

Endoscopic Treatment and Outcome Analysis of Biliary Stricture After Orthotopic Liver Transplantation: A Single Center Retrospective Study

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Purpose: The incidence of biliary stricture (BS) after liver transplantation (LT) significantly increases the risks of retransplantation and mortality. Although various endoscopic treatment strategies are available, a consensus is lacking in certain aspects, and the impact of endoscopic treatment on overall survival has yet to be studied. This retrospective study aims to explore factors influencing the efficacy of initial endoscopic treatment for BS after deceased donor orthotopic liver transplantation (OLT) and to analyze outcomes.

Patients and Methods: This research conducted a retrospective analysis of 89 patients who developed BS after OLT at The First Hospital of Jilin University between 01/01/2014 and 01/01/2022. Patients were categorized into a successful group (59 patients) and a failed group (30 patients) based on the success or failure of initial endoscopic treatment. Risk factor analysis for initial endoscopic treatment failure in patients with BS after OLT was performed using univariate and multivariate logistic regression analysis. The survival analysis for patients with BS after OLT was conducted using Cox regression and Kaplan-Meier methods.

Results: The failure rate of initial endoscopic treatment was 33.7%. Independent risk factors for failure included the proximal and distal bile duct angle $\leq 145^\circ$ ($OR=16.667$, 95% CI : 3.279–83.333, $P=0.001$), severe stricture ($OR=9.009$, 95% CI : 1.590–50.000, $P=0.013$), and non-anastomotic stricture (NABS) type ($OR=20.049$, 95% CI : 2.663–150.953, $P=0.004$). Furthermore, failed initial endoscopic treatment ($HR=3.205$, 95% CI : 1.350–7.634, $P=0.008$) emerged as an independent risk factor for mortality in patients with BS after OLT.

Conclusion: Initial endoscopic treatment for BS in patients after OLT is effective, safe, and has a high success rate. However, patients with the proximal and distal bile duct angle $\leq 145^\circ$, NABS, and severe strictures exhibit poorer initial endoscopic treatment effect. Those whose initial endoscopic treatment fails demonstrate significantly worse prognoses.

Keywords: liver transplantation, biliary stricture, endoscopic treatment, prognosis

Introduction

Liver transplantation is currently the optimal treatment modality for acute or chronic liver failure, primary or secondary liver tumors, and certain metabolic liver diseases. The number of liver transplants performed in China has risen to the second highest worldwide, trailing only behind the United States.¹ Despite continual advancements in surgical techniques in recent years, biliary stricture remains one of the most common complications post-liver transplantation, typically worsening progressively. The incidence of biliary stricture in deceased donor orthotopic liver transplantation (OLT), the classical form of liver transplantation, is reported between 10% and 25%.² Factors contributing to biliary complications after liver transplantation can generally be categorized into donor-related, recipient-related, graft-related, surgical-related, and postoperative-related factors.³ The occurrence of these complications directly impacts patient prognosis, with some patients requiring retransplantation, making them a significant factor influencing long-term survival after liver transplantation.⁴

Various treatment modalities exist for biliary stricture after liver transplantation, including endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), magnetic compression anastomosis (MCA), and surgical approaches such as stricture resection or reconstruction.⁵ PTC showed a good primary cure rate for biliary strictures, and only 13% of the benign strictures had recurrence,⁶ while, the MCA also has a good therapeutic effect on biliary stenosis, especially for other means are invalid.⁷ Given that endoscopic treatment for biliary stricture after liver transplantation is characterized by safety, effectiveness, minimal invasiveness, reduced discomfort, and rapid recovery, it is currently recognized as the preferred method for treating biliary stricture.^{8,9} Initially, balloon dilation (BD) was used in isolation during endoscopic treatment; however, due to the high rates of restenosis and the significant risk of bile duct rupture, it has gradually been supplanted by BD in combination with stent placement. The evolution of stent placement has progressed from single plastic stents to advancements such as multiple stents, fully covered self-expandable metal stents (FCSEMS), anti-migration FCSEMS, steroid-eluting FCSEMS, and biodegradable biliary stents.^{10,11} The effectiveness of different treatment modalities varies across studies, there exists a recognized need for further exploration.¹²

The reported success rates of endoscopic therapy for BS vary significantly across studies, ranging from 46.7% to 94%, likely reflecting differences in treatment modalities.¹³ A meta-analysis of 30 studies by Fan et al demonstrated pooled clinical success rates of 0.69 (95% CI: 0.63–0.74) for multiple plastic stents (MPS) versus 0.66 (95% CI: 0.60–0.72) for FCSEMS.¹² However, in initial endoscopic therapy specifically, Kim et al reported a 55.8% initial success rate in their analysis of 147 patients with BS after LT.¹⁴ This aligns with findings from Lee YY et al's study of 137 LT recipients, where only 46.7% (64/137) achieved successful resolution through initial endoscopic therapy.¹⁵ Although they primarily explored the success rate of initial endoscopic treatment, they did not analyze the impact of the effect of initial endoscopic treatment on prognosis of biliary stricture after liver transplantation.

Despite the array of endoscopic treatment options available, some patients with biliary stricture after liver transplantation require multiple endoscopic interventions and may remain incurable, even potentially leading to retransplantation or mortality.¹⁶ Furthermore, limited research exists regarding the risk factors affecting the efficacy of endoscopic treatment for BS after OLT, with most studies focusing on combined endoscopic and percutaneous techniques, and fewer reports addressing solely endoscopic treatment. Therefore, investigating the factors influencing the efficacy of initial endoscopic treatment for BS after OLT and its impact on prognosis is highly significant. This study conducts a retrospective analysis of data from 89 patients with BS after OLT at The First Hospital of Jilin University, aiming to elucidate factors affecting the outcomes of initial endoscopic treatment and its prognostic implications.

