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Safety and indications for endoscopic retrograde cholangiopancreatography in liver transplant patients: an analysis of the United States' National Inpatient Sample database

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Abstract

Background Endoscopic retrograde cholangiopancreatography (ERCP) is performed to treat biliary complications after a liver transplantation; however, the previously available literature on the safety of ERCP in liver transplant patients is limited. We aimed to study the safety of ERCP in liver transplant patients.

Methods We used a National Inpatient Sample database from 2016-2019 to identify patients who underwent ERCP and had a history of a liver transplantation, using the international classification of diseases, 10th revision. Multivariate logistic regression analysis was conducted to determine the odds of post-ERCP complications in liver transplant recipients.

Results Liver transplant patients who underwent ERCP had a higher rate of post-ERCP pancreatitis and bleeding compared to the general adult population (11.39% vs. 9.19%, 0.83% vs. 0.53%, respectively). However, the adjusted odds of post-ERCP pancreatitis (adjusted odds ratio [aOR] 1.13, 95% confidence interval [CI] 0.86-1.49; P=0.36) and bleeding (aOR 1.41, 95%CI 0.58-3.46; P=0.45) were similar in both the liver transplant and no-transplant groups. There was no difference in the odds of post-ERCP cholangitis (aOR 1.26, 95%CI 0.80-2.01; P=0.32), and sepsis (aOR 0.94, 95%CI 0.66-1.34; P=0.76) between liver transplant and no transplant groups. Biliary stricture was the most common indication for ERCP in the liver transplant group, whereas choledocholithiasis was the main reason for ERCP in the general adult population.

Conclusions ERCP is a safe procedure for treating biliary complications in liver transplant patients. The odds of post-ERCP complications (pancreatitis, bleeding, sepsis, cholangitis) in liver transplant patients are comparable to those in patients with no transplantation.

Keywords Endoscopic retrograde cholangiopancreatography, liver transplant, pancreatitis, cholangitis, bleeding

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Conflict of Interest: None

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Introduction

Liver transplantation, first performed in 1963, is on a rising trend worldwide, resulting in significant improvements in the management of end-stage liver disease. Although surgical techniques and post-transplant care have been improving, the rate of complications is relatively high [1]. Biliary complications represent a substantial cause of post-liver transplant morbidity and mortality, affecting 6-34% of patients [2]. The most common biliary complications reported are biliary leaks and stricture formation. The bile leaks usually develop within 3 months of transplantation and are reported in

1-25% of cases, whereas stricture is a late complication with a reported frequency of 3-15% in deceased donor liver transplant recipients and about 28-32% in living liver donor cases [3-5]. The other notable biliary complications seen in liver transplant recipients are the formation of stones, casts, sludge, fistula, and sphincter of Oddi dysfunction [1,6].

Endoscopic retrograde cholangiopancreatography (ERCP) has emerged as the cornerstone of management for biliary complications in patients with liver transplantation, especially bile leaks and bile duct strictures, with a success rate of more than 90% [7,8]. However, ERCP entails the risk of adverse events, such as pancreatitis, cholangitis, perforation, bleeding and infection, in both general and liver transplant patient populations [6].

ERCP in post-liver transplant patients is considered safe. However, the existing data on ERCP complications in liver transplant patients lack consensus, while studies have shown a varying incidence of complications associated with ERCP [9,10]. Therefore, we analyzed the data from the National Inpatient Sample (NIS) and assessed the burden of complications in liver transplant recipients undergoing ERCP compared to the general adult population. We further investigated the most common indications for ERCP in both groups.

Materials and methods

Study design

This is a retrospective analysis of the data obtained from NIS, the largest publicly available all-payer database maintained by the healthcare cost and utilization agency (HCUP) [11]. The data include one primary and 39 secondary discharge diagnoses and 25 procedure codes, as well as other patient- and hospital-level information. The patient-level information includes age, sex, race, insurance status and median household income in the patient's zip code, while the hospital-level information is arranged in 4 hierarchical categories: hospital location, size, teaching status and ownership. A 20% probability sample of patients from all hospitals is collected. Each discharge is then weighted (weight=total number of discharges from all acute care hospitals in the United States divided by the number of discharges included in the 20% sample), making it nationally representative. We recorded up to 40 discharge diagnoses and 25 procedures. The dataset from 2016-2019 consists of more than 7 million weighted discharges each year, which is a 20% stratified sample from over 4500 nonfederal acute care hospitals in more than 48 states of the United States. This is equivalent to about 35 million yearly discharges nationwide when weighted and representative of 95% of hospital discharges nationwide.

