의학석사 학위논문

Clinical Outcomes According to Anatomical Classification of Biliary Strictures Including Intrahepatic Biliary Tree in Adult Living Donor Liver Transplantation

성인간 생체간이식 후 담도 협착의 해부학적 분류에 따른 예후

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서울대학교 대학원

의학과 외과학

박 한 상

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지도 교수 이 남 준

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의학과 외과학
박 한 상

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위 원 장 ______________________ (인)

부위원장 ______________________ (인)

위 원 ______________________ (인)

Abstract

Although intrahepatic biliary stricture (IHBS) after living donor liver transplantation (LDLT) is uncommon, IHBS requires intensive care. The purpose of this study is to classify anatomical types of biliary strictures including both anastomotic stricture (AS) and IHBS after adult right liver LDLT and to evaluate their prognosis. According to cholangiography, biliary strictures requiring interventions were classified into 4 types based on level and number of involved ducts; type 1 (anastomosis), type 2 (the 2nd order branch; a. single / b. two or more / c. extended to the 3rd order branch), type 3 (multifocal), type 4 (diffuse necrosis). IHBS was defined as non-anastomotic stricture (type 2, 3 and 4). We evaluated incidence of AS and IHBS, intervention frequency per year, biliary intervention free period more than one year (IFY) after last intervention, clinical relapse after IFY and grafts survival outcomes according to types of biliary stricture. The mean follow-up period was 62.0 (1.7-118.6) months. Among 692 adult right liver LDLT recipients, the rates of AS and IHBS were 17.6% (n=122) and 11.0% (n=76). The most common type of biliary stricture was type 1 (n=122, 61.6%) followed by type 2 (n=66, 33.3%), 3 (n=6, 3.0%) and 4 (n=4, 2.0%). The most common type of IHBS was type 2 (86.8%; 2a (10.5%), 2b (19.7%), 2c (56.6%)), followed by 3 (7.9%) and 4 (5.3%). Intervention frequency per year was significantly different according to types; 1 (2.3), 2a (2.3), 2b (2.8), 2c (4.3), 3 (5.7) and 4 (9.5), respectively (P=0.001). IFY was different according to types; type 1 (84.4%), 2a (87.5%), 2b (86.7%), 2c (72.1%), 3 (66.7%), and 4 (25.0%), respectively (P=0.032). Among IHBS group, clinical relapse after IFY was more common in type 3 and 4 (60.0%) than type 2 (31.8%) (*P*=0.026). The graft survival rate of type 3 and 4 (80.0%) was significantly lower than others (*P*=0.001). In conclusion, the incidence of IHBS was not rare in adult right liver LDLTs. Although type 3 and 4 IHBSs were uncommon, they required more intensive care with poorer graft survival rates.

Keyword : Intrahepatic biliary stricture, Living donor liver transplantation
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Chapter 1. Introduction

Living donor liver transplantation (LDLT) is the ultimate treatment for end−stage liver disease and an accepted therapeutic option for acute liver failure and primary liver tumors. In South Korea, about 20 cases of LDLT per million population are implemented in a year, which is the highest rate in the world [1−2]. Among the various complications that can occur after LDLT, biliary complications account for the largest proportion, so called “Achilles Heel” of liver transplantation. Although there are differences between literatures, it is reported that biliary complications after liver transplantation is more common in LDLT than deceased donor liver transplantation (DDLT) (19−32% versus 13%) [3−6]. In the case of asymptomatic mild biliary stricture, observation without intervention may be possible. However, depending on the degree or pattern of biliary strictures, the prognosis varies from cases that are resolved with one or two interventions to cases that result in failed interventions that lead to retransplantation or death [7−9]. Biliary strictures are a significant source of long−lasting morbidity after liver transplantation and sometimes causes mortality.

Although intrahepatic biliary stricture (IHBS) is not common, it is clinically important because it requires intensive care and shows poor response to treatment. IHBS generally has a lower incidence compared to anastomotic stricture (AS) in liver transplantation. However, the level and extent of strictures appear in various forms at initial presentation that it is difficult to establish a treatment strategy. For this reason, while AS shows a higher treatment success rate (70−100%), IHBS often requires more repeated endoscopic and radiologic interventions as well as retransplantation for a longer follow up period [4,7,9−13]. In a previous study, Buis et al. presented a new anatomical classification of non−anastomotic biliary stricture that occurs after brain−dead donor liver transplantation [14], Lee et al. developed a classification of IHBS and evaluated prognosis in donation after circulatory death (DCD) liver transplantation [7].

There have been few reports of IHBS studies targeting LDLT to date. Therefore, the purpose of this study is to classify IHBS after LDLT and to evaluate the prognosis to establish an appropriate management strategy for individual patients with IHBS.

Chapter 2. Methods

Patients

Adult patients (≥18 years old) who underwent LDLT at Seoul National University Hospital in Korea between August 2011 and December 2018 were included in the study. During this period, 719 adult LDLTs were performed, and 27 cases using left liver graft were excluded. Among 692 adult patients of right liver LDLTs, 210 patients who were diagnosed with biliary stricture were retrospectively reviewed. Among 210 patients, 12 patients were excluded because of lack of follow-up cholangiography (n = 11) and limited access to medical record (n = 1). Finally, 198 patients who underwent biliary intervention due to biliary stricture were enrolled in this study (Figure 1). During this period, these patients were followed up every 3-6 months post operatively, unless they have any problems.

Stricture was defined when liver function test results was abnormal without evidence or suspicion of rejection and stricture was confirmed by either percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography. In duct-to-duct anastomosis, endoscopic retrograde intervention was the first attempt to resolve the strictures. If it failed, percutaneous transhepatic approach was tried. In hepaticojejunostomy cases, percutaneous transhepatic approach was tried first. For IHBSs, we did not apply surgical treatment. An initial intervention applied to navigate and decompress the upstream ducts. After then, duct dilatation was tried within one week. If there is no clinical issue related to biliary stricture, we usually waited 3 months after the previous session to stabilize the tract and patient condition. If not, we applied more frequent sessions of biliary intervention to solve the clinical issues related to biliary stricture. The mean follow−up period of this cohort was 62.0 (1.7−118.6) months.

Classification of biliary stricture after LDLT

The classification of biliary strictures was determined according to anatomical locations and numbers through analysis of interventional cholangiography. In the analysis, two radiologists and three surgeons were participated.

Biliary strictures were classified into 4 types based on levels and number of involved branches (Figure 2). AS was classified as type 1 (Figure 3A). If AS was definite at the level of the 2nd order branches in cases of reconstruction of double ducts, it was also classified as type 1. When biliary stricture was presented at the 2nd order branch level and it was not AS, it was classified as type 2. Type 2 was subclassified into 3 subtypes based on the number and extent of involved branches. Type 2a is IHBS on single duct (one of the 2nd order branches) (Figure 3B). Type 2b is IHBSs on two or more ducts (Figure 3C). Type 2c is IHBSs extended to the 3rd order branch (Figure 3D). Type 3 was defined as multifocal type at multi−level IHBSs with skip lesions (Figure 3E). Finally, diffuse necrosis type was classified as type 4 (Figure 3F). IHBS was defined non−anastomotic stricture as type 2, 3 and 4.

We evaluated frequency of biliary interventions per year and intervention-free period at any time point after biliary intervention initiation as a prognosis of biliary stricture. Resting period without biliary intervention more than one year after the last intervention was defined as the intervention free year (IFY) present. Clinical relapse was defined as a restart of biliary intervention due to symptoms or signs related to biliary stricture after IFY. Finally, we evaluated grafts and patients survival outcomes according to types of biliary stricture.

