

Analysis of risk factors associated with endoscopic retrograde cholangiopancreatography for patients with liver cirrhosis: a multicenter, retrospective, clinical study

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Abstract

Background: Endoscopic retrograde cholangiopancreatography (ERCP) is the endoscopic modality of choice for the treatment of biliary and pancreatic diseases. However, patients with cirrhosis, particularly those with decompensated cirrhosis, are believed to be at increased risk for complications associated with ERCP. There is a paucity of literature describing the outcomes of ERCP for patients with cirrhosis. This study aimed to investigate the outcomes of ERCP for cirrhosis patients, especially adverse events, and evaluated its safety and efficacy.

Methods: We performed a multicenter, retrospective study of all patients at Beijing Friendship Hospital affiliated to Capital Medical University, Xijing Hospital affiliated to Air Force Military Medical University, Beijing Youan Hospital affiliated to Capital Medical University, and the Fifth Medical Center of the People's Liberation Army General Hospital from June 2003 to August 2019. The adverse events of inpatient ERCP for patients with ($n = 182$) and without liver cirrhosis (controls; $n = 385$) were compared.

Results: A total of 567 patients underwent ERCP between January 2003 and December 2019 were enrolled in this study. Compared to patients without cirrhosis, patients with cirrhosis were at higher risk for postoperative complications (odds ratio [OR], 4.172; 95% confidence interval [CI], 1.232–7.031; $P < 0.001$) such as postoperative pancreatitis (OR, 2.026; 95% CI, 1.002–4.378; $P = 0.001$) and cholangitis (OR, 3.903; 95% CI, 1.001–10.038; $P = 0.036$). The main indications for ERCP for patients with cirrhosis in this study included choledocholithiasis (101 cases; 55.5%), benign bile duct strictures (46 cases; 25.3%), and malignant bile duct strictures (28 cases; 15.4%). Among them, 23 patients (12.6%) underwent balloon dilation and 79 patients (43.4%) underwent sphincterotomy. Of the patients with cirrhosis, delayed bleeding occurred in ten patients (5.5%), postoperative pancreatitis occurred in 80 patients (44.0%), and postoperative cholangitis occurred in 25 patients (13.7%). An additional multivariate analysis showed that the total bilirubin (TBIL) level (OR, 4.58; 95% CI, 2.37–6.70) and Child-Pugh score of C (OR, 3.11; 95% CI, 1.04–5.37) were risk factors for postoperative complications in patients with cirrhosis.

Conclusions: Compared with the general population of patients undergoing ERCP, patients with cirrhosis were more prone to postoperative pancreatitis and cholangitis. TBIL levels and Child-Pugh scores were risk factors for postoperative complications in patients with cirrhosis.

Keywords: Risk factors; Endoscopic retrograde cholangiopancreatography; Liver cirrhosis

Introduction

For many endoscopists, performing endoscopic retrograde cholangiopancreatography (ERCP) for patients with cirrhosis is challenging, especially at small medical centers. Patients with cirrhosis are at higher risk for adverse events

during ERCP because of underlying ascites, coagulopathy, encephalopathy, esophageal varices, and other problems. In addition, patients with cirrhosis who undergo endoscopy are at higher risk for dysfunction, portal hypertension, coagulopathy, and other difficulties.^[1] However, many patients with cirrhosis and a variety of other

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diseases, especially obstructive jaundice caused by cholelithiasis and malignant bile duct obstruction, develop medical problems that are best treated using ERCP.^[2,3] They are also at increased risk for adverse events because of underlying liver dysfunction and esophageal varices. Surgery has been considered a contraindication for advanced liver disease because cirrhosis is a significant risk factor for postoperative perioperative complications.^[4-6] The safety and outcomes of ERCP for patients with cirrhosis are unclear because the literature regarding the safety of ERCP with cirrhosis mainly comprises small retrospective studies or database studies.^[7] The objective of this large, multicenter, retrospective study was to determine the efficacy and safety of therapeutic ERCP for patients with cirrhosis.

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the local ethics committee of Beijing Friendship Hospital (No. 2020-P2-078-01). Written informed consent was obtained from all patients before enrollment in the study.