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Study population

We analyzed the NIS from 2016-2019 and recruited all patients who underwent diagnostic or therapeutic ERCP. We used the international classification of diseases, 10th revision (ICD-10), to identify these patients. We further subdivided the study population into 2 groups based on the history of a liver transplantation. We excluded patients under the age of 18 and those admitted for a new liver transplantation.

Study outcomes and variable definition

The outcomes of interest were post-ERCP pancreatitis, bleeding, and acute cholangitis. We also investigated the most common causes of ERCP in both groups. We also analyzed the resource utilization, including mean length of stay and total hospital charges.

Statistical analysis

Analysis was performed using STATA version 17. Categorical variables were compared using the chi-square test, and a *t*-test was performed to find the difference between continuous variables. Multivariate analysis was conducted to obtain adjusted odds ratios. Variables included in the multivariate regression model were age, race/ethnicity, hospital teaching status, hospital size, hospital location, median household income, insurance status, Charlson's comorbidity index, and history of chronic kidney disease, cerebrovascular accident, coronary artery disease, congestive heart failure, hyperlipidemia, obesity, alcohol use, cigarette smoking or malnutrition. These variables were selected as confounders in multivariable regression analysis based on the significant association seen in univariate analysis with a cutoff P-value of 0.2. Logistic regression analysis was performed for categorical variables (post-ERCP pancreatitis, bleeding, acute cholangitis, infection/sepsis). In contrast, linear regression was used for continuous variables (mean length of stay and total charges). Deyo's modification of the Charlson comorbidity index was used to assess the comorbidity burden and was included in regression models [12].

Results

Patient characteristics

There were 28 million hospital discharges between the years 2016-2019, of which 580,040 received diagnostic or therapeutic

ERCP. Five thousand three hundred ninety-five patients were under age 18, so they were excluded from the study. Of the adult patients who underwent ERCP, 0.53% (3030) had a history of a liver transplantation. Fig. 1 shows the inclusion and exclusion criteria of the study population. 66.34% patients in the transplant group were male compared to 43.52% in the no-transplant group. Most patients in the study and control groups were White (66.43% vs. 67.23%, P=0.51), followed by Hispanic and Blacks. Most patients with a history of liver transplantations had high Charlson comorbidity index scores compared to the control group (57.10% vs. 30.38%, P<0.001). Medicare insured most patients in both transplant and no-transplant groups (47.19% vs. 49.57%, P<0.001), followed by private/self-insurance. The liver transplant patients underwent their ERCP predominantly in large urban teaching hospitals; similar trends were seen in the patients without transplant history (Table 1).

Liver transplant patients were more likely to have diabetes mellitus, cerebrovascular accidents, chronic kidney disease, and malnutrition. Dyslipidemia, congestive heart failure, coronary artery disease, and hypertension were present more often in patients without a liver transplantation (Fig. 2).

Post-ERCP complications

The overall incidence of post-ERCP pancreatitis in liver transplant recipients was 11.39%, compared to 9.19% in the general population. On multivariate regression analysis, the odds of post-ERCP pancreatitis in transplant patients were 13% more, but these results did not achieve statistical significance (adjusted odds ratio [aOR] 1.13, 95% confidence interval [CI] 0.86-1.49; P=0.36). Post-ERCP bleeding was seen in 0.83% of transplant patients, while only 0.53% of non-transplant patients developed bleeding. On adjusted analysis, higher odds of bleeding were seen in transplant patients, but the results were non-significant (aOR 1.41, 95%CI 0.58-3.46; P=0.45). Of the general adult population, 2.40% developed acute cholangitis after the ERCP, while 3.45% of liver transplant patients had acute cholangitis. On multivariate regression analysis, no significant difference in cholangitis was seen in both groups (aOR 1.26, 95%CI 0.80-2.01; P=0.32). Liver transplant patients had more cases of post-ERCP sepsis (6.27% vs. 4.58%) in comparison to the general patient population, but the adjusted odds were similar in both study groups (aOR 0.94, 95%CI 0.66-1.34; P=0.76) (Table 2, Fig. 3).

