ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2018; 23: 190-196
DOI: 10.12659/AOT.907240

Received: 2017.09.22
Accepted: 2017.12.07
Published: 2018.03.20

Clinical Analysis of Classification and Prognosis of Ischemia-Type Biliary Lesions After Liver Transplantation

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This study was funded by the Projects of Application Foundation and Frontier Technologies of Tianjin (14JCYBJC24800) and the National Natural Science Foundation of China (81370576)

Background: The aim of this study was to classify ischemia-type biliary lesions after liver transplantation according to their imaging findings and severity of clinical manifestations and to analyze the relationship between such classification and prognosis.

Material/Methods: We collected clinical data of patients with ischemia-type biliary lesions (ITBL) after liver transplantation in the Organ Transplantation Center, the First Central Hospital of Tianjin, from August 2012 to July 2013; all patients were classified according to their imaging findings and relevant clinical data to analyze the relationship between their classification and prognosis.

Results: The mean postoperative survival time, as well as the 1-, 3-, and 5-year survival rate, in Group ITBL showed statistical significance when compared with those in Group NITBL (log rank=12.13, P<0.001), but the mean postoperative survival times among the mild, moderate, and severe ITBL cases showed no statistical significance. The incidence rates of 1-, 3-, and 5-year adverse prognosis in Group ITBL showed statistical significance when compared with Group NITBL with <2% patients who had anastomotic biliary obstruction (log rank=277.06, P<0.001), among which the difference in the incidence rate of adverse prognosis between severe and moderate ITBL cases showed no statistical significance. The difference in the incidence rate of adverse prognosis between mild and moderate ITBL cases showed statistical significance (log rank=6.01, P=0.014), and the difference in the incidence rate of adverse prognosis between mild and severe ITBL cases showed statistical significance (log rank=10.98, P=0.001).

Conclusions: ITBL classification based on the severity of biliary imaging and bilirubin level can predict the prognosis of ITBL.

MeSH Keywords: **Liver Transplantation • Prognosis • Statistics as Topic • Transplantation, Homologous**

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/907240

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Organs that have been successfully transplanted many times include the kidneys, liver, heart, lungs, pancreas, intestine, and thymus [1]. Liver transplantation is thought to be the most effective way to treat end-stage liver diseases, including hepatic carcinoma [2], cirrhosis caused by harmful alcohol consumption, viral hepatitis B and C, and metabolic syndromes related to overweight and obesity [3]. In the last 4 decades, liver transplantation has developed from an experimental approach with a very high mortality to an almost routine procedure with good short- and long-term survival rates [4]. However, there still exist some complications that can threaten the survival of grafts, as well as affect patient quality of life [5]. Despite significant advances in orthotopic liver transplantation (OLT), biliary tract reconstruction is still a major source of complications [6], and ischemia-type biliary lesions (ITBL) is a severe, graft-threatening complications after liver transplantation [7], which is associated with worse graft survival and poor prognosis [8]. This complication develops in up to 25% of patients, with a 50% re-transplantation rate in affected patients [9], and there are 3 main outcomes. The first one is to achieve the final remission through biliary support treatment; the biliary support tube can then be removed, and liver function can return to normal. The second one needs to continue biliary support treatment to get more normal liver function, but the biliary support tube cannot be pulled out, which will form the status of long-term tube-bearing survival. The third treatment is ineffective, which may cause recurrent cholangitis and eventually lead to liver failure [10]. The dysfunction of the graft normally leads to re-transplantation and death, so treatment protocols should be developed as soon as possible to improve the patient survival rate. This study analyzed and classified the features of ITBL to achieve the goal of properly estimating the prognosis of ITBL, determining the treatment program, and improving the patient survival rate [11].

Material and Methods

Subjects

The clinical data of patients with ITBL after liver transplantation in the Organ Transplantation Center, the First Central Hospital of Tianjin, from August 2012 to July 2013 were collected and assessed, as well as the biliary imaging results such as T-tube cholangiography, endoscopic retrograde cholangiography (ERC), percutaneous trans-hepatic cholangiography (PTC), and magnetic resonance cholangiopancreatography (MRCP). This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of the First Central Hospital of Tianjin. Written informed consent was obtained from all participants.