Statistical Analysis

Univariate analysis with the chi square test and ANOVA for categorical variables was performed and expressed as numbers and percentages. For multivariate analysis, factors which were significant in univariate analysis and age and sex were put into a logistic regression analysis to determine associated factors for severe types of biliary stricture. Continuous variables without equal variance were compared using Student's t-test and expressed as mean ± standard deviation. Categorical variables were expressed as numbers with percentages. Survival rates were calculated using the Kaplan-Meier method and the data of survival rates and clinical relapse incidence after IFY were compared using the log-rank test. A P-value ≤ 0.05 was considered statistically significant. Statistical analysis was done using SPSS software (version 25; SPSS Inc., Chicago, IL).

Ethical consideration

The institutional review board of Seoul National University Hospital approved this study (institutional review board no. 2011-117-1173). The requirement for informed consent was waived because of the retrospective nature of the study.

Chapter 3. Results

The clinical characteristics of recipients with biliary strictures

Table 1 shows the clinical characteristics of 198 cases of biliary strictures. The mean ages of donor and recipient were 34.7 ± 11.3 and 55.5 ± 9.1 years, respectively. There were more males in both groups (65.7% and 76.8%). Among the recipients, the most common underlying liver disease was hepatitis B virus (n=125, 63.1%). The mean medical model for end-stage liver disease (MELD) score was 14.2 ± 7.0. Hepatocellular carcinoma was the most common indication for liver transplantation (n=134, 67.7%). Among all cases, 14.6% of the biliary strictures were occurred after ABO incompatible liver transplantation. 48.0% of donor hepatectomy was laparoscopically performed. The average operation time of liver transplantation was 397.3 ± 101.8 minutes, and the average cold ischemic time and warm ischemic time were 84.8 ± 29.8 minutes and 31.1 ± 13.5 minutes. Surgical complications were noted in total number of 29 patients; 10 cases (5.1%) showed post-operative hepatic artery thrombosis before diagnosis of biliary stricture. Portal vein complications (n=12, 6.1%) included 5 cases of portal vein thrombosis and 7 cases of portal vein stenosis. Hepatic vein thrombosis was presented in 3 cases and the other 4 hepatic vein complications were hepatic vein stenosis among hepatic vein complications (n=7, 3.5%). Liver biopsy was performed on patients suspected of rejection, and rejection was defined as a case with a rejection activity index (RAI) score of 3 or higher according to Banff grading [28]. Total number of 29 patients (14.6%) showed a biopsy proven graft rejection.

Incidence of biliary strictures according to the type of biliary strictures

The overall incidence of biliary stricture including IHBS was 28.6% in right liver adult LDLTs (n=198). Among the BS, incidence of IHBS was 11.0% which was lower than that of AS (17.6%). The most common type of stricture was type 1 (n=122, 61.6%) followed by type 2 (n=66, 33.3%), 3 (n=6, 3.0%) and 4 (n=4, 2.0%). The most common type of IHBS was type 2 (n=66, 86.8%), followed by 3 (n=6, 7.9%) and 4 (n=4, 5.3%). Type 2 sub-classification consisted of 2a (n=8, 10.5%), 2b (n=15, 19.7%), 2c (n=43, 56.6%). Among IHBS, the incidence of type 2c was dominant, more than a half of cases.

When the clinical characteristics among the types of biliary strictures were compared, donor age was significantly different among types (P=0.0031), the incidence of autoimmune hepatitis was significantly higher in type 3 and 4 (P=0.021) and the rate of hepatic artery thrombosis was significantly higher in type 4 (P<0.001) (Table 2).

Prognosis of biliary strictures according to the type of biliary strictures

The biliary intervention free survival after transplantation was analyzed using the Kaplan-Meier method (Figure 4) and median time to the 1st symptomatic biliary stricture were within 1 year in all types of biliary stricture. The overall median onset time of BS was 177 days after transplantation and there were no statistically significant differences in biliary stricture onset time among types of BS (P=0.152) (Table 3). The earliest onset of BS was occurred at 13 days postoperatively and the latest onset was 2489 days after transplantation.

Intervention frequency was significantly different among types of biliary stricture (Figure 5) (P=0.001). Type 4 biliary stricture required the most frequent interventions per year (9.5), followed by type 3 (5.7). IFY was different among types of biliary strictures; type 1 (84.4%), 2a (87.5%), 2b (86.7%), 2c (72.1%), 3 (66.7%), and 4 (25.0%), respectively (P=0.032) (Table 3). More than 50% of patients with type 3 and 4 experienced symptomatic relapse after IFY (Figure 6A). Among IHBSs, the rates of clinical relapse after IFY in type 3 and 4 were significantly higher than type 2 (31.8%) (P=0.026) (Figure 6B).

During follow-up period, there were 27 mortalities among 198 adult right liver LDLT recipients (13.6%) which did not show statistically significant differences among the types of biliary stricture; type 1 (89.3%), 2 (81.8%), and 3 and 4 (80.0%) (Figure 7A) (P=0.295). However, the graft survival rate of patients with type 3 and 4 biliary strictures was significantly lower than those of other types of biliary strictures (P=0.001) (Figure 7B).

Chapter 4. Discussion

To our knowledge, this is the first study to analyze IHBS classification in LDLT patients. In this particular LDLT cohort, multifocal type IHBS (type 3) and diffuse necrosis type IHBS (type 4) required persistent need of interventions, and the intervention free period was less than type 2 IHBS and type 1 AS. In addition, there were more clinical relapses in those type 3 and 4 patients, which is highly likely to impair patients' quality of life. Since types 3 and 4 IHBS have a higher risk of graft failure than other types, more careful attention is needed and early re-transplantation might be considered in case of deterioration.

Lee et al. reported that multifocal type IHBS and diffuse necrosis type IHBS showed poor prognosis in DCD liver transplantation [7]. Since LDLT mainly uses the right or left hemiliver as a graft in adults, it is clearly different in the surgical method including bile duct anastomosis compared to DCD liver transplantation which uses a whole liver. In addition, we used detailed sub-classification of the 2nd and 3rd order branch level strictures; type 2a, 2b and 2c, which were classified all together into 'confluence type' in the previous study. The present study's IHBS classification was technically based on stricture sites, i.e., anastomosis or level and number of intrahepatic biliary tree. The outcome of treatment and graft survival was well reflected according to this classification.

Despite the remarkable advances in the surgical techniques, immunosuppressive therapy and postoperative care including complication management, biliary stricture after LDLT remains unsolved major cause of morbidity and mortality [2, 15]. As previous studies reported that the incidence range of biliary stricture after LDLT was 13−36%, our study showed that incidence of biliary stricture including IHBS in adult right liver LDLTs was 28.6% [3−6]. The incidence of IHBS in LDLT was uncommon compared to AS in LDLTs and IHBS in DDLTs. That would be related to relatively shorter cold ischemic time and younger live donors in LDLTs.

We hypothesized before data analysis that type 1 biliary stricture of AS would have the best prognosis in all outcomes. Although not statistically significant, type 1 showed the possibility of more frequent clinical relapse (33.6%) than type 2a (12.5%) (P=0.436). It was analyzed whether double duct anastomosis, which was included as type 1 as one of these causes, might have had an effect. Among type 1 patients, double duct accounted for a total of 23.8%, and there was no significant difference in other results including IFY present between single duct anastomosis and double duct anastomosis (Supplement Table 1). On the other hands, type 1 of AS showed more frequent clinical relapse after IFY than type 2a of single duct in the 2nd order branch. This might be related to selection bias of this study cohort with symptomatic biliary strictures and biliary interventions. Single duct stricture usually shows attenuated symptoms and signs related to biliary stricture than AS because of another intact and functioning biliary tree.