Materials and Methods

General Information

This study involved a retrospective cohort analysis of 495 patients who underwent deceased donor orthotopic liver transplantation performed between 01/01/2014 and 01/01/2022, with 89 cases of BS after OLT included in the study. All patients received comprehensive preoperative evaluations, and clinical diagnoses were clearly established. Throughout the study, all patient data were anonymized and accessed for research purposes in 01/02/2024. Data collected included pre-transplant conditions, surgical details, endoscopic treatment metrics, and survival follow-up data for all patients. Follow-up was conducted in an outpatient setting, beginning from the day of liver transplantation until 01/01/2024.

Ethics Statement

This study was approved by the Ethics Committee of The First Hospital of Jilin University, with approval number 2024–034. This study had been conducted according to the principles expressed in the Declaration of Helsinki. The studies were conducted by the local legislation and institutional requirements. All of the participants were adults, and the participants provided their written informed consent to participate in this study. All organs were donated voluntarily with written informed consent, and these were conducted in accordance with the Declaration of Istanbul.

Inclusion and Exclusion Criteria

Inclusion Criteria

Patients who underwent deceased donor orthotopic liver transplantation at The First Hospital of Jilin University; patients who received end-to-end biliary anastomosis during surgery; patients who developed biliary stricture after transplantation; aged ≥ 18 years; complete clinical data; and patients followed regularly with follow-up duration exceeding two years.

Exclusion Criteria

Patients who died within one month post-surgery; incomplete clinical data; patients who were not re-evaluated or lost to follow-up.

Diagnostic Criteria

Diagnostic criteria for BS included: ① presence of fever or jaundice, elevated liver function enzymes and bilirubin, and MR cholangiopancreatography (MRCP) (Figure 1) or abdominal ultrasound indicating BS; ② confirmation of BS via ERCP (Figure 2) or percutaneous transhepatic biliary drainage (PTBD) imaging.

Definition of Initial Endoscopic Treatment Success: No further endoscopic intervention required for over three months, near-normal liver function, and absence of clinical symptoms related to cholangitis or jaundice.

Definition of Initial Endoscopic Treatment Failure: Failure of ERCP treatment, necessitating intervention via PTCD or re-treatment within three months post-initial therapy, accompanied by significant liver function abnormalities or onset of cholangitis and jaundice-related clinical symptoms.

Endoscopic Treatment

Using ERCP, a guidewire was selectively advanced through the stricture to enter the donor bile duct, confirming the presence of biliary stricture under fluoroscopy after administration of contrast agent. In cases of failure during guidewire selection via ERCP, percutaneous transhepatic biliary drainage (PTBD) may be performed, followed by combined percutaneous/endoscopic treatment. Endoscopic treatment involved balloon dilation using a balloon catheter (balloon diameter determined by the degree of stricture and the diameter of the bile ducts proximal and distal to the stricture), with dilation lasting three minutes. The decision regarding the placement and number of stents (plastic or covered metal stents) was left to the discretion of the endoscopist based on the stricture condition. There were two ERCP operators in our center, both of whom were mature ERCP surgeons and had performed more than 500 ERCP ordinary procedures. If the initial endoscopic therapy fails, our center will most likely perform ERCP again; Otherwise we will perform PTCD combined with ERCP, SpyGlass combined with ERCP, Magnetic Compression Anastomosis or liver transplantation.



Figure 1 Magnetic Resonance Cholangiopancreatography (MRCP) Findings of Biliary Strictures Following Liver Transplantation.



Figure 2 Endoscopic Retrograde Cholangiopancreatography (ERCP) Findings of Biliary Strictures Following Liver Transplantation.

The Immunosuppressive Therapy

1. Early Postoperative Phase: Tacrolimus + Mycophenolate Mofetil + Prednisone. 2. Intermediate Postoperative Phase: Gradually reduce the dose of Prednisone while maintaining Tacrolimus and Mycophenolate Mofetil. 3. Long-Term Postoperative Phase: Prednisone may be discontinued, and maintenance therapy can be continued with Tacrolimus or Cyclosporine as monotherapy, or in combination with Mycophenolate Mofetil.

Statistical Methods

Statistical analysis and graphical representation were performed using SPSS version 19.0 and R version 4.1.3. Normality tests were first conducted on continuous data; normally distributed measurements were expressed as mean $\pm$ standard deviation and analyzed using the Student *t* test. Non-normally distributed data were expressed as M (P25~P75) and compared using the Mann–Whitney *U*-test. Count data between groups were compared using the chi-squared test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to identify risk factors for failure of initial endoscopic treatment for BS after OLT. Univariate and multivariate Cox regression analyses were employed to determine risk factors associated with decreased survival in patients with BS after OLT, using the Kaplan-Meier method to analyze the impact of initial endoscopic treatment efficacy on survival. $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics Comparison

During the entire study period, 406 patients did not develop BS after OLT, while 89 patients underwent ERCP treatment for BS after OLT, yielding an incidence rate of 17.98%. Among the 89 patients undergoing initial ERCP, 59 had successful outcomes and 30 had treatment failures, resulting in a failure rate of 33.7%. A comparison of baseline characteristics between the successful and failed groups is presented in Table 1. The failed group exhibited a higher proportion of non-anastomotic strictures (10 of 30, 33.3% versus 6 of 59, 10.2%, $P=0.020$), the proximal and distal bile duct angle $\leq 145^\circ$ (22 of 30, 73.3% versus 16 of 59, 27.1%, $P<0.001$), more severe strictures (28 of 30, 93.3% versus 28 of 59, 47.5%, $P<0.001$), and stricture segments measuring ≤ 13 mm in length (16 of 30, 53.3% versus 46 of 59, 78.0%,

Table 1 Baseline Characteristics Comparison of Patients with BS After Liver Transplantation