Criteria of imaging classification

Using data from 124 ITBL patients diagnosed by clinical and imaging results, we performed the imaging severity classification, treatment strategy analysis, and prognostic assessment. Among the 124 ITBL patients, 98.3% had hilar bile duct stenosis and 93.2% had intrahepatic bile duct stenosis. According to the biliary imaging morphology and the total bilirubin level, these ITBL patients were divided into 3 categories: mild, moderate, and severe. Imaging scores and clinical criteria for ITBL after liver transplantation are shown in Table 1, and the criteria of mild, moderate, and severe ITBL are shown in Table 2.

Observation indexes

The mean postoperative survival time and the 1-, 3-, and 5-year incidence rates of adverse prognosis were recorded during the follow-up. Risk factors included anhepatic time, intraoperative use of erythrocytes and plasma, cold ischemic time of donor, and donor weight, and these were compared among the mild, moderate, and severe ITBL patients.

Table 1. Imaging and clinical criteria for ITBL after liver transplantation.

Score	Imaging evaluation		Total bilirubin level
	Hilar injury	Intrahepatic injury	
1 point	Stenosis occurred only at the joint of left and right hepatic ducts while not involved in the secondary bile duct	There was no intrahepatic lesion or only scattered lesions	The total bilirubin level was not normal while not beyond 2-fold
2 points	Unilateral hepatic duct stenosis, and stenosis involved in the secondary bile duct	Half hepatic duct existed severe lesions, but more than half hepatic duct was complete	The total bilirubin level was not normal and >2-fold, but not more than 100 umol/L
3 points	All the hepatic ducts occurred stenosis, and stenosis involved in the secondary bile duct	Intrahepatic biliary lesions involved in the whole liver, and less than half hepatic duct was complete	The total bilirubin level was not normal and >100 umol/L

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Table 2. Classification of ITBL after liver transplantation.

Classification	Points	Conditions
Mild ITBL	1–3	The hilar injury and intrahepatic conditions didn't exceed mild injury, and no obvious jaundice
Moderate ITBL	4–6	At least one item of hilar injury and intrahepatic conditions reached moderate injury, but no severe injury, and the bilirubin level was slightly elevated
Severe ITBL	7–9	At least one item of hilar injury and intrahepatic conditions reached severe injury, and the bilirubin level was severely increased

