Recipients' Biliary Complications after Living Donor Liver Transplantation: Risk Factors and Management

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ABSTRACT

Background: Biliary complications remain one of the most worrisome problems in recipients after liver transplantation, so it is important to study risk factors of biliary complications and to evaluate the efficacy of different management modalities. **Aim**: To investigate the risk factors and management strategies of biliary complications in recipients of LDLT.**Patients and Methods**: Over our two years study period from May 2019 to May 2022, 70 patients underwent adult-to-adult living-donor liver transplant with right hepatic lobe graft. Patients were divided into 2 groups, with group A having biliary complications and group B without biliary complications.**Results**: Group A included 17 patients (24.3%), whereas group B included 53 patients (75.7%). Biliary complications included bile leak in 6 patients (8.6%), biliary stricture in 9 patients (12.9%), and combined bile leak with biliary stricture in 2 patients (2.9%). Cold ischemia time was significantly longer in group A (P= 0.009). Warm ischemia time was significantly longer in group A (P= 0.013). Postoperative cholangitis was significantly longer in group A (P= 0.001).Technical success rates of endoscopic management alone was 83.3%.**Conclusion**: proper donor selection with favourable anatomy and careful intraoperative technique in donor bile duct division and recipient biliary reconstruction decrease the risk of biliary complications. Early diagnosis and proper management of biliary complications decrease their effect on both the graft and the patient survival.

Keywords: Biliary Complication; Living donor liver transplantation; Bile leakage; Biliary Stricture; Endoscopic management.

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Introduction

Liver transplantation (LT) is currently the only definitive treatment for end-stage liver disease (ESLD) and also becomes the standard therapy for patients with early hepatocellular carcinoma(HCC)[(1)].Biliary reconstruction is the Achilles heel of LT with duct-to-duct anastomosis (DDA) has developed into the preferred biliary reconstruction method due to its benefits of a shorter total operative time, less incidence of post-operative infections, more physiological enteric functions and the enablement of access to the biliary tree in case of complications [(2)].

Despite considerable progress in surgical performance in liver transplantation and perioperative management, post-LT biliary complications (BC) remain a considerable cause of morbidity and mortality.If BCs not managed properly, it leads to cholestasis, secondary biliary cirrhosis and eventually graft failure [(3)].

Early diagnosis and proper management are the keys to prevent graft failure. The management of BCs depends on a multidisciplinary approach including endoscopic, percutaneous and surgical interventions[(4)]. The preferred imaging method for the biliary tract is MRCP; it provides a guide for further interventional approaches. Currently, ERCP is the preferable first-line therapeutic modality in cases of DDA [(5)].

Patients and Methods

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This study included70 patients underwent LDLT at the Liver Transplant Units, Zagazig University Hospitals and Gastro-Intestinal surgery Center, Mansoura Universityduring the period from May 2019 to May 2022,.Ethical committee approval was obtained from institutional review board (IRB) and written consent was obtained for the surgical procedure from all patients.

Patients included in this study were recipients with ESLD with MELD score ≥15, recipients with HCC within Milan criteria, defined as a single lesion ≤5 cm or up to three lesions of ≤3 cm each with the absence of vascular invasion and extrahepatic metastases and biliary reconstruction in the form of duct to duct anastomosis.

All donors were subjected to a preoperative multistep evaluation protocol, including a precise study of the graft vascular and biliary anatomy by CT angiography, venography and portography as well as MRCP. Both CT volumetry and liver biopsy were performed preoperatively and at least a 30% residual liver volume together with a graft-to recipient weight ratio of at least 0.8%. In all donor operations, right hepatic lobe without the middle hepatic vein graft was harvested with the aid of duplex ultrasonography mapping. Dissection of hepatic inflow pedicle under loop magnification to ensure good vascularity of graft bile ducts, Minimal dissection of the pericholedochal tissue is done with fine scissors to identify the right hepatic duct and to maintain its blood supply. The right hepatic duct is usually transected 2 mm from the bifurcation under cholangiographic guidance.