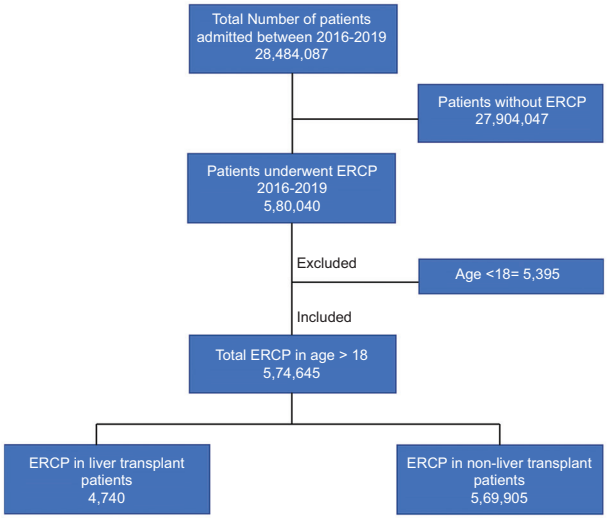


Figure 1 Criteria for the study population. Patients were selected from National Inpatient Sample using ICD-10 codes
ERCP, endoscopic retrograde cholangiopancreatography

Indications for ERCP

Indications for ERCP in both groups were similar but with different frequencies. The main presentation for ERCP in the liver transplant group was biliary stricture. In that group 44.71% of patients underwent ERCP for biliary stricture, while only 18.99% in the no-transplant group underwent the ERCP for stricture. In contrast, 46.63% of patients in the no-transplant population underwent ERCP for choledocholithiasis, while only 10.56% of patients in the transplant group underwent ERCP for that reason. Acute cholangitis was the reason for ERCP in 25.74% of liver transplant patients, whereas 14.64% of patients without liver transplant history underwent ERCP for cholangitis. ERCP was performed for bile leak in 8.25% of cases in the transplant group, compared to only 3.94% in the no-transplant group. Biliary acute pancreatitis was a much more common reason for ERCP in the no-transplant group compared to transplant patients (13.74% vs. 1.00%) (Fig. 4A, B).

