Diagnostic and Therapeutic Management Algorithm for Biliary Complications in Living Liver Donors

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Abstract

Background: Complications in living liver donors are one of the main concerns about living donor liver transplantation and the most important of all are biliary complications. Objective: To present the diagnostic and therapeutic algorithm developed for the postoperative biliary complications in living liver donors (LLDs). Methods: Between September 2005 and October 2019, 2120 living liver donor candidates underwent living donor hepatectomy and postoperative biliary complications developed in 167 (7.87%). Management algorithm for various biliary complications and living liver donors who required hepaticojejunostomy were evaluated for this retrospective cohort study. Results: Fifty-one LLDs underwent 53 relaparotomy procedures due to biliary peritonitis. Endoscopic retrograde cholangiopancreatography (sphincterotomy± stenting) was performed in 104 donors but due to persistent bile duct stricture ± bile leaks, percutaneous transhepatic biliary tract drainage catheter was inserted in six donors following a failed endoscopic retrograde cholangiopancreatography assisted treatment. Ninety-seven LLDs underwent interventional radiologic procedure and twelve of them were percutaneous transhepatic biliary tract drainage. HJ was performed in 10 LLDs with right lobe LDH and 2 LLDs with left lobe LDH. Ten of the 12 LLDs underwent percutaneous transhepatic biliary tract drainage catheter assisted HJ in a median of 50 days after LDH. Following HJ, 11 LLDs did not have any complication along the median of 978 days (min-max: 139-3578) of follow-up. Conclusion: As living donor liver transplantation will continue to be performed in countries with low cadaveric organ supply and biliary complications will be encountered following LDH. Timing of management of the biliary complication is vital and HJ procedure is the ultimate treatment modality for biliary complications that cannot be solved by other minimally invasive methods especially percutaneous transhepatic biliary tract drainage.

ORIGINAL ARTICLE

Diagnostic and Therapeutic Management Algorithm for Biliary Complications in Living Liver Donors

Running Head: Management algorithm for donor biliary complications

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ABBREVIATIONS

LDH- Living donor hepatectomy; LLD- Living liver donors; LDLT- Living donor liver transplantation; ERCP- Endoscopic retrograde cholangiopancreatography; PTBD- Percutaneous transhepatic biliary tract drainage; HJ - Hepaticojejunostomy; MDCT- Multidetector computed tomography; MRCP- Magnetic resonance cholangio pancreatography; US- Ultrasonography; ALP- Alkaline phosphatase; GGT- Gamma-glutamyl transferase; BMI- Body mass index

ABSCTRACT

Background: Complications in living liver donors are one of the main concerns about living donor liver transplantation and the most important of all are biliary complications.

Objective: To present the diagnostic and therapeutic algorithm developed for the postoperative biliary complications in living liver donors (LLDs).

Methods: Between September 2005 and October 2019, 2120 living liver donor candidates underwent living donor hepatectomy and postoperative biliary complications developed in 167 (7.87%). Management algorithm for various biliary complications and living liver donors who required hepaticojejunostomy were evaluated for this retrospective cohort study.

Results: Fifty-one LLDs underwent 53 relaparotomy procedures due to biliary peritonitis. Endoscopic retrograde cholangiopancreatography (sphincterotomy± stenting) was performed in 104 donors but due to persistent bile duct stricture ± bile leaks, percutaneous transhepatic biliary tract drainage catheter was inserted in six donors following a failed endoscopic retrograde cholangiopancreatography assisted treatment. Ninety-seven LLDs underwent interventional radiologic procedure and twelve of them were percutaneous transhepatic biliary tract drainage. HJ was performed in 10 LLDs with right lobe LDH and 2 LLDs with left lobe LDH. Ten of the 12 LLDs underwent percutaneous transhepatic biliary tract drainage catheter assisted HJ in a median of 50 days after LDH. Following HJ, 11 LLDs did not have any complication along the median of 978 days (min-max: 139-3578) of follow-up.

Conclusion: As living donor liver transplantation will continue to be performed in countries with low cadaveric organ supply and biliary complications will be encountered following LDH. Timing of management of the biliary complication is vital and HJ procedure is the ultimate treatment modality for biliary complications that cannot be solved by other minimally invasive methods especially percutaneous transhepatic biliary tract drainage.

