



Liver biochemistry profile, significance and endoscopic management of biliary tract complications post orthotopic liver transplantation

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Abstract

AIM: To correlate the significance of liver biochemical tests in diagnosing post orthotopic liver transplantation (OLT) biliary complications and to study their profile before and after endoscopic therapy.

METHODS: Patients who developed biliary complications were analysed in detail for the clinical information, laboratory tests, treatment offered, response to it, follow up and outcomes. The profile of liver enzymes was determined. The safety, efficacy and outcomes of endoscopic retrograde cholangiography (ERC) were also analysed.

RESULTS: 40 patients required ERC for 70 biliary complications. GGT was found to be > 3 times (388.1 ± 70.9 U/mL vs 168.5 ± 34.2 U/L, $P = 0.007$) and SAP > 2 times (345.1 ± 59.1 U/L vs 152.7 ± 21.4 U/L, $P = 0.003$) the immediate post OLT values. Most frequent complication was isolated anastomotic strictures in 28 (40%). Sustained success was achieved in 26 (81%) patients.

CONCLUSION: Biliary complications still remain an important problem post OLT. SAP and GGT can be used as early, non-invasive markers for diagnosis and also to assess the adequacy of therapy. Endoscopic management is usually effective in treating the majority of these biliary complications.

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Key words: Liver biochemistry; Biliary lesion; Ischemic

INTRODUCTION

Chronic liver diseases are an important cause of morbidity and mortality, the impact of which can be judged by the mortality rates due to these diseases. The highest deaths rates per 100 000 populations (in Europe) from chronic liver disease have been reported from Austria (37.9) while the lowest are those from Iceland (0.9)^[1].

Only a small fraction of these patients with end stage liver disease end up obtaining a suitable liver transplant. Despite standardization of biliary reconstruction, biliary complications after orthotopic liver transplantation (OLT) occur in 7% to 51% of cases and are an important cause of early and late postoperative morbidity and mortality^[2-11]. The commonest are bile duct strictures and biliary leaks. The biliary anastomosis has been rightly termed the 'Achilles' heel' of the OLT. Early diagnosis, followed by prompt and adequate treatment of biliary complications will not only reduce the unnecessary diagnostic procedures but will also be necessary to reduce hospital stays, morbidity, mortality and to improve outcomes related to OLT. Some of these patients may ultimately experience graft loss. Diagnosing and localizing these obstructive biliary complications post OLT could be very challenging to the clinician because of following reasons: (1) hepatic denervation leading to right upper quadrant abdominal pain, which is normally a feature of Charcot's triad is usually not seen in these patients^[12], (2) clinical symptoms that may be non-specific like fever, anorexia etc., (3) recurrence of the underlying pretransplant liver illnesses (like HBV, HCV reactivation, PSC recurrence etc.) or graft rejection which could lead to the elevation of liver biochemical parameters and can be misleading, (4)

epithelial casts fill up the biliary system thus making its visualization difficult by indirect imaging e.g. USG/CT scan, (5) the time for the biliary system to dilate upstream after being obstructed as compared to that of native biliary system.

Direct cholangiography by endoscopic retrograde cholangiography (ERC) or PTC still remains the gold standard to diagnose biliary complications; however it is an invasive procedure associated with morbidity. There are multitudes of studies reporting the role of endoscopy in diagnosis and management of biliary complications. Shah, *et al*^[13] demonstrated ERC to have a sensitivity and specificity of 53% and 98%; respectively in predicting overall biliary complications post OLT. But there is a scarcity of information in the literature evaluating the significance of serum levels of liver biochemistry panels, i.e. AST (aspartate aminotransferase), ALT (alanine aminotransferase), gamma glutamyl transferase (GGT), and serum alkaline phosphatase (SAP) in diagnosing these biliary complications. The present study had the primary aim to analyse the significance of deranged liver biochemistry for early suspicion of biliary complications, and also to study their profile during post endoscopic therapy and follow up.