	Failed Group (n=30)	Successful Group (n=59)	P	Statistical Value
Gender			0.471	0.524
Female	12(40.0%)	18(30.5%)		
Male	18(60.0%)	41(69.5%)		
Age	48.800±11.047	52.880±8.122	0.051	3.913
Surgical Date			0.104	2.733
Before 2020	13(43.3%)	15(25.4%)		
After 2020	17(56.7%)	44(74.6%)		
Cirrhosis			0.315	1.030
No	8(26.7%)	10(17.0%)		
Yes	22(73.3%)	49(83.1%)		
Hepatitis B			0.703	0.146
No	14(46.7%)	25(42.4%)		
Yes	16(53.3%)	34(57.6%)		
Malignant Tumor			0.483	0.496
No	17(56.7%)	38(64.4%)		
Yes	13(43.3%)	21(35.6%)		
Previous Abdominal Surgery History			0.332	0.950
No	13(43.3%)	34(57.6%)		
Yes	17(56.7%)	25(42.4%)		
Suture wire Type			0.688	0.162
Polypropylene Suture wire	18(60.0%)	39(66.1%)		
Other Suture wire Types	12(40.0%)	20(33.9%)		
Suture Method			0.074	3.333
Interrupted anterior wall and continuous posterior wall	16(53.3%)	46(78.0%)		
Interrupted anterior and posterior walls	8(26.7%)	7(11.9%)		
Continuous anterior and posterior walls	6(20.0%)	6(10.2%)		
Donor-Recipient Bile Duct Matching			0.505	0.100
Yes	22(73.3%)	47(79.7%)		
No	8(26.7%)	12(20.3%)		
CHILD Classification			0.167	1.960
A	4(13.3%)	12(20.3%)		
B	24(80.0%)	46(78.0%)		
C	2(6.7%)	1(1.7%)		
Cold Ischemia Time (min)	439.870±122.052	391.880±109.525	0.064	3.828
Warm Ischemia Time (s)	102.600±50.401	82.410±39.461	0.061	3.571
Blood Loss (mL)	4846.670±3777.495	3364.410±3213.687	0.110	2.609
ERCP Time Post-Liver Transplant (days)	338.600±624.158	183.881±301.858	0.118	1.606
Stricture Type			0.020	5.808
Anastomotic Stricture	20(66.7%)	53(89.8%)		
Non-Anastomotic Stricture	10(33.3%)	6(10.2%)		
Stent Type			0.820	0.052
Metal	3(10.0%)	5(8.5%)		
Plastic	27(90.0%)	54(91.5%)		
Number of Stents			0.172	1.909
1	23(76.7%)	37(62.7%)		
2	7(23.3%)	22(37.3%)		
Proximal & Distal Bile Duct Angle			<0.001	21.083
≤145	22(73.3%)	16(27.1%)		
>145	8(26.7%)	43(72.9%)		

(Continued)

Table 1 (Continued).

	Failed Group (n=30)	Successful Group (n=59)	P	Statistical Value
Stricture Severity			<0.001	32.656
Mild	28(93.3%)	28(47.5%)		
Severe	2(6.7%)	31(52.5%)		
Proximal Bile Duct Width (mm)	8.413±3.627	9.542±3.491	0.158	2.026
Distal Bile Duct Width (mm)	5.813±2.032	6.258±2.155	0.351	0.880
Bile Duct Width Ratio	1.627±0.907	1.702±0.893	0.707	0.142
Stricture Length (mm)			0.026	5.256
≤13	16(53.3%)	46(78.0%)		
>13	14(46.7%)	13(22.0%)		
Length from Stricture to Hepatic Duct (mm)			0.061	3.599
≤20	18(60.0%)	23(39.0%)		
>20	12(40.0%)	36(61.0%)		
AST (U/L)	101.847±99.773	80.346±65.463	0.226	1.489
ALT (U/L)	121.343±246.711	106.715±111.854	0.701	0.149
γ-Glutamyltransferase (U/L)	394.087±344.752	360.436±305.358	0.639	0.221
Alkaline Phosphatase (U/L)	338.337±219.171	304.324±189.676	0.450	0.575
Direct Bilirubin (μmol/L)			0.028	5.080
≤35	15(50.0%)	44(74.6%)		
>35	15(50.0%)	15(25.4%)		
Total Bile Acids (μmol/L)	94.650±105.360	74.103±85.476	0.325	0.980
White Blood Cells (10 ⁹ /L)	5.474±2.966	4.737±2.282	0.198	1.684
Absolute Neutrophil Count (10 ⁹ /L)	3.774±2.366	3.113±2.019	0.172	1.893
Red Blood Cells (10 ⁹ /L)	3.844±0.893	3.566±0.859	0.158	2.028
Platelets (10 ⁹ /L)	119 (80, 161)	145 (103.5,200.5)	0.516	0.801

$P=0.026$). Additionally, the preoperative direct bilirubin levels were ≤ 35 $\mu\text{mol/L}$ in a higher proportion of the failed group (15 of 30, 50.0% versus 44 of 59, 74.6%, $P=0.028$).

Complications of Endoscopic Treatment for BS After OLT

A total of 218 ERCP procedures were performed among the 89 patients, averaging 2.45 procedures per patient. The incidence of complications after endoscopic treatment was 11% (24 occurrences in total, including 15 cases of mild pancreatitis, 6 cases of bacterial cholangitis, and 3 cases of biliary bleeding). The complication rate after initial endoscopic treatment was 16.9% (15 occurrences in total, including 9 cases of mild pancreatitis, 4 cases of bacterial cholangitis, and 2 cases of biliary bleeding), as shown in Table 2. All adverse events were successfully treated conservatively, with no patient mortality attributable to endoscopic-related complications.