In the previous study, anatomic variants of donor's right posterior bile duct influenced the biliary complications of recipients in adult right liver LDLT [27]. We analyzed the outcomes of right posterior duct stricture among patients with sub−classification of type 2 and type 1 biliary strictures. However, in our cohort study, there were few cases of biliary stricture only in the right posterior bile duct among type 2 and type 1.

IHBS in LDLT were related to consequences of hepatic artery complications or ABO incompatible liver transplantation [19, 23, 25]. However, recent advances of surgical techniques as well as perioperative care reduced the incidence of hepatic artery complications and proper desensitization protocol in ABO incompatible LDLTs attenuated severity and reduced incidence IHBS [24].

In our cohort analysis, the rates of hepatic artery complications and autoimmune hepatitis were higher in severe damage of IHBS types, 3 and 4. IHBSs without hepatic artery thrombosis have been reported to be rare in DDLT [19]. Although the number of cases was small, hepatic artery thrombosis showed potential as an associated factor to the occurrence of diffuse necrosis type IHBS from this study. Since blood supply to the major intrahepatic bile duct is derived solely from the hepatic artery, this theory seems reasonable that further large scale of research should be considered.

Underlying disease like autoimmune hepatitis which has potential activity of immunological attack to the graft was more frequently observed in patients with type 4 IHBS. Although the cause of IHBS has not yet been clearly elucidated, one of the suggested varieties of possible causes is the resultant endothelial cell damage during cold preservation that activate a coagulation cascade and subsequent thrombosis [16, 17]. It was also found that donor warm ischemia increased the incidence of ischemic type stricture in controlled DCD liver transplantation [18]. However, in the results of this study, cold ischemic time and warm ischemic time were not identified as statistically significant factor because of very short ischemic time in LDLTs. As other related factors, autoimmune hepatitis and primary sclerosing cholangitis have been suggested in previous studies [20-21]. Because there was no primary sclerosing cholangitis in this study, so there was a limitation to verifying the statistical significance.

It seems clear that type 3 and 4 are a severe type of biliary stricture and have worse prognosis than other types of biliary strictures in terms of graft survival outcomes and impair the patient's quality of life in terms of more frequent interventions and clinical relapse even after IFY. Type 2c was the most frequent IHBS and considered to be relatively worse outcome than type 1 of AS, and type 2a and 2b of IHBS although it showed a similar graft survival outcome. Further detailed analysis to figure out any statistically significant results regarding intervention outcomes, type 3 and type 4 biliary stricture showed poor graft survival outcome at the results than type 2c (Supplement Figure 1) (P=0.003). For this reason, we defined these types 3 and 4 as 'severe' type of IHBS' compared to types 2a and b as 'mild' type of IHBS which were comparable outcome to type 1 of AS. Type 2c was defined as 'moderate' type of IHBS which was less difficult to control than severe type of IHBS (Supplement Table 2). However, there was no significant difference between type 2c and other IHBS in terms of clinical relapse (Supplement Figure 2). In addition, we analyzed associated factors with severe types of biliary stricture were autoimmune hepatitis, donor's sex (female), and hepatic artery thrombosis in multivariate analysis (Supplement Table 3). However, this study has small sample size, especially in severe type of IHBS. The associated factors related to severe type of IHBS should be evaluated more in prospective large cohort studies.

At our institution, laparoscopic donor hepatectomy has been performed in earnest since 2015 and is currently being performed routinely [22, 26]. While conducting this study, we wondered whether factors that can be affected by laparoscopic maneuver like warm ischemia time during donor surgery affects incidence of biliary strictures [22]. However, this study has a limitation of retrospective nature analysis, small cohort of a single center and only in adult right liver LDLTs. In this regard, a more in-depth analysis of the associated factors related to the occurrence of IHBS is planned in the future.

The strengths of this study were as follows; this was the first try to classify IHBS in adult LDLT series, analyzed the outcomes according to this classification, and came from a well-established large number LDLT center and biliary interventions. On contrary, this study had several limitations; it was a retrospective study of a small sample size with patients having symptomatic biliary strictures based on cholangiography. It was also limited to analysis of adult right liver LDLT series. Thus, additional research with large prospective cohort is needed to validate this classification in the future. If this kind of effort is valuable in real world practice, the extended classification including left liver LDLT can be proceeded.

In conclusion, IHBS was not rare in adult right liver LDLTs. Although severe type of IHBS (type 3 and type 4) was uncommon, they required more frequent interventions with less resting period and the graft survival rates of type 3 and 4 IHBS were eventually worse. This classification of biliary stricture including IHBS in right liver LDLTs gave more information related to prognosis and help to guide a treatment plan of IHBS for both patients and physicians regardless of causes of IHBS.

Bibliography

1. IRODaT: International Registry in Organ Donation and Transplantation. World liver transplant from living donors 2019 (PMP). Available at: https://www.irodat.org/?p=database
2. Boeva I, Karagyozov PI, Tishkov I. Post-liver transplant biliary complications: Current knowledge and therapeutic advances. World J Hepatol 2021; 13(1): 66-79
3. Calne RY, McMaster P, Portmann B, Wall WJ, Williams R. Observations on preservation, bile drainage and rejection in 64 human orthotopic liver allografts. Ann Surg 1977; 186: 282-290 [PMID: 329780 DOI: 10.1097/00000658-197709000-00006]
4. Moser MA, Wall WJ. Management of biliary problems after liver transplantation. Liver Transpl 2001;7(Suppl):S46-S52.
5. Verdonk RC, Buis CI, Porte RJ, van der Jagt EJ, Limburg AJ, van den Berg AP, et al. Anastomotic biliary stictures after liver transplantation: causes and consequences. Liver Transpl 2006;12:726-735.
6. Akamatsu N, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. Transpl Int 2011;24:379-392.
7. Lee HW, Suh KS, Shin WY, Cho EH, Yi NJ, Lee JM, Han JK, Lee KU. Classification and prognosis of intrahepatic biliary stricture after liver transplantation. Liver Transpl. 2007 Dec;13(12):1736-42. doi: 10.1002/lt.21201. PMID: 18044761.
8. Coté GA, Slivka A, Tarnasky P, Mullady DK, Elmunzer BJ, Elta G, et al. Effect of covered metallic stents compared with plastic stents on benign biliary stricture resolution: A randomized clinical trial. JAMA 2016;315:1250–1257. doi: 10.1001/jama.2016.2619.
9. Lee HW, Shah NH, Lee SK. An update on endoscopic management of post-liver transplant biliary complications. Clin Endosc 2017;50:451–463. doi:10.5946/ce.2016.139.

10. Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. Liver Transpl 2008; 14: 759-769 [PMID: 18508368 DOI: 10.1002/lt.21509]

11. Arain MA, Attam R, Freeman ML. Advances in endoscopic management of biliary tract complications after liver transplantation. Liver Transpl 2013; 19: 482-498 [PMID: 23417867 DOI:10.1002/lt.23624]

12. Balderramo D, Navasa M, Cardenas A. Current management of biliary complications after liver transplantation: emphasis on endoscopic therapy. Gastroenterol Hepatol 2011; 34: 107-115 [PMID:20692731 DOI: 10.1016/j.gastrohep.2010.05.008]

13. Choi JH, Lee SK. Percutaneous transhepatic cholangioscopy: does its role still exist? Clin Endosc 2013; 46: 529-536 [PMID: 24143316 DOI: 10.5946/ce.2013.46.5.529]

14. Buis CI, Verdonk RC, Van der Jagt EJ, van der Hilst CS, Slooff MJ, Haagsma EB, Porte RJ. Nonanastomotic biliary strictures after liver transplantation, part 1: Radiological features and risk factors for early vs. late presentation. Liver Transpl 2007; 13: 708-718 [PMID:17457932 DOI: 10.1002/lt.21166]

15. Yoshida EM, Haque M, Scudamore CH. Adult live donor liver transplantation: routine, commonplace, standard care for end stage liver disease (we hope) Ann Hepatol. 2010;9:89–90.