Biliary complications post OLT are usually evaluated and treated now-a-days by ERC or by percutaneous transhepatic biliary drainage (PTBD); surgical intervention (including placement of T tube drainage)^[14] is reserved for lesions not managed by the above 2 techniques. ERC being the less invasive and safer intervention is generally the preferred mode of management^[2,3,15,16]. The secondary aim of this study was to study the efficacy, safety and outcomes of ERC in diagnosing and managing biliary complications post OLT from our centre.

MATERIALS AND METHODS

This study included 162 patients (109 males, age 52 ± 10 years; 53 females, age 49 ± 14 years) who underwent OLT between 1994 and 2004, 84 of these patients were transplanted between January 2002 through December 2004, and who were followed up regularly at Frankfurt Liver Transplantation Center. The mean time since OLT was 3 ± 2 years. Indications for OLT were as depicted in Figure 1. 154 patients received biliary continuity by choledocho-choledochostomy (40 with side-to-side technique and 114 with end to side technique). Eight patients underwent OLT with primary biliary reconstruction by Roux-en-Y choledocho-jejunostomy.

Routine measurements for liver biochemistry (ALT, AST, GGT, AP, and bilirubin) were performed in all patients being followed up post OLT at our centre, and also before and after initial ERC and on subsequent visits thereafter. Rise in values of these liver biochemical tests were further evaluated by doing ultrasonography (USG). All these patients except for those with obvious biliary leak underwent liver biopsy to exclude rejection and or reinfection of graft with hepatitis B or C virus. This was followed by cholangiography which was performed through the T tube, if present at the time of occurrence of biliary complications (as usually it is removed 6 wk post transplantation), ERC or PTC (if ERC had

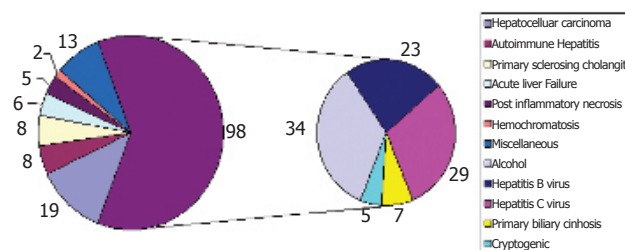


Figure 1 Indications of OLT.

failed or was not technically feasible e.g. patients with cholecystojejunostomy). ERC was carried out under standard conditions with Propofol and midazolam sedation. All the patients received preprocedure antibiotic prophylaxis 30 min before ERC with intravenous infusion of 500 mg ciprofloxacin. The diagnosis made by ERC, methods of therapeutic intervention, success rates and complications were analyzed. Centre practice of endoscopic treatment for post OLT biliary complications has been biliary sphincterotomy, balloon dilatation, placement of single or multiple (if indicated) plastic biliary endoprosthesis [routinely 10 French (F)]. Balloon dilatation of the stricture was done using 6-8 mm biliary balloon dilator (Maxforce; Microvasive Boston Scientific, Ireland). Fluoroscopic image of duodenoscope was used as the rough guide to assess the diameter of bile duct and the stricture. Dilatation is started with a 6 mm balloon and was upsized until attainment of adequate dilatation which is judged by disappearance of waist of dilating balloon under fluoroscopy control. The pressure used for dilation was 6-8 ATM/BAR for 2 min. Before placing all 10 F biliary endoprosthesis (stent), standard endoscopic biliary sphincterotomy was performed. On individual basis, patient's biliary strictures (anastomotic and non anastomotic e.g. ITBL) were treated sequentially with balloon dilation and/or consecutive stent placement. Those patients with biliary stents underwent elective biliary stent exchange every 10-12 wk for 12 mo. All patients were followed up regularly (every 3 mo) for signs and symptoms suggesting recurrence of biliary tract complications and other relevant issues associated with liver transplant throughout the study period. Success of the therapy performed was primarily assessed by evaluating the serum levels of liver biochemistry panel and secondarily on cholangiography of these biliary lesions before and after endoscopic treatment. PTBD was resorted to in cases of ERC failures (inability to reach the papilla endoscopically), which were performed by the endoscopists themselves.

