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Cohort Study

Biliary complications after adult to adult right-lobe living donor liver transplantation (A-ARLLDLT): Analysis of 245 cases during 16 years period at a single high centre- A retrospective cohort study

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ABSTRACT

Objectives: Biliary complications (BCs) after adult to adult living donor liver transplantation (A-ALDLT) result in poor graft and patient survival. This study aimed to analyze these complications.
Methods: We retrospectively analyzed BCs in 245 recipients who underwent A-ALDLT using the right–lobe graft during 16 years period in our centre. The overall male/female ratio was 215/30.
Results: One hundred fifty-five BCs affected 102 of our recipients (95 early (≤3months) and 60 late (≥3months)). They were classified as 67/245(27.3%) early bile leak, 10/245(4.1%) early biliary stricture, 44/245(17.9%) late biliary stricture, 4/245(1.6%) early cholangitis, 10/245(4.1%) late cholangitis, 14/245(5.7%) early biloma, and 6/245(2.4%) late cholangitic abscesses. Multiple biliary anastomoses were independently correlated with Post liver transplantation (LT) overall BCs; moreover, post LT hepatic artery thrombosis or stenosis (HAT/S) was an independent predictor of overall BCs, strictures and leaks. The mortality affected 96(39.2%) cases mostly due to sepsis, bleeding and multi-organ failure (MOF). On the other hand, the biliary related mortality was 10.6% of cases. Multiple cholangitic hepatic abscesses were significant predictors of poor graft and patient outcomes.
Conclusions: Multiple biliary anastomoses and post LT HAT/S lead to a poor biliary outcome, furthermore, cholangitis, cholangitic abscesses and sepsis lead to poor graft and patient outcomes, so proper management of those variables is mandatory to improve outcomes after A-ARLLDLT.

1. Introduction

Despite improved surgical techniques, perioperative care, organ preservation and immunosuppression in living donor liver transplantation(LDLT); biliary complications(BCs) (I.e. bile leaks, biliary strictures, cholangitis, biloma, cholangitic abscesses, bile duct stones/casts, ischemic biliary injury, hemobilia, sphincter of Oddi dysfunction (SOD), etc) remain a significant catastrophe after adult to adult right lobe LDLT (A-ARLLDLT) leading to post-transplant morbidities, dysfunctions and mortalities. [1,2]; they may reach up to 60% of recipients [3–11].

They are related to various sources (i.e. Graft bile ducts (sizes, numbers and anatomic variations), biliary ischemic damage (hepatic artery complications, warm and cold ischemia times, ischemia-reperfusion injury (IRI), etc), biliary reconstruction related factors (reconstruction type and number, suture methods and materials and t-tube/stent use/non-use), immunologic issues (ABO incompatibility) and infections (biliary sepsis and cytomegalovirus (CMV) infections)) [1,12,13].

They can be identified clinically (abdominal pain, distension, bilious drains or wound, jaundice, fever, sepsis, etc), biochemically(abnormal liver function tests(LFT), etc) and by imaging(abdominal ultrasonography(US) including Doppler US, abdominal computed tomography(CT) including CT angiography, magnetic resonance(MR) imaging (magnetic resonance cholangiopancreatography(MRCP) and MR angiography), external stent/t-tube cholangiography, percutaneous transhepatic cholangiography(PTC) and endoscopic retrograde cholangiopancreatography(ERCP) [1,12].

There are different treatment options for those complications (i.e.

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List of abbreviations

A-ALDLT	Adult to adult living donor liver transplantation
A-ARLLDLT	Adult to adult right lobe living donor liver transplantation
ABO	Blood group
AIH	Autoimmune hepatitis
ARDS	Adult respiratory distress syndrome
BCs	Biliary complications
BDs	Bile ducts
BMI	Body mass index
CHD	Common hepatic duct
CIT	Cold ischemia time
CMV	Cytomegalo virus
CNIs	Calcineurin inhibitors
CT	Computed tomography
CTP	Child-Turcotte-Pugh
CUSA	Cavitron ultrasonographic surgical aspirator
D-D	Duct to duct
ERCP	Endoscopic retrograde cholangiopancreatography
GRWR	Graft recipient weight ratio
HA	Hepatic artery
HAT/S	Hepatic artery thrombosis or stenosis
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HJ	Hepaticojejunostomy
HPB	Hepatopancreatobiliary
HTK	Hydroxytryptophan ketoglutarate
IRB	Institutional review board
IRI	Ischemia-reperfusion injury
LDLT	Living donor liver transplantation
LFT	Liver function tests
LHDs	Left hepatic ducts
LT	Liver transplantation
MELD	Model for End-stage Liver Disease
MHV	Middle hepatic vein
MMF	Mycophenolate mofetil
MOF	Multi-organ failure
MRCP	Magnetic resonance cholangiopancreatography
MR	Magnetic resonance
NLI	National liver institute
PBC	Primary biliary cirrhosis
PDS	Polydioxanone
PHN	Portal hypertension
POD	Postoperative day
PPF	Peri-portal fibrosis
PSC	Primary sclerosing cholangitis
PTBD	Percutaneous transhepatic biliary drainage
PTC	Percutaneous transhepatic cholangiography
PVT	Portal vein thrombosis
RHA	Right hepatic artery
RHDs	Right hepatic ducts
RL	Right lobe
RPV	Right portal vein
SFSS	Small for size syndrome
SOD	Sphincter of Oddi dysfunction
SRL	Sirolimus
US	Ultrasonography
WIT	Warm ischemia time

conservative treatment (i.e. wait and see), endoscopic management (i.e. ERCP), percutaneous interventions (i.e. percutaneous drainage (pigtail) and percutaneous transhepatic biliary drainage (PTBD) and lastly surgeries (i.e. surgical drainage, external biliary diversion and hepaticojejunostomy(HJ)) [2,12]. However, the non-surgical management of these catastrophic complications became the commonest therapeutic option after advances in endoscopy and interventional radiology measures [2].

In the literature of a large number of cases; the analysis of BCs after A-ARLLDLT is scarce, so our aims and objectives were to analyze those complications and their predictors as well as patients outcomes during 16 years period at a single high tertiary Egyptian centre.

2. Materials and methods

After approval of our institutional review board (IRB), we did this cohort study which is a retrospective analysis of a prospectively collected database done in a single institution. It analyzed BCs after A-ARLLDLT in the department of hepatopancreatobiliary (HPB) surgery, National liver Institute (NLI), University of Menoufiya, Menoufiya, Egypt; in the period from December 2003 to December 2019 where patients were observed from POD1 until the end of December 2019 or until the death of patients with a median follow up period of 34(range; 0.03–192) months.

Our study included 245 patients after exclusion of cases that refused research, cases with loss of data and those who did not complete the follow-up. The data were collected from our liver transplant (LT) unit. The recipients and their donors gave written informed consent regarding surgeries and research, furthermore, our work was registered in the research registry with registration NO of researchregistry4596(www.researchregistry.com) as well as it was reported in line with the STROCSS 2021 criteria [14]. All our donors were ≥19 years old and were pre-operatively assessed clinically, psychologically, biochemically ((LFT), virology, etc), pathologically (liver biopsy), and by imaging (abdominal US, CT volumetry, CT angiography, and MRCP; Fig. (1: A, B)) [15–17].