16. Caldwell-Kenkel JC, Currin RT, Tanaka Y, et al. Reperfusion injury to endothelial cells following cold ischemic storage of rat livers. Hepatology 1989; 10: 292.

17. Furukawa H, Wu TM, Zue Y, et al. Disturbance of microcirculation associated with prolonged preservation of dog livers under University of Wisconsin solution. Transplant Proc 1993; 25: 1591.

18. Abt P, Crawford M, Desai N, et al. Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. Transplantation 2003; 75: 1659.

19. Nakamura N, Nishida S, Neff GR, Vaidya A, Levi DM, Kato T, et al. Intrahepatic biliary strictures without hepatic artery

thrombosis after liver transplantation: analysis of 1,113 liver transplantations at a single center. Transplantation 2005; 79: 427–432.

20. Guichelaar MM, Benson JT, Malinchoc M, Krom RA, Wiesner RH, Charlton MR. Risk factors for and clinical course of non-anastomotic biliary stricutures after liver transplantation. Am J Transplant 2003;3:885-890.

21. Letourneau JG, Day DL, Hunter DW, Ascher NL, Najarian JS, Thompson WM, et al. Biliary complications after liver transplantation in patients with preexisting sclerosing cholangitis. Radiology 1988;167:349-351.

22. Hong SK, Tan MY, Worakitti L, Lee JM, Cho JH, Yi NJ, Lee KW, Suh KS. Pure Laparoscopic Versus Open Right Hepatectomy in Live Liver Donors: A Propensity Score-matched Analysis. Ann Surg: April 20, 2020

23. Song GW, Lee SG, Hwang S, Kim KH, Ahn CS, Moon DB, Ha TY, Jung DH, Park GC, Kang SH, Jung BH, Yoon YI, Kim N. Biliary stricture is the only concern in ABO-incompatible adult living donor liver transplantation in the rituximab era. J Hepatol. 2014 Sep;61(3):575-82.

24. Natsuda K, Murokawa T, Lee KW, Yoon KC, Hong SK, Lee JM, Cho JH, Yi NJ, Suh KS. No diffuse intrahepatic biliary stricture after ABO-incompatible adult living donor liver transplantation using tailored rituximab-based desensitization protocol. Ann Transl Med. 2021 Jan;9(1):30.

25. Egawa H, Teramukai S, Haga H, Tanabe M, Mori A, Ikegami T, Kawagishi N, Ohdan H, Kasahara M, Umeshita K. Impact of rituximab desensitization on blood-type-incompatible adult living donor liver transplantation: a Japanese multicenter study. Am J Transplant. 2014 Jan;14(1):102-14.

26. Suh KS, Hong SK, Lee KW, Yi NJ, Kim HS, Ahn SW, Yoon KC, Choi JY, Oh D, Kim H. Pure laparoscopic living donor hepatectomy: Focus on 55 donors undergoing right hepatectomy. Am J Transplant. 2018 Feb;18(2):434-443.

27. Jeon YM, Lee KW, Yi NJ, Lee JM, Hong G, Choi Y, et al. The

right posterior bile duct anatomy of the donor is important in biliary complications of the recipients after living-donor liver transplantation. Ann Surg 2013; 257: 702- 707.
28. Banff schema for grading liver allograft rejection: an international consensus document. Hepatology. 1997 Mar;25(3):658-63.

Abstract

Introduction

담도 합병증은 생체간이식 후 발생하는 해결되지 않는 문제로 남아있다. 생체간이식 후의 간내 담도 협착(IHBS)은 흔하지 않지만 발생할 경우 집중 치료가 필요하다. 이 연구의 목적은 LDLT 후 발생하는 간내 담도 협착을 분류하고, IHBS 의 예후를 평가하는 것이다.

Methods

서울대학교병원에서 2011 년 8 월부터 2018 년 12 월까지 우간 생체 간이식을 받은 692 명의 환자 중 담관조영술을 통해 담도협착으로 있는 198 명을 대상으로 한 후향적 연구이다. 담관 협착의 유형은 담관 조영학적 소견에 따라 침범된 분지의 위치와 수에 따라 4 가지로 분류하였다; 1 형 (문합부 협착), 2 형 (제 2 분지 협착; a. 단독 / b. 2 개/ c. 제 3 분지로의 확장), 3 형 (다발성 협착), 4 형 (미만성 괴사). 이 중 간내 담도 협착은 2 형, 3 형 그리고 4 형으로 정의하였다. 담도 협착 유형에 따른 IHBS 발생률, 연간 중재 빈도, 마지막 중재시술 후 1 년 이상 담도 시술이 없는 휴지기(IFY), 그리고 IFY 후 임상적 재발 및 이식편 생존 결과를 평가하였다. 평균 추시 기간은 62.0 개월이었다.

Results

692 명의 성인 우간 생체간이식 환자 중 문합부 협착과 IHBS 의 비율은 17.6% (n=122) 및 11.0% (n=76)였다. IHBS 의 가장 흔한 유형은 2 형(86.8%; 2a(10.5%), 2b(19.7%), 2c(56.6%))이었고, 3 형(7.9%) 및 4 형(5.3%)이 순이었다. 연간 중재 빈도는 각 유형별로 1 형(2.3), 2a 형(2.3), 2b 형(2.8), 2c 형(4.3), 3 형(5.7), 4 형(9.5)로 유의미하게 차이를 보였다(*P*=0.001). IFY 는 유형에 따라 유의미한 차이를 보였으며, 1 형(84.4%), 2a 형(87.5%), 2b 형(86.7%), 2c 형(72.1%), 3 형(66.7%) 및 4 형(25.0%)으로 각각

나타났다(P=0.032). IHBS 군 중 IFY 후 임상적 재발은 3 형(66.7%)과 4 형(50.0%)에서 2 형(31.8%)보다 더 많았다(P=0.026). 이식편 생존율은 3 형과 4 형 IHBS(80.0%)에서 다른 유형보다 유의하게 낮았다(P=0.001).

Conclusion

성인 우간 생체간이식에서 IHBS 의 발생은 드물지 않았다. 3 형 및 4 형 IHBS 는 흔하지 않지만 중재가 더 빈번하고 이식편 생존율이 더 낮았다.