Table 2 Complications of Endoscopic Treatment for BS After OLT

Complication	Total Endoscopic Treatments (n=218)	Initial Endoscopic Treatment (n=89)
Mild Pancreatitis	15 (6.88%)	9 (10.11%)
Bacterial Cholangitis	6 (2.75%)	4 (4.49%)
Biliary Bleeding	3 (1.38%)	2 (2.25%)
Total Complications	24 (11.01%)	15 (16.85%)

Efficacy Analysis of Initial ERCP Treatment for BS After OLT

To explore the risk factors associated with failure of initial endoscopic treatment for BS after OLT, univariate and multivariate logistic regression analyses were conducted (Table 3). Univariate analysis revealed statistically significant differences in stricture type, angle between proximal and distal bile ducts, stricture severity, stricture segment length, and preoperative direct bilirubin levels. Multivariate analysis identified that the proximal and distal bile duct angle ≤ 145 ($OR=16.667$, 95% CI : 3.279–83.333, $P=0.001$), severe stricture ($OR=9.009$, 95% CI : 1.590–50.000, $P=0.013$), and non-anastomotic stricture type ($OR=20.049$, 95% CI : 2.663–150.953, $P=0.004$) were independent risk factors for initial endoscopic treatment failure in patients with BS after OLT. To provide a more intuitive understanding, we have constructed a nomogram delineating the risk factors associated with the failure of initial endoscopic treatment in patients with BS after OLT (Figure 3).

Table 3 Univariate and Multivariate Logistic Regression Analysis of Initial Endoscopic Treatment Efficacy for BS After OLT

Factor	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Gender	1.404 (0.564–3.494)	0.466		
Age	1.049 (0.999–1.102)	0.057		
Surgical Date	0.680 (0.279–1.656)	0.395		
Cirrhosis	1.782 (0.619–5.128)	0.284		
Hepatitis B	1.190 (0.492–2.880)	0.700		
Malignant Tumor	0.723 (0.295–1.773)	0.478		
Previous Abdominal Surgery History	0.643 (0.266–1.557)	0.328		
Suture wire Type	0.829 (0.336–2.047)	0.684		
Suture Method	0.370 (0.105–1.304)	0.122		
Donor-Recipient Bile Duct Matching	0.839 (0.291–2.415)	0.745		
CHILD Classification	0.653 (0.190–2.242)	0.498		
Cold Ischemia Time (min)	0.996 (0.992–1.000)	0.058		
Warm Ischemia Time (s)	0.991 (0.980–1.001)	0.075		
Blood Loss (mL)	1.000 (1.000–1.000)	0.116		
ERCP Time Post-Liver Transplant (days)	0.998 (0.996–1.000)	0.111		
Stricture Type	4.417 (1.419–13.745)	0.010	20.049 (2.663–150.953)	0.004
Stent Type	0.833 (0.185–3.750)	0.812		
Number of Stents	1.954 (0.721–5.295)	0.188		
Proximal & Distal Bile Duct Angle	7.407 (2.740–20.000)	<0.001	16.667 (3.279–83.333)	0.001
Stricture Severity	15.385 (3.378–71.429)	<0.001	9.009 (1.590–50.000)	0.013
Proximal Bile Duct Width (mm)	1.110 (0.893–1.379)	0.348		
Distal Bile Duct Width (mm)	1.104 (0.664–1.835)	0.704		
Bile Duct Width Ratio	1.104 (0.962–1.267)	0.160		
Stricture Length (mm)	3.096 (1.203–7.937)	0.019	1.795 (0.491–6.579)	0.377
Length from Stricture to Hepatic Duct (mm)	2.347 (0.956–5.780)	0.063		
AST (U/L)	0.997 (0.991–1.002)	0.230		
ALT (U/L)	1.000 (0.997–1.002)	0.699		
γ -Glutamyltransferase (U/L)	1.000 (0.998–1.001)	0.635		
Alkaline Phosphatase (U/L)	0.999 (0.997–1.001)	0.447		
Direct Bilirubin (umol/L)	2.933 (1.163–7.407)	0.023	2.033 (0.549–7.519)	0.288
Total Bile Acids (umol/L)	0.998 (0.993–1.002)	0.323		
White Blood Cells ($10^9/L$)	0.895 (0.754–1.061)	0.201		
Absolute Neutrophil Count ($10^9/L$)	0.870 (0.710–1.065)	0.178		
Red Blood Cells ($10^9/L$)	0.676 (0.393–1.165)	0.159		
Platelets ($10^9/L$)	0.999 (0.998–1.001)	0.414		

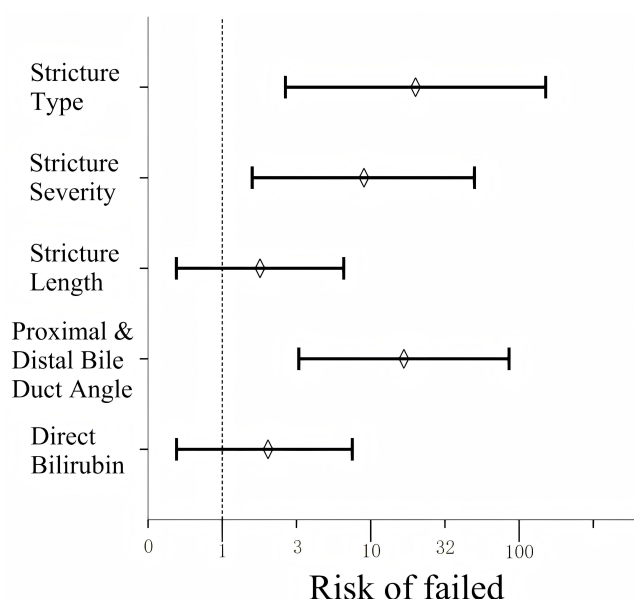


Figure 3 The risk factors for initial endoscopic treatment failure in patients with BS after OLT nomogram.