The collected variables included: A- Preoperative variables: Donors parameters (i.e. age, gender, donor liver biopsy, etc), and recipients' parameters (i.e. age, weight, gender, Child-Pugh(CTP) and Model for end-stage liver disease (MELD) scores, original liver disease, comorbidities, pre- LT portal hypertension(PHN) and portal vein thrombosis(PVT), etc) [15–17]. B- Intra-operative variables: Graft type, No of hepatic artery (HA) anastomoses and their difficulties, No of biliary anastomoses; their types and suture types, as well as liver graft bile ducts (BD) No, ductoplasty, using biliary stents, actual graft weight, and graft recipient weight ratio (GRWR), cold, warm ischemia and HA anastomosis times per minute, blood and plasma transfusion per units and operative time per hours [15–17].

-Donor procedure: It was done by a qualified team; in brief; After mobilization of the right lobe (RL) of the liver and dissection of IVC, an intra-operative cholangiogram was performed routinely through the cystic duct after cholecystectomy and before parenchymal transection to delineate the biliary anatomy and the correct point of biliary transaction (Fig. 1**:C).** The right portal vein (RPV) and right HA (RHA) were isolated without excessive peri-ductal dissection to minimize ischaemic damage to the BD. The cavitron ultrasonographic surgical aspirator (CUSA) + bipolar devices were used to divide the liver parenchyma without inflow occlusion. After parenchymal transection, minimal dissection of hilar peribiliary soft tissue was done without cauterization. Then, the right BD/s was/were divided with sharp scissors maintaining more than 2–3 mm safe margin from biliary bifurcation to prevent stricture of the remnant donor liver duct. Then, we closed the opening of the remnant liver BD using continuous 6-0 prolene sutures. A final cholangiogram was then performed at the end of the operation to ensure biliary tract

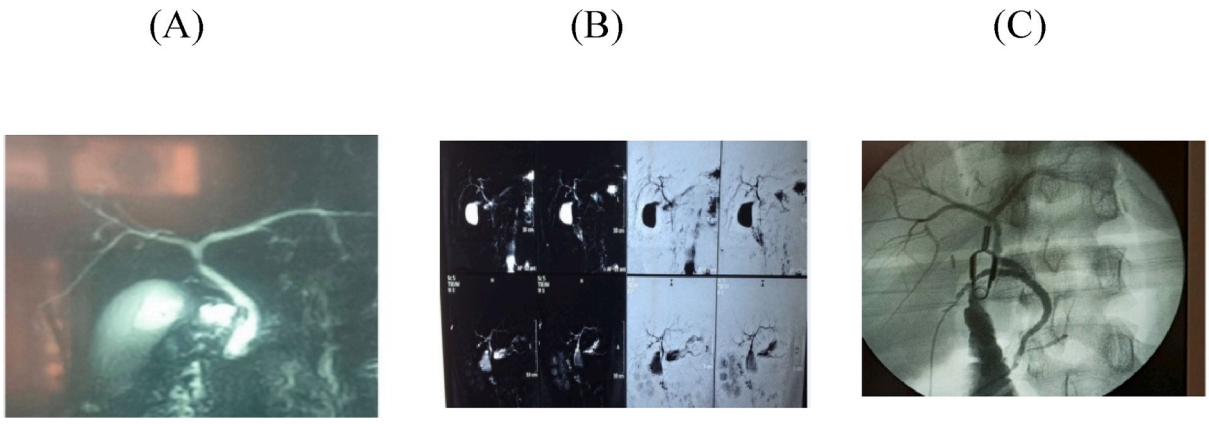

Fig. 1. (A), (B) Donor MRCP showing RL graft with single and double BDs respectively, (C) IOC showing single RL graft BD.

integrity. Then, on the back table; the harvested graft was flushed and preserved in Hydroxytryptophan ketoglutarate (HTK) solution and weighted to determine the actual graft weight and GRWR. Moreover, in grafts with multiple BDs; ductoplasty of the adjacent ducts was done to obtain a single orifice using a continuous 7-0 prolene suture [15–18].

-Recipient procedure: It was done by a qualified team; In short; the recipient BD was prepared by doing a minimal dissection of the peri-choledochal soft tissue aiming to leave as much of the vascular connections between the BD and the HA intact as possible and to preserve the 3 and 9 o'clock arteries; moreover, sharp scissors were used for BD transection above the hilar bifurcation. The biliary anastomosis was performed using loupe magnifications after completing vascular anastomoses. Tension-free duct to duct (D-D) or R-Y HJ reconstruction was selected according to graft and recipient BDs site and size matching. The recipient common hepatic duct (CHD) was mostly used for a single anastomosis, however, the right hepatic ducts (RHDs) and left HD (LHDs) were mostly used for double anastomoses. The posterior and anterior layers of biliary anastomoses were performed using interrupted 6-0 Polydioxanone(PDS)/prolene sutures keeping a 1mm distance between stitches, furthermore, an external 4–6 Fr polyethylene tube (external stent) was used selectively by the surgeon's decision for biliary decompression and to drain bile for 1month after LT before being clamped and then removed at the 6th–8th months from LT after ensuring absent BCs by repeated cholangiography [15–18].

C- Postoperative management: 1- Prophylactic antibiotics: By giving preoperative 3rd generation cephalosporine, then intra/postoperative tazobactam plus metronidazole or imipenem plus metronidazole until culture results. 2- Prophylactic anticoagulants: Starting with heparin infusion until POD8; the time of giving dipyridamole. 3- Immunosuppression regimens consisted of a triple-drug therapy that included calcineurin inhibitors (CNIs)(tacrolimus or cyclosporine), mycophenolate mofetil (MMF), and steroids. When CNIs were contraindicated or had side effects; sirolimus (SRL) or everolimus were given. Steroids and MMF were completely withdrawn at the end of the 3rd and 6th post-operative months respectively. In late cases; an interleukin-2 receptor blocker (Simulect) was administered on POD0 and 4 for reducing the CNI dose [15–17].

D- Postoperative follow-up (by a team consisting of transplant surgeons, hepatogastroenterologists, and radiologists) was done daily until hospital discharge, then monthly during the 1st 6 months, then every 3 months until the end of 1st year, then every 6 months until the end of the follow-up period for detecting: A-HA thrombosis or stenosis (HAT/S) that were diagnosed when the LFTs became abnormal or when doppler US showed poor or no blood flow within HA and were confirmed by doing CT angiography, MR angiography or formal conventional angiography if needed. B– BCs that were known by clinical assessment (i.e. bilious drains, etc), abnormal LFTs and/or the abdominal US and were confirmed by external stent cholangiography, MRCP; Fig. 2, and when

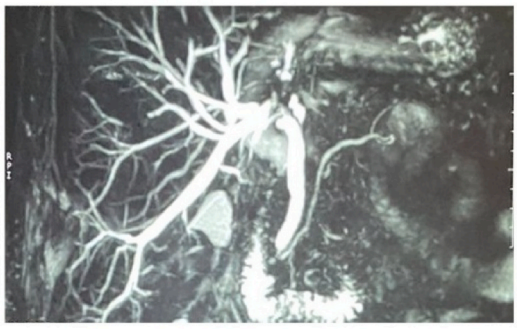

Fig. 2. MRCP showing D-D anastomotic stricture.

necessary ERCP (for D-D cases), PTC (for HJ cases) or abdominal CT (for bile leak, biloma and cholangitic abscesses cases); they were classified into early and late complications if occurred (≤3months) and (≥3months) from LT respectively [15–17].

