ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2021 September 16; 13(9): 356-450

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

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The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database. The 2021 edition of Journal Citation Reports® cites the 2020 Journal Citation Indicator (JCI) for *WJGE* as 0.36.

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NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Anastasios Koulaouzidis, Bing Hu, Sang Chul Lee

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5190/editorialboard.htm

PUBLICATION DATE
September 16, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/GerInfo/287

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https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2021 September 16; 13(9): 371-381

DOI: 10.4253/wjge.v13.i9.371

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Outcomes of inpatient cholecystectomy among adults with cystic fibrosis in the United States

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Author contributions: Ramsey ML designed and performed the research and wrote the paper; Sobotka LA, Krishna SG designed the research and supervised the report; Hinton A performed the statistical analysis and supervised the report; Kirkby SE, Li SS, Meara MP, Conwell DL supervised the report; Stanich PP designed and performed the research and supervised the report; all authors approved the final version of the article.

Institutional review board statement: As the NIS is a publicly available database of de-identified patients, The Ohio State University Institutional Review Board deemed studies utilizing this resource as exempt.

Informed consent statement: This study was completed using a de-identified dataset, which does not

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Abstract

BACKGROUND

Symptomatic biliary and gallbladder disorders are common in adults with cystic fibrosis (CF) and the prevalence may rise with increasing CF transmembrane conductance regulator modulator use. Cholecystectomy may be considered, but the outcomes of cholecystectomy are not well described among modern patients with CF.

AIM

To determine the risk profile of inpatient cholecystectomy in patients with CF.

METHODS

The Nationwide Inpatient Sample was queried from 2002 until 2014 to investigate outcomes of cholecystectomy among hospitalized adults with CF compared to controls without CF. A propensity weighted sample was selected that closely matched patient demographics, patient's individual comorbidities, and hospital

meet criteria for human subject research. Therefore, there is no risk to any individual subject so informed consent is not necessary and was not obtained.

Conflict-of-interest statement: Stanich PP receives research support from Emtora Biosciences, Janssen Pharmaceuticals Inc., Pfizer Inc. and the PTEN Research foundation. Ramsey ML, Sobotka LA, Krishna SG, Hinton A, Kirkby SE, Li SS, Meara MP, Conwell DL has no conflicts of interest to report.

Data sharing statement: The data is available online from the Healthcare Costs and Utilization Project.

Manuscript source: Invited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 13, 2021
Peer-review started: February 13, 2021
First decision: March 28, 2021
Revised: April 20, 2021

characteristics. The propensity weighted sample was used to compare outcomes among patients who underwent laparoscopic cholecystectomy. Hospital outcomes of open and laparoscopic cholecystectomy were compared among adults with CF.

RESULTS

A total of 1239 inpatient cholecystectomies were performed in patients with CF, of which 78.6% were performed laparoscopically. Mortality was < 0.81%, similar to those without CF (P = 0.719). In the propensity weighted analysis of laparoscopic cholecystectomy, there was no difference in mortality, or pulmonary or surgical complications between patients with CF and controls. After adjusting for significant covariates among patients with CF, open cholecystectomy was independently associated with a 4.8 d longer length of stay (P = 0.018) and an $18449 increase in hospital costs (P = 0.005) compared to laparoscopic cholecystectomy.

CONCLUSION

Patients with CF have a very low mortality after cholecystectomy that is similar to the general population. Among patients with CF, laparoscopic approach reduces resource utilization and minimizes post-operative complications.

Key Words: Laparoscopic cholecystectomy; Nationwide Inpatient Sample; Cystic fibrosis; Mortality; Length of stay; Symptomatic biliary disorders

Core Tip: Cholecystectomy has been considered to be a high-risk intervention in adults with cystic fibrosis (CF). Our study used a sample of adults with closely matched baseline characteristics to compare hospital outcomes among patients with and without CF. There was no difference in mortality or pulmonary or surgical complications between adults with and without CF. Patients with CF who underwent an open cholecystectomy had a longer length of stay than those who underwent a laparoscopic cholecystectomy. This study suggests that cholecystectomy is safe in selected adults with CF and that a laparoscopic approach should be preferred.

