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Patients with cystic fibrosis do not have an increased risk of adverse events after endoscopic retrograde cholangiopancreatography: a propensity-matched analysis

Mahmoud Y. Madi[a], Saqr Alsakarneh[b], Yassine Kilani[c], Ryan Plunkett[c], Razan Aburumman[d], Farah Heis[c], Christopher Nguyen[a], Christine Hachem[a], Wissam Kiwan[a]

Saint Louis University School of Medicine; University of Missouri-Kansas City, MO, USA; Mayo Clinic, Rochester, MN; Henry Ford Hospital, Detroit, Michigan, USA

Abstract

Background Cystic fibrosis (CF) is a common life-limiting genetic disease often associated with hepatobiliary complications. Endoscopic retrograde cholangiopancreatography (ERCP), though valuable, carries procedural risks. We assessed the safety of ERCP in CF patients using real-world data.

Methods A retrospective cohort study using the TriNetX database (2010-2024) identified adults (≥18 years) with CF who underwent ERCP. Propensity-score matching adjusted for confounders, including age, sex, race, and hospitalization history. The primary outcome was post-ERCP pancreatitis (PEP); secondary outcomes included bleeding and infection. Subgroup analysis evaluated outcomes in patients with choledocholithiasis.

Results Among 534 matched CF patients (mean age 44.6 years; 48.3% female), rates of PEP (8.3% vs. 4.9%, adjusted odds ratio [aOR] 1.76, 95% confidence interval [CI] 0.937-3.315; P=0.075), bleeding (3.1% vs. 2.1%, aOR 1.52, 95%CI 0.674-3.409; P=0.31), and infection (3.7% vs. 2.4%, aOR 1.55, 95%CI 0.638-3.785; P=0.33) were not significantly different compared to non-CF controls. Subgroup analysis of choledocholithiasis patients similarly showed no significant differences.

Conclusions ERCP in CF patients demonstrated comparable adverse event rates to non-CF controls. These findings support the procedural safety of ERCP in this population, though further prospective studies are needed to validate these results and clarify risk by indication.

Keywords Cystic fibrosis, endoscopic retrograde cholangiopancreatography (ERCP), post-ERCP pancreatitis, hepatobiliary complications, ERCP complications

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[a]Division of Gastroenterology and Hepatology, Department of Medicine, Saint Louis University School of Medicine, St Louis, USA (Mahmoud Y. Madi, Christopher Nguyen, Christine Hachem, Wissam Kiwan); [b]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN (Saqr Alsakarneh); [c]Division of General Internal Medicine, Department of Medicine, Saint Louis University School of Medicine, St Louis, MO, USA (Yassine Kilani, Ryan Plunkett, Farah Heis); [d]Department of Medicine, Henry Ford Hospital, Detroit, Michigan, USA (Razan Aburumman)

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Correspondence to: Mahmoud Y Madi, MD, Division of Gastroenterology and Hepatology, Saint Louis University School of Medicine, St Louis, MO, USA, e-mail: mahmood_madi@hotmail.com

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Introduction

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive disease in North America, affecting approximately 30,000 individuals in the United States [1]. The disease results from mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene, leading to dysfunction of the chloride channel and impaired ion transport across epithelial cell membranes [2]. While respiratory manifestations are often the focus of clinical attention, hepatobiliary involvement is increasingly recognized as a significant concern, occurring in 15-30% of CF patients [3].

Hepatobiliary manifestations in CF include cholelithiasis, gallbladder dysfunction, biliary strictures and stenosis [3]. Additionally, CF-related liver disease can progress to portal hypertension and cirrhosis in 5-10% of patients, representing the third leading cause of death in this population [4]. The pathophysiology involves CFTR protein expression in

cholangiocytes, leading to dysfunctional water and bicarbonate secretion into bile, resulting in thickened secretions, biliary obstructions, inflammation, and progressive fibrosis within the portal system [5].