For recipients, total hepatectomy was performed. The graft hepatic and portal venous reconstruction followed by graft reperfusion, then hepatic arterial reconstruction was undertaken. Intraoperative duplex ultrasonography was used to exclude any graft inflow or outflow problems before starting biliary anastomosis. Biliary reconstruction was the final anastomosis to be carried out in the form of DDAanastomosing the graft single bile duct into the recipient CHD in an interrupted end to end fashion using absorbable polydioxanone (PDS-II; Ethicon) 6-0 sutures. When two bile ducts were present in the liver graft, ductoplasty was undertaken by approximating both ducts together when the 2 graft ducts were too close to each other (ie, < 2 mm apart) allowing the performance of a single 2-in-1 anastomosis. A routine external biliary stent was inserted either trans-cystic or upward into the biliary anastomosis through the wall of the common hepatic duct whichever was more technically feasible witha routine intraoperative cholangiogram (IOC) was performed after completion of biliary anastomosis.

Immunosuppression protocol was tailored for each patient. After discharge, regular follow-up visits were scheduled at the outpatient clinic. Each follow-up visit included thorough history evaluation, clinical examination and serum laboratory tests including serum trough level of immunosuppression drugs. Also, duplex was routinely performed to evaluate the patency of hepatic vasculature and any potential complications. Stent cholangiogram was routinely done at least 2 months post-transplant.

Our study divided patients into two groups: **group A** consisted of patients with biliary complications in the form of biliary leakage and/or stricture and **group B** consisted of patients without biliary complications. Both groups were compared in terms of recipient, donor, graft factors and postoperative events.

The diagnosis of BL was based on the presence of bile drainage from a surgical drain or the presence of bile in a postoperative fluid collection (biloma) and/or confirmation of BL as evidenced by extravasation of contrast either from the anastomosis or the cut surface of the liver at the time of cholangiography. Management plan for BL was; first conservative measures in cases with stable general condition with minor leak. When indicated sonar guided aspiration with/without catheter insertion was done for drainage of biloma. ERCP was reserved for cases with frank bile with failed previous measures, followed by surgery when indicated.

The diagnosis of BS was made on the basis of liver function laboratory findings, noninvasive imaging studies in the form of MRCP and

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subsequently confirmed during contrast based cholangiography. ERCP was the initial step in all cases with BS with ballon dilatation with stenting. ERCP with Spyglass technique was used when indicated and available. Precutaneous stenting or Rendezvous technique was initiated in case of failed ERCP. Conversion to side to side Reux-en Y hepatico-jejonostomy (RYHJ) was reserved as the last resort for intractable cases of BS with failed or unsatisfactory results of previous interventions (Fig. 1-3).