Citation: Ramsey ML, Sobotka LA, Krishna SG, Hinton A, Kirkby SE, Li SS, Meara MP, Conwell DL, Stanich PP. Outcomes of inpatient cholecystectomy among adults with cystic fibrosis in the United States. *World J Gastrointest Endosc* 2021; 13(9): 371-381
URL: https://www.wjgnet.com/1948-5190/full/v13/i9/371.htm
DOI: https://dx.doi.org/10.4253/wjge.v13.i9.371

INTRODUCTION

Cystic fibrosis (CF) is a multisystem disease resulting from defects in the CF transmembrane conductance regulator (CFTR) apparatus. The highest incidence of CF is seen in people of northern European descent, where CF occurs in one out of 3000 live births and approximately one in 25 people carry a pathogenic allele[1]. When initially described in the 1930s, median survival was only a few months but advances in pulmonary treatments have since increased the median predicted survival beyond 40 years[2,3]. While the natural history and treatment of pulmonary and pancreatic diseases in CF have been well characterized, other affected organs, such as the biliary tree and gallbladder, have less epidemiologic and clinical data to guide care. Management of these other organ systems which affect quality of life will become increasingly important as median survival improves.

Biliary disorders are thought to be common in CF due to the high expression of the CFTR gene in the gallbladder and biliary tree[4]. The mechanism of gallstone formation in CF is incompletely understood, but is likely the result of biliary stasis due to gallbladder dysmotility and prolonged transit through the bile ducts[4,5]. Cholelithiasis is reported in 20%-30% of patients with CF, and symptomatic biliary colic is experienced by 4% to 40% of subjects in retrospective studies[6-8]. One case

Accepted: August 9, 2021
Article in press: August 9, 2021
Published online: September 16, 2021

P-Reviewer: Tebala GD
S-Editor: Zhang H
L-Editor: A
P-Editor: Liu JH

series suggested that the incidence of cholelithiasis increases with age, from 0.1% in those less than 5 years of age, to nearly 10% in those aged 30-40[8]. Additionally, the use of CF transmembrane conductance regulator (CFTR) modulators may increase the risk of biliary colic[9]. The population of patients with CF are aging and CFTR modulators are increasingly used, which are leading to a greater number of patients at risk for biliary and gallbladder disorders.

In patients without CF, symptomatic biliary disorders are managed surgically by cholecystectomy. However, few CF patients undergo cholecystectomy, due at least in part to concerns for perioperative complications[3,10]. The few published case series of cholecystectomy show an aggregate mortality rate of 4% (3/71) among patients with CF, which is considerably higher than the 0.15% mortality reported in the general population[6,8,10-15]. However, the CF surgical case series were completed over 25 years ago, and surgical technique and patient characteristics have changed dramatically since then. We hypothesized that the outcomes of cholecystectomy in a modern cohort of subjects with CF will be no different than the general population, especially when controlling for comorbidities. We aimed to evaluate the safety of cholecystectomy in subjects with CF compared to non-CF controls using a large national database.

MATERIALS AND METHODS

Data source

A retrospective analysis was performed using the Nationwide Inpatient Sample (NIS) (2002 to 2014), available through the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. The NIS represents more than 35 million individual hospitalizations annually across the United States and is one of the largest publicly available databases. This database can be used to evaluate patient and hospital characteristics as well as resource utilization such as costs, mortality, and length of stay[16]. As the NIS is a publicly available database of de-identified patients, The Ohio State University Institutional Review Board deemed studies utilizing this resource as exempt.

Study sample

Subjects were required to have a procedure code for cholecystectomy, defined as open, laparoscopic, or laparoscopic converted to open (Supplementary Table 1). Subjects were excluded if they were under the age of 18, pregnant, had cirrhosis, or underwent a partial cholecystectomy. Patients who underwent laparoscopic converted to open approach were categorized as open cholecystectomy. The cohorts were then defined by the presence or absence of CF diagnosis codes.