E– HAT/S was managed by anticoagulant therapy, angiographic (dilatation, thrombectomy, thrombolytic therapy and/or stenting) or surgical thrombectomy and/or reconstruction. On the other hand; BCs were managed by conservative therapy, percutaneous drainage (single or multiple pigtails insertions), ERCP shinectrotomy ± dilatation ± Stenting; Fig. 3, PTBD; Fig. 4, open surgical drainage, external biliary diversion and/or by R-Y HJ; Fig. 5. Graft and patient survivals, as well as mortality causes, were recorded during the follow-up period [15–17].

SPSS 21 software was used for the statistical measures. Qualitative data were expressed in frequency and percentage and analyzed with the Chi-square or Fisher exact tests. Quantitative data were expressed as the mean and standard deviation or median (range) and were compared with the t- or Mann- Whitney U tests. Univariate and then multivariate analyses were performed for determining predictors of BCs as well as predictors of graft and patient survival. The Kaplan–Meier method was applied for survival analysis and comparisons were done using log-rank tests. In all tests, a P-value of <0.05 was significant [15–17].

3. Results

3.1. The patients' characteristics

They were classified as 215(87.8%) males and 30(12.2%) females. Their median age and body weight reached 47 (range; 22–66) years and 80 (range; 43–120) kg respectively. Their donors were categorized into 176(71.8%) males and 69(28.2%) females, where, median age and BMI were 26 (range; 18–45) years and 26 (range; 18–35) respectively. The 1st-degree donor to recipient relation was the most frequent 121

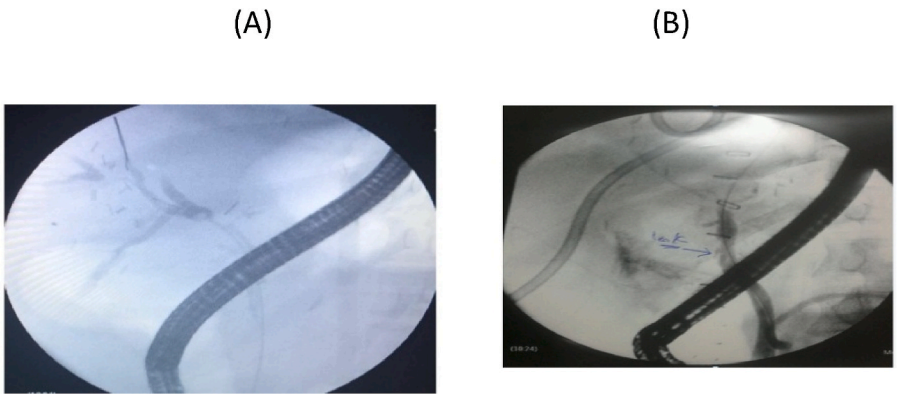

Fig. 3. (A) ERCP + stent For D-D stricture, (B) ERCP + stent for Bile leak.

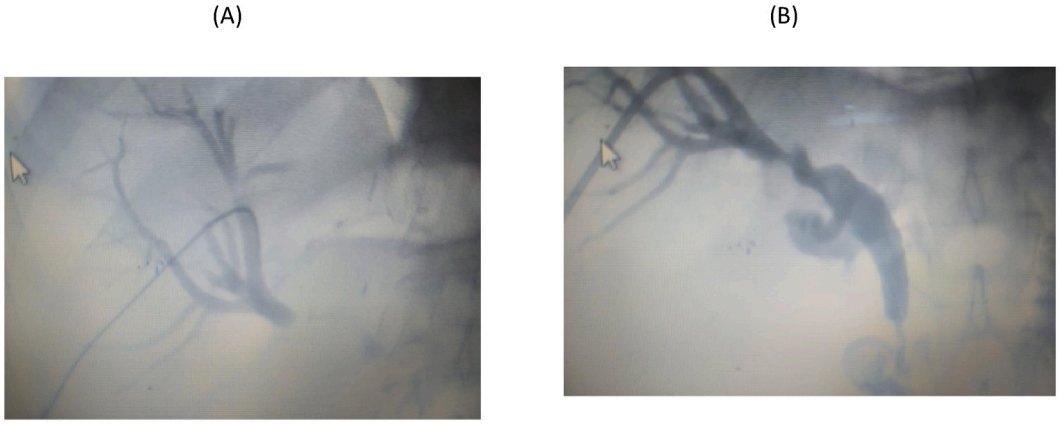

Fig. 4. (A),(B) PTD for D-D stricture.

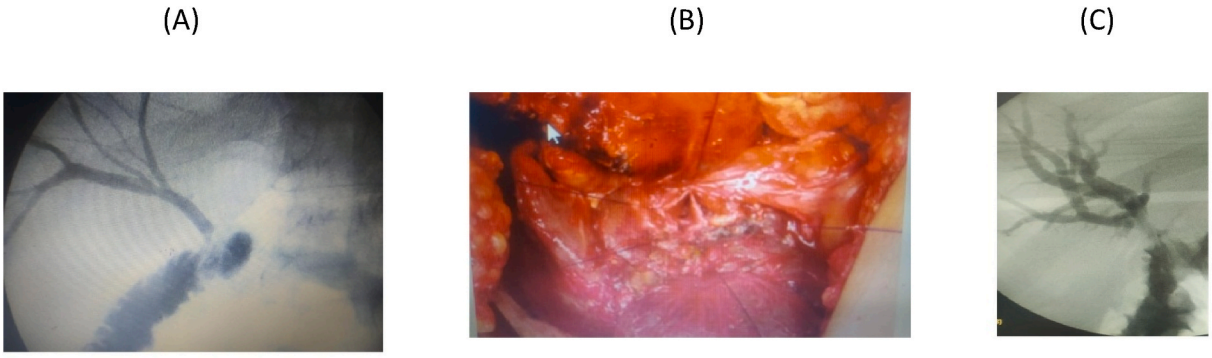

Fig. 5. (A),(B),(C) Intra-operative pictures of HJ for cases with D-D stricture.

(49.4%). The normal, peri-portal fibrotic (PPF), and steatotic donor liver biopsies were 85.7%, 9.8%, and 4.5% respectively. The recipients' median MELD score was 16(range; 7–34), moreover, CTP scores A, B, and C were 13(5.3%), 64(26.1%), and 168(68.6%) respectively. The comorbidities (DM, hypertension, cardiac disease, etc) affected 26.1% of them while Pre LT PVT and PHN affected 15.5% and 91.4% of them respectively. Table 1.

The compatible and identical donor to recipient blood group matching were 73(29.8%) and 172(70.2%) respectively. The RL-middle hepatic vein (MHV), RL + MHV and Segments VI, VII liver grafts were given to 234(95.5%), 10(4.1%) and 1(0.4%) of them respectively. The single and double HA anastomoses were performed in 229(93.5%) and 16(6.5%) of them respectively, however, the anastomosis was difficult in 5(2%) of patients. The single and multiple liver graft BDs involved 121(49.4%) and 124(50.6%) of them respectively, moreover; Ductoplasty of the near multiple BDs was performed in 42(17.1%) of them, furthermore; the single, double and triple biliary anastomoses were done in 147(60%), 87(35.5%), and 11(4.5%) of them respectively. These anastomoses were classified into D-D(142 single, 80 double and 10 triple), HJ (5single, 6 double and 1 triple) and D-D + HJ(one double) biliary reconstructions in 232(94.7%), 12(4.9%) and 1(0.4%) of patients respectively, moreover, prolene and PDS 6/0 sutures were used in 106 (43.3%) and 139(56.7%) of them respectively and external biliary stents were put in 224(91.4%) of them, the median actual graft weight and GRWR were 900 (range, 340–1250) gms and 1.1 (range, 0.6–1.7) respectively. Table 1.