In addition to hepatobiliary manifestations, pancreatic involvement is a hallmark of CF. Approximately 85-90% of CF patients develop exocrine pancreatic insufficiency due to fibrotic replacement of pancreatic tissue. Interestingly, this destruction of acinar cells appears to confer a reduced risk of acute pancreatitis compared to the general population. However, individuals with milder *CFTR* mutations or pancreatic sufficiency retain some acinar function and may be at increased risk of recurrent acute or even chronic pancreatitis [6,7]. Thus, the pancreatic phenotype in CF may paradoxically influence pancreatitis risk, depending on the degree of residual pancreatic parenchyma.

The prevalence of cholelithiasis in CF patients ranges from 15-30%, driven by altered bile composition, reduced gallbladder motility and mucus hypersecretion. CF patients may also develop choledocholithiasis, although the incidence relative to the general population remains uncertain. Some studies suggest a potentially reduced risk due to bile stasis and altered enterohepatic circulation, but these findings are inconsistent [8,9].

Endoscopic retrograde cholangiopancreatography (ERCP) is a valuable diagnostic and therapeutic tool for hepatobiliary diseases in the general population. There are limited data regarding the safety and efficacy of ERCP specifically in CF patients [10]. This raises concerns, given that ERCP carries inherent risks, including post-ERCP pancreatitis ([PEP] occurring in 3-10% of cases), bleeding, infection, and perforation [11]. Additionally, CF patients present unique challenges due to their increased susceptibility to respiratory infections, potential for anesthesia-related complications, and underlying pancreatic insufficiency [6].

Current management guidelines for CF-related hepatobiliary complications lack consensus regarding the optimal approach to interventional procedures such as ERCP [11]. While ursodeoxycholic acid has been used as a pharmacological intervention, its efficacy remains questionable [12]. *CFTR* modulators may theoretically improve cholangiocyte function, but supportive evidence is limited [13]. These therapeutic gaps highlight the potential importance of ERCP in managing hepatobiliary manifestations of CF.

Despite the clinical relevance, research examining the safety profile of ERCP specifically in CF patients remains sparse. Given the aging CF population, as a result of better survival [14] and the significant burden of hepatobiliary disease in these patients, understanding the risk–benefit profile of ERCP is crucial for informed clinical decision-making. This study aims to investigate the safety of ERCP in CF patients compared to non-CF controls using real-world data, with a focus on postprocedural complications, including PEP, bleeding, perforation and infection.

Materials and methods

Data source

We conducted a retrospective cohort analysis using the US-Collaborative TriNetX Analytics Network Platform (Cambridge, USA), a comprehensive global federated research network, incorporating demographic and administrative data from 69 healthcare organizations for more than 110 million patients in the US. The TriNetX platform facilitates cohort selection and the application of propensity-score matching (PSM), allowing for comparative analysis while accounting for potential confounders. PSM was performed to adjust for confounding variables, including age, sex, race/ethnicity and number of hospitalizations. Known risk factors for post-ERCP adverse events, such as younger age, female sex and history of acute pancreatitis, were prioritized [11]. Unfortunately, ERCP-specific procedural variables, such as ductal dilation or cannulation technique, were not available in TriNetX and thus could not be included in the PSM. This was a limitation of the study. A rigorous quality assurance process is enforced during the extraction of electronic health records, ensuring that the data are systematically formatted and standardized before their inclusion in the database. In accordance with the guidelines from the National Human Research Protections Advisory Committee, this study was exempt from Institutional Review Board (IRB) approval, as it involved publicly available, de-identified data [15]. The de-identification process, as stipulated by the Health Insurance Portability and Accountability Act Privacy Rule, is meticulously executed at the network level by a qualified expert within the TriNetX framework [16].

Study population and variables

A real-time search and analysis of the US Collaborative Network in the TriNetX platform were conducted from 2010-2024. We analyzed records of adults (≥18 years) who were hospitalized and underwent ERCP. We then stratified patients by the presence of CF into 2 groups, those who had CF and those who did not (control group), using codes from the International Classification of Diseases, Ninth or Tenth Edition, Clinical Modification (ICD-10-CM) (ICD-10: E84).