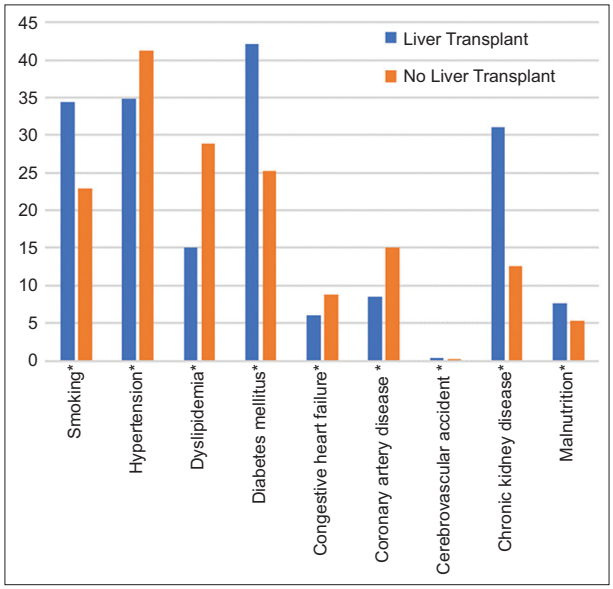


Figure 2 Disease burden in the study population
*P<0.05

Table 1 Baseline characteristics of the study population

Baseline characteristics	Total number of ERCP (574,645)		P-value
	Liver transplant history [n (%) 3030 (0.53%)]	No liver transplant history [n (%) 571,615 (99.47%)]	
Mean age [years]	58 (57-58.9)	61.4 (61.3-61.6)	<0.001
Female sex [n (%)]	1020 (33.66%)	322765 (56.48%)	<0.001
Race [n (%)]			0.51
White	1910 (66.43%)	371425 (67.23%)	
Black	160 (5.57%)	48570 (8.79%)	
Hispanic	530 (18.43%)	85780 (15.53%)	
Asians	150 (5.22%)	23450 (4.24%)	
Native Americans	15 (0.52%)	4395 (0.80%)	
Others	110 (3.83%)	18825 (3.41%)	
Charlson comorbidity index [n (%)]			<0.001
0	0 (0.00%)	204880 (35.84%)	
1	780 (25.41%)	114995 (20.12%)	
2	530 (17.49%)	78075 (13.66%)	
3 or more	1730 (57.10%)	173665 (30.38%)	
Median household income in zip code (quartile)			0.004
$1-42,999	575 (19.39%)	152620 (27.13%)	
$43,000-53,999	785 (26.48%)	146890 (26.11%)	
$54,000-70,999	835 (28.16%)	141570 (25.16%)	
≥$71,000	770 (25.97%)	121525 (21.60%)	
Hospital region [n (%)]			0.67
Northeast	520 (17.16%)	105930 (18.53%)	
Midwest	604 (19.97%)	126930 (22.21%)	
South	1160 (38.28%)	203150 (35.54%)	
West	745 (24.59%)	135604 (23.72%)	
Insurance status [n (%)]			<0.001
Medicare	1430 (47.19%)	283010 (49.57%)	
Medicaid	330 (10.89%)	82755 (14.50%)	
Private/self-pay	1165 (38.45%)	161690 (28.32%)	
Uninsured	30 (1.00%)	27370 (4.80%)	
Hospital size [n (%)]			<0.001
Small	154 (5.12%)	86514 (15.14%)	
Medium	404 (13.37%)	155865 (27.27%)	
Large	2470 (81.52%)	329235 (57.60%)	
Hospital teaching status [n (%)]			<0.001
Rural	10 (0.33%)	17465 (3.06%)	
Urban non-teaching	84 (2.81%)	111435(19.49%)	
Urban teaching	2935(96.86%)	442715 (77.45%)	

ERCP, endoscopic retrograde cholangiopancreatography

Table 2 Adjusted odds of post-ERCP complication in liver transplant patients

Outcomes	aOR	95%CI	P-value
Post-ERCP pancreatitis	1.13	0.86-1.49	0.36
Post-ERCP bleeding	1.41	0.58-3.46	0.45
Post-ERCP cholangitis	1.26	0.80-2.01	0.32
Sepsis	0.94	0.66-1.34	0.76

ERCP, endoscopic retrograde cholangiopancreatography; aOR, adjusted odds ratio; CI, confidence interval

Complications in patients who underwent biliary sphincterotomy for biliary stricture

We performed a subgroup analysis in patients who underwent ERCP with biliary sphincterotomy for biliary stricture and found that liver transplant patients with biliary stricture had significantly higher rates of post-ERCP pancreatitis (16.9% vs. 10.6%, P=0.001), bleeding (9.3% vs. 5.6%, P=0.002), cholangitis (15.8% vs. 11.6%, P=0.02) and sepsis (2.6% vs. 0.47%, P=0.001) compared to the patient group without a liver transplant (Fig. 5).

Discussion

In the current study, we investigated ERCP complications in liver transplant recipients compared to the general adult population. The study demonstrates that post-ERCP complications, such as bleeding, pancreatitis, cholangitis and sepsis/infections were comparable to those in the general adult population. This study also determined that the most common indication for ERCP in the liver transplant group was biliary stricture, whereas the predominant indication for ERCP in the no-transplant group was choledocholithiasis. To the best of our knowledge, this is the largest study conducted on a nationally representative cohort to determine the safety of ERCP in liver transplant recipients.

The safety of ERCP in patients with liver transplant history is a matter of debate, given the limited published literature on the topic. Previous studies assessing the risk of ERCP complications in transplant recipients yielded conflicting evidence. Our study's overall rate of post-ERCP pancreatitis in liver transplant recipients was 11.39%, compared to 9.19% in the general adult population. In our study, we found non-significantly higher odds of post-ERCP pancreatitis in liver transplant patients, similar to the analysis performed by Catron *et al*, who concluded that transplant patients had a higher risk of developing pancreatitis, but the results did not achieve significance. However, Li *et al* documented higher odds of post-ERCP pancreatitis in liver transplant patients, and their results were statistically significant [13,14]. Contrary to our results, Singh *et al* reported lower trends of post-ERCP pancreatitis in liver transplant patients [15]. Our results are also reinforced by those of Alomari *et al*, who conducted a meta-analysis and reported non-significantly higher pooled odds of post-ERCP pancreatitis in liver transplant patients [16].