Data source

We performed a multicenter, retrospective search of all patients with and without cirrhosis who underwent therapeutic ERCP at Beijing Friendship Hospital Affiliated to Capital Medical University, Xijing Hospital of Air Force Military Medical University, Beijing Youan Hospital affiliated to Capital Medical University, and the Fifth Medical Center of People's Liberation Army General Hospital between June 2003 and August 2019.

All patients who underwent ERCP were admitted to the hospital. We collected data regarding the demographic characteristics, patient history, pre-procedural laboratory values, post-procedural laboratory values, ERCP indications, procedural details, procedure-related adverse events, and patient mortality. The severity of post-ERCP adverse events was noted in accordance with standard definitions. Follow-up information was obtained through a review of medical records after the procedure to assess immediate adverse events and subsequent complications. The diagnosis of liver cirrhosis was based on the patient's history of cirrhosis, the results of a series of viral hepatitis tests, abdominal imaging examination data (including abdominal plain scan plus enhanced computed tomography [CT]), portal vein CT reconstruction data, and the exclusion of non-cirrhotic portal hypertension such as Budd-Chiari syndrome, idiopathic portal hypertension, and other diseases. For patients with cirrhosis, we collected data regarding the etiology of cirrhosis, Child-Pugh (CP) scores at the time of the procedure, gastrointestinal bleeding history, esophageal varices history, and severity of the disease. Before ERCP, all patients with cirrhosis underwent general gastroscopy to determine the extent of esophagogastric varices and whether there was active bleeding. A preoperative plan for treating esophageal and

gastric varices rupture and bleeding was created. Prophylactic pancreatic ductal stent placement was performed if the pancreatic duct was cannulated during the third attempt or later. We focused special attention on the application of indomethacin for post-ERCP pancreatitis prevention during data collection. None of the included patients confirmed the application of indomethacin supposition or other non-steroidal anti-inflammatory drugs for post-ERCP pancreatitis prevention.

Some patients received prophylactic antibiotics before ERCP because ERCP is an invasive procedure associated with a high risk of bacterial infections, especially for patients anticipated to have non-drainable (or difficult to drain) obstructed duct segments (primary sclerosing cholangitis, hilar tumors, chronic pancreatitis strictures), pseudocysts, and bile leakage, and those who have undergone liver transplantation.

Outcomes, inclusion criteria, and exclusion criteria

The primary outcomes evaluated were ERCP-related adverse events (pancreatitis, bleeding, infection, perforation, and mortality). All enrolled patients were required to meet the following inclusion criteria: age 18 to 90 years; indication for ERCP; diagnosis of cirrhosis with or without esophageal varices. The exclusion criteria were as follows: severe heart disease; cerebrovascular, liver, kidney, or hematopoietic system disorders; mental disorders, intellectual and language disabilities; unable to undergo surgery; pregnancy or trying to become pregnant; breastfeeding; active gastrointestinal bleeding within 2 weeks before ERCP; obstruction of the upper gastrointestinal tract; and missing medical data.

Statistical analysis

Quantitative data are described as the mean and standard deviation for normal distribution, and as the median (quantile) for non-normal distribution. Categorical data are reported as frequency and percentages. Student's *t*-test (normally distributed variables) or the Mann-Whitney test (non-normally distributed variables) was used for continuous variables to compare differences. The chi-square test or Fisher's exact test was used for categorical variables.

A binary logistic regression analysis was used to construct a logit model to assess the factors related to postoperative complications. The probability values for conditional stepwise selection were 0.05 and 0.10 for removal predictors. These analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $P < 0.05$.

Results

Characteristics of enrolled patients

The baseline characteristics of the enrolled patients are summarized in Table 1. A total of 385 patients without cirrhosis and 182 patients with cirrhosis were enrolled. Among the 182 patients with cirrhosis, there were 120

Table 1: Baseline information of patients who underwent therapeutic ERCP.

