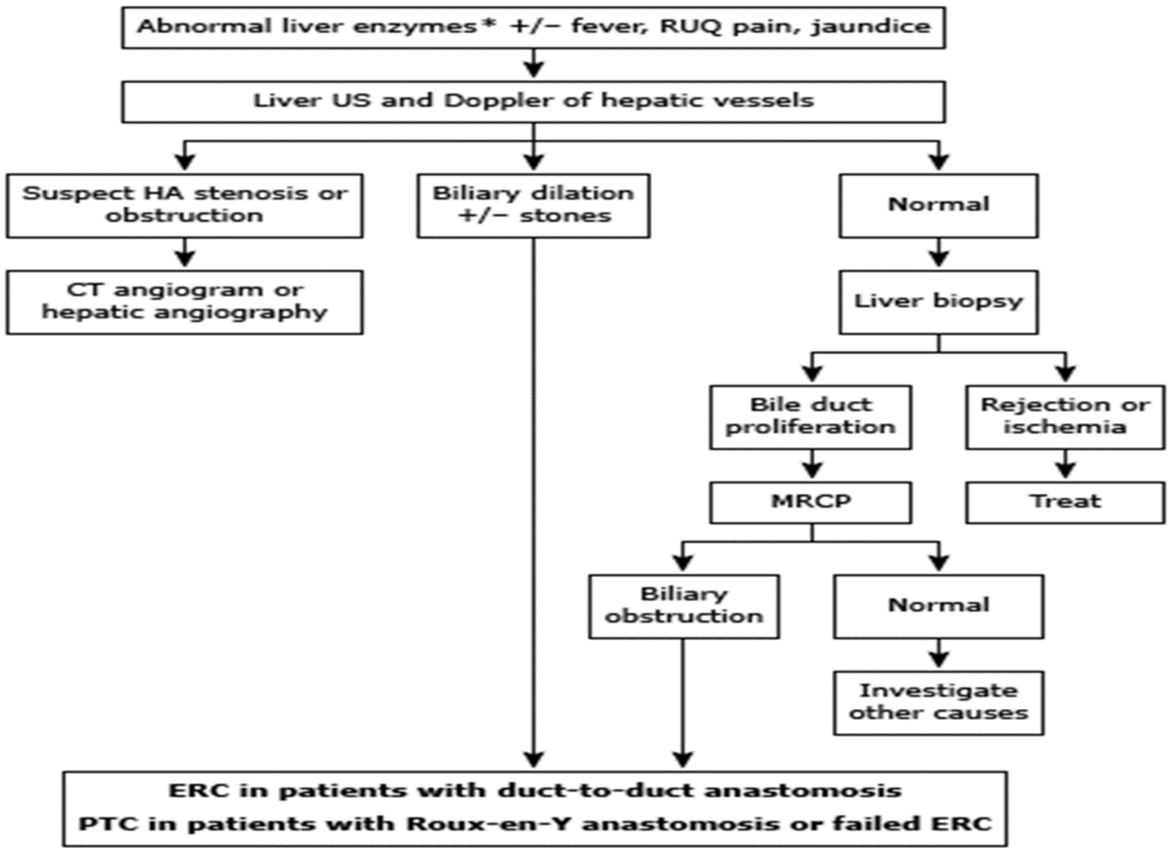

Figure (1): Diagnostic algorithm for the evaluation of suspected biliary obstruction after liver transplantation. HA: hepatic artery; CT: computed tomography; RUQ: right upper quadrant; US: ultrasound; MRCP: magnetic resonance cholangiopancreatography; ERC: endoscopic retrograde cholangiography; PTC: percutaneous transhepatic cholangiography. * Abnormal liver enzymes include: aspartate aminotransferase; alanine aminotransferase; total bilirubin; alkaline phosphatase, and gamma glutamyl-transferase (8).

Results

Table (1): Comparison between both group (1) and (2) according to patients' characteristics.

Population	Group (1)		Group (2)		Significance	
Gender	**No.**	**%**	**No.**	**%**	χ^2	**P**
• Males (n=160)	40	83.3	120	78.9	0.189	0.192
• Females (n=40)	8	16.7	32	21.1	0.267	0.103
• Total (n=200)	48	100	152	100		
Age:					**t**	**P**
• Range	28 – 68		19 – 67			
• Mean ±SD	50.08 ± 7.97		47.636 ± 10.76		0.0358	0.631
MELD score:					**t**	**P**
• Range	7 – 26		6 – 21			
• Mean ±SD	17.046 ± 3.078		15.61 ± 3.195		0.2963	**0.044***

SD: standard deviation, χ^2= Chi square test, t= paired t-test, P >0.05 = non-significant, * P <0.001 = highly significant.