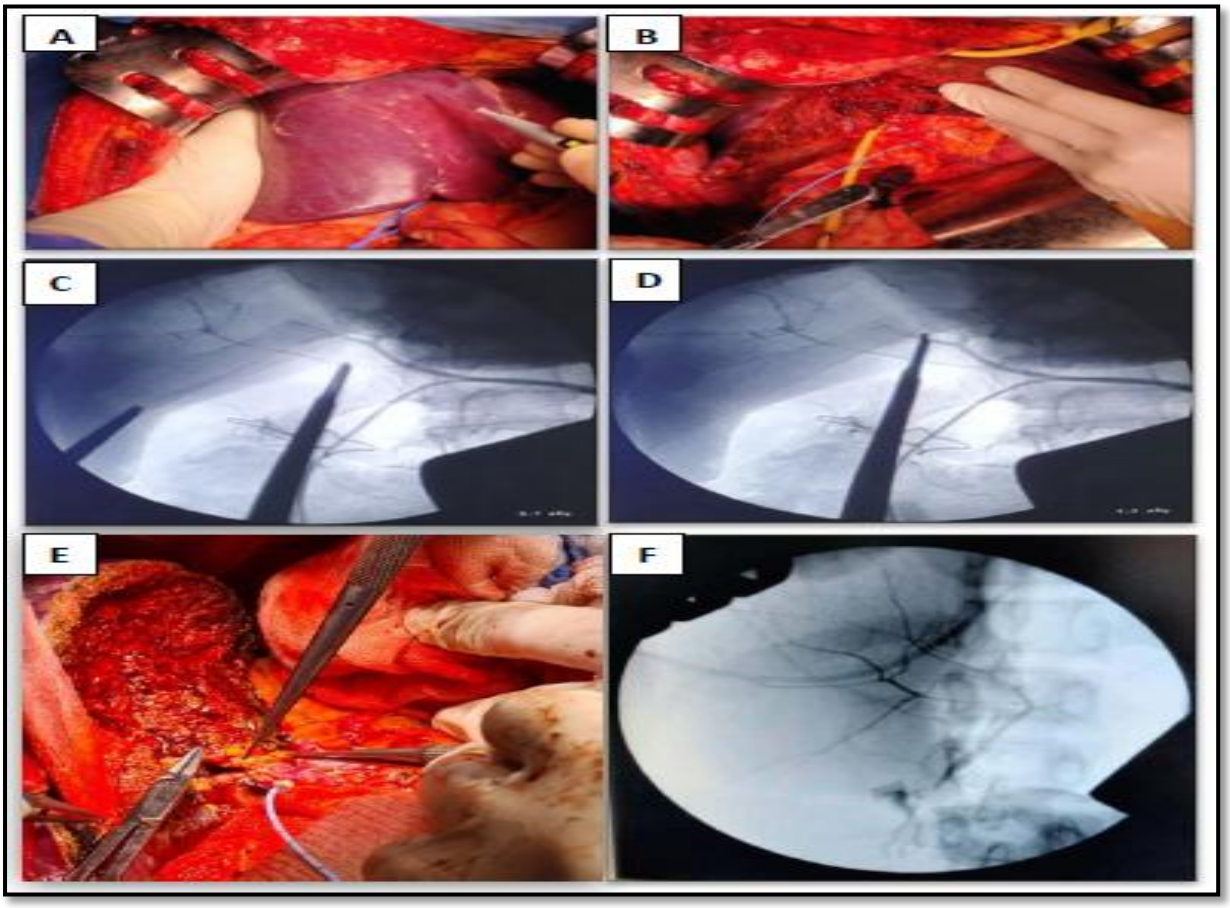

Figure 1:Donor hepatic maping for a right lobe graft followed by parenchymal dissection(A)(B), donor intraoperative cholangiogram before bile duct division showing Huang A4 type (C)(D) befor division under cholangiographic guidance, DDA with transcystic external biliary stent, followed by intraoperative stent cholangiogram (E)(F).

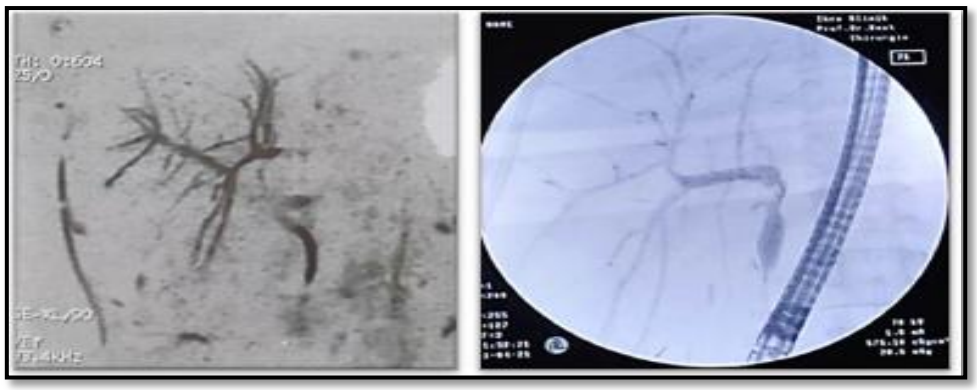

Figure 2: MRCP showing anastomotic BS, followed by ERCP with successful wire passage and insertion of two plastic stents into RPHD and RAHD 8 and 6 Fr respectively.