Key Words; Living donor liver transplantation; Living Donor Hepatectomy; Biliary Complications; Percutaneous transhepatic biliary tract drainage; Hepaticojejunostomy

INTRODUCTION

Living donor liver transplantation (LDLT) is the method of choice for expanding the liver donor pool in many countries where the cadaveric organ supply is insufficient. [1,2] The most important advantages of LDLT are an easily available liver graft, ability to perform a planned and elective surgery, and a shorter cold ischemia time. [1,2] Despite of these advantages, safety of living liver donors (LLDs) is still a matter of debate. Increase in the number of studies addressing with morbidity and mortality in LLDs reduced the interest and a motivation in performing LDLT in the western world; significantly. Studies in current literature reported an overall morbidity and mortality following living donor hepatectomy (LDH) as 0-67% and 0.1-1%, respectively. [1-3] Biliary complications following the LDH procedure are the most common of all the complications. Management of intraoperative or postoperative biliary complications vary from a strategy of "wait and see" to a complex and technically demanding surgical procedure such as hepaticojejunostomy (HJ). Percutaneous transhepatic biliary tract drainage (PTBD: external-internal, external), percutaneous perihepatic bilioma drainage (transhepatic or transperitoneal) and endoscopic retrograde cholangiopancreatography (ERCP) are among the treatment options for biliary complications. However, there is a lack of consensus regarding timing and choice of treatment algorithm and which LLDs should undergo HJ. This study aims to present our treatment algorithm of biliary complications in LLDs and our technique for PTBD catheter assisted HJ in necessary cases.

MATERIAL AND METHODS

Study Design

Demographic, clinical and radiological data of 2120 LLDs who underwent LDH at the Inonu University Liver Transplant Institute between September 2005 and October 2019 were prospectively collected and retrospectively analyzed (retrospective cohort). This study was designed to emphasize two major points. First, to assess the diagnostic and therapeutic management algorithm for biliary complications following LDH. Second, to present our interventional radiology assisted HJ technique for biliary stricture and bile leaks which were not successfully treated with endoscopic and interventional radiologic procedures.

Donor Evaluation Protocol

Turkish Ministry of Health allows living organ donation from the first to fourth relatives of the recipient. Any relative beyond the fourth degree or non-next of kin donor (samaritan donors) are evaluated by the state ethic committee in order to rule out commercial organ donation. Our detailed donor evaluation scheme and information regarding our aborted donor hepatectomies were emphasized in a recent study from our institute. [4] Currently, LLDs are chosen among individuals aged between 18 to 60 years of age with normal renal and liver functions. However, in the early years of our experience, donors [?] 60 years old were used. The individuals must also have negative viral serology (except for those individuals that have antibody against the hepatitis B core antigen) and matched blood group compatible. We routinely perform multi-detector computerized tomography to determine the volume of the graft and the future remnant liver, to delineate the vascular anatomy of the intended vascular graft. Also, we routinely perform magnetic resonance assisted cholangiography and dynamic magnetic resonance imaging to evaluate the biliary anatomy and the quality of the liver parenchyma.

Donor Hepatectomy Technique

The technique for LDH that we prefer was described in the previous studies from our liver institution. [5-7] The procedure starts with cholecystectomy and we perform intraoperative cholangiography routinely. It is performed as the initial step of the procedure in order to decide to proceed with LDH. We also perform intraoperative cholangiography as the last step the procedure following hemostasis in order to determine any unrecognized injuries to the biliary tract.

Data acquisition

Data of 167 (7.87 %) LLDs with postoperative biliary complications (one intraoperative) diagnosed clinically and radiologically were reviewed in terms of age, sex, body mass index (BMI: kg/m2), blood group, relation of LLDs to the recipient, type of LDH (right, left, segment II-III), time from LDH to ERCP, time from LDH to interventional radiologic procedures, time from LDH to relaparotomy or HJ. In the following sections we will define LDH related biliary complications and PTBD catheter assisted HJ technique in accordance with the objectives of the present study. Ethical approval was obtained from the Inonu University Institutional Review Board for non-interventional studies (Approval No: 2019/10-23).

Definition of Biliary Complications

Physical examination findings, biochemical parameters, ultrasonography (US), multidetector computed tomography (MDCT), magnetic resonance cholangiopancreatography (MRCP) and ERCP were used to identify and classify biliary complications following LDH. All of the components listed below are regarded as postoperative biliary complications: (i) radiologic diagnosis of fluid collection suggesting perihepatic bilioma in LLDs with cholangitis or abscess formation with abdominal pain, fever, chills or rarely, bilioma incidentally detected in LLDs without clinical findings (ii) prolonged biliary fluid drainage from surgically inserted drainage tube more than 5 days after the LDH, (iii) prolonged postoperative elevations in serum alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin levels, or a new onset postoperative elevation of the afore mentioned tests (iv) diagnosis of biliary peritonitis with acute abdominal findings.