The median cold ischemia (CIT), warm ischemia (WIT), and HA anastomotic times were 60 (range; 20–340) mins, 50 (range; 25–120)

Table 1
The characteristics of recipients and their donors.

Category	No (%)
	245 (100%)
	Or Median(range)
Donor age(years) (Median(range))	26(18–45)
Donor gender	
males	176(71.8%)
females	69(28.2%)
BMI of the donor (Median(range))	26(18–35)
Donor to recipient relation	
1st degree	121(49.4%)
2nd degree	48(19.6%)
3rd degree	32(13.1%)
4th degree	16(6.5%)
Unrelated	28(11.4%)
Donor liver biopsy	
Normal	210(85.7%)
PPF	24(9.8%)
Steatosis	11(4.5%)
Recipient age(years) (Median(range))	47(22–66)
Recipient weight(KG) (Median(range))	80(43–120)
Recipient gender	
Males	215(87.8%)
Females	30(12.2%)
MELD score (Median(range))	16(7–34)
CTP score	
A	13(5.3%)
B	64(26.1%)
C	168(68.6%)
Co-morbidity	64(26.1%)
Pre LT PVT	38(15.5%)
Pre LT PHN	224(91.4%)
Bl. Group	
Compatible	73(29.8%)
Identical	172(70.2%)
Graft type	
RL-MHV	234(95.5%)
RL + MHV	10(4.1%)
Segments VI, VII	1(0.4%)
Liver graft HA NO	
1	224(91.4%)
2	20(8.2%)
3	1(0.4%)
HA anastomosis NO	
1	229(93.5%)
2	16(6.5%)
Difficult HA anastomosis	5(2%)
Liver graft BD NO	
1	121(49.4%)
2	100(40.8%)
3	20(8.2%)
4	4(1.6%)
Ductoplasty of liver graft bile ducts	42(17.1%)
Biliary anastomosis NO	
1	147(60%)
2	87(35.5%)
3	11(4.5%)
Biliary anastomosis type	
D-D	232(94.7%)
HJ	12(4.9%)
HJ + D-D	1(0.4%)
Biliary anastomosis suture type	
Prolene 6/0	106(43.3%)
PDS 6/0	139(56.7%)
External biliary stent	224(91.4%)
Actual graft weight(g) (Median(range))	900(1.1–1250)
Actual GRWR (Median(range))	1.1(0.6–1.7)
CIT (min) (Median(range))	60(20–340)
WIT (min) (Median(range))	50(25–120)
HA anastomosis time (min) (Median(range))	60(11–290)
Intraoperative blood transfusion (units) (Median(range))	4(0–40)
Intraoperative plasma transfusion(units) (Median(range))	5(0–53)
Operative time (hours) (Median(range))	12.5(7–29)
Postoperative hospital stay(days) (Median(range))	17(1–120)
Immunosuppression regimen	
Regimen including FK	224(91.4%)
Regimen including MMF	230(93.9%)
Regimen including Cyclosporine	35(14.3%)
Regimen including Sirolimus	33(13.5%)
Regimen including Everolimus	20(8.2%)
Regimen including Simulect	73(29.8)
Post LT HAT/S	34(13.9%)

BMI: Body mass index, PPF: Periportal fibrosis, MELD: Model for end-stage liver disease, CTP: Child-Turcotte-Pugh, Pre LT PVT: Pre liver transplantation portal vein thrombosis, PHN: portal hypertension, RL: Right lobe, MHV: Middle hepatic vein, HA, Hepatic artery, NO: Number, D-D: Duct to duct, HJ: Hepaticojejunostomy, BD: Bile duct, PDS: Polydioxanone, GRWR: Graft recipient weight ratio, CIT: Cold ischemia time, WIT: Warm ischemia time, FK: Tacrolimus, MMF: Mycophenolate mofetil, HAT/S: Hepatic artery thrombosis or stenosis.

mins and 60 (range; 11–290) mins respectively. The median intraoperative blood and plasma transfusions were 4 (range; 0–40) units and 5 (range; 0–53) units respectively, the median operative time and postoperative hospital stays were 12.5 (range; 7–29) hours and 17 (range; 1–120) days respectively, lastly, the post LT HAT/S reached 34 (13.9%) of cases.Table 1.

3.2. The original liver disease

The most frequent original liver diseases were hepatitis C virus (HCV)(51.8%), hepatocellular carcinoma(HCC)(31.8%) and cryptogenic liver cirrhosis(5.3%). Table 2.

3.3. BCs and their management

One hundred fifty-five BCs affected 102 (41.6%) of our recipients (95 early (≤3months) and 60 late (≥3months)). They were classified as 67/245(27.3%) early bile leak, 10/245(4.1%) early biliary stricture, 44/245(17.9%) late biliary stricture, 4/245(1.6%) early cholangitis, 10/245(4.1%) late cholangitis, 14/245(5.7%) early biloma, and 6/245 (2.4%) late cholangitic abscesses. Table 3.

Regarding early bile leaks, they affected 27.3% of our patients at a median of 0.5 (range, (0.03–2)) months. The Clavien grades II, III and V affected 6, 45 and 16 of them respectively. They were classified regarding leak site into anastomotic, cut surface and cystic stump leaks in 51, 16 and one of them respectively. They were managed by conservative treatment, percutaneous drainage, ERCP ± stent, open

Table 2
The original liver disease.

Category	No (%)
	245(100%)
HCV	127(51.8%)
HCC	78(31.8%)
Cryptogenic liver cirrhosis	13(5.3%)
HBV	7(2.9%)
AIH	4(1.6%)
PBC	3(1.2%)
PSC	6(2.4%)
Budd Chiari syndrome	2(0.8%)
Wilson's disease	2(0.8%)
Alcoholic cirrhosis	1(0.4%)
Caroli's disease	1(0.4%)
HCV + HBV	1(0.4%)

HCV: Hepatitis C virus, HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus, AIH: Autoimmune hepatitis, PBC: Primary biliary cirrhosis, PSC: Primary sclerosing cholangitis.

Table 3
BCs and their management.