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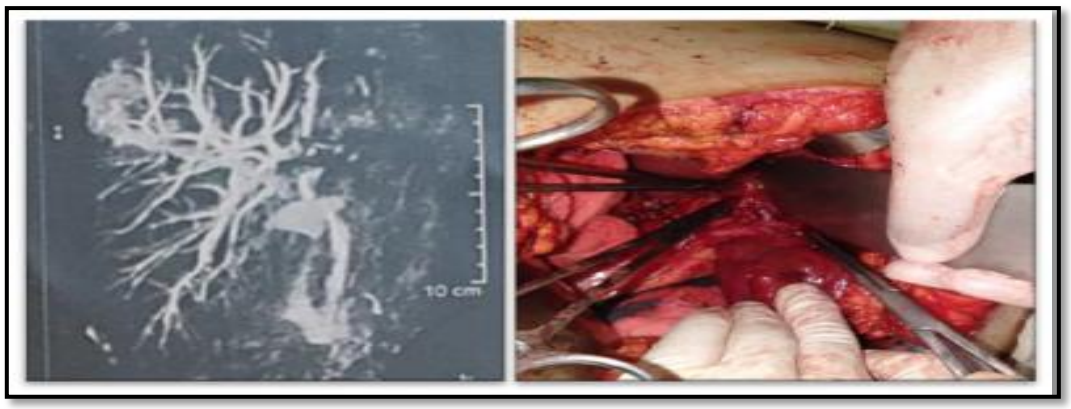

Figure 3: MRCP showing marked dilatation of right posterior and anterior hepatic ducts with absence of signal at site of anastomosis, that necessitates a conversion side to side RYHJ.

Statistical Analysis:

Continuous variables are presented as means and range. Categorical and ordinal variables are presented as proportions. Continuous variables were compared with the 2-tailed Student t test, whereas categorical variables were compared with the chi-square test. Logistic regression was used to detect independent factors affecting the development of postoperative biliary complications. A P value < .05 was considered statistically significant, whereas a value < .01 was considered highly significant. All analyses were performed in SPSS 17.0 for Windows (SPSS, Chicago, IL).

Results

This study included 70 adult recipients, the mean patients age at the time of operation was 44 years ranged from 17 to 63 years, 43 patients (61.4%) were male and 27 patients (38.57%) were female. The mean recipients body mass index (BMI) 28 ranged from 18 to 37 Kg/m^2. The range of MELD score at time of transplantation was 11 to 24. The ABO blood groups were identical in 57 patients (81.42%) and compatible13 patients (18.57%).The indications for LT were HCC [19 patients (27.14%)] and liver cirrhosis because of HCV [26 patients (37.14%)], hepatitis B virus (HBV) [5 patients (7.14%)], HCV and HBV coinfection [3 patients (4.28%)], autoimmune hepatitis [11 patients (15.71%)], cryptogenic cirrhosis [4 patients (5.71%)] and other aetiologies including Wilson syndrome and Budd Chiarri syndrome [1 patient (1.42%)] for each. The donors age ranged from 21 to 43 years with male to female ratio 53 to 27. Preoperative ultrasound guided liver biopsy showed no steatosis in 54 donors (77.14%) and steatosis of less than 10% in 16 donors (22.86%). Donor recipient relationship were, as shown in figure 21, son in 29 (41.43%), daughter in 13 (18.57%), nephew in 9 (12.85%), wife in 6 (8.57%), cousin in 4 (5.71%), sister in 3 (4.29%), mother in 3 (4.29%), father in 2 (2.86%) and husband in 1 (1.43%)(Table 1).

Table 1: Recipients and donors demographic data.

Variable		Data [All cases (n=70)]
Recipient age (years)	Mean (Range)	44 (17-63)
Recipient sex	Male	43 (61.43%)
	Female	27 (38.57%)
Recipient BMI (Kg/m2)	Mean (Range)	28 (18-37)
MELD score	Mean (Range)	14 (11-24)

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ABO matching [n (%)]	**Identical**	**57 (81.43%)**
	Compatible	**13 (18.57%)**
Donor age (years	**Mean (Range)**	**30 (21-43)**
Donor sex [n (%)]	**Male**	**53 (75.71%)**
	Female	**27 (38.58%)**
Steatosis [n (%)]	**No**	**54 (77.14%)**
	Less than 10%	**16 (22.86%)**