Statistical analysis

Continuous variables are reported as medians and ranges. Categorical and continuous variables were compared by using the Fisher's exact test and Wilcoxon rank-sum test as appropriate^[17]. *P* values of 0.05 or less were considered as significant.

RESULTS

Out of all patients undergoing OLT, 40 (24.7%) underwent ERC to diagnose and treat biliary complications. The

Table 1 Liver biochemical profile in 40 Patients with biliary complications post OLT depending on time of presentation [Median, (range); mean \pm SD]

Liver biochemical parameters	Post OLT / before any biliary complication	On the day of presentation	Ist Follow-up (avg-1 mo) after endoscopic therapy	IIInd Follow-up (avg-3 mo) after endoscopic therapy
Bilirubin, mg/dL (< 1.3)	1.3 (0.5-13.7) 2.8 \pm 0.6	1.3 (0.4-35.0) 5.1 \pm 1.3	0.9 (0.3-29.0) 2.8 \pm 1.0	1 (0.4-26.2) 3.0 \pm 1.0
< 30 d	3.3	4.2	1.2	1.4
1-3 mo	1.1	1	0.7	0.7
4-12 mo	1.1	1.2	0.9	0.7
> 12 mo	0.8	1	1.2	1.1
AST, U/L (< 32)	22.5 (6.0-378.0) 54.4 \pm 14.1	48.5 (8.0-313.0) 75.4 \pm 12.2	20.5 (4.0-179.0) 38.8 \pm 6.5	29.5 (12.0-142.0) 42.3 \pm 5.7
< 30 d	37	64	18	25
1-3 mo	19	40	18	20
4-12 mo	20	46	20	25
> 12 mo	17	40	34	38
ALT, U/L (< 31)	26.5 (4.0-126.0) 98.8 \pm 22.0	90.5 (4.0-891.0) 145.7 \pm 33.1	30 (4.0-216.0) 46.1 \pm 8.0	24 (5.0-142.0) 37.2 \pm 5.7
< 30 d	125	102	23	25
1-3 mo	97	89	32	23
4-12 mo	26	97	24	24
> 12 mo	19	58	37	30
GGT, U/L (< 38)	74.5 (14.0-182.0) 168.5 \pm 34.2	236 (19.0-1748.0) 388.1 \pm 70.9	123 (9.0-1697.0) 282.2 \pm 63.9	117 (9.0-1294.0) 233.4 \pm 60.4
< 30 d	152	296	123	54
1-3 mo	82	157	96	38
4-12 mo	45	367	103	63
> 12 mo	39	182	235	266
Alkaline phosphatase, U/L (< 104)	107 (24.0-671.0) 152.7 \pm 21.4	242 (32.0-1799.0) 345.1 \pm 59.1	141 (47.0-1435.0) 270.7 \pm 51.3	127.5 (46.0-1267.0) 287.3 \pm 53.8
< 30 d	107	240	144	120
1-3 mo	130	100	138	117
4-12 mo	75	244	125	110
> 12 mo	107	263	286	423

median time between OLT and the first suspicion of biliary complications was 10 mo (range-1 to 54 mo).

The relevant liver biochemistry panel along with its time profile is summarized in Table 1. The initially elevated values of bilirubin, AST and ALT might be caused by ongoing reperfusion injury after OLT and/or early viral re-infection of the transplant or rejection (which was ruled out by performing liver biopsy). In patients presenting with biliary complications it was found that GGT values were found to be > 3 times (388.1 ± 70.9 U/mL *vs* 168.5 ± 34.2 U/L, $P = 0.007$) and SAP values > 2 times (345.1 ± 59.1 U/L *vs* 152.7 ± 21.4 U/L, $P = 0.003$) the immediate post OLT values. In the subgroup of patients with an early onset (≤ 3 mo) of biliary complications a normalisation of GGT and SAP at the end of treatment could be achieved. In contrast the group of patients with late onset (> 3 mo) of biliary complications showed no normalisation in SAP and GGT, although sufficient decrease in laboratory values was obvious as compared to these values before treatment. 70 different biliary tract complications were identified in these 40 patients. 20 (50%) patients developed only one biliary complication post OLT whereas in 14 (35%) patients two types of complications were seen and the remaining 6 (15%) patients had more than two complications. The number and type of complications are