Category	Early bile leak	Early biliary stricture	Late biliary stricture	Early cholangitis	Late cholangitis	Early biloma	Late cholangitic abscesses	Total
No (% of totall patient NO)	67(27.3%)	10(4.1%)	44(17.9%)	4(1.6%)	10(4.1%)	14(5.7%)	6(2.4%)	155 (63.3%)
Onset per months								
Early(≤3months)	67(27.3%)	10(4.1%)	0	4(1.6%)	0	14(5.7%)	0	95(38.8%)
Late(≥3months)	0	0	44(17.9%)	0	10(4.1%)	0	6(2.4%)	60(24.5%)
Median(Range)	0.5(0.03–2)	2(2–2)	6(3.5–36)	2(1–2)	4(3–14.5)	0.75 (0.06–2)	4.5(3–7)	
Clavien grade								
II	6(2.4%)	0	0	1(0.4%)	0	3(1.2%)	0	10(4.1%)
III	45(18.4%)	7(2.8%)	39(15.9%)	1(0.4%)	3(1.2%)	7(2.9%)	0	102 (41.6%)
V	16(6.5%)	3(1.2%)	5(2%)	2(0.8%)	7(2.9%)	4(1.6%)	6(2.4%)	43(17.6%)
Treatment								
*1- Conservative	25(10.2%)	0	0	1(0.4%)	4(1.6%)	5(2%)	2(0.8%)	37(15.1%)
2- Intervention								
Percutaneous drainage	54(22%)	0	0	0	0	11(4.5%)	5(2%)	70(28.6%)
PTBD	0	0	2(0.8%)	0	0	0	0	2(0.8%)
ERCP ± Stent	26(10.6%)	9(3.6%)	43(17.5%)	3(1.2%)	7(2.9%)	2(0.8%)	0	88(35.9%)
Open surgical drainage	5(2%)	0	0	0	0	0	2(0.8%)	7(2.9%)
External biliary diversion	3(1.2%)	0	0	0	0	0	0	3(1.2%)
HJ	1(0.4%)	3(1.2%)	13(5.3%)	0	0	0	0	17(7%)
Treatment outcome								
Recovery	51(20.8%)	7(2.8%)	39(15.9%)	2(0.8%)	3(1.2%)	10(4.1%)	0	112 (45.7%)
No recovery	16(6.5%)	3(1.2%)	5(2%)	2(0.8%)	7(2.9%)	4(1.6%)	6(2.4%)	43(17.6%)

BCs: Biliary complications, NO: Number, PTBD: Percutaneous transhepatic biliary drainage, ERCP: Endoscopic retrograde cholangeopancreatography, HJ: Hepaticojejunostomy.* Conservative: Wait and see with medication therapy (ie antibiotics, IV fluids, electrolytes, etc); if succeeded OK but if failed proceed with intervention.

surgical drainage, external biliary diversion and HJ in 25, 54, 26, five, three and one of them respectively with favourable outcomes in 51 of them. Table 3.

All early biliary strictures that affected 4.1% of recipients occurred at the 2nd post LT month where Clavien grades III and V affected 7 and three of these strictures respectively. ERCP ± stent and HJ were the treatment options in 9 and three of them respectively with a successful outcome in seven of them. On the other hand, late biliary stricture affected 17.9% of our patients at a median of 6 (range, 3.5–36) months where 39 and five of them were Clavien grades III and V respectively. They were managed by PTBD, ERCP ± stent and HJ in two, 43 and 13 of them respectively where recovery occurred in 39 of them. Table 3.

Early and late cholangitis affected 4(1.6%) and 10(4.1%) of our patients respectively at a median of 2(range, 1–2) months, and 4(range; 3–14.5) months respectively. Clavien grades II, III and V affected one, one and two of early cases respectively; however, three and seven of late cases had Clavien grades III and V respectively. The conservative treatment and ERCP ± stent were the treatment options in one and three of the early cases respectively; however, they were the treatment options in four and seven of the late cases respectively. The outcome was favourable in two and three of the early and late cases respectively. Table 3.

We had 14 cases of early bilomas that occurred at a median of 0.75 (range; 0.06–2) months post-transplant; Clavien grades II, III and V affected three, seven and four of them respectively. The conservative treatment, percutaneous drainage and ERCP ± stent were the treatment options in five, eleven and two of them respectively with favourable outcomes in 10 of them. Table 3.

Lastly, late cholangitic abscesses affected 6(2.4%) of our patients at a median of 4.5 (range; 3–7) months; they all were Clavien grades V. Regarding their treatment; the conservative treatment(antibiotics), percutaneous drainage and open surgical drainage were the management strategies in two, five and two of them respectively with unfortunately unfavorable outcome in all of them (N.B two of them had associated HAS managed by angiographic dilatation and stenting, however, one of them had associated HAT managed by angiographic thrombolytic therapy and stenting). Table 3.

3.4. Predictors of BCs

On univariate analysis, heavier recipient weight, multiple graft BDs, multiple biliary anastomoses and post-LT HAT/S were significant predictors of BCs, however, multiple biliary anastomoses and post LT HAT/S were independent predictors of those complications on multivariate analysis. Table 4.

3.5. Predictors of biliary leaks

On univariate analysis, multiple graft BDs, multiple biliary anastomoses and post-LT HAT/S were significant predictors of biliary leaks, however, post-LT HAT/S was the only independent predictor of those complications on multivariate analysis. Table 5.

3.6. Predictors of biliary strictures

On univariate analysis, D-D biliary anastomosis, and post-LT HAT/S were significant predictors of biliary strictures, however, post-LT HAT/S was the only independent predictor of those complications on multivariate analysis. Table 6.

3.7. The outcome of patients

Our 6-months, 1-year, 3-year, 5-year, 10-year and 16-year graft survival were 167(68.2%), 159(64.9%), 150(61.2%), 149(60.8%),149

Table 4
Pre- and intra-operative variables as predictors of BCs.

Category	BCs	No BCs	P-value	P-value
	No (%)	No (%)	Univariate analysis	Multivariate analysis
	102 (100%) or	143 (100%)		
	(Mean ± SD)	Or (Mean ± SD)		
Donor age	27.1 ± 6.9	26.9 ± 5.9	0.9	
BMI of donor	25.4 ± 3.1	25.6 ± 3.4	0.58	
Donor liver biopsy			0.05	0.06
Normal	81 (79.4%)	129 (90.2%)		
PPF	15 (14.7%)	9(6.3%)		
Steatosis	6(5.9%)	5(3.5%)		
Recipient age	47.4 ± 7.7	46.7 ± 7.9	0.5	
Recipient weight(kg)	82.5 ± 13.3	79.2 ± 11.4	0.043	0.13
Recipient gender			0.055	0.15
Males	94 (92.2%)	121 (84.6%)		
Females	8(7.8%)	22 (15.4%)		
Cholestatic or immunological 1ry disease	5(4.9%)	10(7%)	0.59	
MELD score	15.6 ± 3.9	16.6 ± 4.1	0.06	
CTP score			0.56	
A	7(6.9%)	6(4.2%)		
B	28 (27.5%)	36 (25.2%)		
C	67 (65.7%)	101 (70.6%)		
Pre LT PVT	11 (10.8%)	27 (18.9%)	0.1	
Pre LT PHN	93 (91.2%)	131 (91.6%)	0.9	
Bl. Group			0.33	
Compatible	27 (26.5%)	46 (32.2%)		
Identical	75 (73.5%)	97 (67.8%)		
Graft type			0.25	
RL-MHV	100 (98%)	134 (93.7%)		
RL + MHV	2(2%)	8(5.6%)		
Segments VI,VII	0	1(0.7%)		
Difficult HA anastomosis	4(3.9%)	1(0.7%)	0.08	
Liver graft BD NO			0.021	0.3
1	44 (43.1%)	77 (53.8%)		
2	48 (47.1%)	52 (36.4%)		
3	6(5.9%)	14(9.8%)		
4	4(3.9%)	0		
Ductoplasty of liver graft BDs	15 (14.7%)	27 (18.9%)	0.39	
Biliary anastomosis NO			0.034	0.03
1	52(51%)	95 (66.4%)		
2	43 (42.2%)	44 (30.8%)		
3	7(6.9%)	4(2.8%)		
Biliary anastomosis type(excluding HJ + D-D)			0.2	
D-D	99 (97.1%)	133 (93%)		
HJ	3(2.9%)	9(6.3%)		
Biliary anastomosis suture type			0.1	
Prolene 6/0	49(48%)	57 (39.9%)		
PDS 6/0	53(52%)	86 (60.1%)		
External biliary stent	92 (90.2%)	132 (92.3%)	0.56	
Actual graft weight (g)	882.4 ± 153.7	865.3 ± 141.8	0.37	
Actual GRWR	1.1 ± 0.2	1.1 ± 0.2	0.33	
CIT (min)	69.9 ± 39.5	72.5 ± 51.2	0.65	
WIT (min)	52.9 ± 17	51.2 ± 17	0.55	
HA anastomosis time (min)	72.5 ± 29	69 ± 36	0.37	
Intraoperative blood transfusion (units)	5.1 ± 4.6	5.5 ± 6.7	0.55	
Intraoperative plasma transfusion (units)	6.1 ± 6.5	6.9 ± 8.2	0.40	
Operative time (hours)	12.7 ± 3.2	12.4 ± 3.1	0.58	
Post LT HAT/S	24 (23.5%)	10(7%)	0.000	0.005