Patient and hospital characteristics

We retrieved data from the TriNetX database, including age (reported as mean ± standard deviation) and race/ethnicity (categorized as White, Black, Hispanic/Latino, and Not Hispanic/Latino). Based on one-to-one (1:1) PSM variables, we matched records of patients with or without a diagnosis of CF, who were hospitalized and underwent ERCP (Table 1).

Table 1 A comparative analysis of covariates, before and after propensity matching, for hospitalizations of patients with and without cystic fibrosis who underwent endoscopic retrograde cholangiopancreatography in the United States

Demographics	Before propensity score matching				After propensity score matching			
	Cystic fibrosis	No cystic fibrosis	P-value	Standard difference	Cystic fibrosis	No cystic fibrosis	P-value	Standard difference
No. of hospitalizations	534	186337			480	480		
Sex								
Male	208	76470	0.880	0.007	208	208	>0.99	<0.001
Female	258	94565	0.798	0.012	258	258	>0.99	<0.001
Age (years), mean±standard deviation	44.6±20.9	59.4±18.6	<0.001	0.746	44.6±20.9	44.6±20.9	>0.99	<0.001
Race								
White	354	126972	0.252	0.053	354	354	>0.99	<0.001
Hispanic or Latino	50	20413	0.467	0.034	50	50	>0.99	<0.001
Black or African American	43	15492	0.847	0.009	43	43	>0.99	<0.001
Not Hispanic or Latino	362	124476	0.009	0.122	362	362	>0.99	<0.001

Study aims and outcomes

The primary outcome was PEP. Secondary outcomes included gastrointestinal bleeding, and infection (Tables 2, 3). Furthermore, we performed subgroup analyses for patients who were undergoing ERCP for choledocholithiasis (Table 4). Adjustments were made to account for potential confounding factors (age, sex, race, number of hospitalizations). The reporting of this study adheres to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) reporting guidelines [17].

Statistical analysis

Statistical analyses were performed using the TriNetX Advanced Analytics Platform. The characteristics of both groups are presented as mean ± standard deviation (SD) or frequency and proportion. One-to-one PSM was performed to control for covariates between the 2 comparison groups and for subgroup analyses. Propensity scores generated were used to match patients using greedy nearest-neighbor algorithms, with a caliper width of 0.1 for the pooled standard deviations. Comparative analyses were performed to assess patients within the 2 comparison groups. PSM was employed to estimate the adjusted odds ratio (aOR) of post-ERCP complications, with a 95% confidence interval (CI), while adjusting for potential confounders. Baseline characteristics were compared using a t-test for continuous variables and a chi-square test for categorical variables. Two-sided P-values <0.05 were set as the threshold to determine statistical significance.

Results

Patient characteristics

We identified 534 patients in the CF cohort and 186,337 controls who underwent ERCP during the study period (Table 1). Controls were older (59.4 vs. 44.6 years, P<0.001) and although the proportion of non-Hispanic/Latino patients was similar between the CF cohort (67.8%) and the control group (66.8%), this small absolute difference reached statistical significance (P=0.009), likely due to the large sample size of the control cohort. We note that while statistically significant, the clinical relevance of this difference is minimal. There was no significant difference in sex, or in the proportion of Whites, Hispanics and Blacks, between the control cohort and the CF cohort.

Risk of ERCP complications

After PSM, we found no significant difference in PEP (8.3% vs. 4.9%, aOR 1.763, 95%CI 0.937-3.315; P=0.075), bleeding (3.1% vs. 2.1%, aOR 1.516, 95%CI 0.674-3.409; P=0.311), or infection (3.7% vs. 2.4%, aOR 1.554, 95%CI 0.638-3.785; P=0.328) rates between the CF cohort and controls (Table 2). The low rates of perforation meant that no statistical analysis could be conducted to assess the difference.