Table 1. Clinical characteristics (n = 198)	
Characteristic	**Value**
Recipient variables	
Age (year)	55.5 ± 9.1 (22-76)
Sex (male/female)	152/46 (76.8%/23.2%)
Underlying liver disease	
Hepatitis B	125 (63.1%)
Hepatitis C	18 (9.1%)
Alcoholic	34 (17.1%)
Autoimmune hepatitis	6 (3.0%)
Primary biliary cirrhosis	2 (1.0%)
Child-Pugh classification (A/B/C)	87/56/55 (43.9%/28.3%/27.8%)
Medical MELD score	14.2 ± 7.0 (6-41)
Hepatocellular carcinoma	134 (67.7%)
Donor variables	
Age (year)	34.7 ± 11.3 (16-63)
Sex (male/female)	130/68 (65.7%/34.3%)
GRWR (%)	1.10 ± 0.29 (0.09-1.79)
ABO incompatibility	29 (14.6%)
Laparoscopic donor hepatectomy	95 (48.0%)
Surgical variables	
Ischemic time (minutes)	
Cold	84.8 ± 29.8 (31-200)
Warm	31.1 ± 13.5 (12-149)
Operation time (minutes)	397.3 ± 101.8 (185-777)
Surgical complications	
Hepatic artery	10 (5.1%)
Portal vein	12 (6.1%)
Hepatic vein	7 (3.5%)
Medical variables	
Rejection	29 (14.6%)

Abbreviations: MELD, model for end−stage liver disease; GRWR, graft−to−recipient weight ratio

Table 2. Comparison of clinical characteristics according to the type of biliary stricture							
Characteristic	**1 (n=122)**	**2a (n=8)**	**2b (n=15)**	**2c (n=43)**	**3 (n=6)**	**4 (n=4)**	**P value**
Recipient variables							
Age (year)	55.9±8.7	55.9±5.8	57.2±9.9	53.7±10.1	53.7±14.6	56.0±2.0	0.769
Sex (male/female)	95/27	8/0	12/3	32/11	3/3	2/2	0.241
Underlying liver disease							
Hepatitis B	79 (64.8)	5 (62.5)	8 (53.3)	28 (65.1)	2 (40.0)	3 (75.0)	0.818
Hepatitis C	14 (11.5)	1 (12.5)	1 (6.7)	2 (4.7)	0 (0)	0 (0)	0.705
Alcoholic	20 (16.4)	2 (25.0)	5 (33.3)	5 (11.6)	2 (40.0)	0 (0)	0.243
Autoimmune hepatitis	2 (1.6)	0 (0)	0 (0)	2 (4.7)	1 (20.0)	1 (25.0)	**0.021**
Primary biliary cirrhosis	1 (0.8)	0 (0)	0 (0)	1 (2.3)	0 (0)	0 (0)	0.953
Child-Pugh classification (A/B/C)	60/30/32	2/4/2	4/6/5	18/13/12	2/1/3	1/2/1	0.630
Medical MELD score	13.9±6.9	16.2±8.2	15.3±9.0	14.5±6.8	12.6±4.5	12.5±8.5	0.869
Hepatocellular carcinoma	87 (71.3)	6 (75.0)	10 (66.7)	26 (60.5)	3 (50.0)	2 (50.0)	0.064
Donor variables							
Age (year)	35.5±11.7	26.5±5.9	30.4±9.9	34.8±10.3	43.2±12.2	27.5±5.2	**0.031**
Sex (male/female)	76/46	6/2	12/3	32/11	3/3	1/3	0.197
GRWR (%)	1.09±0.29	1.08±0.15	1.18±0.26	1.09±0.31	1.24±0.18	1.02±0.24	0.674
ABO incompatibility	16 (13.1)	0 (0)	2 (13.3)	7 (16.3)	3 (50.0)	1 (25.0)	0.153
Laparoscopic donor hepatectomy (%)	45.8	62.5	40.0	51.2	66.7	50.0	0.893
Surgical variables							
Ischemic time (minutes)							
Cold	86.4±31.6	86.7±19.7	80.1±38.0	83.4±24.2	78.8±28.0	72.7±7.4	0.912
Warm	32.4±14.8	29.4±11.1	32.1±15.3	28.0±9.1	24.7±8.6	32.0±10.0	0.400
Operation time (minutes)	398.0± 91.3	376.5± 86.6	386.9± 125.8	402.3± 117.9	385.8± 159.3	419.8± 111.2	0.973
Surgical complications (%)							
Hepatic artery	6 (4.9)	0 (0)	2 (13.3)	0 (0)	0 (0)	2 (50.0)	**<0.001**
Portal vein	8 (6.6)	0 (0)	3 (20.0)	1 (2.3)	0 (0)	0 (0)	0.193
Hepatic vein	3 (2.5)	1 (12.5)	0 (0)	3 (7.0)	0 (0)	0 (0)	0.452
Medical variables (%)							
Rejection	16 (13.1)	1 (12.5)	2 (13.3)	8 (18.6)	2 (33.3)	0 (0)	0.672

Abbreviations: MELD, model for end−stage liver disease; GRWR, graft−to−recipient weight ratio

Table 3. Outcomes of biliary stricture according to the type of biliary stricture					
Type	**Incidence, n (%)**	**Median time to 1st BS after transplant, days (range)**	**Intervention frequency per year (range)**	**IFY present (%)**	**Clinical relapse after IFY (%)**
Type 1. Anastomosis	122 (61.6)	177 (13-2489)	2.3 (0.1-24.0)	84.4	33.6
Type 2. The 2nd order branch	66 (33.3)				
2a. Single	8 (4.0)	167 (63-406)	2.3 (0.3-8.2)	87.5	12.5
2b. Double	15 (7.6)	161 (21-704)	2.8 (0.4-9.1)	86.7	40.0
2c. Extended to the 3rd order branch	43 (21.7)	178 (19-1085)	4.3 (0.5-32.6)	72.1	32.6
Type 3. Multifocal	6 (3.0)	168 (51-499)	5.7 (1.7-14.1)	66.7	66.7
Type 4. Diffuse necrosis	4 (2.0)	242 (21-1383)	9.5 (2.0-24.0)	25.0	50.0
		P=0.152	***P*=0.001**	***P*=0.032**	P=0.391

Abbreviations: BS, biliary stricture; IFY, intervention free period more than one year

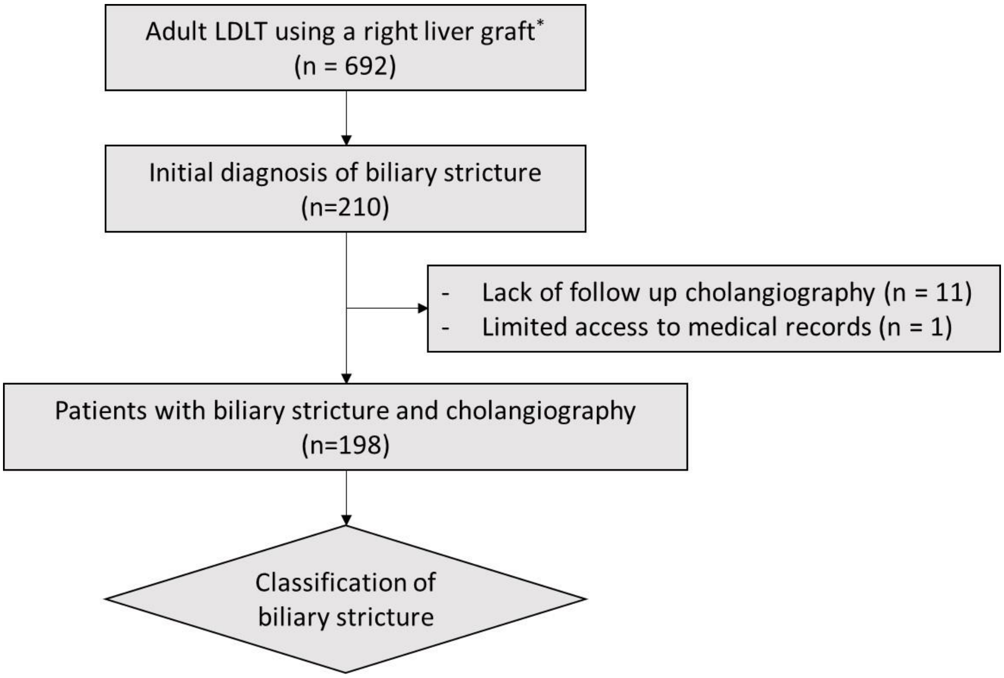


Figure 1. Flowchart of the patient enrollment

*Right liver graft includes modified or extended right liver graft as well as conventional right liver graft. There was no case of right anterior or posterior section graft in this particular cohort.
Abbreviation: LDLT, living donor liver transplantation