BCs: Biliary complications, MELD: Model for end-stage liver disease, CTP: Child-Turcotte-Pugh, Pre LT PVT: Pre liver transplant PVT, Pre LT PHN: Pre liver transplantation portal hypertension, BMI: Body mass index, PPF: Peri-portal fibrosis, RL: Right lobe, MHV: Middle hepatic vein, HA, Hepatic artery, D-D: Duct to duct, HJ: Hepaticojejunostomy, NO: Number, BDs: Bile ducts, PDS: Polydioxanone, GRWR: Graft recipient weight ratio, CIT: Cold ischemia time, WIT: Warm ischemia time. HAT: Hepatic artery thrombosis or stenosis.

(60.8%), and 149(60.8%) respectively, however, the 6-months, 1-year, 3-year, 5-year, 10-year and 16-year patient survival were 171(69.8%), 164(66.9%), 152(62%),150(61.2%),149(60.8%), and 149(60.8%) respectively. The mortality reached 96(39.2%) mostly due to sepsis, bleeding and multi-organ failure (MOF). On the other hand, the biliary related mortality was 26(10.6%).Table 7.

3.8. BCs as predictors of outcome

The overall BCs were not significantly associated with graft or patient survival; however, recurrent cholangitis and multiple cholangitic hepatic abscesses were significant predictors of poor both graft and patient survival when using the fisher's exact tests. However, the abscesses were the only significant predictors of poor survival when using the log-rank tests.Table 8, Fig. 6.

4. Discussion

BCs after LDLT; especially A-ARLLDLT are a common problem reaching up to 60% of recipients [3–11,19]. Their management should be through a multidisciplinary team of transplant surgeons, hepatogastroenterologists, and intervention radiologists [1,20]. In similar; they affected 102 (41.6%) of our patients and were treated with the aid of our multidisciplinary team (i.e. Our treatment approaches started with the conservative measures (wait and see), but if failed; ERCP for leaks or strictures and/or pigtail and/or open surgical drainage for leaks were tried; however if failed PTBD or lastly HJ were allowed).

Table 5
Predictors of biliary leaks.

Category	Biliary leaks	No leaks	P-value	P-value
	No (%) 67 (100%) or (Mean ± SD)	No (%) 178 (100%) Or (Mean ± SD)	Univariate analysis	Multivariate analysis
Liver graft HA NO			0.10	0.3
1	58 (86.6%)	166 (93.3%)		
2	8(11.9%)	12(6.7%)		
3	1(1.5%)	0		
Liver graft BD NO			0.006	0.94
1	23 (34.3%)	98 (55.1%)		
2	36 (53.7%)	64(36%)		
3	5(7.5%)	15(8.4%)		
4	3(4.5%)	1(0.6%)		
Biliary anastomosis NO			0.005	0.14
1	30 (44.8%)	117 (65.7%)		
2	31 (46.3%)	56 (31.5%)		
3	6(9%)	5(2.8%)		
Biliary anastomosis suture type			0.06	0.21
Prolene 6/0	35 (52.2%)	71 (39.9%)		
PDS 6/0	32 (47.8%)	107 (60.1%)		
Recipient weight(kg)	82.6 ± 13.8	79.8 ± 11.7	0.10	0. 22
Intraoperative plasma transfusion (units)	5.2 ± 5.6	7.1 ± 8.1	0.08	0.20
Post LT HAT or HAS	16 (23.9%)	18 (10.1%)	0.007	0.029

HA, Hepatic artery, NO: Number, BDs: Bile ducts, HAT/S: Hepatic artery thrombosis or stenosis.

Table 6
Predictors of biliary strictures.

Category	Biliary strictures	No biliary strictures	P-value	P-value
	No (%) 54 (100%) or (Mean ± SD)	No (%) 191(100%) Or (Mean ± SD)	Univariate analysis	Multivariate analysis
Ductoplasty of liver graft BDs	5(9.3%)	37(19.4%)	0.057	0.1
Biliary anastomosis type(excluding HJ + D-D)			0.046	1
D-D	54(100%)	178(93.7%)		
HJ	0	12(6.3%)		
WIT (min)	55.2 ± 16.9	50.8 ± 16.6	0.09	0.1
Bile leak	20(37%)	47(24.6%)	0.053	0.1
Post LT HAT/S	14(25.9%)	20(10.5%)	0.005	0.02

D-D: Duct to duct, HJ: Hepaticojejunostomy, BDs: Bile ducts, WIT: Warm ischemia time. HAT/S: Hepatic artery thrombosis or stenosis.

Bile leaks occur mostly during the 1st two months post LDLT and their rate may reach up to 37% of recipients [3,9,21], moreover, they may come from the anastomotic site, the cut surface of the liver graft

Table 7
Recipients' outcome.

Category	No(%) 245(100%)
Graft survival	
6 months survival	167(68.2%)
1-year survival	159(64.9%)
3-year survival	150(61.2%)
5-year survival	149(60.8%)
10-year survival	149(60.8%)
16-year survival	149(60.8%)
Graft survival per months Median(Range)	31(0.03–192)
Patient survival	
6 months survival	171(69.8%)
1-year survival	164(66.9%)
3-year survival	152(62%)
5-year survival	150(61.2%)
10-year survival	149(60.8%)
16-year survival	149(60.8%)
Patient survival per months Median(Range)	34(0.03–192)
Mortality	96(39.2%)
Main causes:	
Sepsis	36(14.6%)
Biliary sepsis	18(7.3%)
Sepsis from pneumonia	18(7.3%)
Bleeding	13(5.3%)
MOF	11(4.5%)
HCC recurrence	7(2.8%)
HAT	6(2.4%)
ARDS	4(1.6%)
Graft failure	4(1.6%)
PVT	4(1.6%)
Renal impairment	3(1.2%)
SFSS	3(1.2%)
Chronic rejection	2(0.8%)
CMV infection	1(0.4%)
HAT + PVT	1(0.4%)
Ischemic reperfusion injury	1(0.4%)
Biliary related mortality	26(10.6%)

MOF: Multiorgan failure, HCC: Hepatocellular carcinoma, HAT: Hepatic artery thrombosis, ARDS: Adult respiratory distress syndrome, PVT: Portal vein thrombosis, SFSS: Small for size syndrome, CMV: Cytomegalovirus.