Table 2 Type and number of complications in patients post OLT ($n = 40$)

No. of complications	No. of patients	Type of complication
1	20	10 biliary leakage (50%), 7 anastomotic strictures(35%), 1 vanishing bile duct syndrome,ITBL, and abscess (5%) each
2	14	5 anastomotic strictures and biliary leakage (36%), 5 anastomotic strictures and ITBL (36%), 4 other combinations (28%)
> 2	6	2 anastomotic strictures and stones and secondary cholangitis (33%), 4 other combinations (66%)

shown in Table 2.

Due to our experience and with regard to ERC findings, spectrum of biliary tract complications along with their treatment is classified as shown in Table 3. The most frequently diagnosed complication was isolated anastomotic stricture (IAS) in 24 (40%) of the patients. Upon analysing the complications on time profile, maximum number 22 (31.4%) were seen between 4-12

Table 3 Spectrum of biliary tract complications (*n* = 70) and their treatment post OLT

Classification	No. of complications <i>n</i> (%)	Type of treatment
<i>Isolated bile leak</i>	17 (24.3)	Stent +/- Stent exchange PTBD (2 patients) Primary re-operation (3 patients)
<i>Isolated anastomotic stricture</i>	28 (40)	Stent +/- Stent exchange Multiple stenting Bougienage, Balloon dilatation PTBD (2 patients) Primary re-operation (1 patients)
<i>Ischemic type biliary lesion (ITBL)</i>	6 (8.6)	Stent +/- Stent exchange Bougienage, Balloon dilatation
<i>Miscellaneous</i>	19 (27.1)	Stent +/- Stent exchange
Stones	7 (10)	Multiple stenting
Vanishing bile duct Syndrome	2 (2.8)	Bougienage, Balloon dilatation
Ductopenic rejection	1 (1.4)	Stone extraction
Abscess	5 (7.1)	
Secondary cholangitis	2 (2.8)	
Ampullary dyskinesia (SOD)	2 (2.8)	

SOD: sphincter of Oddi; PTBD: percutaneous transhepatic biliary drainage.

Table 4 Type of complications related to time post OLT

Time elapsed between OLD & complication	No. of complication	Type of complication (%)			
		IBL	IAS	ITBL	Misc.
≤ 30 d	20	11 (55.0)	7 (35.0)	1 (5.0)	1 (5.0)
1-3 mo	13	5 (38.5)	4 (30.1)	1 (7.7)	3 (23.0)
4-12 mo	22	1 (4.5)	11 (50.0)	2 (9.0)	8 (36.4)
> 12 mo	15	-	6 (40.0)	2 (13.3)	7 (46.7)
Total	70	17 (24.3)	28 (40.0)	6 (8.6)	19 (27.1)