Table 1 showed that there was no statistically significant difference between the two groups as regard sex and age (P >0.05). Abnormal biliary ducts showed elevated MELD score than normal ducts with statistically significant difference (p=0.044).

Table (2): Types of biliary complications as detected by MRCP.

Finding	No.	%
Biliary stricture (anastomotic stricture)	46	95.83
Biliary leak	2	4.17
Total	48	100

* At the end of the follow-up period. χ^2: Chi square test. P <0.05 = significant.

Table 2 showed that biliary stricture (anastomotic) was the most prominent complication found in 46 patients (95.8%), while only 2 patients (4.17%) had biliary leak.

Table (3): Comparison between the two studied groups as regard laboratory findings at baseline.

	Group 1 (n = 48)	**Group 2 (n = 152)**	**Significance**	
			t	**P**
ALT (U/L)	86.64 ± 22.26	64.51 ± 27.87	0.367	**0.031***
AST (U/L)	81.86 ± 36.28	59.8 ± 30.12	0.349	**0.035***
Alk. ph (U/L)	293.18 ± 99.7	130.07 ±23.95	0.928	**0.001***
GGT (U/L)	281.2 ± 152.4	59.97 ± 35.19	16.27	**0.000***
Albumin (g/dl)	3.523 ± 0.517	3.632 ± 0.572	0.065	0.282
T. bilirubin (mg/dl)	7.805 ± 4.97	0.846 ± 0.192	12.49	**0.000***
D. bilirubin (mg/dl)	6.568 ± 4.34	1.005 ± 0.573	10.22	**0.000***
S. creatinine (mg/dl)	0.94 ± 0.258	0.931 ± 0.229	0.009	0.875
S. urea (mg/dl)	39.0 ± 14.03	39.54 ± 12.71	0.018	0.692
Hemoglobin (g/dL)	11.37 ± 1.78	11.12 ± 1.70	0.024	0.638
WBC (x100/UL)	7.923 ± 28.24	11.17 ± 44.26	-0.394	**0.021***
Platelets ($x10^3$/UL)	223 ± 133.8	198.34 ±146.1	0.387	**0.025***
INR	1.16 ± 0.188	1.13 ± 0.19	0.146	0.075
ISL (Tacrolimus)	7.309 ± 1.44	7.938 ± 1.565	-0.274	**0.042***

ISL: Immunosuppressive level (Tacrolimus), * p <0.05 = statistically significant.

The laboratory findings showed that liver enzymes and bilirubin were significantly higher in patients with biliary complications. In addition, WBCs, platelets and drug immunosuppressive level had statistically significant values (P <0.05) in comparison between both groups.

Table (4): Outcome of surgery of group (1) patients.

	Patients		Duration (months)	Mortality		Success rate
	No.	%		No.	%	
Surgery	7	100	3-12	2	28.5	71.4 %

Table 4 showed that, in the surgical group (n = 7), the overall success rate was 71.4%.

Table (5): Comparison of patients with biliary complications before and 12 months after treatment as regard laboratory findings (mean ± SD).

	Before treatment	After treatment	Significance	
			t	p
ALT (U/L)	86.64 ± 22.26	55.64 ± 12.75	0.762	**0.002***
AST (U/L)	81.86 ± 36.28	51.59 ± 14.24	0.537	**0.004***
Alk. ph (U/L)	293.18 ± 99.7	171.8 ± 47.07	0.477	**0.011***
GGT (U/L)	281.2 ± 152.4	141.2 ± 78.85	6.544	**0.000***
Albumin (g/dl)	3.523 ± 0.517	4.095 ± 0.459	0.099	0.314
T. bilirubin (mg/dl)	7.805 ± 4.97	2.581 ± 0.248	1.977	**0.000***
D. bilirubin (mg/dl)	6.568 ± 4.34	2.464 ± 2.206	1.398	**0.000***
S. creatinine (mg/dl)	0.94 ± 0.258	0.957 ± 0.093	0.003	0.687
S. urea (mg/dl)	39.0 ± 14.03	38.81 ± 4.057	0.019	0.692
WBC (x100)	11.37 ± 1.78	54.13 ± 17.17	1.047	**0.008***
PT	79.23 ± 28.24	11.38 ± 0.399	8.092	**0.000***
PC (%)	223 ± 133.8	82.86 ± 13.05	0.731	**0.000***
INR	1.16 ± 0.188	0.968 ± 0.078	0.036	0.231
ISL	7.309 ± 1.44	8.314 ± 0.903	0.008	0.614

PT: prothrombin time, PC: Prothrombin concentration, ISL: Immunosuppressive level, P <0.05 = statistically significant.