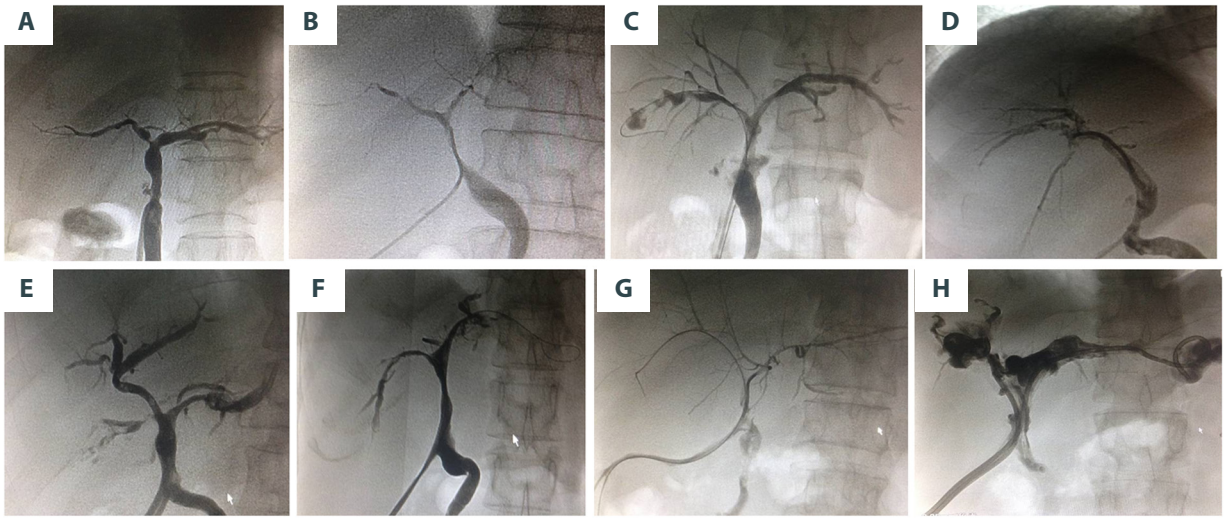

Figure 1. (**A**) Mild ITBL: only the opening of the right hepatic duct has stenosis; the bilirubin is normal and a biliary stent support is required (1+1=2 points). (**B**) Mild ITBL: only scattered intrahepatic lesions with stage expansion and local stenosis; stent support is required. Total bilirubin<30 umol/L (1+1+1=3 points). (**C**) Moderate ITBL: the right hepatic duct has stenosis; the bile duct dilatation and stenosis alternates in the right liver and show bead-like changes; the biliary tract tree in the left liver is still normal. Total bilirubin <40 umol/L (2+2+2=4 points). (**D**) Moderate ITBL: the left hepatic duct occurs stenosis, and the left biliary tract tree disappears. The right hepatic duct opening has stenosis, but the right hepatic bile duct is still intact. Total bilirubin <30 umol/L (2+2+1=5 points). (**E**) Severe ITBL: the main hepatic ducts occur stenosis, so long-term catheter support is required for drainage; the partial biliary tract tree in the anterior right liver lobe is normal. The patient survives bearing the tube; cholangitis is intermittent, and the liver function is abnormal. Total bilirubin <60 umol/L (3+2+2=7 points). (**F**) Severe ITBL: the main hepatic ducts occur stenosis, so long-term catheter support is required for drainage; the partial biliary tract tree can be seen in the liver. The patient survives bearing the tube; cholangitis is intermittent, and the liver function is abnormal. Total bilirubin <80 umol/L (3+3+2=8 points). (**G**) Severe ITBL: the biliary tract tree in the whole main liver trunk becomes thin and has stenosis. Partial end branches are stiff. The patient has been transplanted twice. Total bilirubin <100 umol/L (3+3+3=9 points). (**H**) Severe ITBL: the intrahepatic biliary tract tree disappears. The hilar biliary tract has cystic dilatation; the patient is waiting for re-transplantation. Total bilirubin >100 umol/L (3+3+3=9 points).

Statistical analysis

SPSS22.0 statistical software was used for the analysis. The measurement data are expressed as mean±standard deviation ($\bar{\chi}\pm s$). The comparison of the average values at the same time point among different groups was analyzed by one-way ANOVA. The LSD test was used for multiple comparisons, and the *t* test was used for intergroup comparisons. The Kaplan-Meier method was used to analyze survival time among patients with different classifications, with $P<0.05$ considered as statistical significance.

Results

Classification of ITBL

According to the classification criteria in Table 2, the 124 ITBL patients were divided into mild ITBL in 28 cases (22.6%), moderate ITBL in 59 cases (47.6%), and severe ITBL in 37 cases (29.8%). The imaging examples of different levels of ITBL are shown in Figure 1.

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Table 3. Relationship between ITBL classification and different risk factors.

Group	Mild ITBL (n=28)	Moderate ITBL (n=59)	Sever ITBL (n=37)	H	*P*
Anhepatic time (min)	51.79±10.1	53.69±25.7	56.08±24.5	1.277	0.528
Erythrocyte (U)	13.02±9.7	15.17±11.7	16.42±10.95	2.174	0.337
Plasma (ml)	2390.6±1036.6	2607.1±887.02	2813.5±1166.0	3.721	0.156
Cold ischemic time (min)	558.8±181.1	559.6±164.5	605.6±171.5	1.787	0.409