Survival Analysis of Patients Post-OLT

Through a median follow-up period of 7.78 years, the 1-year, 3-year, and 5-year survival rates for the 89 patients with BS after OLT were 94.4%, 79.0%, and 72.9%, respectively. To identify detrimental prognostic factors, univariate and multivariate Cox regression analyses were conducted regarding mortality in patients with BS after OLT (Table 4). Univariate analysis indicated that surgical date, preoperative direct bilirubin, and efficacy of initial endoscopic treatment were correlated with mortality in this patient group. Multivariate analysis revealed that failure of initial endoscopic treatment ($HR=3.205$, 95% CI : 1.350–7.634, $P=0.008$) was an independent risk factor for mortality among patients with BS after OLT. Kaplan-Meier survival analysis was performed to assess the impact of the efficacy of initial endoscopic treatment on survival, illustrated in Figure 4. Patients in the initial endoscopic treatment failure group demonstrated 1-year, 3-year, and 5-year survival rates of 96.7%, 56.3%, and 50.7% respectively. In contrast, the treatment success group showed substantially better survival outcomes at corresponding intervals: 96.6%, 87.9%, and 80.6%. Comparative analysis indicated that the treatment failure group had significantly lower overall survival rates compared to their successfully treated counterparts.

Discussion

In recent years, advancements in medical technology, perioperative care, immunosuppressants, and organ preservation have led to a decline in the incidence of postoperative complications such as bleeding, infection, primary graft failure, vascular complications, and immune rejection. These improvements have significantly enhanced the survival rates of liver transplant patients.¹⁷ However, biliary stricture continues to be one of the most common complications after liver transplantation, with progressive severity, severely affecting post-transplant survival and quality of life for patients.⁴ In this study, the incidence of BS was found to be 17.98%, which aligns with previous reports indicating a rate of 15%–25%.¹⁸ A retrospective study by Senter-Zapata et al involving 1041 adult liver transplant recipients demonstrated comparable survival rates between patients with biliary complications (92%, 81%, and 75% at 1, 3, and 5 years, respectively) and those without complications (90%, 84%, and 78%; $P=0.93$), suggesting no significant impact of biliary complications on overall survival.¹³ Notably, subgroup analysis revealed markedly reduced survival rates in patients with bile leakage (83.6%, 70.6%, and 68%; $P=0.04$) compared to the complication-free group. Similarly, Jarlot-Gas et al reported no survival difference between anastomotic stricture patients (98% and 81% at 1 and 5 years) and non-stricture controls (93% and 77%; $P=0.75$). The researchers emphasized that while anastomotic strictures often require multiple

Table 4 Survival Analysis of Patients with BS After OLT

Factor	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender	1.799 (0.713–4.537)	0.213	0.552 (0.220–1.389)	0.207
Age	0.979 (0.941–1.018)	0.284		
Surgical Date	0.368 (0.149–0.907)	0.030		
Cirrhosis	0.761 (0.283–2.044)	0.587		
Hepatitis B	1.986 (0.823–4.792)	0.127		
Malignant Tumor	2.229 (0.995–4.995)	0.051		
Previous Abdominal Surgery History	1.090 (0.489–2.429)	0.832		
Suture wire Type	1.615 (0.720–3.622)	0.245		
Suture Method	1.326 (0.443–3.970)	0.614		
Donor-Recipient Bile Duct Matching	0.273 (0.064–1.163)	0.079		
CHILD Classification	0.826 (0.306–2.227)	0.705		
Cold Ischemia Time (min)	1.001 (0.998–1.005)	0.487		
Warm Ischemia Time (s)	1.005 (0.997–1.013)	0.238		
Blood Loss (mL)	1.000 (1.000–1.000)	0.093		
ERCP Time Post-Liver Transplant (days)	0.999 (0.997–1.001)	0.455		
Stricture Type	0.440 (0.182–1.065)	0.069		
Stent Type	0.792 (0.186–3.375)	0.753		
Number of Stents	1.007 (0.416–2.440)	0.987		
Proximal & Distal Bile Duct Angle	0.760 (0.341–1.692)	0.501		
Stricture Severity	0.935 (0.824–1.062)	0.301		
Proximal Bile Duct Width (mm)	1.005 (0.831–1.216)	0.958	2.144 (0.938–4.902)	0.071
Distal Bile Duct Width (mm)	0.863 (0.522–1.426)	0.565		
Bile Duct Width Ratio	1.238 (0.529–2.897)	0.622		
Stricture Length (mm)	1.635 (0.714–3.746)	0.245		
Length from Stricture to Hepatic Duct (mm)	1.105 (0.496–2.462)	0.807		
AST (U/L)	0.998 (0.992–1.004)	0.505		
ALT (U/L)	0.997 (0.992–1.002)	0.197		
γ -Glutamyltransferase (U/L)	1.001 (0.999–1.002)	0.366		
Alkaline Phosphatase (U/L)	1.001 (0.999–1.003)	0.500		
Direct Bilirubin (umol/L)	2.773 (1.240–6.201)	0.013		
Total Bile Acids (umol/L)	1.005 (1.001–1.009)	0.058	3.205 (1.350–7.634)	0.008
White Blood Cells ($10^9/L$)	0.877 (0.721–1.067)	0.191		
Absolute Neutrophil Count ($10^9/L$)	0.969 (0.799–1.174)	0.746		
Red Blood Cells ($10^9/L$)	1.059 (0.671–1.670)	0.806		
Platelets ($10^9/L$)	1.000 (1.000–1.001)	0.364		
Effect of primary endoscopic treatment	4.065 (1.776–9.346)	0.001	3.205 (1.350–7.634)	0.008
Complications after ERCP	2.042 (0.809–5.153)	0.131		

surgical interventions, they do not adversely affect long-term survival outcomes.¹⁴ The critical determinant of clinical outcomes may lie not in the mere presence or absence of biliary strictures, but rather in the implementation of proactive therapeutic strategies and the achievement of favorable initial treatment responses following stricture diagnosis. Over the past two decades, the management of biliary stricture after liver transplantation has transitioned from surgical treatment to primarily endoscopic treatment with adjunctive interventional radiology. The safety and efficacy of endoscopic treatment for BS after liver transplantation have been consistently recognized in earlier studies.^{12,19} Similarly, in our study, 218 ERCP procedures were performed with a total of 24 postoperative complications reported, with no mortality attributed to these complications, thus affirming the safety of the procedure. The overall success rate of initial endoscopic treatment in our cohort was 66.3%, which is consistent with prior findings.¹² Unlike previous studies evaluating the long-