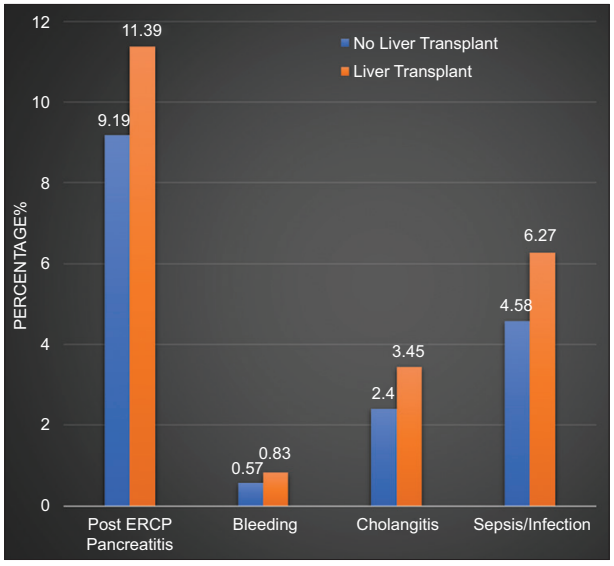


Figure 3 Post-ERCP complication rate in liver transplant vs. no-transplant group
ERCP, endoscopic retrograde cholangiopancreatography

The overall rate of bleeding in our study population was 0.83%, compared to 0.53% in the general adult population. On multivariate regression analysis, we did not find any difference in the odds of post-ERCP bleeding between liver transplant and no-transplant group which is in accordance with the result found in the study performed by Sanna *et al* [17].

ERCP carries a high risk of infection compared to other diagnostic procedures, and in the case of transplant recipients on long-term immunosuppressive agents, this risk increases even further [7,18]. In view of the high risk of infection, the American College of Gastroenterology recommends antibiotic prophylaxis in all liver transplant recipients undergoing ERCP [19]. Previously Kohli *et al* conducted a retrospective analysis of liver transplant patients and found that the odds of post-ERCP infection in liver transplant recipients are low [7]. We also found that 3.45% of liver transplant patients developed post-ERCP cholangitis, similar to the incidences of 4.5% and 3.3% reported in the previous studies by Ambrus *et al* and Law *et al* [20,21]. Furthermore, we found that the odds of post-ERCP cholangitis in liver transplant patients are comparable to the general adult population, reinforcing previously available studies [10,16].

We also noted that indications to perform ERCP were significantly different between the liver transplantation and the general adult population. Bile duct anastomotic stricture, bile leak and cholangitis are commonly reported indications