Rates of PEP, bleeding or infection in the CF cohort were not influenced by age or sex (Table 3). However, when assessing the odds of post-ERCP outcomes in controls, we found that younger patients (for example, 18-45) were at higher risk of PEP (7.2% vs. 6.0%, aOR 1.213, 95%CI 1.128-1.303; P<0.001), bleeding (2.1% vs. 1.4%, aOR 0.673, 95%CI 0.594-0.761; P<0.001), and infection (3.0% vs. 1.2%, aOR 0.402, 95%CI 0.353-0.457; P<0.001) compared to patients in the ≥46-year age group. Among non-CF controls, females had a slightly higher incidence of PEP compared to males (6.3% vs. 5.7%, aOR 0.907, 95%CI 0.865-0.951; P<0.001), whereas males were more likely to experience bleeding (2.3% vs. 1.7%, aOR 1.341, 95%CI 1.247-1.442; P<0.001), or infection (3.3% vs. 2.5%, aOR 1.340, 95%CI 1.253-1.434; P<0.001).

Table 2 Clinical outcomes for propensity-matched hospitalizations of patients with and without cystic fibrosis (CF) who underwent endoscopic retrograde cholangiopancreatography in the United States

Outcomes	Cohort	Incidence		Adjusted odds ratio	95% confidence interval	P-value
		N	%			
Post-ERCP pancreatitis	CF	24	8.3	1.763	0.937-3.315	0.075
	Control	18	4.9			
Bleeding	CF	15	3.1	1.516	0.674-3.409	0.311
	Control	10	2.1			
Perforation	CF	10	2.1	--	--	--
	Control	0	0			
Infections	CF	10	3.7	1.554	0.638-3.785	0.328
	Control	10	2.4			

ERCP, endoscopic retrograde cholangiopancreatography

Table 3 Subgroup analysis of clinical outcomes for hospitalization of patients with and without cystic fibrosis (CF) who underwent endoscopic retrograde cholangiopancreatography in the United States

		Subgroup analysis				
Outcomes	Cohort	Incidence		Adjusted odds ratio	95% confidence interval	P-value
		N	%			
Post-ERCP pancreatitis						
With CF	Age 18-45	10	8.1	1.140	0.476-2.731	0.768
	Age ≥46	12	7.1			
	Male	10	8.8	0.837	0.333-2.103	0.704
	Female	10	10.3			
Without CF	Age 18-45	1703	7.2	1.213	1.128-1.303	<0.001
	Age ≥46	1479	6.0			
	Male	3440	5.7	0.907	0.865-0.951	<0.001
	Female	3884	6.3			
Bleeding						
With CF	Age 18-45	10	4.6	1	0.408-2.453	>0.99
	Age ≥46	10	4.6			
	Male	10	5.6	1	0.406-2.464	>0.99
	Female	10	5.6			
Without CF	Age 18-45	428	1.4	0.673	0.594-0.761	<0.001
	Age ≥46	632	2.1			
	Male	1730	2.3	1.041	1.247-1.442	<0.001
	Female	1298	1.7			
Perforation						
With CF	Age 18-45	0	0	--	--	--
	Age ≥46	10	4.6			
	Male	0	0	--	--	--
	Female	10	5.6			
Without CF	Age 18-4	82	0.3	0.660	0.499-0.873	0.003
	Age ≥46	24	0.4			
	Male	267	0.4	0.821	0.698-0.965	0.017
	Female	325	0.4			
Infection						
With CF	Age 18-45	10	8.3	1.495	0.603-3.711	0.083
	Age ≥46	10	5.7			
	Male	10	9.9	1.033	0.411-2.099	0.945
	Female	10	9.6			
Without CF	Age 18-45	339	1.2	0.402	0.353-0.457	<0.001
	Age ≥46	756	3.0			
	Male	1967	3.3	1.340	1.253-1.434	<0.001
	Female	1561	2.5			

ERCP, endoscopic retrograde cholangiopancreatography

Table 4 Subgroup analysis of clinical outcomes for hospitalization of p6 atients with and without cystic fibrosis (CF) who underwent endoscopic retrograde cholangiopancreatography (ERCP) for an indication of choledocholithiasis in the United States