Table 5 showed that liver enzymes as well as bilirubin level improved significantly 12 months after treatment in patients who had biliary complications.

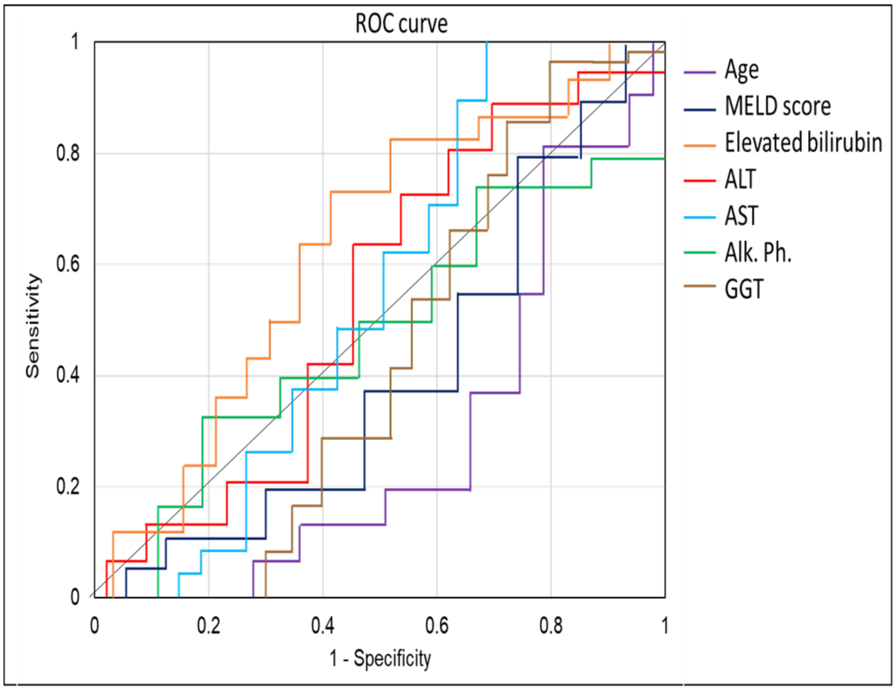

Figure (2): ROC curve of different variables for prediction of biliary complications.
Figure 2 showed that elevated bilirubin had more sensitivity and accuracy (98.6%, 73.5%, respectively) followed by ALT, AST, MELD score, alkaline phosphatase, then GGT and age.