Management Algorithm for Biliary Complications (Graphic-1)

(I) Majority of the LLDs who had a radiological perihepatic bilioma with findings of cholangitis or abscess without acute abdomen underwent percutaneous transhepatic drainage and in rare occasions (Fig.1a), a percutaneous transperitoneal (non-hepatic) drainage was performed (Fig.1b). A drainage catheter was not placed in the perihepatic fluid collections or perihepatic abscess like fluid collections without abdominal findings when there is no bile in the aspirated fluid and these cases were generally followed-up with US. In rare cases with recurrent collection, the procedure was repeated. LLDs who received a drainage catheter were controlled with pouchography following couple of days to provide a decrease of pressure in the collection and reduction of the edema. In cases without any bile duct connection, "wait and see" strategy was chosen (Fig.1c). In majority of these cases the bilioma was caused by minor bile duct draining the caudate lobe (Fig.1d). Cases with a bile duct connection were evaluated and treated according to the communication of

the bile leaks either to the main or isolated major segmental branches of hepatic duct (Fig.2). Cases with a communication with the main bile ducts were treated primarily with ERCP+ sphincterotomy +- stent placement. If ERCP failed due to technical reasons or bile leaks persisted despite ERCP, an external-internal or external PTBD catheter was inserted. In LLDs with bile leaks from an isolated segmental bile duct located on the cut surface of remnant liver without any communication with a major bile duct, treatment method is chosen according to daily amount of bile drainage. In LLDs with bile drainage less than 50 mL/day are mostly related to minor segmental bile duct; thus close follow-up without any invasive intervention is preferred but very rarely fibrin glue plug is applied to the bile duct through percutaneous placed catheter in cases with prolonged low volume drainage less than 20ml/days. In LLDs with prolonged bile drainage more than 50 ml/days can be related to major segmental bile duct which require PTBD catheter. If bile leaks was communicated with major segmental bile duct in PTC, PTBD assisted HJ can be considered. Even if the external-internal PTBD catheter is inserted, the most appropriate approach is PTBD guided HJ in cases with persistent bile leaks from the site of bile duct stumps. The reason for this is due to the fact that ischemic defects in the bile duct stump that often unsuitable for primary repair.

(II) For LLDs with a biliary drainage from the perihepatic surgical drain without acute abdomen, wait and see for first postoperative five days is the preferred management strategy. Early relaparotomy is beneficial in cases with pure bile flow more than 300 ml/day within the postoperative first two days, which we preferred in two cases in the present study. In LLDs with persistent biliary drainage prolonged ([?]5 days), bile duct injury is usually evaluated with MRCP and/or occasionally with fluoroscopy enhanced with contrast media delivered from surgical drain where placed in the perihepatic space. In patients whose MRCP was unsuccessful to show the remnant biliary tract, diagnostic ERCP was considered and, stent was inserted in necessary cases. Wait and see strategy was chosen in LLDs without any evident relation with the bile ducts. If any relation with the bile ducts was diagnosed, first column of the algorithm was chosen (see Graphic-1).

(III) For LLDs with isolated enzyme elevation and without any clinical or ultrasonographic findings, MRCP is utilized to evaluate the biliary tract. LLDs without any biliary stricture diagnosed with MRCP require further investigation for evaluation of any possible parenchymal disease (transient elastography, biopsy, genetic analysis etc). LLDs with biliary stricture on MRCP undergo ERCP+- sphincterotomy and a stent is inserted for the treatment of the stricture. In LLDs whom ERCP failed, PTBD is performed and external-internal PTBD catheter is inserted and during the follow-up period stent 'renewal is performed with ERCP. If external-internal PTBD procedure failed to pass through the stricture, external PTBD catheter is inserted and re-evaluated a few days later. If the repeated attempt fails again, PTBD catheter assisted HJ is performed.

(IV) Relaparotomy was performed for LLDs with acute abdomen. Following irrigation of abdominal cavity, cut surface of remnant liver, left or right hepatic duct stumps, cystic duct stump and main bile duct are evaluated thoroughly and minor bile leaks points on cut surface of the remnant liver are sutured with polypropylene. Cholangiography is performed via catheter inserted into cystic duct. When major bile leaks are detected during cholangiography, catheter is sent through the cystic duct to the remnant liver bile ducts. After this procedure, bile leaks points are repaired with polypropylene suture materials. Postoperative cholangiography is performed two to four weeks later and catheter was withdrawn if no bile leak is observed.

Definition of Hepaticojejunostomy Procedure

Laparotomy is performed through the previous Makuuchi incision and cholangiography is performed following catheterization of cystic duct stump. In LLDs with an external PTBD catheter, radiologist place a guide-wire through the catheter. The PTBD catheter is withdrawn with care and the rigid guide-wire is pushed-forward slowly under fluoroscopic observation (Fig.3a). The bile duct is determined by the bulging at the closest point on the cut surface. A bile duct orifice that is wide enough to perform an anastomosis is obtained using cavitron ultrasonic surgical aspirator to dissect the periductal liver parenchyma. Following retraction of guide-wire, PTBD catheter was inserted and HJ anastomosis was performed. In cases that have external-internal PTBD catheter, it is easy to see the catheter after the damaged extrahepatic bile duct is explored. In these cases, HJ is performed over the PTBD catheter and distal end of the catheter was

advanced into the Roux limb (Fig.3b). HJ anastomoses are performed with interrupted suture using 6/0 monofilament polydioxanone sutures, stiches remained outside. Following the anastomosis, patency of bile ducts is controlled with intraoperative cholangiography via PTBD catheter. PTBD catheters are with-drawn in LLDs without bile leaks on cholangiography performed on postoperative week 4-6.