Outcomes of interest

The primary outcome of interest was mortality following cholecystectomy. As secondary outcomes, we evaluated length of stay, cost of hospitalization, and the rates of post-operative complications based on a validated set of diagnosis and procedure codes (Supplementary Table 1)[17,18]. Additionally, we analyzed the indications for cholecystectomy among patients with CF using previously defined diagnosis codes (Supplementary Table 1)[19-21]. Patients with choledocholithiasis and gallstone pancreatitis were included in the category of gallstone disease without cholecystitis (Supplementary Table 1). All outcomes were compared between patients with and without CF using survey weighting and propensity weighting and between patients with CF who received open or laparoscopic cholecystectomy using univariate and multivariate analyses. A study flowchart of patient inclusion and analyses is presented in Figure 1.

Definition of variables

Other variables evaluated include age, gender, race, income, type of insurance, hospital size, type of hospital, and hospital region. The presence of comorbid conditions were evaluated using the Elixhauser comorbidity index, which has been used widely since it was developed in 2005[22].

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, United States) on weighted data and accounted for the complex survey designs of the NIS.

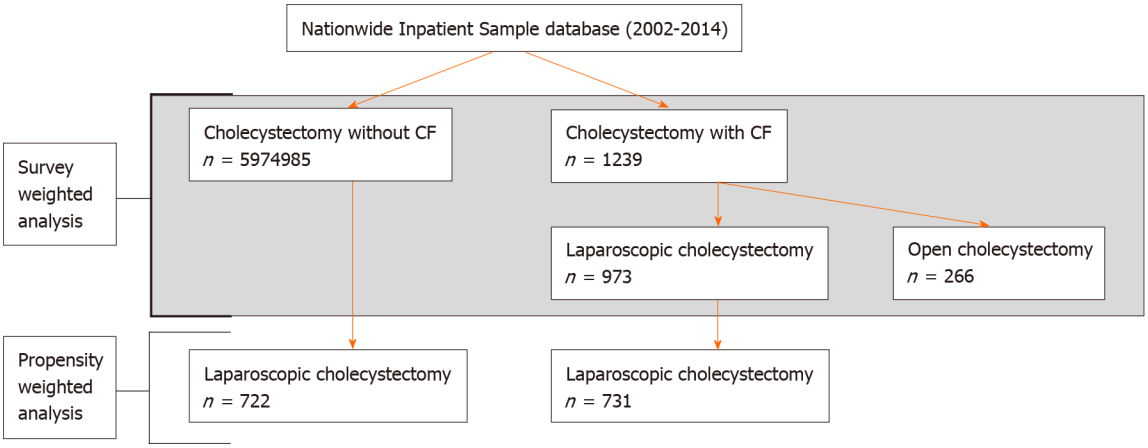

Figure 1 Study flowchart demonstrating survey weighted and propensity weighted analyses. CF: Cystic fibrosis.

Differences between patient characteristics, hospital characteristics, and outcomes were compared between patients with and without CF through the use of chi-square tests for categorical variables and *t*-tests for continuous variables. Similar comparisons were made between the populations of patients with CF who underwent open or laparoscopic cholecystectomy. Multivariate linear regression models were created for length of stay and hospital costs using a stepwise selection process. Where less than 10 observations are recorded, the exact number is censored to protect subject privacy, per NIS regulations. Missing data is listed in Supplementary Table 2.

Propensity weighted analysis

Among patients who underwent a laparoscopic cholecystectomy, propensity scores were calculated using a multivariable logistic regression model for CF containing all patient and hospital characteristics and indications for cholecystectomy as well as all individual Elixhauser comorbidities. The logistic regression model was weighted and accounted for all aspects of the complex survey design.

After deriving propensity scores (e) for each subject, propensity score weights were defined as 1 for subjects with CF and as $e/(1-e)$ for subjects without CF. These propensity score weights were then multiplied by the original survey weights defined by HCUP to arrive at the new weights which were used in place of the original HCUP weights in the following propensity weighted analysis, as previously described[23]. After propensity weighting was applied, all variables were well balanced between the two groups. The propensity weights were then used to evaluate differences in outcomes between patients with and without CF.