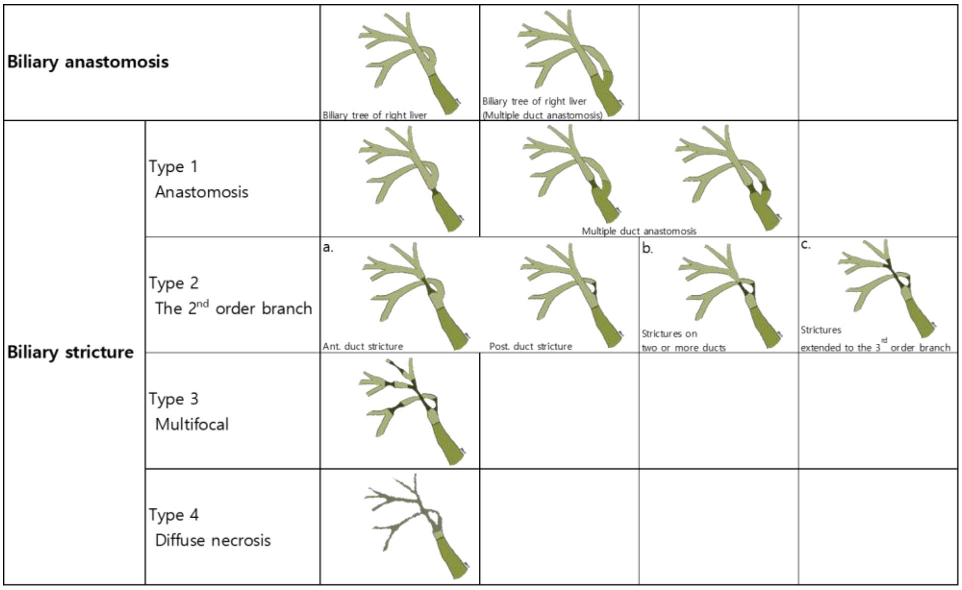


Figure 2. Classification of biliary stricture in right liver transplantation

Type 1: Anastomosis stricture

Type 2: 2nd order branch stricture (number)

Type 2a: 2nd order branch (one)

Type 2b: 2nd order branch (two or more)

Type 2c: 2nd order branch extended to 3rd order branch

Type 3: Multifocal strictures

Type 4: Diffuse necrosis

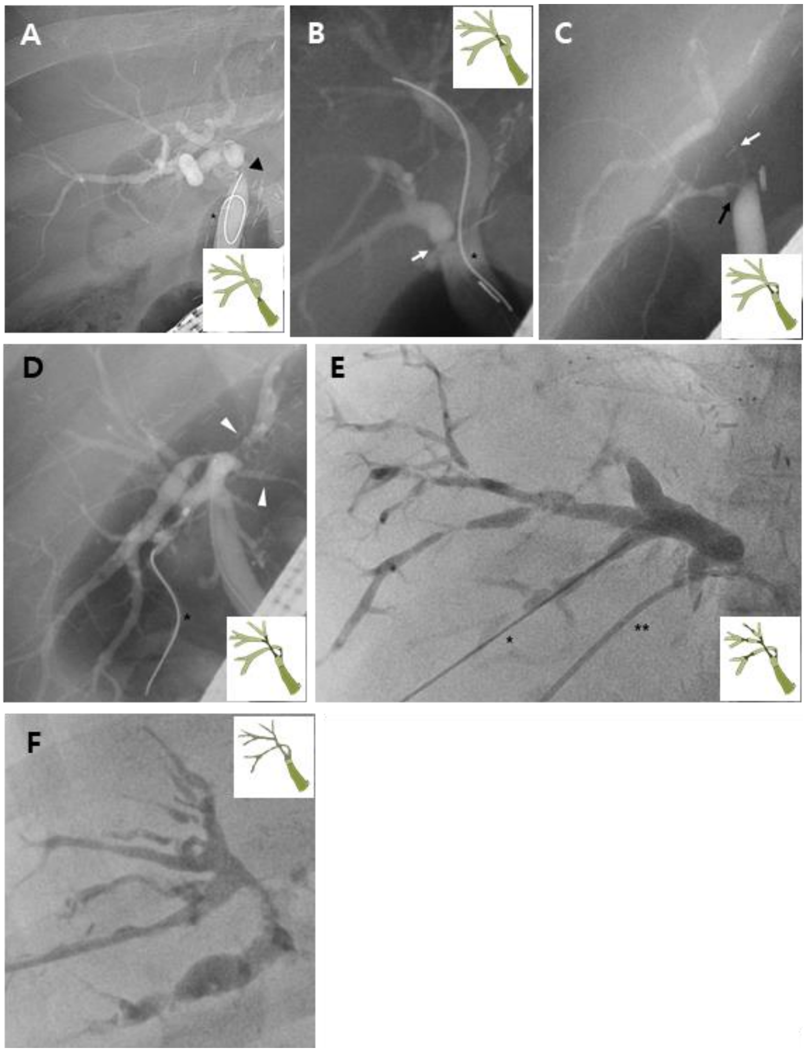


Figure 3. Cholangiography of patients with biliary stricture

A. Type 1: Anastomosis stricture (arrowhead)

B. Type 2a: 2^{nd} order branch (one)

Right anterior duct stricture is presented (white arrow)

C. Type 2b: 2^{nd} order branch (two or more)

Right anterior duct stricture (white arrow) and right posterior duct stricture (black arrow) are presented

D. Type 2c: 2^{nd} order branch extended to 3^{rd} order branch (arrowhead)

E. Type 3: Multifocal strictures

F. Type 4: Diffuse necrosis

* : Guide wire or catheter used for intervention

** : Previous internal stent

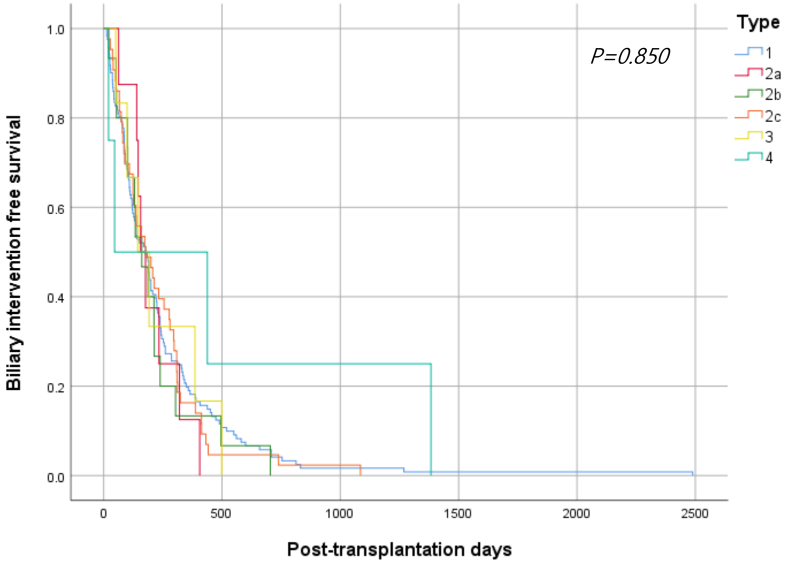


Figure 4. Biliary intervention free survival according to biliary stricture classification

The biliary intervention free survival was not different significantly between the types of biliary strictures using the Kaplan–Meier method (*P*=0.850).