Postoperative follow-up of LLDs with Hepaticojejunostomy

A surgical drain is inserted to the perihepatic or perianastomotic site and these drainage tubes were with-drawn postoperatively when drainage is not bilious and the output volume is < 50 mL/day. PTBD catheters are irrigated at least once each day with 5-10 cc saline solution. A cholangiography is performed between on postoperative 5th to 7th days and LLDs without clinical, laboratory and radiological findings of bile leaks are discharged. Another cholangiography is performed on postoperative fourth and sixth weeks and catheters are withdrawn in LLDs without any biliary leaks.

RESULTS

General Assessment

A total of 167 (7.87 %) LLDs (male: 103, female: 64, median age: 30, min-max: 18-63 yr) developed biliary complications. Right hepatectomy was performed in 134 LLDs while segment II-III resection was performed in 25 LLDs. Left hepatectomy was performed in the remaining 8 LLDs. No statistically difference was found between the LLDs with (n=167) and without (n=1953) biliary complications in terms of liver graft type (n=0.153), preoperative Anti HBc total positivity (p=0.716), sex (p=0.403), age (p=0.328), BMI (p=0.443) and preoperative total bilirubin level (p=0.280).

Assessment of the ERCP Results

ERCP was performed in 104 LLDs in a median of 21 days (min-max: 5-104 days) following LDH for one to eight sessions. Among these 104 LLDs, six LLDs underwent PTBD +- stenting due to unsuccessful ERCP or persistent biliary leak despite ERCP. Due to persistent bile duct stricture or bile leaks, two of these six LLDs underwent PTBD catheter assisted HJ thereafter. Six of twelve LLDs who underwent HJ had a history of failed ERCP attempts. One ERCP session resulted in duodenal perforation, management report of this LLD is previously published.[8] Five LLDs with biliary complications had mild-to-moderate pancreatitis following ERCP, all of which recovered with fluid resuscitation and medical treatment. No other complications were observed all along median of 1119 days (min-max: 15-3536) of follow-up after ERCP.

Assessment of the Percutaneous Procedures Results

Ninety-seven LLDs with biliary complications underwent one to four sessions of interventional radiology assisted percutaneous procedures. Eighty-five of them underwent transhepatic or transperitoneal perihepatic bilioma drainage and no any drainage catheter was placed in 18 of these patients because the aspirated fluid was serous/purulent rather than bilious. Median time from LDH to percutaneous bilioma drainage was 21 days (min-max: 6-317 days). Median time from LDH to PTBD catheter insertion was 33 days (min-max: 24-78 days). Among 12 LLDs had a PTBD catheter insertion, ten underwent PTBD catheter assisted HJ, of which 7 had external and 3 had internal-external PTBD catheters.

Assessment of the Hepaticojejunostomy Results

HJ procedure was performed in 12 LLDs who had postoperative (n=11) or intraoperative (n=1) biliary complications. (i) Intraoperative biliary complication consisted of iatrogenic segment IV bile duct injury. In this patient, HJ anastomosis was performed to the bile duct draining segment 4 and the main bile duct was left intact (Fig.4). (ii) Isolated major segmental duct obstruction was present in 4 LLDs and there was no problem in the main bile duct. In these LLDs, these isolated bile ducts were probably unnoticed in the first operation and ligated accidentally. HJ anastomosis was performed in these patients as described above. (iii) Two patients had obstruction in the main bile duct that could not be resolved by percutaneous interventional procedures and the treatment required HJ. In the above-mentioned 7 LLDs, single orifice HJ was performed. (iv) In 3 patients, large ischemic defective area was found on the ductal stump area which was caused by

an obstruction in the main biliary tract. Side-to-side HJ was performed and ductal continuity was achieved in these 3 cases (Fig.5). (v) Two patients had both major biliary tract and isolated segmental major biliary tract obstruction. These patients underwent double orifice HJ (Fig.6). In other words, there were 14 HJ ostium in 12 cases. One of these 12 cases was unfortunate. Isolated major segmental duct obstruction was noticed after HJ was performed to the main biliary tract in the re-operation. Another HJ was performed to this bile duct on the same Roux limb in the second reoperation.