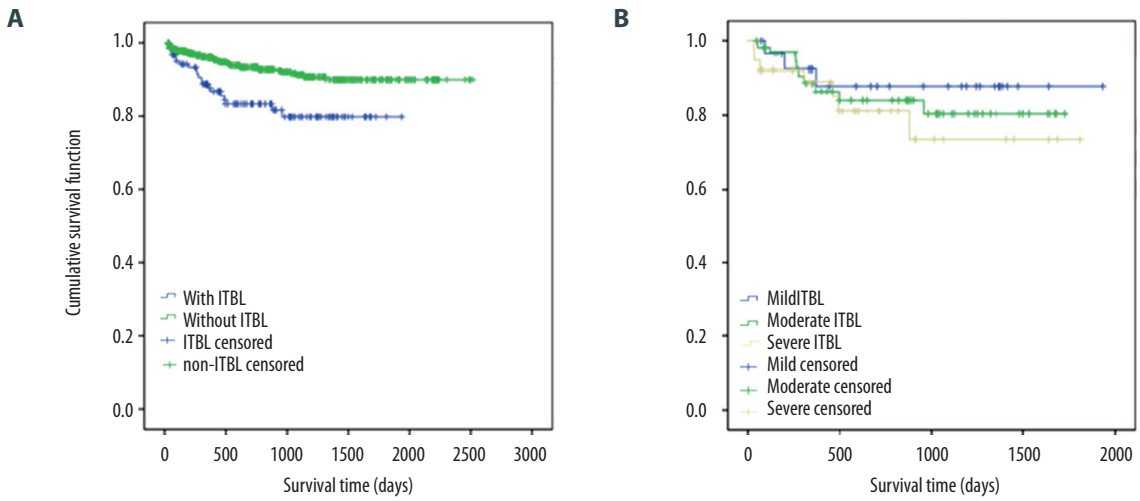

Figure 2. Comparison of survival times between Group ITBL and Group NITBL (**A**) and among the patients with different levels of ITBL (**B**).

Relationship between ITBL classification and different risk factors

The anhepatic time, intraoperative use of erythrocytes and plasma, cold ischemic time of donor, and donor weight were compared among the mild, moderate, and severe ITBL patients, and the differences showed no statistical significance (P=0.528, 0.37, 0.156, 0.409) (Table 3).

Relationship between ITBL classification and postoperative survival

At the end of the follow-up, all the 886 OLT recipients we investigated were divided into Group ITBL and Group NITBL and we analyzed their survival using the Kaplan-Meier method. The mean postoperative survival time in Group ITBL was 16.9.06±64.07 days, and the 1-year, 3-year, and 5-year survival rates were 87.7±3.1%, 79.8±4.2%, and 78.1±4.8%, respectively, exhibiting statistical significance when compared with those in Group NITBL (2314.44±29.02 days, 95.8±0.8%, 91.2±1.4%, and 90.0±2.3%, respectively, log rank=12.13, P<0.001) (Figure 2A).

The mean postoperative survival times in the mild, moderate, and severe ITBL patient groups were 1726.10±113.22 days, 1464.77±78.46 days, and 1442.43±124.87 days, respectively. The 1-year, 3-year, and 5-year survival rates in mild ITBL cases were 92.1±5.3%, 87.8±6.6%, and 87.8±6.6%, respectively; the 1-year, 3-year, and 5-year survival rates in moderate ITBL cases were 86.4±4.8%, 80.3±6.1%, and 80.3±6.1%, respectively; and the 1-year, 3-year, and 5-year survival rates in severe ITBL cases were 85.0±6.3%, 73.0±10.0%, and 73.0±10.0%, respectively (Figure 2B). For all results, we found no significant differences among the mild, moderate, and severe groups (mild *vs.* moderate: p=0.573; mild *vs.* severe: p=0.307; moderate *vs.* severe: p=0.555).