Table 8
BCs as predictors of outcome.

Category	Graft or patient survival	Graft or patient loss	P-value	P-value
	No (%) 149(100%)	No (%) 96 (100%)	Univariate analysis	Multivariate analysis
Overall BCs	58(38.9%)	44(45.8%)	0.2	
Bile leak	39(26.2%)	28(29.2%)	0.61	
Bile stricture	32(21.5%)	22(22.9%)	0.8	
Cholangitis	4(2.7%)	10(10.4%)	0.01	0.7
Biloma	7(4.7%)	7(7.3%)	0.4	
Cholangitic abscesses	0	6(6.3%)	0.003	0.2

BCs: Biliary complications.

[22–24], or the cystic duct stump [22,25] and can be managed conservatively [26] and/or by Percutaneous drainage [23,25,26], and/or by ERCP ± sphinectrotoy ± stenting [5,22,23,25–27] and/or by re-operation [5,22,25–27]. Similarly, biliary leaks that affected 27.3% of our patients occurred during the 1st two post-transplant months (median 0.5 (range, (0.03–2) months) from the anastomotic site (51/67; 76%), the graft cut surface(16/67; 24%), and the cystic duct stump (1/67; 1.5%), and were treated conservatively(25/67; 37%), by percutaneous drainage(54/67; 81%), by ERCP ± Stenting (26/67; 39%) and/or by surgery(surgical drainage, external biliary diversion and HJ) (9/67; 13%) with favourable outcomes in 51/67(76%) of them.

Post-LDLT biliary strictures are a common catastrophe reaching up to

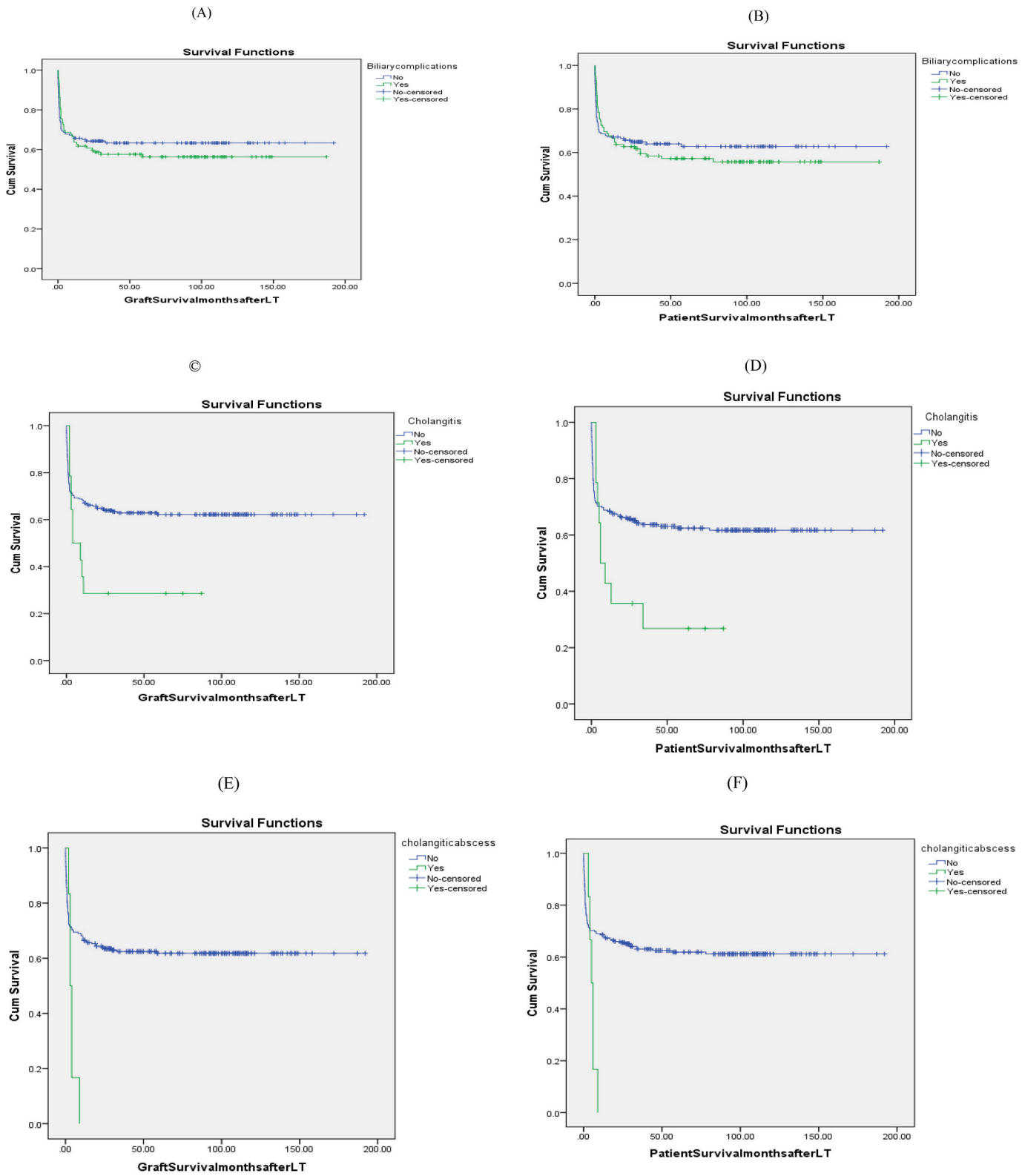

Fig. 6. Kaplan-Meier survival curves. A: Biliary complications and graft survival (Log rank = 0. 62). B- Biliary complications and patient survival (Log rank = 0. 65). C- Cholangitis and graft surival(Log rank = 0.05). D- Cholangitis and patient surival(Log rank = 0.06). E− Cholangitic abscesses and graft surival (Log rank = 0.006). F- Cholangitic abscesses and patient surival (Log rank = 0.008).

40% of patients [2,3]. They are anastomotic-/non-anastomotic ones; moreover, they may be angulated, tortuous, twisted, fork-shaped, trident-shaped, multi-branched, long and/or complicated strictures leading to more challenging therapy [28–30]. However, they can be managed successfully by endoscopy(ERCP ± sphinectrotomy ± ballon dilatation ± stenting) [5,7,9,11–13,21,23,27,30–34], by PTBD [2,7,9,11–13,21,23,31–33] and/or by surgery (HJ) [7,12,21,32,33]. In the same way; the post LT biliary strictures (early and/or late) that affected

54(22%) of our recipients at a median of 5 (range, 2–36) months were managed by ERCP ± Stent(52/54; 96.3%), by PTBD (2/54; 3.7%), and/or by surgery(HJ)(16/54; 29.6%) with favourable outcome in 46/54(85.2%) of them.