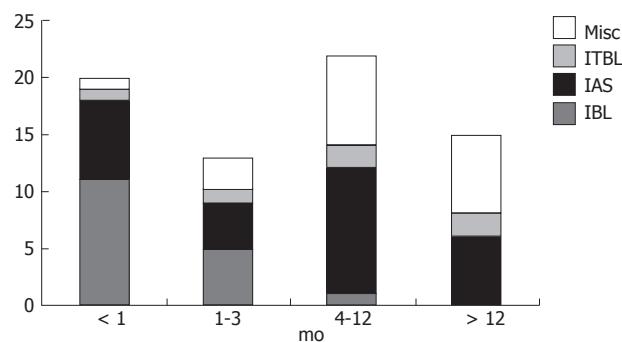
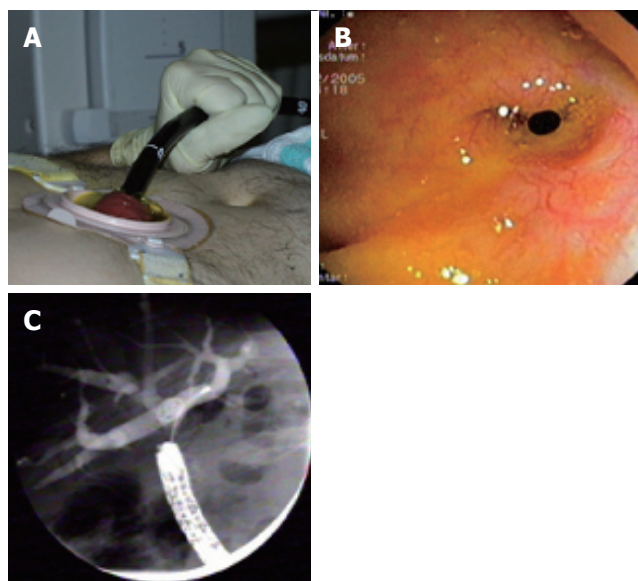
IBL: isolated bile leak; IAS: isolated anastomotic stricture; ITBL: ischemic type biliary lesion; Misc.: miscellaneous.

mo post OLT and amongst them IAS was the commonest one (Table 4 and Figure 2). Out of 6 ITBL patients 2 had hepatic artery thrombosis.

32 patients were treated endoscopically, 4 patients were treated via the percutaneous route while 4 patients had to be referred back for surgery. Nasobiliary drain (NBD) was placed in 4 patients and in 7 patients we had to resort to multiple 10 F biliary stent placements (2 stents).

Out of 32 endoscopically treated patients sustained success was achieved in 26 (81%) of cases and failure in 6 (19%). From this failed group, 3 patients needed to be re-operated upon with surgical revision of anastomosis, one died while waiting for retransplantation (because of intracerebral bleed), two are still under endoscopic treatment and out of these, 1 young patient with severe ITBL had a co-existent development of advanced lung carcinoma and therefore is unfit for retransplantation. To date, none of these patients had undergone retransplantation.

Total numbers of ERC performed were 302. Number of ERCs performed per patient ranged from 2 to 35, in 23 (72%) patients up to 4 ERCs were needed, and in the remaining 9 (28%) patients more than 4 ERCs were

**Figure 2** Type of complications related to time post OLT.**Figure 3** A patient with recurrent intrahepatic stones had a jejunal stoma made so as to reach the bilio-enteric anastomosis endoscopically. A: Jejunostoma; B: Endoscopic view of the bilioenteric anastomosis; C: Fluoroscopic film after stone extraction.

needed to achieve sustained success. There were 5 (1.65%) ERC related complications, 2 patients had mild pancreatitis i.e. abdominal pain with elevation of amylase and lipase (3 times the upper limit of normal) and only required conservative management including intravenous fluid and bowel rest. 3 patients presented with gastrointestinal bleeding from biliary sphincterotomy, out of which 1 required 2 units of blood transfusion whereas other 2 settled with endoscopic injection of epinephrine. There was no procedure related death.

31 (27.1%) out of 114 patients with end to end anastomosis, 4 (10%) of 40 patients with side to side anastomosis and 5 (62.5%) out of 8 with Roux en Y anastomosis developed biliary complications. All the 3 patients with total thrombosis of hepatic artery later developed IAS.

Late bile leaks are quite rare and we encountered only 1 patient presenting with this complication in the 5th month post OLT. Patient developed abscess and secondary cholangitis for which hepaticojejunostomy had to be performed.

7 (10%) patients had choledocholithiasis, most of

which was late complication developing mean 11.1 mo (range 3-26 mo) post OLT. 6 of these had anastomotic stricture distal to the stone which was dilated prior to stone extraction.