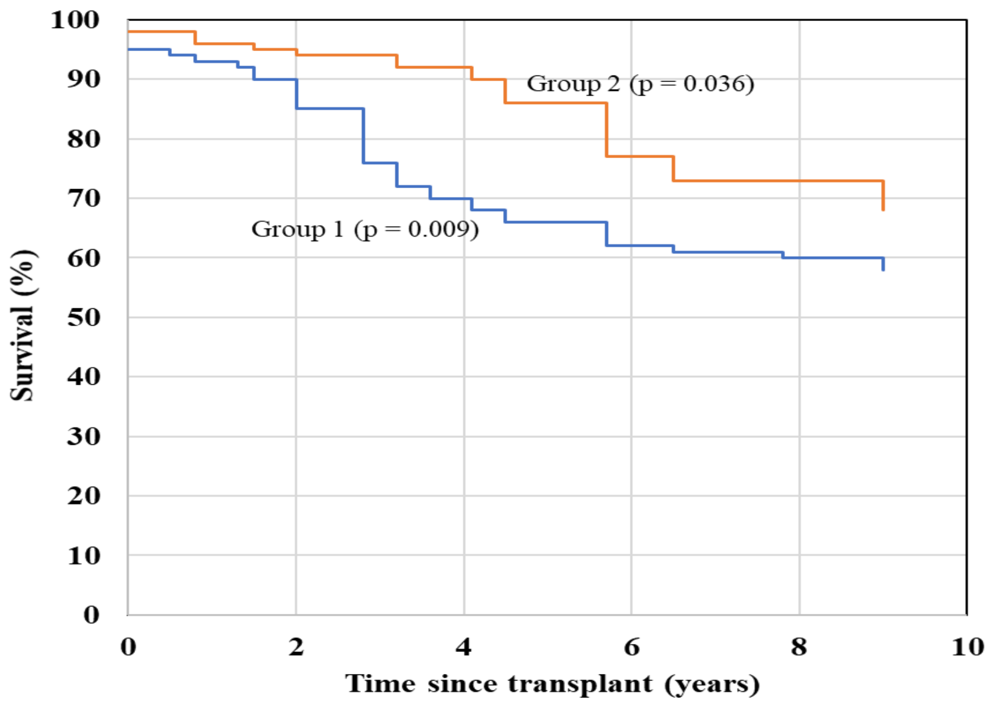

Figure (3): Kaplan Meier curves showing survival comparison between both groups.
Figure 3 showed that there was good improvement of survival rate of group (1) and group (2) (p = 0.009, 0.036, respectively) after treatment.

Discussion

Our results showed that males were more prominent than females in both groups with no statistically significant difference between the two groups as regard sex and age (P >0.05). Abnormal biliary ducts showed elevated MELD score than normal ducts with statistically significant difference (p=0.044).

In this respect **Villa and Harrison** stated that the most common risk factors for anastomotic strictures in patients undergoing DDLT are advanced recipient age (9).

In contrast to ours, **Sundaram et al.,** found that the MELD score was not a significant risk factor in their analysis of 1798 LTs for anastomotic biliary strictures. These contrasting results may be owing to well-documented limitations of the MELD score in reflecting post-transplant outcomes (10).

The laboratory findings showed that liver enzymes and bilirubin were significantly higher in patients with biliary complications. In addition, WBCs, platelets and drug immunosuppressive level had statistically significant values (P <0.05) in comparison between both groups. In our study of biliary complication rate was similar to several reports such as **Nemes et al.** (11)**; Akamatsu et al.** (12), found an incidence of biliary complications of 26.9% which was also similar to the other studies. Living donor liver transplantation was almost two times the rate of cadaveric transplantation. In addition to the small size of the biliary duct in the living donor transplantation, some patients have two or more small ducts that need anastomosis.

The current study showed that the most prominent biliary complication was biliary stricture (68.2%) followed by biliary leak (4.55%).

This was coinciding with previous reports that stated that the most common biliary complication was stenosis, followed by fistula. Healing of fistula may cause biliary stenosis (13). Biliary fistula occurs earlier than stenosis (14). In this study, all fistulas were diagnosed in the 1st month post-transplantation, while stenosis were recognized on average of the 11^{th} month.

Our results showed that liver enzymes as well as bilirubin level improved significantly 12 months after treatment in patients who had biliary complications

This is agreed by **Venu et al.** who found the same results, however, they added that serum alkaline phosphatase level remained elevated even after successful endoscopic therapy (15). Also, **Boeva et al.** illustrated that there is general laboratory improvement after treatment of biliary complications which agreed with our results (16).

Our results showed that, in the surgical group (n = 7), the overall success rate was 71.4%.

which was more than the study of **Buxbaum et al.,** who found a long-term success 68%. This may be due to our selected cases of younger age and lower complications (17).

Analysis of predictors of biliary complications after living donor liver transplantation in our study shows that elevated bilirubin had more sensitivity and accuracy (98.6%, 73.5%, respectively) followed by ALT, AST, MELD score, alkaline phosphatase, then GGT and age.

Other factors associated to biliary complications included acute rejection, immunosuppression, ABO incompatibility, cytomegalovirus infection, and technical factors (18). Acute rejection causes reduction of blood flow and increase of liver volume that predispose to arterial thrombosis. Immunosuppression changes the inflammatory response necessary to healing and formation of normal fibrotic tissue. Cytomegalovirus infection causes vasculitis that reduces hepatic vascularization (19).

Kaplan Meier curves showing survival comparison between both groups. It shows more improvement of survival rate in group (1) than group (2) (p = 0.009, 0.036, respectively) in comparison between before and after treatment.

Also, we have better resolution rate for treatment of biliary complications than **Coelho et al.** (20) who had resolution rate of 62.5%, and it was higher than most reports (21, 22). This is possibly due to limitations and restrictions of our public hospital.

Conclusion

The incidence of biliary complications in LDLT is high. Higher MELD score, prolonged ischemia time and multiplicity of bile duct anastomoses could be risk factors for development of biliary strictures in our series. Thesis complications can be successfully managed by non-operative treatment in most of patients. Overall success rate is high (92%). Overall survival is improved after successful management of biliary complications.

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