Characteristics	Patients without cirrhosis (n = 385)	Patients with cirrhosis (n = 182)	P values
Age (years)	63 ± 15	58 ± 13	0.001
Female, n (%)	227 (58.9)	120 (65.9)	0.112
Complications, n (%)			
Coronary disease	72 (18.7)	7 (3.8)	<0.001
Hypertension	162 (42.1)	23 (12.6)	<0.001
Diabetes mellitus	81 (21.0)	28 (15.4)	0.154
Cerebral infarction	34 (8.8)	2 (1.1)	0.001
ERCP indications, n (%)			
Cholelithiasis	174 (45.2)	101 (55.5)	0.032
Benign bile duct stricture	53 (13.8)	46 (25.3)	0.001
Malignant bile duct stricture	54 (14.0)	28 (15.4)	0.722
Management of biliary sphincter, n (%)			
Balloon dilation	40 (10.4)	23 (12.6)	0.379
Sphincterotomy	245 (63.6)	79 (43.4)	<0.001
Laboratory test			
Hemoglobin (g/L)	123.7 ± 48.9	104.8 ± 22.4	0.007
Platelets (×10 ⁹ /L)	202.2 ± 94.0	150.4 ± 108.1	<0.001
WBC (×10 ⁹ /L)	7.8 ± 9.0	6.4 ± 8.0	0.077
INR	1.2 ± 0.6	1.2 ± 0.2	0.404
ALT (U/L)	61 (26, 141)	57 (33, 87)	0.098
AKP (U/L)	177 (105, 344)	226 (131, 408)	0.030
Total bilirubin (μmol/L)	36.3 (17.2, 123.5)	91.0 (33.5, 226.9)	<0.001
Creatinine (μmol/L)	76.5 ± 62.9	74.2 ± 28.5	0.653
BUN (mmol/L)	4.5 ± 1.8	5.9 ± 7.2	<0.001

Values were shown as n (%), mean ± standard deviation, or median (quantile). ALT: Alanine aminotransferase; AKP: Alkaline phosphatase; BUN: Blood urea nitrogen; ERCP: Endoscopic retrograde cholangiopancreatography; INR: International normalized ratio; WBC: White blood cell.

women (65.9%). The mean patient age was 58 years (standard deviation, ± 13 years). Patients had the following comorbidities: cognitive disease (seven cases; 3.8%); cognitive disease (23 cases; 12.6%); diabetes mellitus (28 cases; 15.4%); and cerebral parameters (two cases; 1.1%). The ERCP indications were cholelithiasis (101 patients; 55.5%), benign bile duct strictures (46 patients; 25.3%), and malignant bile duct strictures (28 patients; 15.4%). Twenty three patients (12.6%) underwent balloon dilation and 79 patients (43.4%) underwent sphincterotomy for the management of the biliary sphincter during ERCP.

During this study, the baseline characteristics of cirrhosis patients were assessed according to the following laboratory test results: hemoglobin, 104.8 ± 22.4 g/L; platelets, 150.4 ± 108.1 × 10⁹/L; white blood cell count, 6.4 ± 8.0 × 10⁹/L; international normalized ratio, 1.2 ± 0.2; alanine aminotransferase, 57 U/L (range, 33–87 U/L); red blood cell count, 6.4 ± 8.0 × 10⁹/L; alkaline phosphatase 226 U/L (range, 131–408 U/L); TBIL, 91.0 μmol/L (range, 33.5–226.9 μmol/L); creatinine, 74.2 ± 28.5 μmol/L; and blood urea nitrogen, 5.9 ± 7.2 mmol/L. No cirrhosis results are shown in Table 1.

A comparison of the baseline characteristics of patients with and without cirrhosis showed that 12 patients had statistically significant differences. Patients with cirrhosis who were treated with ERCP were younger. Patients without cirrhosis were more likely to have coronary disease, hypertension, and cerebral infarction. More

patients underwent ERCP because of cholelithiasis and benign bile stricture. Fewer patients chose sphincterotomy. Patients with cirrhosis had different hemoglobin, platelet, alkaline phosphatase, TBIL, and blood urea nitrogen levels, suggesting that patients with cirrhosis had worse anemia, coagulation, liver function, and kidney function. These features are worthy of attention, but no significant differences in the other features were observed. Statistical significance was set at *P* < 0.05 [Table 1].

Postoperative complications

We first analyzed postoperative complications experienced by patients with cirrhosis. Of these, 115 patients (63.2%) had postoperative complications: ten patients (5.5%) had delayed bleeding; 25 patients (13.7%) had postoperative cholangitis; and 80 patients (44.0%) had postoperative pancreatitis.