1 patient presenting with biliary abscess had bile leak communicating with biliary system so was managed with ERC sphincterotomy and drainage. Another 3 patients with liver abscess underwent CT-guided drainage while the one with late bile leak needed hepaticojejunostomy.

DISCUSSION

Various serum cholestasis indicating liver enzymes have been used to predict early outcomes post OLT^[18]. However there are mixed results about their utility in predicting biliary complications. One study reported that these non-invasive blood tests are often not sensitive and accurate enough to detect any biliary complications post OLT^[12]. While Hintze, *et al*^[19] had shown in 1999 that ITBLs may be diagnosed using alkaline phosphatase levels. Zoepf *et al*^[20] found that liver biochemical values do provide a clue towards the existence of post transplant biliary strictures but they further stated that it is of no help in differentiating various lesions like IAS or ITBLs. The drawback of their study design was that they performed biochemical values at the point of presentation of complications and it was not a continuum like in the present study in which these tests were performed immediately after OLT and thereafter regularly on every follow up and also before and after endoscopic interventions. In fact, ours is the first study in which such a detailed and systematic analysis of liver biochemical values have been reported in post OLT patients.

Contrary to the understanding we found GGT and SAP to be quite sensitive in predicting biliary complications on the other hand liver transaminases (AST\ALT) and bilirubin were not of any clinical significance in diagnosing these complications. Also there was significant fall in serum levels of SAP and GGT following endoscopic therapy to about 0.5 and 0.6 times the preprocedure levels respectively but not that of serum bilirubin. This was also reported by Mahajani *et al*^[21]. Thus GGT and SAP can be used as early, non-invasive and inexpensive markers for diagnosing biliary complications post OLT and can also be used to assess adequacy of endoscopic treatment in the group of patients presenting early (≤ 3 mo).

Abdominal USG is a non invasive, easily available, portable and an economical modality for imaging. However it has low sensitivity (59%-68%)^[20] and specificity; and also it has been shown to be a poor diagnostic technique to detect biliary obstruction post transplant unlike in non transplant population. It has been shown to have a sensitivity of around 50% in diagnosing biliary congestion^[22-24]. Various reasons, like acute onset occlusion not allowing sufficient time to allow dilatation of prestenotic biliary duct^[22-24], inability to assess biliary dimensions secondary to their filling with epithelial casts^[20] etc. have been implicated in this shortcoming of USG.

Although MRI and MRCP are highly sensitive and specific^[25] modalities to diagnose biliary complications and have been shown to be the most accurate indirect

techniques to do so^[20]. However they have certain drawbacks; expensive, not available at all the centres, will not be practically feasible to repeat during each follow up, contraindicated in certain patient groups (metallic implants, pacemakers etc.) and last but not the least, inability to perform any therapeutic intervention.

One of the studies has reported the occurrence of one third of all biliary complications within a month post OLT^[4] which was 28.5% in our study.

IBL has been reported to occur in the range of 1%-25% of patients post OLT^[9,26]. It has been arbitrarily subdivided in the literature in to, early-presenting within 1-3 mo and late- beyond 3 mo. IBL was found in 17 (24.3%) of our patients, 11 (64.7%) presented early within 1 mo while 5 (35.3%) manifested within 3 mo post OLT. ERC plus placement of biliary endoprosthesis with or without endoscopic sphincterotomy has been shown to achieve a success rate of over 90%^[7,27,28] in treating IBL. We failed to treat bile leakage in 1 patient (success rate 95.5%) while 3 other patients were shown to have complete dissociation and necrosis of common bile duct on ERC, hence were not considered for endoscopic therapy. These patients were managed with wide surgical debridement of necrotic and infected tissue and conversion to bilio-enteric anastomosis, similar to the management done in previous studies also^[26,29,30].