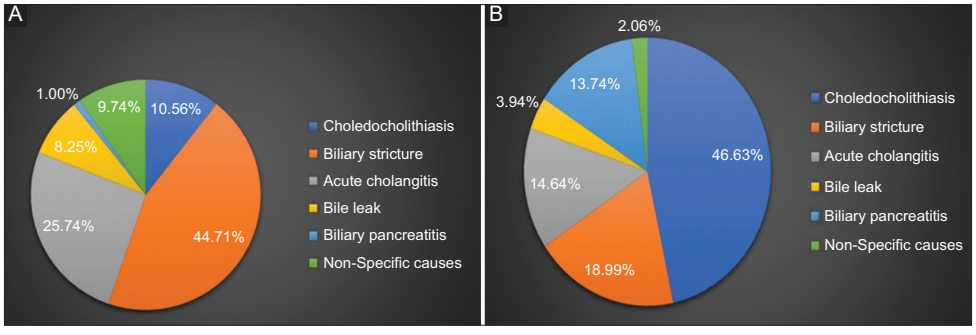
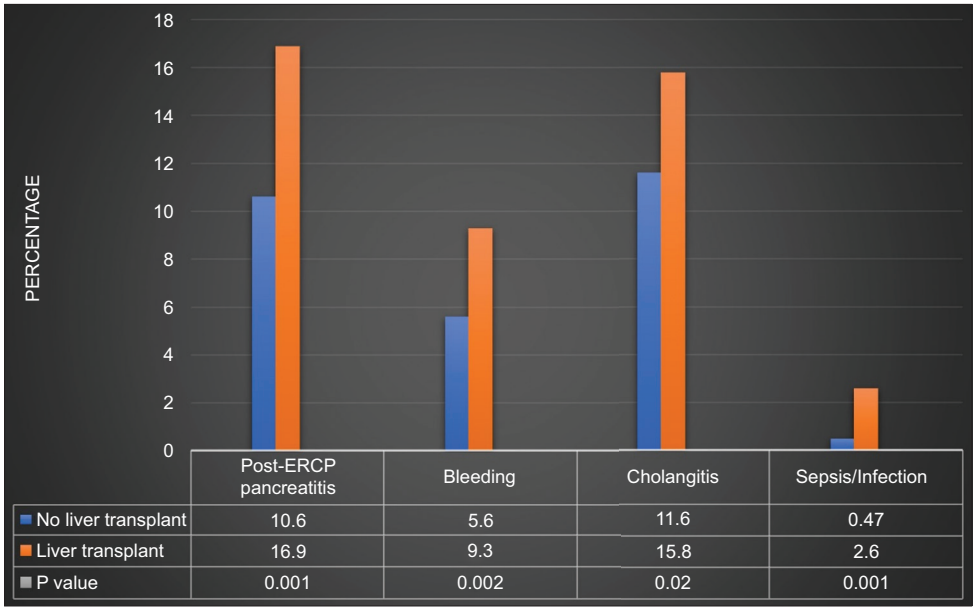


Figure 4 (A) Indications for ERCP in liver transplant patients. (B) Indications for ERCP in patients without a liver transplant
ERCP, endoscopic retrograde cholangiopancreatography



	Post-ERCP pancreatitis	Bleeding	Cholangitis	Sepsis/Infection
No liver transplant	10.6	5.6	11.6	0.47
Liver transplant	16.9	9.3	15.8	2.6
P value	0.001	0.002	0.02	0.001

Figure 5 Post-ERCP complications in biliary stricture patients in liver transplant vs. no-transplant group
ERCP, endoscopic retrograde cholangiopancreatography

in liver transplant patients, while choledocholithiasis, biliary pancreatitis and cholangitis are the most common indications in the general adult population for ERCP, according to previous studies [22-24]. Like these studies, bile duct stricture was the most common indication for ERCP in our study in transplant patients, while choledocholithiasis was the main reason for performing ERCP in the general adult population.

There are various shortcomings to our study. First, the retrospective nature of our study meant that the exposure was not entirely randomized. However, we employed multivariate regression, including diverse patient and hospital-level characteristics in the model to control for confounders. Second, using ICD-10 codes instead of clinical parameters can result in misclassification of the diagnosis. Third, data on laboratory parameters are not stored in the NIS; therefore, the severity of complications could not be accounted for. Regardless of these constraints, our study has numerous strengths. We used the NIS database, which includes data on patients and various hospital-level characteristics from more than 45 states, resulting in better external validity and generalizability; hence we believe that the results should reflect the patient population admitted to hospitals across the United States.

Moreover, NIS eliminates the commonly encountered limitation of single-center studies by allowing the use of a nationally representative large sample size. Another striking feature of our study is that we excluded patients admitted for new transplants, given the high comorbidity burden in the peri-transplant period. This resulted in a bias-free assessment of the outcomes.

Summary Box

What is already known:

- Biliary complications represent a substantial cause of post-liver transplant morbidity and mortality, affecting about 6-34% of patients
- Biliary stricture and bile leak are the 2 most common complications seen in liver transplant recipients
- Endoscopic retrograde cholangiopancreatography (ERCP) is the main treatment modality for biliary complications in liver transplant recipients

What the new findings are:

- In our analysis we found that ERCP is safe in live transplant recipients
- No difference in the adjusted odds of post-ERCP pancreatitis, bleeding, cholangitis and sepsis was seen between the liver transplant and no-transplant groups
- Biliary stricture was the most common indication for ERCP in liver transplant patients
- Biliary stricture patients who underwent sphincterotomy have a higher rate of complications in the liver transplant group compared to no-transplant patients

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