We further explored the differences in the incidence of complications experienced by patients with and without cirrhosis. Based on the multifactor logistic regression model and after adjusting for the age and sex of the patients, it was found that patients with cirrhosis were at higher risk for postoperative complications (odds ratio [OR], 4.172; 95% confidence interval [CI], 1.232–7.031; *P* < 0.001) such as postoperative pancreatitis (OR, 2.026; 95% CI, 1.002–4.378; *P* = 0.001) and cholangitis (OR, 3.903; 95% CI, 1.001–10.038; *P* = 0.036) [Table 2].

Table 2: The multivariate logistic regression for the postoperative complications in patients with and without cirrhosis.

Models	OR	95% CI	P values
Model 1: Postoperative complications (n = 115) Cirrhosis vs. no cirrhosis	1.172	1.232–7.031	<0.001
Model 2: Delayed bleeding (n = 10) Cirrhosis vs. no cirrhosis	1.037	0.199–5.405	0.966
Model 3: Postoperative pancreatitis (n = 80) Cirrhosis vs. no cirrhosis	2.026	1.002–4.378	0.001
Model 4: Postoperative cholangitis (n = 25) Cirrhosis vs. no cirrhosis	3.903	1.001–10.038	0.036

From Model 1 to Model 4, different types of postoperative complications were considered outcomes in each logistic regression, which have been adjusted for patients' age and sex. CI: Confidence interval; OR: Odds ratio.

Table 3: Univariate analysis of cirrhosis characteristics between patients with and without postoperative complications.

Characteristics	Patients with postoperative complications (n = 115)	Patients without postoperative complications (n = 67)	P values
Age (years)	69 ± 13	63 ± 16	0.006
Male	75 (65)	43 (64)	0.887
WBC (×10 ⁹ /L)	5.04 ± 3.32	5.32 ± 2.59	0.554
PT (seconds)	15.56 ± 2.01	15.16 ± 2.34	0.225
INR	1.24 ± 0.22	1.21 ± 0.24	0.392
ALT (U/L)	77.16 ± 29.28	84.97 ± 40.93	0.152
AST (U/L)	88.58 ± 35.92	86.55 ± 36.51	0.715
ALB (g/L)	46.55 ± 20.92	32.67 ± 13.91	0.001
TBIL (μmol/L)	229.42 ± 79.11	146.10 ± 78.30	0.001
Child-Pugh			<0.001
A	12 (10)	51 (76)	
B	36 (31)	13 (19)	
C	67 (59)	3 (5)	
Complicated with gastric varices	46 (40)	9 (13)	<0.001
Previous gastrointestinal bleeding	23 (20)	4 (6)	0.010
Combined with ascites	69 (60)	29 (43)	0.029
Combined with hepatorenal syndrome	6 (5)	0	0.058

Values were shown as n (%) or mean ± standard deviation. ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio; PT: Prothrombin time; TBIL: Total bilirubin; WBC: White blood cell.

Risk factors for postoperative complications in cirrhosis patients

These results suggest that patients with cirrhosis are at higher risk for postoperative complications. To determine which factors are responsible for the increased risk of complications in patients with cirrhosis, we further analyzed these patients by performing a single-factor analysis including 14 features. Among these 14 features, seven showed statistically significant differences [Table 3]: age (P = 0.006); albumin level (P = 0.001); TBIL level (P = 0.001); CP score (P < 0.001); gastric varices (P = 0.010); previous gastrointestinal bleeding (P < 0.001); and ascites (P = 0.029).

These seven features were incorporated in the multifactor logistic regression analysis model [Figure 1] including the TBIL level (OR, 4.58; 95% CI, 2.37–6.70) and CP score C (OR, 3.11; 95% CI, 1.04–5.37). Higher TBIL levels were associated with a higher risk of postoperative complica-

tions with ERCP. Patients with CP score C were more likely to have postoperative complications than those with score A and score B. According to our multivariate analysis, the TBIL level and CP score were risk factors for postoperative complications in patients with cirrhosis.