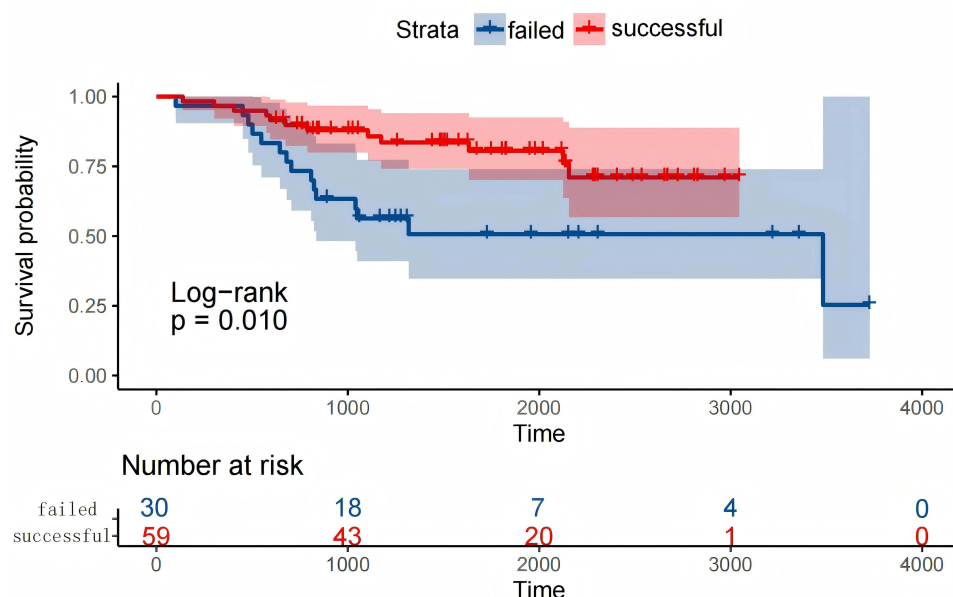


Figure 4 Survival Analysis Comparison between Successful and Failed Initial Endoscopic Treatment Groups for BS after OLT.

term outcome of endoscopic treatment, this study focus was primarily on evaluating the efficacy of initial endoscopic treatment for BS after OLT.

Through risk factor analysis for initial endoscopic treatment efficacy in our cohort, we identified that the proximal and distal bile duct angle $\leq 145^\circ$ ($OR=16.667$, 95% CI : 3.279–83.333, $P=0.001$), severe stricture ($OR=9.009$, 95% CI : 1.590–50.000, $P=0.013$), and NABS ($OR=20.049$, 95% CI : 2.663–150.953, $P=0.004$) were independent risk factors for treatment failure. Compared to anastomotic strictures, NABS present greater challenges for endoscopic management, yielding lower success rates and poorer prognoses.²⁰ This disparity is rooted in the mechanisms of occurrence, as anastomotic strictures result from surgical techniques and local ischemic fibrotic responses, while NABS may result from ischemia or immune-mediated injury to the biliary system. Morphologically, NABS tend to be more complex and have longer segments compared to anastomotic strictures, which can impede effective treatment.²¹ Patients with severe of biliary stricture exhibit poorer outcomes with ERCP treatment, likely because tissues in those with mild strictures are softer and thus more amenable to endoscopic reshaping and correction.²² Lee YY et al similarly suggest that the diameter of the lumen at the stricture site is closely related to the feasibility of initial endoscopic treatment.¹⁵

Moreover, our findings indicate that the angle between proximal and distal bile ducts is a significant determinant of endoscopic treatment efficacy for BS after OLT. A smaller angle complicates the selection and passage of guidewires during endoscopic procedures, thereby increasing procedural difficulty and failure rates. Meanwhile the patients with smaller angles in proximal and distal bile duct may still struggle with correct their biliary angle after multiple endoscopic stent placement treatments. It is supported by research of Yazumi et al that noted very low success rates for endoscopic treatment in patients exhibiting sharp angles or kinked duct structures after living donor liver transplantation.²³ Similarly, Lee YY et al reported that the angle between the proximal and the distal catheter influences the efficacy of primary endoscopic therapy in BS.¹⁵ Moreover, when the angle between the proximal and distal bile duct of the stricture is excessively acute, biliary drainage may slow, resulting in bile stasis and bacterial proliferation, which can lead to recurrent cholangitis. The bile duct mucosa then experiences a cycle of inflammatory injury, repair, reinjury, and subsequent repair, alongside persistent proliferation of surrounding connective tissue, resulting in scar formation. This not only diminishes the efficacy of stricture endoscopic treatment but may also contribute to the recurrence of biliary stricture.

While a consensus has been established regarding the use of stents in treating BS after OLT, debate persists over whether to employ metallic stents (FCSEMS) or plastic stents. Some scholars advocate for the superiority of FCSEMS,²⁴

while others find comparable efficacy.^{25,26} Meanwhile, recent guidelines from the American Society for Gastrointestinal Endoscopy recommend prioritizing FCSEMS for initial intervention in extrahepatic biliary strictures.²⁷ However, this study observed no difference in outcomes between FCSEMS and plastic stents, potentially due to the limited economic access in our patient population restricting the use of FCSEMS. The timing of intervention since BS onset has also been indicated in the former literature as an important factor influencing initial endoscopic treatment efficacy;¹⁵ however, our study did not substantiate this link, possibly due to irregular follow-up intervals leading to inaccurate capturing of treatment timelines.