Ten LLDs underwent PTBD catheter assisted HJ and the distal tip of the catheters were advanced through the anastomosis into the Roux limb. In one patient who received an emergency laparotomy in the postoperative early period and did not have a PTBD catheter, a trans-anastomotic catheter was inserted and distal tip of the catheter was advanced into the intrahepatic bile ducts (Fig.7). In the remaining one patient with HJ, it was found that there was an iatrogenic injury to the segment 4 bile duct during parenchymal transection. Therefore, end-to-side HJ was performed between Roux limb and bile duct that drained segment IV and a trans-anastomotic catheter was used to protect the anastomosis in this patient. The details of the of the patients underwent HJ are given in Graphic-2.

Twelve LLDs with biliary complications underwent HJ at a median of 50 days (min-max: 0-97 days) after the LDH. HJ was performed in 10 LLDs with right lobe LDH and 2 LLDs with left lobe LDH. None of the LLDs underwent segment II-III resection required HJ anastomosis. There was no statistically significant difference between LLDs, who have biliary complications, with (n=12) and without (n=155) HJ procedure in terms of sex (p=0.805), age (p=0.714), graft type (right vs left; p=0.820), BMI (p=0.330), bile duct anatomy (p=0.066) and bile leaks (p=0.137). LLDs with a biliary complication following LDH were followed-up for a median of 1141 days (min-max: 21-4201 days). Following HJ, 11 LLDs did not have any complication all along the median 978 days (min-max: 139-3578 days) of follow-up. For a patient who suffered from HJ anastomosis stricture on long-term follow-up, an internal biliary drainage catheter was inserted and then the catheter was withdrawn following three sessions of balloon dilation.

Assessment of the Relaparotomy Results

Fifty-one LLDs (2.4 %) with a median age 27 years (min-max: 20-51 years) underwent 53 relaparotomy due to various biliary complications. A sum of 107 relaparotomy procedures were performed and 53 of them were related with various biliary complications. Median time from LDH to relaparotomy was 20 days (min-max: 1-97 days). Thirteen of the relaparotomies received HJ (one LLD had twice relaparotomy for a second HJ). Only two LLDs underwent HJ during relaparotomy for acute biliary peritonitis. One of these two LLDs underwent early relaparotomy due to a bilioma which was 10 cm in diameter resulted in peritonitis. An ischemic section consisting right ductal stump of the main bile duct was diagnosed, and a HJ was performed between the ischemic section of the bile duct and a jejunal Roux limb, preserving the continuity of bile flow via common bile duct. Although external-internal PTBD catheter was inserted in another LLD to prevent postoperative bile leaks, bile leaks persisted and acute abdomen findings developed. Therefore, PTBD catheter assisted HJ was performed in the laparotomy performed for acute abdomen findings. Remaining 40 patients that underwent re-laparotomy, the indications were biliary peritonitis, drainage of fluid/bilioma, high output bile leaks in the early postoperative period ([?]300 cc pure bile leaks) and duodenal perforation due to ERCP. A biliary drainage catheter extending from the cystic duct stump to the intrahepatic bile ducts was placed in 13 LLDs for bile leaks from cut surface or bile duct stump. Procedure for repair of bile leaks was mentioned above. Following bilioma drainage and a drainage tube placement, surgical procedure was finalized in 26 LLDs. Remaining one LLD underwent relaparotomy due to duodenal perforation following ERCP.

DISCUSSION

Biliary complications following LDH are common and the incidence has been reported to range from 0 % to 38.6 %. [9]Ghobrial and colleagues [10] have reported a retrospective study conducted by the A2ALL study group conducted in conjunction with 9 centers that perform LDLT and they have reported that complications are the second most common complications that are encountered in LLDs in the postoperative

period with an incidence of 9.2%. Our complications are a bit lower than that has been reported in their study. However, a recent review by Simoes and colleagues[11] have stated that the incidence of biliary complications among the donors ranged between 6% to 18%. Wide variations of biliary complications in LLDs reported in various studies may be due to the lack of uniform definition of these complications. In centers who report low postoperative biliary complications can be due to low rate of abdominal drains use, negligence of the subclinical bile leaks, and early discharges because of cost problems in these centers.[12-14] In the present study, overall postoperative biliary complications following LDH is 7.8 %. Total biliary complication rates in LLDs have been shown to be higher in right lobe harvesting (6.6 % versus 2.9 %).[9] Biliary anatomic variations of the right lobe of the liver are more frequently encountered which may explain the high complication rates observed in the present study. In our study, no statistically significant difference between right and left lobe donors in terms of biliary complications may be due to advanced experience of approximately 250-300 LDLTs annually.