Discussion

ERCP is the first choice for the examination and treatment of biliary and pancreatic diseases. With the progress in surgical techniques, its effectiveness and safety have become increasingly high. However, because it is invasive, ERCP still has certain risks, such as pancreatitis, which is the most common complication of ERCP.^[8,9] Cirrhosis is a common gastroenterological disease. Cirrhosis patients often have ascites, portal hypertension, gastric fundus esophageal varices, hypoproteinemia, coagulation dysfunction, and other problems.^[10,11] Cirrhosis is an end-stage liver disease caused by multiple factors, and its pathophysiological processes are consistent. Cirrhosis caused by

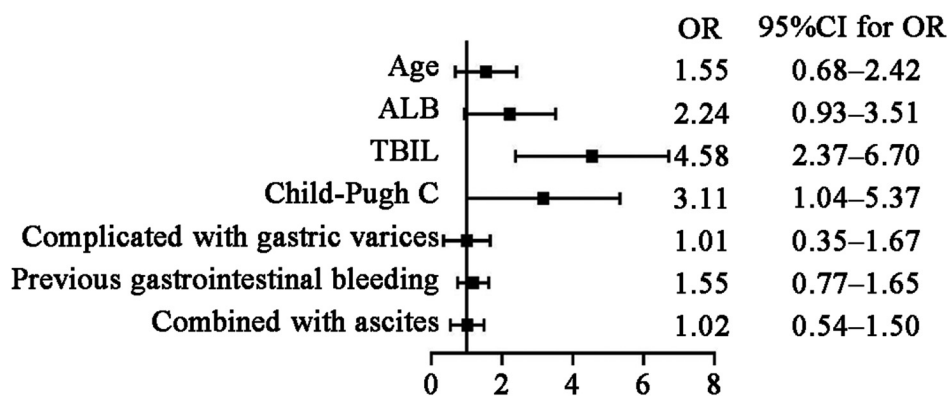


Figure 1: Multivariate logistic regression for the postoperative complications in cirrhosis patients. A stepwise analysis shown TBIL and Child-Pugh were the related factors in our model. ALB: Albumin; CI: Confidence interval; OR: Odds ratio TBIL: Total bilirubin.

different factors exhibits two clinical signs: abnormal liver function and portal hypertension. Therefore, there is no correlation between cirrhosis of different causes and ERCP outcomes. A few studies have specifically examined the role and risk of ERCP for patients with cirrhosis.^[1]

Previous studies have found that patients with cirrhosis are at high risk for postoperative complications such as bleeding, post-ERCP pancreatitis, and infection.^[12] However, a multicenter study conducted by Alder *et al*^[11] found that the risk associated with ERCP for patients with cirrhosis is not significantly higher than that for the general population.

Our study preliminarily showed that the risk of postoperative complications for patients with cirrhosis was higher than that for patients without cirrhosis. This is consistent with the results of previous studies that showed that many patients with cirrhosis require ERCP in clinical practice.^[11-3] Patients with cirrhosis are considered unsuitable for ERCP because of poor hepatic synthesis often associated with platelet dysfunction and coagulopathy, which places them at a higher risk for intraoperative bleeding. Poor coagulation during sphincterotomy can result in acute or delayed bleeding. Our baseline study also found anemia, coagulation deficiency, liver function deficiency, and renal function deficiency in patients with cirrhosis. Patients with cirrhosis also exhibit poor cardiopulmonary function. We analyzed the comorbidities of the patients, including hypertension, coronary artery disease, diabetes, and cerebral infarction, and found a difference in the incidence of comorbidities for patients with and without cirrhosis. Because cirrhosis can lead to the portal pulmonary syndrome, pulmonary hypertension, and hepatic encephalopathy, the probability of high-risk cardiopulmonary events is high.

After adjusting for certain variables, such as sex and age, patients with cirrhosis were found to be at higher risk for developing postoperative pancreatitis and cholangitis. Patients with cirrhosis have poor coagulation function and are at risk for bleeding; therefore, they require more care during surgery, resulting in longer operative times and an increased risk of postoperative pancreatitis. Studies have

shown that cholangitis, coagulation disorders, cholecystectomy, history of jaundice, emergency procedures, intramural sphincter injection, sphincter pressure measurement, and biliary drainage are not risk factors for postoperative pancreatitis.^[13,14] A controversial point is whether the experience of endoscopic operators is meaningful to the occurrence of pancreatitis after ERCP. Notably, a lack of experience and a lower skill level of the operator will significantly increase the occurrence of errors and the risk of postoperative complications. In addition, postoperative monitoring of amylase changes, timely detection, and timely treatment are important for reducing complications.^[15]