The mean actual graft volume was 925 (480-1483) gram with actual GRWR ranged from 0.82 to 2.1 %. All grafts included in the study were right hepatic lobe without the MHV. Single graft bile duct was found in 29 grafts (41.42%) and two ducts in 41 grafts (58.57%). The mean cold ischemia time was 33 (10-55) minutes while the mean warm ischemia time was 42 (24-110) minutes. Ductoplasty was feasible in 9 grafts (12.86 %), thus single DDA was done in 38 cases (54.29%) and two DDA in 32 cases (45.71%). External biliary stent were placed routinely in all cases, single stent was placed in 57 cases (81.43%) and two stents in 13 cases (18.57%).Postoperative biliary complications, biliary leakage occurred in 8 patients (11.43%) while biliary stricture developed in 11 patients (15.71%). Taking into consideration 2 cases with BS were diagnosed previously with BL, i.e. 2 patients (2.86%) with biliary leakage and stricture. So the overall number of recipients without biliary complications was 53 (75.71%) and the overall incidence of biliary complications was 17 cases (24.29%)(Table 2).

Diagnosis of biliary leakage was established in 8 patients (11.43%). Conservative treatment was tried first in all 8 patients which succeeded in 6 patients without need for further interventions. Biloma developed in 2 patients (2.86%) when ultrasound guided percutaneous catheter drainage was done, followed by ERCP with only sphincterotomy in one patient while in the other patient, laparoscopic drainage of intraperitoneal biliary collections was needed with successful outcome.Biliary stricture was diagnosed in 11 patients (15.71%), of them 2 patients (4.29%) with previous history of biliary leakage. ERCP was attempted as the first modality of treatment in all 11 patients which was successful alone in management of 9 patients with BS. PTBD was tried in 2 patients with failed initial ERCP with success to pass the stricture in only one patient. Rendezvous technique was done two times with success to pass a wire by percutaneous method followed by ERCP and successful stent placement. In one patient, respond to these interventions were unsatisfactory and conversion RYHJ was done(Table 3).

Table 2: risk factors for developed BC.

Variable	Patients with BC	Patients without BC	P value
Recipient's age (years)	**44 (21-63)**	**43 (17-62)**	**0.961**
Recipients' sex			**0.704**
Male	**36%**	**64%**	
Female	**32%**	**68%**	
Recipient's BMI (kg/m2)	**28 (19-37)**	**28 (18-37)**	**0.219**
MELD score	**14 (11-24)**	**14 (12-24)**	**0.588**

Indication for LT Cirrhosis	35.8%	64.2%	0.142
HCC	63.3%	36.7%	0.815
Donors' age (years)	29 (21-43)	30 (21-43)	0.927
Donors' sex			0.884
Male	36%	64%	
Female	37%	63%	
Donors' BMI (kg/m2)	25 (21-32)	24 (22-32)	0.845
Steatosis			0.702
No	37%	63%	
Less than 10%	39%	61%	
Size of bile ducts (mm)	1.7 (1-2)	1.7 (1-2)	0.819
Number of ducts			0.139
One	36%	64%	
two	33%	67%	
Ductoplasty	67%	33%	0.061
Number of anastomoses			0.680
One	36%	64%	
Two	37%	63%	
Number of stents			0.578
One	39%	61%	
Two	36%	64%	
Cold ischemia time (min)	37 (18-55)	17 (10-30)	0.009
Warm ischemia time (min)	42 (35-75)	36 (20-55)	0.013
Graft arterialization time (min)	155 (90-205)	120 (90-220)	0.027
Early biliary infection			< 0.001
Yes	72%	28%	
No	18%	82%	
Frequency of cholangitis			< 0.001
No	16%	84%	
1-2 episodes	73%	27%	
≥ 3 episodes	89%	11%	

Table 3: Overall management strategy for biliary complications.

Variable	BL (n=6)	BL followed by BS (n=2)	BS (n=9)	All BCs (n=17)
Conservative measures	6	2	0	8
Successful	4	2		6
Failed	2	0		2
Percutaneous drainage for biloma	2	0	0	2
Successful	2			2
Failed	0			0

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ERCP	**0**	**1**	**9**	**10**
Successful		**1**	**7**	**10**
Failed		**0**	**2**	**0**
PTBD	**0**	**1**	**1**	**2**
Successful		**0**	**1**	**1**
Failed		**1**	**0**	**1**
Rendezvous technique	**0**	**1**	**1**	**2**
Successful		**1**	**1**	**2**
Failed		**0**	**0**	**0**
Treated by surgery	**1**	**0**	**1**	**2**
Successful	**1**		**1**	**2**
Failed	**0**		**0**	**0**

Discussion

Liver transplantation is considered a lifesaving therapeutic modality for patients with ESLD and early stage HCC. Despite considerable progress in LT surgical performance and peri-operative management, post-LT biliary complications remain a considerable cause of morbidity, mortality and graft loss [(6)].