Relationship between ITBL classification and poor prognosis

Death, graft dysfunction, and long-term biliary stent treatment were considered as poor prognosis for analyzing the survival difference between Group ITBL and Group NITBL. The 1-, 3-, and 5-year incidence rates of adverse prognosis in Group ITBL were 24.7±3.9%, 66.2±4.5%, and 73.5±4.3%, respectively, and

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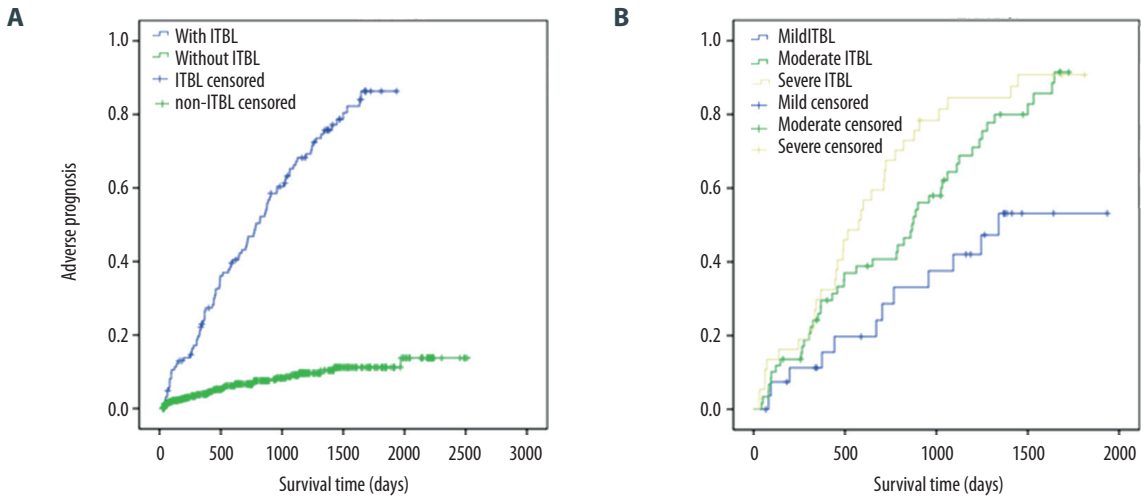

Figure 3. Comparison of incidence rates of adverse prognosis between Group ITBL and Group NITBL (**A**) and among the patients with different levels of ITBL (**B**).

those in Group NITBL were 4.2±0.8%, 8.1±1.4%, and 11.2±1.8%, respectively. The differences in this risk function was statistically significant (log rank=277.06, P<0.001) (Figure 3A).

The 1-, 3-, and 5-year incidence rates of adverse prognosis in mild ITBL cases were 15.5±7.1%, 42.0±10.2%, and 53.1±10.9%, respectively. The 1-, 3-, and 5-year incidence rates of adverse prognosis in moderate ITBL cases were 27.8±5.9%, 64.4±6.6%, and 91.4±4.5%, respectively; and the 1-, 3-, and 5-year incidence rates of adverse prognosis in severe ITBL cases were 32.4±7.7%, 84.6±6.1%, and 90.7±5.0%, respectively (Figure 3B). There was no significant difference in the incidence rate of adverse prognosis between severe and moderate ITBL cases, but the difference in the incidence rate of adverse prognosis between mild and moderate ITBL cases was statistically significant (log rank=6.01, P=0.014).

Discussion

ITBL after liver transplantation is unexplained and is characterized by intrahepatic and hilar biliary stricture and disappearance, which is an important part of biliary complications after liver transplantation. The criterion standard of diagnosing ITBL is trans-T tube PTC or trans-ERC cholangiography, which can show details of different lesions, such as biliary thinning, stenosis, expansion, or disappearance, in the non-anastomotic part of the donor liver [12]. It may be accompanied by liver function abnormalities, including increased levels of bilirubin, alkaline phosphatase, and glutamyl transpeptidase [13,14].

Previous studies have failed to provide definite conclusions regarding the classification of ITBL. Some studies divided it into extrahepatic type, intrahepatic type, and mixed type [15,16]. This classification based only on locations seems simple, but it cannot reflect the severity of ITBL. Most ITBL patients have both extra- and intrahepatic lesions, and only a small number of mild patients do not have intrahepatic lesions. However, regardless of intrahepatic lesions or extrahepatic lesions, they both have significant differences in the degree of severity. ITBL should be categorized from the perspective of prognosis, and the goal is to predict the 3 very different prognoses of ITBL: recovery, long-term survival, and graft dysfunction (i.e., liver failure).