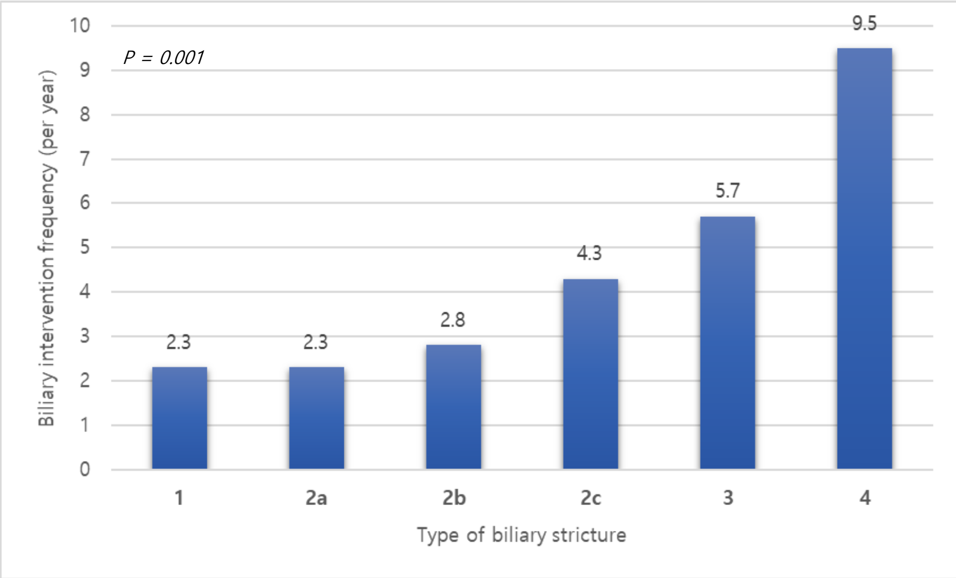
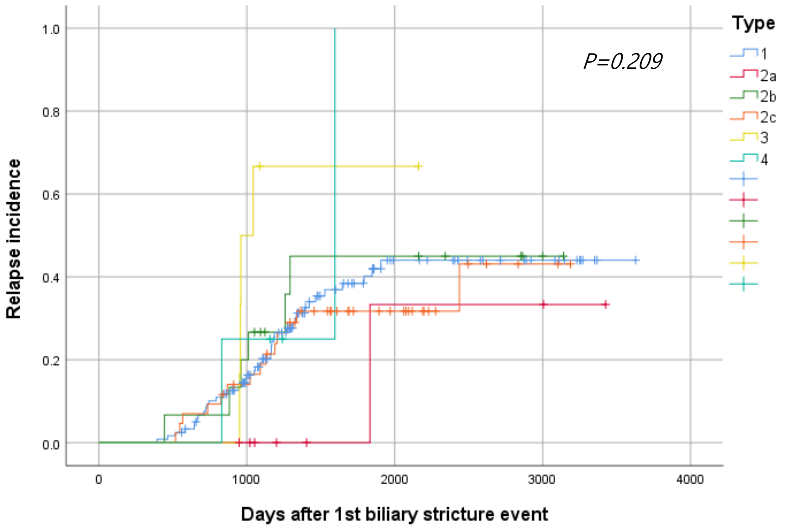


Figure 5. Comparison of intervention frequency per year according to biliary stricture classification

Intervention frequency was significantly different among types of biliary stricture (P=0.001). Type 4 biliary stricture required the most frequent interventions per year (9.5).

A.



B.

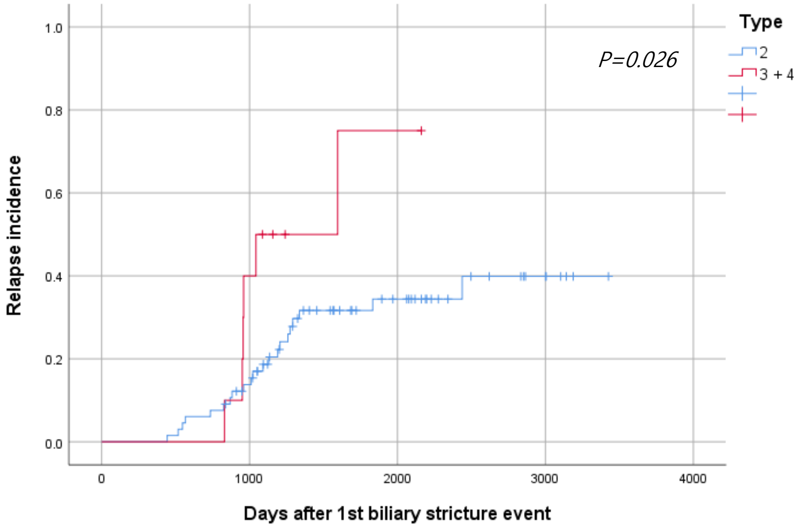
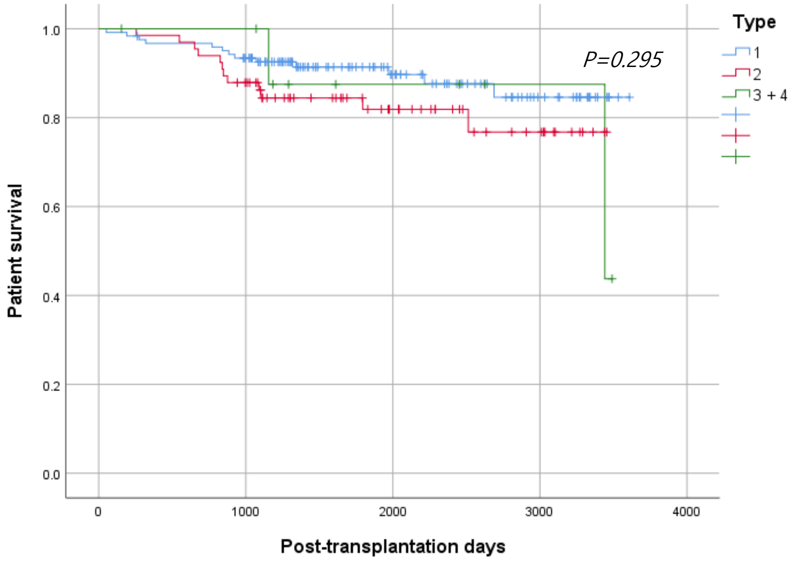


Figure 6. Clinical relapse incidence after one year intervention free period according to biliary stricture classification

A. Clinical relapse incidence in all types of biliary strictures

B. Clinical relapse incidence among IHBS (type 2 *versus* type 3 & 4)

A.



B.