Ultimately, our study encompassing 89 patients with a median follow-up of 7.78 years revealed that the survival rates at 1, 3, and 5 years were 94.4%, 79.0%, and 72.9%, respectively. Survival analysis identified surgical date, preoperative direct bilirubin levels, and efficacy of initial endoscopic treatment as significant risk factors associated with poor prognosis in patients with BS after OLT. Notably, patients undergoing OLT after 2020 exhibited lower mortality risks, which may reflect advancements in surgical techniques and postoperative care that enhance overall patient outcomes.²⁸ Yu YD et al identified serum bilirubin levels as a significant predictor of 12-month survival in their retrospective analysis of 785 liver transplant recipients.²⁹ However, this finding was not corroborated in Liu Y et al's study of 2,964 pediatric transplant cases, potentially attributable to age differences in bilirubin levels and inter-center heterogeneity.³⁰ From the pathophysiological perspective, the association appears biologically plausible, as elevated preoperative direct bilirubin levels may reflect more severe hepatic injury, consequently increasing postoperative mortality risk.

Importantly, only initial endoscopic treatment failure (HR=3.205, 95% CI: 1.350–7.634, $P=0.008$) was identified as an independent predicting factor for mortality in this patient cohort. The 1-, 3-, and 5-year survival rates for the failed initial endoscopic treatment group were 96.7%, 56.3%, and 50.7%, respectively, in contrast to 96.6%, 87.9%, and 80.6% for the successful group. This stark decline in survival rate among those with failed initial treatment underscores the critical impact of intervention success on overall prognosis. Successful initial treatments significantly improve survival and quality of life, potentially even surpassing that of patients with no biliary strictures after OLT.²⁰

In conclusion, severe stricture, the proximal and distal bile duct angle $\leq 145^\circ$, and non-anastomotic strictures are independent risk factors for the failure of initial endoscopic treatment of BS after OLT. Patients who experience failure of the initial endoscopic intervention for BS after OLT exhibit significantly poorer survival outcomes. Therefore, proactive follow-up and treatment should be undertaken, particularly for those at risk of initial endoscopic failure. A combination of various therapeutic approaches may be considered to enhance survival duration.

This study acknowledges certain limitations. Some data utilized were derived from past records rather than specifically collected for this research purpose, resulting in incomplete or unavailable data that might introduce selection bias, thus potentially affecting the accuracy and reliability of findings. Consequently, these results may need validation through prospective studies. Additionally, the single-center nature of this study may limit the generalizability of its outcomes due to potential heterogeneity across different institutions. Finally, the relatively small sample size necessitates further investigation in larger cohorts in future research.

Conclusion

Initial endoscopic treatment for BS in patients after OLT is effective, safe, and has a high success rate. However, patients with the proximal and distal bile duct angle $\leq 145^\circ$, NABS, and severe strictures exhibit poorer initial endoscopic treatment effect. Those whose initial endoscopic treatment fails demonstrate significantly worse prognoses.

Acknowledgments

This study was supported by Scientific Research Program of Jilin Provincial Department of Education (No. JJKH20231194KJ); Scientific Research Project of Jilin Provincial Department of Finance (No. JLSWSRCZX2020-0030; No. JLSWSRCZX2021-074); Research Project of Undergraduate Teaching Reform in Jilin University (No. 2021XZC087); Research Projects of Higher Education in Jilin Province (No. JGJX2021D53); Scientific Research Project of Jilin Provincial Department of Finance (No. JLSWSRCZX2025-068).

Author Contributions

Decai Kong is responsible for designing the thesis framework and drafting the thesis; Decai Kong, Xiaojing Zhang, Yangguang Yuan and Haoyu Duan were responsible for the implementation of the research process, data collection, statistical analysis, and charting; Junfeng Ye is responsible for revising the paper, formulating writing ideas, guiding the writing of the article and finalizing the draft. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