There are differences in hilar biliary stricture and intrahepatic biliary stricture. Firstly, ITBL appears much more commonly in the porta hepatis than inside the liver. Secondly, the difference in the anatomical blood supply between these 2 parts is significantly different. The classic anatomy of the extrahepatic biliary duct is from the left and right hepatic ducts to the left and right liver lobes, and the right and left hepatic ducts fuse into the general hepatic duct. The intrahepatic bile duct can be further subdivided into the greater and smaller bile ducts [17,18]. The epithelium of grade 4–5 biliary ducts is lined with the basement membrane, together with tight junctions among the cells and microvilli extending into the bile duct [19]. The vascular plexus of the hilar biliary system is supplied directly through the arteries, consisting of the right and left hepatic arteries and indirect gastroduodenal artery-originated branches [20,21]. The surface veins on the bile duct closely attach to the arterial plexus and drain into other veins. The blood in the peripheral vascular plexus of the smaller bile duct connects to the sinusoid, which then connects to the portal vein system through both the lobular branches and the peri-biliary branches. Through the very small capillaries in

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the portal area, oxygen and nutrients can finally be transported to the sinusoid through the distal arterial branches of the hepatic artery [22]. In severe ITBL patients, all the hilar biliary ducts may collapse [11,23]. If there is simple hilar stenosis instead of intrahepatic injury, which is equivalent to a hilar biliary obstructive disease, biliary stent treatment can be performed for control. The degree of destruction of the hilar biliary tract determines whether the stent can be removed from ITBL patients, and the degree of the intrahepatic biliary injury determines whether ITBL patients will have graft dysfunction. The intrahepatic biliary blood supply can be easily recovered through the intrahepatic lobular tissue and portal blood supply. However, the destruction of the intrahepatic biliary duct caused by cholangitis is fatal. Patients with liver transplantation need life-long immunosuppressive agents, so once the support tube is blocked in such ITBL patients, it is extremely easy to cause cholangitis. Repeated biliary tract infections then further injure the biliary duct (repair and then re-stenosis), thus forming a malignant cycle of stenosis, obstruction, infection, scar repair, and aggravated stenosis [23]. Therefore, the treatment of patients with moderate ITBL (i.e., with severe hepatic portal stenosis but sufficient liver function to ensure liver metabolism) should break this malignant cycle; infection is the most easily controlled clinical aspect, so preventing the occurrence of infection is as crucial as anti-infective treatment [24,25].

The significance of the classification in this study for treatment lies in that we propose the patient group with moderate ITBL, and hope clinicians to pay more attention to this group. The prognosis of such patients can be infection-induced death or good quality of life. Many people think that once ITBL occurs, no treatment should be performed, so studies, treatment, or care toward this group of patients is ignored. It is often thought that there is no therapeutic meaning in such patients, and a necessary liver transplantation is irresponsible. In fact, it is precisely this type of patient who needs the most careful treatment, immunosuppressive agent adjustment, infection control, and biliary drainage observation. Improving biliary interventional treatment techniques, developing new biliary support equipment, and extending graft survival can even cure them.

In this study, the classification of ITBL is based on our retrospective analysis. The sample is relatively limited, and the standards among different groups still need to undergo long-term evolution and adjustment. However, classifying ITBL is of great necessity and requires more clinician attention so as to refine the diagnosis, standardize the treatment, and improve the prognosis. ITBL is not a surgical complication, and due to its higher morbidity and poorer prognosis, it is known as the "Achilles heel" of liver transplantation; furthermore, its pathogenesis is still unclear. ITBL should be studied as a separate disease, and transplantation surgeons should focus more attention on such studies and treatment of ITBL rather than feeling discouraged and ignoring it.

Conclusions

By analyzing the features of ITBL classification, our results suggest that ITBL classification can be used to predict the prognosis of ITBL based on the severity of biliary imaging and bilirubin level, and further contribute to determining the treatment program and improving survival of ITBL patients.

Conflicts of interest

None.

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