Subgroup analysis of patients with choledocholithiasis						
Outcomes	Cohort	Incidence		Adjusted odds ratio	95% confidence interval	P-value
		N	%			
Post-ERCP pancreatitis	With CF	10	6.9	1.193	0.482-2.951	0.703
	Without CF	10	5.8			
Bleeding	With CF	10	4.6	1	0.408-2.453	0.99
	Without CF	10	4.6			
Perforation	With CF	10	4.6	--	--	--
	Without CF	0	0			
Infection	With CF	10	9.3	1.806	0.727-4.493	0.198
	Without CF	10	5.3			

Choledocholithiasis and risk of complications

On subgroup analyses, among patients who underwent ERCP for an indication of choledocholithiasis (Table 4), there was no significant difference between the CF cohort and the controls in rates of PEP (6.9% vs. 5.8%, aOR 1.193, 95%CI 0.482-2.951; P=0.703), bleeding (4.6% vs. 4.6%, aOR 1, 95%CI 0.408-2.453; P>0.99), or infections (9.3% vs. 5.3%, aOR 1.806, 95%CI 0.727-4.493; P=0.198). The low rates of perforation meant that no statistical analysis could be conducted to assess the difference.

Discussion

This study examined the US Collaborative Network, a large national database within the TriNetX platform, to evaluate post-ERCP complications in CF while including one of the largest cohorts to date. Over a 15-year study period, analysis of our matched cohorts showed no difference between CF patients and controls with regard to post-ERCP complication rates (for example, PEP, bleeding and infections). Our results are consistent with findings from a pair of prior large database studies, which demonstrated the risks of ERCP to be generally no different between CF patients and controls [10,18].

The frequency and extent of hepatobiliary manifestations of CF inevitably leads to complications necessitating the use of ERCP. Despite ERCP's utility as a diagnostic and therapeutic tool, it is not without risks, as ERCP is noted to have a higher risk of adverse events compared to other endoscopic procedures [17-19]. While anesthesiology guidelines have made CF-specific recommendations, largely regarding procedural safety considerations [20,21], there are no guidelines regarding ERCP safety, efficacy or prevention measures in CF patients.

Our study showed no significant difference in rates of PEP, bleeding or infection in CF patients. Two recent database studies using the National Inpatient Sample database have found similar outcomes in CF patients in the US. Asfari *et al* investigated 73 ERCPs in CF patients from 2011-2014 and also found no significant difference in PEP or bleeding [18]. Haider *et al* analyzed 535 ERCPs in CF patients from 2016-2020 and discovered no significant difference in PEP, bleeding or perforation, with a higher likelihood of infection in CF patients [10]. In contrast, our data showed no significant difference in infection rates following ERCP in CF patients compared to controls. This may warrant further investigation, as CF patients are known to be at high risk for infection, which has led to CF-specific guidelines that predominantly focus on hygiene and isolation precautions [22,23]. Given the infectious risks associated with endoscopic procedures, and the potential biliary involvement in CF (for example, cholelithiasis, biliary strictures) [24], we conducted a subgroup analysis of patients who underwent ERCP specifically for choledocholithiasis. This analysis revealed no significant differences in the complication rates between the CF and non-CF cohorts. When considered alongside the prior literature, these findings may offer reassurance to endoscopists that the presence of CF does not inherently confer an increased risk of post-ERCP complications.

It is worth exploring how CF phenotype severity may impact ERCP outcomes. Individuals with milder *CFTR* mutations tend to retain greater pancreatic parenchyma and are more likely to develop acute pancreatitis, whereas those with severe genotypes often exhibit pancreatic atrophy and are thus paradoxically protected. This spectrum of disease severity may influence ERCP indications, risk stratification and outcomes. Unfortunately, the TriNetX dataset does not include *CFTR* mutation genotype or imaging data on pancreatic morphology, which precluded further exploration of these associations.

It should be noted that both prior database studies reported no cases of post-ERCP perforation in CF patients, while in this study 10 cases of perforation were found in the CF group compared to zero in the controls [10,18]. While statistical analysis of this difference could not be conducted because of the low incidences, it is a notable change from prior findings, and might suggest that larger study populations may be necessary to detect meaningful differences.