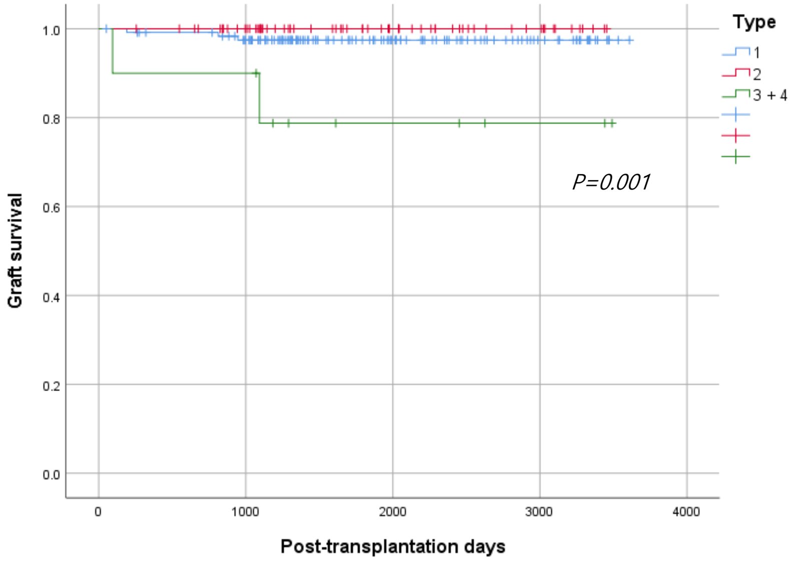


Figure 7. Survival outcomes according to biliary stricture classification

A. Patient survival rates

B. Graft survival rates

Supplement 1. Outcomes of type 1 biliary stricture (single duct *versus* double duct)				
Number of anastomoses	**Incidence, n (%)**	**Intervention frequency per year (range)**	**IFY present (%)**	**Clinical relapse after IFY (%)**
Single	93 (76.2)	2.59 (0.1-24.0)	81.7	32.3
Multiple (two or more)	29 (23.8)	1.48 (0.1-6.2)	93.1	37.9
		P=0.084	*P*=0.140	*P*=0.572

Supplement 1. Outcomes of biliary stricture among type 1 BS (single duct versus multiple ducts)

Supplement 2. Outcomes of biliary stricture according to the type of biliary stricture						
Anatomical type		**Severity**	**Incidence, n (%)**	**Intervention frequency per year (range)**	**IFY present (%)**	**Clinical relapse after IFY (%)**
AS	Type 1	Mild	122 (61.6)	2.3 (0.1-24.0)	84.4	33.6
IHBS	Type 2a + 2b	Mild	23 (11.6)	2.7 (0.3-9.1)	87.0	30.4
	Type 2c	Moderate	43 (21.7)	4.3 (0.5-32.6)	72.1	32.6
	Type 3 + 4	Severe	10 (5.0)	7.2 (1.7-24.0)	50.0	60.0
				***P*<0.001**	***P*=0.022**	*P*=0.367

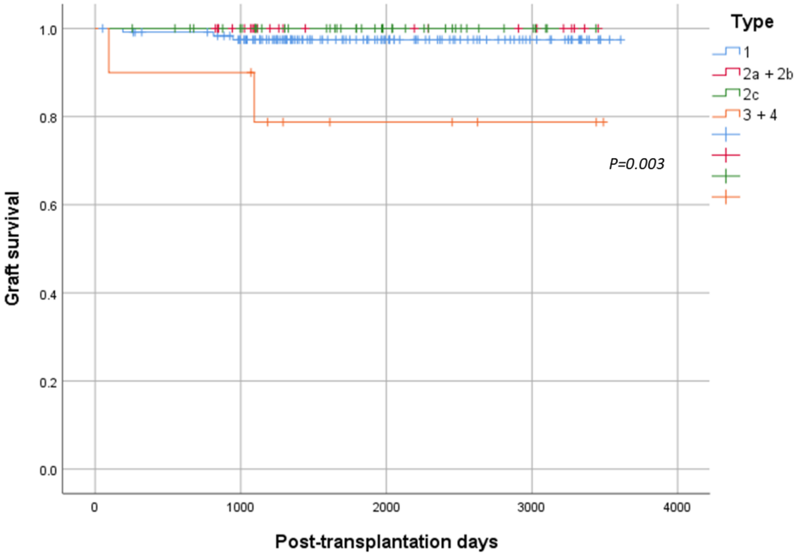
Supplement 2. Outcomes of biliary stricture according to the type of biliary stricture

Supplement 3. Multivariate analysis of factors associated with severe type of biliary stricture

Characteristic	Non-severe BS group (n=188)	Severe BS group (n=10)	*P* value	Multivariate analysis p value	Odds ratio (95% confidence interval)
Recipient variables					
Age (year)	55.5±9.1	54.6±11.0	0.763		
Sex (male/female)	147/41	5/5	0.054	0.227	2.783
Underlying liver disease					
Hepatitis B	120(63.8)	6(60.0)	0.525		
Hepatitis C	18(9.6)	0(0)	0.377		
Alcoholic	32(17.0)	2(20.0)	0.538		
Autoimmune hepatitis	4(2.1)	2(20.0)	**0.031**	**0.032**	**12.892 (1.25 – 132.923)**
Primary biliary cirrhosis	2(1.1)	0(0)	0.901		
Child-Pugh classification (A/B/C)	84/53/51	3/3/4	0.594		
Medical MELD score	14.3±7.1	12.5±5.9	0.449		
Hepatocellular carcinoma	129(68.6)	5(50.0)	0.187		
Donor variables					
Age (year)	34.6±11.2	36.9±12.5	0.522		
Sex (male/female)	126/62	4/6	0.082	**0.045**	**4.792 (1.034 – 22.216)**
GRWR (%)	1.10±0.29	1.17±0.21	0.480		
ABO incompatibility	25(13.3)	4(40.0)	**0.042**	0.070	3.942
Laparoscopic donor hepatectomy (%)	43.1	60.0	0.234		
Surgical variables					
Ischemic time (minutes)					
Cold	85.2±30.1	76.8±22.7	0.410		
Warm	31.3±13.6	27.6±9.45	0.404		
Operation time (minutes)	397.1±100.1	399.4±136.1	0.946		
Surgical complications (%)					
Hepatic artery	8(4.3)	2(20.0)	0.083	**0.037**	**8.800 (1.146 – 67.605)**
Portal vein	12(6.4)	0(0)	0.527		
Hepatic vein	7(3.7)	0(0)	0.692		
Medical variables (%)					
Rejection	27(14.4)	2(20.0)	0.446		

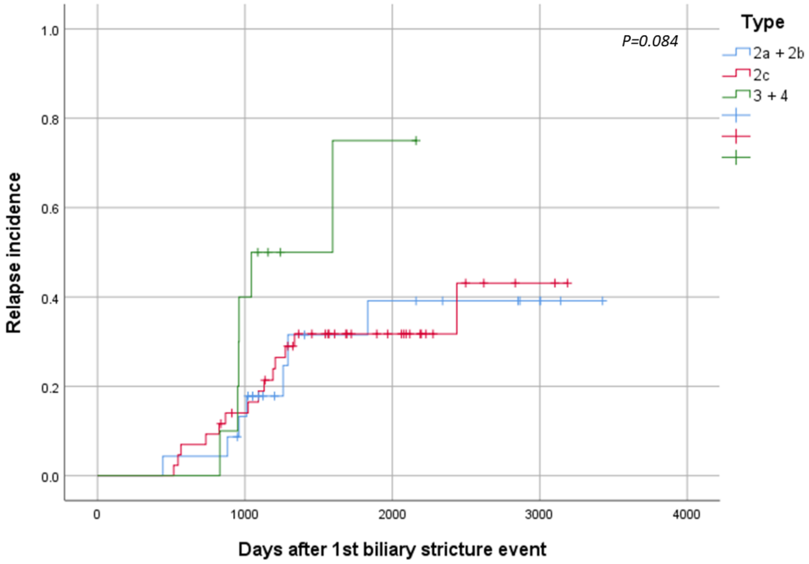
Abbreviations: MELD, model for end-stage liver disease; GRWR, graft-to-recipient weight ratio

Supplement 3. Multivariate analysis of factors associated with severe type of biliary stricture



Supplement Figure 1. Graft survival outcomes according to biliary stricture classification

Type 2c was significantly better survival outcome than type 3 and type 4 (P=0.003).



Supplement Figure 2. Clinical relapse incidence after one year intervention free period according to biliary stricture classification

There was no significant difference between type 2c and other IHBS (*P*=0.084).