Proper understanding of the bile ducts anatomy and their blood supply guarantee lower biliary complications [(7)]. Dissection along the donor bile ducts should be kept to minimum in order to keep the fine arterial plexus that supply the graft using fluoroscopy-guided technique during bile duct transection and this is the procedure adopted in our study [(8)].

Several factors are thought to contribute to this high incidence in LDLT. These include prolonged graft ischemia time, the much smaller size of the bile ducts, the multiplicity of the bile ducts in some grafts, the high incidence of variations in the donor biliary anatomy, the presence of a liver parenchymal cut surface and the impaired vascularity of bile ducts in both donor and recipient operations [(9)]. In our study, the cold and warm ischemia times of the liver grafts were significantly longer in group A than in group B patients (P value = 0.009 and 0.013 respectively). In agreement with **Rammohan et al[(10)],** we identified longer arterialization time as a risk factor for BCs (P value = 0.027). This finding is predictable because biliary tract vascularization is supplied exclusively by the hepatic artery, and a longer arterialization time of the graft may cause biliary ischemia and subsequently BS [(11)].

In addition to surgical techniques, several risk factors for BC have been defined literature such as older recipients and donors, female recipients and recipients of female donors, ABO mismatch and higher MELD score [(12)].However, in our current study we were unable to establish any of these variables as risk factors for development of BCs.

In accordance with **Azzam and Tanaka study[(4)]**, we observed that the occurrence of BCs was not related to the number of bile ducts. In contrast, **Miyagi et al[(13)]**and**Ogiso et al[(14)]** identified the number of bile ducts as a risk factor for BC. Furthermore, **Senter-Zapata et al[(9)]** reported that internal biliary stents and T-tube insertion were risk factors for BC post-LT. However, in our study, we prefer external drainage for easy accessibility of biliary ducts for postoperative cholangiography to manage any strictures.

Simoes et al[(15)] reported that ductoplasty has been shown to increase the risk of bile duct ischemia also its benefit to facilitate biliary reconstruction in the recipient.In our study, ductoplasty was used in a total of 9 patients, with the aim of performing less biliary anastomoses and to obtain a larger luminal diameter for an easier reconstruction.

Biliary infection in postoperative period increases the risk for development of biliary complications due to the resultant inflammatory

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process with progression of fibrosis and stricture formation [16].In agreement with **Guirguis et al.**[17], we observed that occurrence of biliary infection in early postoperative period and the frequency of cholangitis to be a highly significant risk factor for development of biliary complications (P value = 0.001).

A preceding bile leak has also been described as an important risk factor for anastomotic biliary strictures[18], a finding that is consistent with our study results in which 2 of total 11 cases (18.18%) of biliary strictures were preceded by bile leaks.

A high index of suspicion is needed for diagnosis of posttransplant BCs especially when there is difficult adjustment of immunosuppressantsin early posttransplant period [19].In our study, a combination of close clinical surveillance, laboratory investigations and imaging under supervision of a multidisciplinary team, including LT surgeon, hepatologist and radiologist, were sufficient to establish a correct preliminary diagnosis in almost all patients with biliary complications after LDLT.

The overall incidence of biliary complications after liver transplant ranges from 5% to 40%, biliary leaks account for 0 - 22% whereas strictures occur in 4 - 25% of recipients, with anastomotic strictures representing the majority[20]**.** Approximately one third of biliary complications occur within the first month after transplant, two thirds occur within the first 3 months and nearly 80% occur within the first 6 months after liver transplant [20]. We reported BCs in 17 patients with an overall incidence of recipient biliary complications of 24.29%, with nearly half cases (52.63%) manifested in the first three months, while 16 cases (94.12%) were diagnosed during the 1st six months posttransplant period.