Our findings showed a higher proportion of PEP among females in the non-CF group, which aligns with prior literature

identifying female sex as a known risk factor. This should be interpreted carefully, as the absolute differences were small and may reflect residual confounding despite propensity matching.

Lastly, it should be mentioned that CF patients were younger in this study (44.6 vs. 59.4 years), which is unsurprising given the frequent onset of hepatobiliary manifestations of CF early in life [25]. However, subgroup analysis showed ERCP outcomes were not affected by age or sex in the CF group, whereas in the control group younger patients and male patients showed significantly higher rates of PEP, bleeding and infection. Though the literature appears to validate younger age as a risk factor for PEP, female sex has also been previously claimed as a risk factor for this complication [19]. The overall results of this subgroup analysis suggest a lack of demographic impact on ERCP outcomes in CF patients.

Our study had several limitations. First, its retrospective nature precluded causal inferences. Second, the reliance on ICD coding for identification of outcomes might have introduced misclassification bias. Additionally, reliance on ICD coding may result in under-identification of CF patients, particularly those with milder or atypical phenotypes who may be undiagnosed or misclassified. Patients with residual *CFTR* function, or non-classic CF, may present later in life with isolated gastrointestinal manifestations, further complicating accurate case capture in retrospective datasets [1]. Furthermore, differences in ERCP indications, baseline comorbidities and disease severity between CF patients and our non-CF cohort may have introduced potential confounding by indication. Additionally, CF patients are more likely to receive care at specialized centers, where variations in procedural expertise and postoperative monitoring may influence outcomes. Moreover, heightened clinical surveillance in CF may increase the detection of minor complications, contributing to potential detection bias. Although PSM was adjusted for baseline characteristics, residual confounding may have persisted, limiting the generalizability of our findings. Another limitation is the unavailability of procedural indications within the TriNetX dataset. Given that ERCP complications may vary by indication—for example, sphincter of Oddi dysfunction is associated with a higher risk of PEP, while biliary strictures are linked with higher cholangitis risk—we were unable to account for this variability in our PSM. Moreover, a breakdown of ERCP indications across CF and non-CF cohorts was not feasible. This limited our ability to fully assess whether certain subgroups within the CF population might be at disproportionate risk based on procedure indication. Lastly, only 10 CF patients underwent ERCP for choledocholithiasis, which seems low given its general prevalence. This probably reflects data limitations within TriNetX regarding procedure indications, as well as the distinct hepatobiliary profile in CF patients, where non-stone-related indications, such as strictures or cholestasis, may predominate.

This study focuses on a population at considerable risk of hepatobiliary pathology and at elevated risk of infections and complications. Finding no compelling evidence for a greater incidence of adverse events in ERCP is useful in assisting clinical decision-making for care of CF patients. Nonetheless, this remains an underexplored area, and additional data from larger, prospective studies are warranted to validate these findings and inform best practices.

A nuanced understanding of ERCP indications in CF patients is warranted. While biliary complications, such as cholelithiasis or strictures, remain common drivers for ERCP, a subset of CF patients, particularly those with pancreatic sufficiency, may require intervention for pancreatic ductal abnormalities. Future studies should aim to categorize ERCP indications by organ system—biliary vs. pancreatic—and correlate them with genotype, disease severity and procedural outcome.

In conclusion, our study provides real-world evidence regarding the safety of ERCP in CF patients, showing them to have comparable rates of adverse events to the general population. This is encouraging as regards informing care for CF patients, though the evidence remains scarce and further studies are warranted.

Summary Box

What is already known:

- Patients with cystic fibrosis (CF) frequently develop hepatobiliary complications, for which endoscopic retrograde cholangiopancreatography (ERCP) may be indicated
- ERCP carries procedural risks, including pancreatitis, bleeding and infection
- There are only limited data on ERCP safety specifically in CF patients

What the new findings are:

- This study used a large, real-world dataset with propensity-score matching to compare ERCP-related adverse events in CF vs. non-CF patients
- Post-ERCP pancreatitis, bleeding and infection rates were comparable between CF and matched controls
- Subgroup analysis in choledocholithiasis cases confirmed similar safety profiles

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