Post-LDLT bilomas are the collected localized intra- or para-hepatic biliary leaks occurring from bile duct rupture and biliary extravasation into the hepatic parenchyma or the abdominal cavity that can be managed conservatively [1,35,36], by percutaneous pigtail drainage [1, 35–38] and/or by ERCP ± stenting [1,35,39,40]. Also, the bilomas that affected 14(5.7%) of our recipients were managed conservatively (5/14; 36%), by percutaneous pigtail drainage (11/14; 79%) and/or by ERCP ± stenting (2/14; 14%) with effective treatment in 10/14(71.4%) of them.

The pyogenic hepatic abscesses that develop after LT are catastrophic rare events occurring in a range of 1.4–8.9% of patients due to several reasons (i.e. biliary causes (obstruction, reconstruction, drainage procedures (ERCP, PTBD), instrumentation (stents), cholangitis, infected bilomas, etc), HA complications (HAT/S), immunosuppresion, DM, etc) [41–44], however, they can be managed medically (antibiotics) [42, 44], by percutaneous drainage [42–44], and/or by open surgery [41, 45], In the same line; the cholangitic abscesses that affected 2.4% of our recipients occurred at a median of 4.5 (range; 3–7) months after ERCP with stenting and after repeated attacks of cholangitis, also, they were significantly correlated with HAT/S($P = 0.037$), moreover, they were associated with DM but without significance($P = 0.1$); those abscesses were managed medically (2/6; 33.3%), by percutaneous pigtail drainage (5/6; 83.3%), and/or by open surgical drainage (2/6; 33.3%) but unfortunately with unfavorable outcome.

BCs after LDLT are related to different (recipient, donor, graft, operative and/or postoperative factors) [46]; moreover, some of those factors were mentioned in different works of literature (i.e. centre volume/expertise, multiple small and short bile ducts from aberrant biliary anatomy, the type and number of biliary anastomoses, ductal intimal damage, necrosis, or ischemia during donor and recipient operations, HAT/S, CIT, WIT, immunological issues, ABO incompatibility, infections, etc) [7,9,35,47]. In this work; we analyzed the effect of different pre-, intra-, and post-transplant variables on the occurrence of post LT BCs.

Multiple graft BDs were significant predictors of overall BCs and leaks in our work, also, they were significant predictors of biliary strictures in Na et al., 2014 [48] study. However, they were not predictors of stricture or leak in Arikan et al., 2019 [8], Kim, et al., 2009 [18], or Jung et al., 2014 [49] studies.

Multiple biliary anastomoses were independent predictors of overall BCs and significant predictors of biliary leaks in our work; also, they were predictors of BCs in Ogiso et al., 2020 [19] study, however, they were not predictors of stricture or leak in Arikan et al., 2019 [8], Kim, et al., 2009 [18], or Özçelik et al., 2021 [50] studies, and were not associated with biliary stricture in Na et al., 2014 [48] study.

Despite the literature debate regarding the ideal method of biliary reconstruction in LDLT (D-D Vs HJ); D-D reconstruction is the procedure of choice and this is due to several reasons (i.e. being easier, quicker, more anatomic and physiologic, preserves SOD, has eliminated bowel manipulation, and is easy for ERCP post LT) [8,18]. In similar, it was done in 95% of our recipients. However, it was a predictor of biliary stricture in comparison to HJ in ours, Saidi, et al., 2009 [5] and Kawachi et al., 2002 [51] studies, conversely, HJ was a predictor of biliary stricture when compared to D-D reconstruction in Gunawansa et al., 2011 [25] and Icoz et al., 2003 [38] studies. Also, it was a predictor of biliary leaks and overall BCs in comparison with D-D reconstruction with a T-tube in Kobayashi et al., 2009 [52] study. On the other hand, the type of biliary anastomosis was not associated with BCs in Arikan et al., 2019 [8], Na et al., 2020 [13], Ogiso, et al., 2020 [19], Park, et al., 2003 [24], Jung, et al., 2014 [49] or Ramacciato et al., 2006 [53] studies.

We used external biliary stents in most of our cases (91.4%) due to several reasons (i.e. to keep the biliary flow and minimize intraductal pressure in the swollen edematous anastomosis, to keep small biliary lumens open, for assessment of graft function according to early bile production, and for doing simple cholangiography in suspected BCs); however, they had no significant impact on our BCs rate. Similarly, they did not affect the biliary outcome in Ozcelik et al., 2021 [50] study. In contrast, the none use of them was an independent predictor of BCs in Hong et al., 2018 [54] study.

We found an independent correlation between Post LT HAT/S and overall BCs, strictures and leaks; similarly, arterial complications were independent predictors of BCs in Reyes et al., 2020 [10] study, and HAT/S was a significant predictor of biliary stricture in Gunawansa et al., 2011 [25] study. Also, there was a significant association between HAS and biliary stricture in Hann et al., 2020 [55] study. Conversely, HAT was not associated with biliary stricture in Na et al., 2014([48]) study, and HA complications were not predictors of BCs in Ogiso et al., 2020 [19] study.

In our work, and despite non-reaching statistical significance; the biliary stricture rate was higher among leak cases; also, bile leak was an independent predictor of biliary stricture in Na et al., 2014 [48] study.

The overall BCs were not significantly associated with long-term graft or patient survival in ours or Cortez et al., 2020 [27] studies, however; those complications were significant predictors of poor long-term graft and patient survival in Rönning et al., 2019 [56] work, they were also independent predictors of a poor patient but not graft survival in Matar et al., 2021 [57] study. Moreover, the non-resolved biliary complications were significantly associated with poor long-term graft survival in Ogiso et al., 2020 [19] study.

Post LT recurrent cholangitis and cholangitic abscesses were significant predictors of poor graft and patient survival in our work, also, Post LT pyogenic liver abscess was a predictor of poor patient survival in Czerwonko et al., 2018 [41] study, Moreover, cholangitis was a cause of death in Barbaro et al., 2021 [58] recipients; in the same line, biliary sepsis from recurrent cholangitis and a liver abscess was a cause of death in Na et al., 2014 [48] study. Lastly, sepsis either from biliary or non-biliary causes was the main cause of death in our recipients, similarly, it was a cause of death in Na et al., 2020 [13] recipients. In conclusion: Multiple biliary anastomoses and post LT HAT/S lead to poor biliary outcomes, furthermore, cholangitis, cholangitic abscesses and sepsis lead to poor graft and patient outcomes, so proper management of those variables is mandatory to improve outcomes after A-ARLLDLT.

Ethical approval

The approval by National liver institute (IRB), Menoufia university that was done retrospectively.

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Author contribution

Emad Hamdy Gad: Surgical procedures, study design, data collection, writing, analysis and publication.

Eslam Ayoup: Surgical procedures, data collection, and analysis.

Amr M. Aziz: Surgical procedures, and analysis.

Tarek Ibrahim: Surgical procedures, and analysis.

Mostafa Elhelbawy: Endoscopic procedures, and data collection.

Mohammed Al-sayed Abd-elsamee: Intervention radiology procedures, and data collection.

Ahmed Nabil Sallam: Surgical procedures, data collection, and analysis.

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All the authors of this paper accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Declaration of competing interest

No conflict of interest to declare.

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The main limitation of the study is its retrospective nature; so, it is advisable to do further randomized prospective studies of the studied issues.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amsu.2022.103577.

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