The algorithm for the management of postoperative biliary complications presented in our study is the result of extensive experience of our institute, obtained through a long period of time. In some studies, flowchart-like diagrams are presented for the diagnosis and treatment of biliary complications; however, in these studies an development of an algorithm was attempted based on results obtained from low volume experience. [2,15] We think that our flowchart (Graphic-1) is a study that results from a high patient volume series and clearly demonstrates the treatment methods. To give an example, our management algorithm is very clear in the cases with low output bile leaks that stem from isolated minor bile ducts. It is noteworthy to emphasize that 30 years have passed since the first LDLT procedure and little has been published to guide the physicians regarding the management of biliary complications following LDH. We believe that the present study will provide a useful algorithm for management of postoperative living donor biliary complications in centers performing LDLT.

The necessity of HJ for management of the biliary complications in cases that cannot be treated by the interventional methods following LDH is a reality. The publications from centers that perform LDLT have major shortcomings regarding the extent of LLDs that receive HJ following biliary complications. For example, it is not clear whether "the surgical repair" and "repeat biliary reconstruction" referred to in these studies is in fact HJ or not. [15,16] We do not see much emphasis on this issue in the literature. To date, we have tried to find cases of HJ reported in LLDs. A total of 15 HJs were reported in 9 published studies except four cases of HJ that was reported from our institute (Table 1) [4-6,14,17-24] In the present study, the rate of HJ among those who experience biliary complications was 0.56%.

HJ is a major operation performed for the management of biliary complications following LDH. This has emotionally adverse effects on the LLD surgeons. Nevertheless, it is noteworthy that HJ is a life-saving procedure in the management of biliary complications because biliary complications may result in death of the donor. [2,25]Of course, all non-surgical methods should be used to treat biliary complications especially in LLDs. However, unnecessary waiting of the cases that do not recover will only result in a disaster. In biliary leaks that are not resolved with percutaneous radiologic interventions, HJ should be kept in mind as a last resort for the management. In other words, we think that after a few unsuccessful attempts of minimally invasive procedures, we should not underestimate the success of a HJ procedure.

In the operations for biliary stricture, the most difficult part of this operation was to reveal the obstructed biliary duct on the dens structured hepatic hilum. We believe that this difficulty can be overcome with the percutaneous transhepatic biliary drainage catheter assisted HJ described in this study.

Furthermore, if HJ is chosen to treat a biliary complication in an LLD, it should be performed as one step procedure during the reoperation. In the present study, another procedure was needed in one LLD who was operated for biliary complication and HJ was performed. In this LLD, HJ was performed to a sufficiently wide bile duct. Intraoperative cholangiography was performed through a PTBD catheter that has been inserted prior to operation and bile ducts were visualized and the operation was ended. In fact, the visualized bile ducts belong to segment II and IV. Segment III hepatic duct remained obstructed and were not visualized. Unfortunately, we did not compare the final intraoperative cholangiography images with donor MRCP or

intraoperative cholangiography images obtained at the beginning of the LDH procedure. Therefore, this patient required re-laparotomy for a second HJ anastomosis.

In LLDs with early-recognized biliary complication, presence of a skilled endoscopists and interventional radiologists has paramount importance. In this study, we mentioned 12 LLDs whose biliary complications had to be treated with HJ although we had endoscopists and interventional radiologists with extensive experience. Of course, minor bile ducts originating from the cut surface of the remnant liver should be evaluated with extreme caution during the operation. Intraoperative cholangiography should be examined diligently to evaluate any misinterpreted major biliary tract injuries and if necessary, cholangiography should be repeated from different flip angles.

This is the largest LLDs series in the literature and we have described the treatment algorithm for biliary complications and we have frankly presented HJ cases. The results of this study show that postoperative biliary complications are still a major problem following LDH. Furthermore, about 7 % of the LLDs with biliary complications require HJ for management of this complication. Donor safety during LDLT is imperative, however if this concern leads to improper transection of the graft donor, the results may be devastation for the recipient. Therefore, a good balance should be obtained during the LDH procedures. Necessary precautions should be taken to avoid damage to the donor bile ducts but we should also provide sufficient bile ducts for safe anastomosis in the recipient. However, occasionally this balance can be disrupted leading to unfavorable outcome in the donor. In countries with insufficient cadaveric organ supply, LDLT will still continue to be the major source of organ supply and biliary complications will be encountered in the LLDs. In centers performing LDLT, it should be a priority to employ early and accurate management protocol for postoperative donor biliary complications.

AUTHOR CONTRIBUTIONS

Development of the project: Akbulut S, Sahin TT, Yilmaz S and Ozsay O; data collection: Sarici KB, Baskiran A, Gonultas F, Ozdemir F and Ersan V; writing: Akbulut S, Isik B and Yilmaz S; drawing of figures: SU; radiological interventions: Kutlu R; endoscopic interventions: Harputluoglu M; editing; Akbulut S, Isik B, Sahin TT and Yilmaz S

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are avaiable from the corresponding author, (SA), upon a reasonable request

DISCLOSURE

The authors report no conflict of interest.