Patients with cirrhosis often have hypoalbuminemia associated with malnutrition because of abnormal liver synthesis. Low albumin levels can cause duodenal papilledema, which increases the risk of postoperative biliary tract infection and bleeding. Moreover, the poor general condition of the patient can increase the possibility of infection.^[16] Therefore, for patients with cirrhosis and benign biliary tract stenosis, the risk of biliary tract infection after ERCP is relatively high. Our study confirmed this finding. Regular and repeated stent replacement can reduce the incidence of restenosis.^[17] However, repeated biliary inflammation and invasive surgery increase the incidence of cholangitis.

The use of therapeutic ERCP for patients with decompensated cirrhosis has increased significantly. We further analyzed the related clinical factors that lead to complications and found that the TBIL level and CP score were risk factors for postoperative complications. Choledocholithiasis was the most common indication for ERCP. Furthermore, 57% of patients with cirrhosis had indications for ERCP because of gallstones, similar to our results (55.5%).^[18-20] Patients who underwent ERCP during this study had high TBIL levels, regardless of cirrhosis. Impaired glucuronic acid-binding of indirect bilirubin in patients with decompensated cirrhosis promotes an increase in indirect bilirubin, which may be a reason for the increase in the TBIL level.^[21] One study of ERCP for cirrhosis complicated with choledocholithiasis found that increased bilirubin was associated with the total postoperative complications. We believe that higher

TBIL levels indicate poorer liver function because bilirubin is also used as an indicator of the CP score. A few studies have described the relationship between adverse events and CP scores. These studies consistently showed that patients with higher CP scores had more complications overall.^[22-25] Li *et al*^[8] reported 46 cases of choledocholithiasis treated with ERCP in patients with cirrhosis and found that the incidence of clinically significant bleeding after ERCP was very high (25%) for patients with CP score C. Another study found that the amount of blood loss for patients with cirrhosis and CP score C was significantly higher than that for those with CP score A or B.^[26] Patients with cirrhosis may develop varicose veins in the duodenum, which may increase the risk of bleeding after sphincterotomy. Inamdar *et al*^[18] observed a higher incidence of adverse events in patients with decompensated cirrhosis compared with patients with compensatory cirrhosis. Similarly, Adler *et al*^[11] found that patients with CP score A had fewer postoperative adverse events than those with scores B and C, which was statistically significant. Zhang *et al*^[16] found that there was no significant difference in the incidence of adverse events when correlated with the CP score. However, patients with higher Model for End-stage Liver Disease scores had a higher incidence of adverse events. More evaluation criteria should be used to assess the severity of cirrhosis to gain a better understanding of the condition of the patients. In contrast, normal serum bilirubin levels have been found to double the risk of postoperative pancreatitis; this deserves further consideration.^[27-29]

The advantage of our center—Digestive Endoscopic Center, Beijing Friendship Hospital affiliated to Capital Medical University—is that it has a large patient base and the operators have vast experience with ERCP. ERCP is performed at our center in accordance with relevant guidelines^[30] and regulations and in accordance with strict operating specifications, especially for patients with cirrhosis. Furthermore, at our center, ERCP is performed by experienced digestive endoscopists with a physician level of at least associate chief physician or by those with experience performing at least 500 endoscopic procedures per year. Therefore, the complication rate during this study was lower than the average.

This study had some limitations. Because of the lengthy period of our study, the treatment measures and evaluation criteria for ERCP complications did not change; therefore, the results of the analysis on the complications were not sufficiently comprehensive. The definition and severity assessment of cirrhosis are not sufficiently detailed. Therefore, they should be further refined to obtain more clinically significant results.

In conclusion, ERCP is relatively safe and effective for patients with cirrhosis, but the occurrence of postoperative cholangitis and pancreatitis should be noted. Therefore, the preoperative risk factors for complications should be evaluated in detail, the general patient status and disease status should be comprehensively evaluated, and individualized treatment methods should be formulated to avoid complications.

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Conflicts of interest

None.

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