Placement of T tube during OLT is still a controversial issue. There are conflicting results about it in 3 different studies. Two of them demonstrated nearly double the rate of complications in the T tube group as against those without it (33% *vs* 15.5%)^[31,32]. However the third one showed that T tube prevented development of anastomotic strictures, 3.3% *vs* 20% in the group with and without T tube respectively^[33]. Pending this issue we still use a T tube in all of our patients undergoing OLT.

IAS are the most common late complications of OLT and usually follow IBL in chronology^[4,28]. Biliary strictures are usually seen in about 3-14% of all OLT and could constitute up to 40% of total biliary complications^[4,9,34,35]. It constituted 28 (40%) of biliary complications in our patient group and half of these presented between 4-12 mo post OLT. Use of ERC for treating anastomotic stricture in older studies had been disappointing^[36,37], however newer studies have reported the efficacy of endoscopic and percutaneous approaches in managing these complications^[5,36,38-40]. 2 failures of endoscopic treatment for anastomotic stricture in the present study had to undergo hepaticojejunostomy after 7 and 8 mo of OLT. Our success rate of 81% lies between 70%-100% as has been reported in previous studies^[21,39,41].

The severity and number of these anastomotic strictures will increase in coming times as more and more complex biliary anastomoses are being performed (living donor, split liver transplant, etc)^[42-45], mainly because of widening gap of demand and supply of the organ. This would pose tougher challenges to endoscopists in future. Though there are reports of placement of self expandable metal stents^[46,47] we did not place it in any of our patient as it is a controversial therapy in present scenario. It may lead to difficulties in performing surgeries later, if required and also usually undergoes stent blockages which are difficult

to manage. Recently one of the studies has reported placement of T-tube drainage for biliary strictures in patients with failed endoscopic or percutaneous therapy^[14].

Though the exact cause for ITBL is not known but has been postulated to be secondary to microcirculatory problems like ischemia-reperfusion injury. It was a late complication occurring after a mean time period of 33.8 mo (range-1 to 95 mo) post OLT and was observed in 6 (8.6%) which is comparable to the quoted figure of 2.5-19% in the literature^[19,48]. They have been found difficult to treat endoscopically or by PTC^[26,29] so was the case in our experience. Out of 6 patients with ITBL, 4 (66%) could be treated successfully, 1 had to undergo surgery while another one had an interesting clinical course. After 5 ERC with balloon dilatation and biliary stent placement with only partial relief, the patient underwent hepaticojejunostomy. This patient had excessively lithogenic bile and presented within few months with intrahepatic stones and secondary cholangitis. To prevent repeated surgeries for the same, a jejunal stoma (Figure 3) was created so as to reach the biliary-enteric anastomosis easily using the endoscope. Presently the patient gets routine endoscopy through the stoma for removal of biliary stones and sludge and for thorough flushing of the biliary tree every 3-4 mo and thus is saved from retransplantation and has undergone 74 endoscopic procedures till date in last 14 years.

Two (1.4 %) of all patients undergoing OLT manifested with significant dilatation of the bile duct, elevated liver biochemistry but no evidence of obvious obstruction on cholangiography which responded to endoscopic sphincterotomy. This was most probably papillary dyskinesia or sphincter of Oddi dysfunction. It has been reported to occur in 0-7% of patients^[12,49,50]. We did not perform biliary manometry in any of these patients to prove it. 1 patient had partial biliary cast.

In conclusion, biliary complications still remain an important problem in liver transplant recipients. A multidisciplinary approach is required to manage them. Serum GGT and SAP should be closely monitored and can be used as an early, non invasive and cheap markers for diagnosing post OLT biliary complications. They can also be of great help during follow up after endoscopic therapy and correlate with adequacy of therapy in patients presenting with early onset (< 3 mo) biliary complications post OLT. Endoscopic therapy is usually effective in managing majority of these complications but may require multiple procedures especially to treat strictures. Surgical intervention is required only in a few selected cases. There is a definite need of prospective multicenter studies to further evaluate the role of liver biochemical markers in predicting biliary complications post OLT.

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