REFERENCES

1. Akbulut S, Yilmaz S. Liver transplantation in Turkey: historical review and future perspectives. *Transplant Rev (Orlando)*2015;29:161-167. Doi: 10.1016/j.trre.2014.12.002
2. Shaji Mathew J, Manikandan K, Santosh Kumar KY, Binoj ST, Balakrishnan D, Gopalakrishnan U, Narayana Menon R, Dhar P, Sudheer OV, Aneesh S, Sudhindran S. Biliary complications among live donors following live donor liver transplantation. *Surgeon.* 2018;16:214-219. Doi: 10.1016/j.surge.2017.08.005
3. Braun HJ, Ascher NL, Roll GR, Roberts JP. Biliary complications following living donor hepatectomy. *Transplant Rev (Orlando).*2016;30:247-252. Doi: 10.1016/j.trre.2016.07.003.
4. Kutluturk K, Akbulut S, Baskiran A, Gonultas F, Dirican A, Isık B, Yilmaz S. Aborted donor hepatectomy in living donor liver transplantation: lessons learned. *S Afr J Surg.* 2020;58:91-100. Doi:10.17159/2078-5151/2020/v58n2a3143
5. Usta S, Ates M, Dirican A, Isik B, Yilmaz S. Outcomes of left-lobe donor hepatectomy for living-donor liver transplantation: a single-center experience. *Transplant Proc.* 2013;45:961-965. Doi: 10.1016/j.transproceed.2013.02.065

6. Dirican A, Ara C, Kutluturk K, Ozsoy M, Ates M, Baskiran A, Isik B, Yilmaz S. Donor Postoperative Biliary Complications After Living-Donor Liver Transplant. *Exp Clin Transplant.* 2015;13:516-523. Doi: 10.6002/ect.2014.0117
7. Ozgor D, Dirican A, Ates M, Gönültas F, Ara C, Yilmaz S. Donor complications among 500 living donor liver transplantations at a single center. *Transplant Proc.* 2012;44:1604-1607. Doi: 10.1016/j.transproceed.2012.04.002
8. Akbulut S, Isik B, Karipkiz Y, Yilmaz S. Massive Subcutaneous Emphysema, Pneumoperitoneum, Pneumoretroperitoneum, and Pneumoscrotum following Endoscopic Retrograde Cholangiopancreatography in a Living Liver Donor. *Int J Organ Transplant Med* 2018; 9: 132-135.
9. Yuan Y, Gotoh M. Biliary complications in living liver donors.*Surg Today.* 2010;40:411-417. Doi: 10.1007/s00595-009-4143-1
10. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, Fisher RA, Emond JC, Koffron AJ, Pruett TL, Olthoff KM; A2ALL Study Group. Donor morbidity after living donation for liver transplantation.*Gastroenterology.* 2008;135:468-76. Doi: 10.1053/j.gastro.2008.04.018
11. Simoes P, Kesar V, Ahmad J. Spectrum of biliary complications following live donor liver transplantation. *World J Hepatol.* 2015; 7:1856-65. Doi: 10.4254/wjh.v7.i14.1856
12. Hwang S, Lee SG, Lee YJ, Sung KB, Park KM, Kim KH, Ahn CS, Moon DB, Hwang GS, Kim KM, Ha TY, Kim DS, Jung JP, Song GW. Lessons learned from 1,000 living donor liver transplantations in a single center: how to make living donations safe. *Liver Transpl.* 2006;12:920-927. Doi: 10.1002/lt.20734
13. Humar A, Ganesh S, Jorgensen D, Tevar A, Ganoza A, Molinari M, Hughes C. Adult living donor versus deceased donor liver transplant (LDLT versus DDLT) at a single center. Time to change our paradigm for liver transplant. *Ann Surg* 2019;270:444-51. Doi: 10.1097/SLA.0000000000003463
14. Gorgen A, Goldaracena N, Zhang W, Rosales R, Ghanekar A, Lilly L, Cattral M, Greig P, McCluskey S, McGilvray I, Selzner N, Bhat M, Selzner M, Levy G, Grant D, Sapisochin G. Surgical Complications after Right Hepatectomy for Live Liver Donation: Largest Single-Center Western World Experience. *Semin Liver Dis.* 2018;38:134-144. Doi: 10.1055/s-0038-1636932
15. Shio S, Yazumi S, Ogawa K, Hasegawa K, Tsuji Y, Kida M, Yamauchi J, Ida H, Tada S, Uemoto S, Chiba T. Biliary complications in donors for living donor liver transplantation. *Am J Gastroenterol.* 2008;103:1393-1398. Doi: 10.1111/j.1572-0241.2008.01786.x
16. Hashikura Y, Ichida T, Umeshita K, Kawasaki S, Mizokami M, Mochida S, Yanaga K, Monden M, Kiyosawa K. Japanese Liver Transplantation Society. Donor complications associated with living donor liver transplantation in Japan. *Transplantation.* 2009;88:110-114. Doi: 10.1097/TP.0b013e3181aaccb0
17. Iida T, Ogura Y, Oike F, Hatano E, Kaido T, Egawa H, Takada Y, Uemoto S. Surgery-related morbidity in living donors for liver transplantation. *Transplantation.* 2010;89:1276-128. Doi: 10.1097/TP.0b013e3181d66c55
18. Dayangac M, Taner CB, Yaprak O, Demirbas T, Balci D, Duran C, Yuzer Y, Tokat Y. Utilization of elderly donors in living donor liver transplantation: when more is less? *Liver Transpl.*2011;17:548-555. Doi: 10.1002/lt.22276
19. Grewal HP, Thistlewaite JR Jr, Loss GE, Fisher JS, Cronin DC, Siegel CT, Newell KA, Bruce DS, Woodle ES, Brady L, Kelly S, Boone P, Oswald K, Millis JM. Complications in 100 living-liver donors. *Ann Surg.* 1998;228:214-219. Doi: 10.1097/00000658-199808000-00011
20. Taketomi A, Morita K, Toshima T, Takeishi K, Kayashima H, Ninomiya M, Uchiyama H, Soejima Y, Shirabe K, Maehara Y. Living donor hepatectomies with procedures to prevent biliary complications.*J Am Coll Surg.* 2010;211:456-464. Doi: 10.1016/j.jamcollsurg.2010.04.018]
21. Aziz AM, Saleh S, Soliman HE, Shoreem H, Hegazy O, Taha M, Salem EH, Zakaria H, Hamdy S, Abdeldayem H, Ibrahim T, Abuelella K. Evaluation of surgical complications in 204 live liver donors according to the modified clavien classification system. *Egypt J Surg*2016;35:357-366
22. Kim SH, Kim YK, Lee SD, Lee EC, Park SJ. The Impact of a Surgical Protocol for Enhanced Recovery on Living Donor Right Hepatectomy: A Single-Center Cohort Study. *Medicine (Baltimore).* 2016;95: e3227. Doi: 10.1097/MD.0000000000003227
23. Azzam A, Uryuhara K, Taka I, Takada Y, Egawa H, Tanaka K. Analysis of complications in hepatic