Bile leaks usually occur in the early postoperative period due to bile duct necrosis and poor healing, with the anastomotic site being the most common. Other sources include cut surfaces of liver grafts, cystic duct and biliary stent exit sites [21]**.** Similarly, in our study, all bile leaks manifested in the first 2 months after transplant, with the majority being anastomotic leaks (7/8; 87.5%) and a minority being leaks related to biliary stent (1/8; 12.5%). The overall BL rate in our study was 8/70 cases (11.43%), results coincides with these reported in other studies**Azzam and Tanaka[4], Guirguis et al[17],Wahab et al[22]andSarhan et al[23]**ranging from 8.2% to 37.9%. In a similar management plan as other centres [4] [17] [22] [23], minor BLs were treated conservatively while major BLs required percutaneous drainage. ERCP was needed in selected cases while surgical intervention was performed as a last option. In our study, conservative management was attempted in 8 patients diagnosed with biliary leakage, this was successful in 6 cases (75.00%). US guided drainage was needed in two patients with biloma. Endoscopic retrograde cholangiography with biliary drainage by sphincterotomy without need for stenting was attempted with success in only one patients. In one patient stent crack occurred resulting on slipped external biliary stent with resultant multiple intraperitonealbilous collections, this necessitates laparoscopic evacuation of collections with re-insertion of external biliary stent again.

On the other hand, BSis generally classified into anastomotic and nonanastomotic strictures, with anastomotic strictures being much more common [24].All biliary strictures encountered in our study were anastomotic strictures regarding the follow up period in our study of at least 12 months posttransplant. Our study biliary stricture rate was 11/70 cases(15.71%) which coincides with the stricture rates ranging from 9.2% to 35.5% reported in other literatures [4] [17] [22] [23].

A clear understanding of sectoral biliary ductal anatomy and the specific nature of biliary anastomosis in individual patients is essential. Initial endoscopic therapy alone without the need for adjuvant PTC was successful in a high proportion (93%) of patients. Prolonged endoscopic therapy with advanced techniques and multiple stents as needed, resulted in successful treatment in a much higher proportion of patients. Although strictures recurred in some patients, they responded to endoscopic therapy

without the need for surgical revision in any patient [25].

ERCP was the initial choice for BSs, as a similar management plan in other literatures [4] [17] [22] [23], with an overall success rates 81.82%,with 9 patients needing ≥3 ERCP sessions. Although endoscopic approach is usually less invasive than other treatments, acute pancreatitis may be an associated morbidity with this procedure with even possible mortality [26]. Fortunately, no encountered post ERCP complications during the study period.

When the stricture is too tight leading to failed ERCP, an alternative approach is necessary. Thus, PTBD may be performed as second-line therapy[27].We document post-PTBD right sided pleural effusion that was evident to be of biliary nature in one patient. This necessitates US guided percutaneous drainage with catheter insertion into the right pleural cavity. Improvement was evident with adjuvant ERCP that was successful with stent placement.

The conventional rendezvous technique refers to using the percutaneous technique first to gain access to the biliary tracts and passing a guidewire across the stricture and into the duodenum, followed by the endoscopic balloon dilatation and stent placement [28].Rendezvous technique was needed in two occasions when success in one patient was documented. These previous methods only failed in one patient who needed surgical reconstruction of BS with side-to-side RYHJ that was performed with successful results with success to manage this intractable stricture.

Biliary infection was a risk factor for chronic graft rejection and graft failure, which is explained by interrupted immunosuppressive therapy during times of sepsis. This explains that early detection and efficient management of BS can prevent graft loss [5]. Fortunately, no graft loss was documented during the study period.

Conclusion:

A combination of close clinical surveillance, laboratory investigations and imaging studies is important for establishing a correct preliminary diagnosis in patients with suspected biliary complications after LDLT. A combination of measures are crucial in order to decease risk of biliary complications including appropriate donor selection with favourable liver anatomy whenever possible, good surgical technique and close monitoring especially in the early postoperative periods by a multidisciplinary team approach. Bile leak usually manifest during early postoperative period after LT and usually respond well to conservative management while biliary stricture usually present in later periods with good results with endoscopic interventions. Surgery is reserved for patients with intractable biliary complications, in whom other procedures are not able to achieve satisfactory results.

No conflict of interest.

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