- Hibi T, Wei Chieh AK, Chi-Yan Chan A, et al. Current status of liver transplantation in Asia. *Int J Surg*. 2020;82S:4–8. doi:10.1016/j.ijssu.2020.05.071
- Moy BT, Birk J. W A review on the management of biliary complications after orthotopic liver transplantation. *J Clin Transl Hepatol*. 2019;7(1):61–71. doi:10.14218/JCTH.2018.00028
- Fasullo M, Shah T, Zhou H, et al. Post-transplant biliary strictures: an updated review. *Semin Liver Disease*. 2022;42(2):225–232. doi:10.1055/s-0042-1744144
- Matar AJ, Ross-Driscoll K, Kenney L, et al. Biliary complications following adult deceased donor liver transplantation: risk factors and implications at a high-volume US center. *Transplant Direct*. 2021;7(10):e754. doi:10.1097/TXD.0000000000001207
- Michael FA, Friedrich-Rust M, Erasmus HP, et al. Treatment of non-anastomotic biliary strictures after liver transplantation: how effective is our current treatment strategy? *J Clin Med*. 2023;12(10):3491. doi:10.3390/jcm12103491
- Yun G, Yoon CJ, Seong NJ. Percutaneous treatment of benign bilioenteric anastomotic strictures: temporary covered stent placement versus balloon dilatation. *Eur Radiol*. 2019;29(5):2690–2697. doi:10.1007/s00330-018-5776-5
- Jang SI, Lee KH, Yoon HJ, et al. Treatment of completely obstructed benign biliary strictures with magnetic compression anastomosis: follow-up results after recanalization gastrointestinal endoscopy. *Gastrointestinal Endoscopy*. 2017;85(5):1057–1066. doi:10.1016/j.gie.2016.08.047
- Walter D, Laleman W, Jansen JM, et al. A fully covered self-expandable metal stent with antimigration features for benign biliary strictures: a prospective, multicenter cohort study. *Gastrointes Endosc*. 2015;81(5):1197–1203. doi:10.1016/j.gie.2014.10.026
- Park JS, Lee SS, Song TJ, et al. Long-term outcomes of covered self-expandable metal stents for treating benign biliary strictures. *Endoscopy*. 2016;48(5):440–447. doi:10.1055/s-0042-101406
- Conigliaro R, Pigò F, Bertani H, et al. Migration rate using fully covered metal stent in anastomotic strictures after liver transplantation: results from the BASALT study group. *Liver Int*. 2022;42(8):1861–1871. doi:10.1111/liv.15246
- Lam R, Muniraj T. Muniraj T fully covered metal biliary stents: a review of the literature. *World J Gastroenterol*. 2021;27(38):6357–6373. doi:10.3748/wjg.v27.i38.6357
- Fan Z, Zhao X, Ji R, et al. Endoscopic treatment of benign biliary stricture using different stents: a systematic review and meta-analysis. *Wideochir Inne Tech Maloinwazyjne*. 2022;17(1):35–60. doi:10.5114/wiitm.2021.108418
- Roos FJM, Poley JW, Polak WG, et al. Biliary complications after liver transplantation; recent developments in etiology, diagnosis and endoscopic treatment. *Best Pract Res Clin Gastroenterol*. 2017;31(2):227–235. doi:10.1016/j.bpg.2017.04.002
- Kim TH, Lee SK, Han JH, et al. The role of endoscopic retrograde cholangiography for biliary stricture after adult living donor liver transplantation: technical aspect and outcome. *Scand J Gastroenterol*. 2011;46(2):188–196. doi:10.3109/00365521.2010.522722
- Lee YY, Gwak GY, Lee KH, et al. Predictors of the feasibility of primary endoscopic management of biliary strictures after adult living donor liver transplantation. *Liver Transpl*. 2011;17(12):1467–1473. doi:10.1002/lt.22432
- Esser H, Kilpatrick AM, Man TY, et al. Primary cilia as a targetable node between biliary injury, senescence and regeneration in liver transplantation. *J Hepatol*. 2024;S0168-8278;24:02302–X.
- Agostini C, Bucciante S, Risaliti M, et al. Complications in post-liver transplant patients. *J Clin Med*. 2023;12(19):6173. doi:10.3390/jcm12196173
- Rammohan A, Govil S, Vargese J, et al. Changing pattern of biliary complications in an evolving liver transplant unit. *Liver Transpl*. 2017;23(4):478–486. doi:10.1002/lt.24736
- Keane MG, Devlin J, Harrison P, et al. Diagnosis and management of benign biliary strictures post liver transplantation in adults. *Transplantation Rev*. 2021;35(1):100593. doi:10.1016/j.tre.2020.100593
- Zhang CC, Rupp C, Exarchos X, et al. Scheduled endoscopic treatment of biliary anastomotic and nonanastomotic strictures after orthotopic liver transplantation. *Gastrointes Endosc*. 2023;97(1):42–49. doi:10.1016/j.gie.2022.08.034
- Fasullo M, Ghazaleh S, Sayeh W, et al. Prognostic factors for non-anastomotic biliary strictures following adult liver transplantation: a systematic review and meta-analysis. *Dig Dis Sci*. 2023;68(6):2683–2694. doi:10.1007/s10620-023-07861-0
- Bowen H, Wenzhi G, Peihao W, et al. The reasonable therapeutic modality for biliary duct-to-duct anastomotic stricture after liver transplantation: ERCP or PTC? *Front Oncol*. 2022;12:1035722. doi:10.3389/fonc.2022.1035722
- Yazumi S, Chiba T. Chiba T Biliary complications after a right-lobe living donor liver transplantation. *J Gastroenterol*. 2005;40(9):861–865. doi:10.1007/s00535-005-1698-5
- Tal AO, Finkelmeier F, Filmann N, et al. Multiple plastic stents versus covered metal stent for treatment of anastomotic biliary strictures after liver transplantation: a prospective, randomized, multicenter trial. *Gastrointes Endosc*. 2017;86(6):1038–1045. doi:10.1016/j.gie.2017.03.009

25. Martins FP, De Paulo GA, Contini MLC, et al. Metal versus plastic stents for anastomotic biliary strictures after liver transplantation: a randomized controlled trial. *Gastrointes Endosc.* **2018**;87(1):131e1–131e13. doi:10.1016/j.gie.2017.04.013
26. Ramchandani M, Lakhtakia S, Costamagna G, et al. Fully covered self-expanding metal stent vs multiple plastic stents to treat benign biliary strictures secondary to chronic pancreatitis: a multicenter randomized trial. *Gastroenterology.* **2021**;161(1):185–195. doi:10.1053/j.gastro.2021.03.015
27. Amateau SK, Kohli DR, Desai M, et al. American society for gastrointestinal endoscopy guideline on management of post-liver transplant biliary strictures: methodology and review of evidence. *Gastrointes Endosc.* **2023**;97(4):615–637e11. doi:10.1016/j.gie.2022.10.006
28. Han JW, Choi JY, Lee SK, et al. Long-term clinical outcomes and predictive factors for living-donor liver transplant recipients with biliary strictures. *Transplantation.* **2022**;106(10):1990–1999. doi:10.1097/TP.0000000000004201
29. Yu YD, Lee KS, Man Kim J, Korean Organ Transplantation Registry Study Group, et al. Artificial intelligence for predicting survival following deceased donor liver transplantation: retrospective multi-center study. *Int J Surg.* **2022**;106:106838. doi:10.1016/j.ijssu.2022.106838
30. Liu Y, Pan Q, Wang B, et al. Development of a survival predictive model after pediatric liver transplantation: a single-center retrospective cohort study. *Transplantation.* **2025**. doi:10.1097/TP.0000000000005299

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