right lobe living donors. *Ann Saudi Med.* 2010;30:18-24. Doi: 10.4103/0256-4947.59368

24. Kiuchi T, Tanaka K. Liver transplantation from living donors: current status in Japan and safety/long-term results in the donor. *Transplant Proc.* 2003;35:1172-1173. Doi:10.1016/s0041-1345(03)00138-6
25. El-Meteini M, Hamza A, Abdalaal A, Fathy M, Bahaa M, Mukhtar A, Abouelfetouh F, Mostafa I, Shaker M, Abdelwahab S, El-Dorry A, El-Monayeri M, Hobballah A, Sabry H. Biliary complications including single-donor mortality: experience of 207 adult-to-adult living donor liver transplantations with right liver grafts. *HPB (Oxford).*2010;12:109-114. Doi: 10.1111/j.1477-2574.2009.00142.x

TABLE, GRAPHIC AND FIGURE LEGENDS

Table-1 Summarized of the literature about Living liver donors who underwent Roux-en-Y HJ or Choledochojejunostomy due to major biliary complications following living donor hepatectomy

Graphic-1 Diagnostic and therapeutic algorithm for postoperative biliary complications in living liver donors

Graphic-2 Classification of living liver donors undergoing HJ according to anastomosis techniques

Figure-1 Different contrast-enhanced tomography images of postoperative biliary complications. Extrahepatic biloma (a), drainage of extrahepatic biloma via PTBD catheter (b), no communication between the biloma and the bile ducts (c), communication between the biloma and the minor segmnetal bile duct (d).

Figure-2 Pouchography showed that the contrast medium passes both to the left hepatic duct and to the common bile duct.

Figure-3 Demonstration regarding the search of obstructed or ligated bile duct via interventional radiological instruments (a). then, HJ was performed over the PTBD catheter (b).

Figure-4 Demonstration of intraoperative iatrogenic segment IV bile duct injury. HJ was performed over the transanastomotic biliary drainage catheter

Figure-5 Demonstration of the persistent bile leaks from stump despite PTBD catheter placement (a). then, side-to-side HJ was performed over the PTBD catheter (b). Thus, the common bile duct was preserved.

Figure-6 Demonstration of two separate HJ anastomosis on the same Roux limb

Figure-7 Demonstration of end-to-side HJ between roux limb and common bile duct . HJ was performed over the transanastomotic biliary drainage catheter

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