RESULTS

Demographics

From 2002 to 2014, a total of 5976224 adults underwent inpatient cholecystectomy, of which 1239 (0.021%) had CF (Table 1, Figure 1). Subjects with CF were younger and were more likely to be white, have private insurance, be treated at an urban teaching hospital, and have comorbid chronic respiratory failure (Table 1). A laparoscopic approach was used more often in CF subjects than in controls (78.6% *vs* 70.2%, P = 0.003) (Table 1). The indications for surgery between these groups were different: subjects with CF were less likely to undergo cholecystectomy for acute cholecystitis (48.1% *vs* 60.4%, P < 0.001), but more likely to have gallstone disease without cholecystitis (26.6% *vs* 18.0%, P < 0.001) or biliary dyskinesia (5.0% *vs* 1.2%, P < 0.001) (Table 1). Mortality was not significantly different between those with CF and those without (≤ 0.81% *vs* 0.99%, P = 0.719) (Supplementary Table 3). Length of stay and total hospitalization costs were higher for CF patients than controls (10.1 d *vs* 5.4 d, P < 0.001; $27561 *vs* $14059, P < 0.001) (Supplementary Table 3).

Propensity weighted analysis

After propensity weighting was applied to patients who underwent laparoscopic cholecystectomy, the variables were well balanced between groups

Table 1 Comparison of characteristics between subjects with and without cystic fibrosis who underwent cholecystectomy from 2002 to 2014

	Without cystic fibrosis (*n* = 5974985)		With cystic fibrosis (*n* = 1239)		
	n	**%**	***n***	**%**	***P* value**
Patient and hospital characteristics					
Age (mean ± SE)	53.81	0.05	31.28	0.80	< 0.001
Gender					0.342
Male	2113648	35.45	475	38.35	
Female	3848224	64.55	764	61.65	
Race					< 0.001
White	3377462	68.16	917	90.92	
Black	486644	9.82	15	1.51	
Hispanic	784975	15.84	38	3.81	
Other	306042	6.18	38	3.75	
Income quartile					0.669
First	1443591	26.81	270	23.36	
Second	1423075	26.43	322	27.83	
Third	1342530	24.94	313	27.06	
Fourth	1174730	21.82	251	21.76	
Primary payer					< 0.001
Medicare	2013023	33.76	255	20.62	
Medicaid	689680	11.57	215	17.34	
Private insurance	2550634	42.77	646	52.16	
Other	710118	11.91	122	9.88	
Elixhauser co-morbidity score					0.095
< 3	4425355	74.06	974	78.62	
≥ 3	1549630	25.94	265	21.38	
Chronic respiratory failure	16136	0.27	24	1.96	< 0.001
Hospital bed size					0.044
Small	744565	12.50	89	7.27	
Medium	1569622	26.36	306	24.87	
Large	3639976	61.13	835	67.86	
Hospital location/teaching status					< 0.001
Rural	786013	13.20	57	4.67	
Urban non-teaching	2724014	45.75	252	20.52	
Urban teaching	2444135	41.05	920	74.82	
Hospital region					0.184
Northeast	1048152	17.54	210	16.93	
Midwest	1248121	20.89	335	27.00	
South	2369451	39.66	467	37.65	
West	1309262	21.91	228	18.42	
Cholecystectomy approach					0.003

Laparoscopic	4192051	70.16	973	78.55	
Open	1782934	29.84	266	21.45	
Indication for cholecystectomy[1]					< 0.001
Acute cholecystitis	3606140	60.35	597	48.14	
Chronic cholecystitis	317489	5.31	98	7.90	
Gallstone disease without cholecystitis	1077090	18.03	329	26.58	
Biliary dyskinesia	71204	1.19	62	5.03	
Other	903063	15.11	153	12.35	

[1]Hierarchy model.

(Supplementary Table 4). Hospital mortality was low among both groups, with less than 10 events observed (Table 2). Subjects with CF experienced a mean length of stay (LOS) of 9.4 d, compared to 5.2 d in those without CF ($P < 0.001$) (Table 2). Similarly, total hospital costs were greater for subjects with CF ($25891 *vs* $14103, $P = 0.003$) (Table 2). There was no difference between CF and controls in post-operative surgical complications (4.5% *vs* 2.3%, $P = 0.094$) or pulmonary complications (6.6% *vs* 4.1%, $P = 0.109$) (Table 2).

Impact of surgical route on outcomes in CF

Of the 1239 patients with CF who underwent cholecystectomy, 973 (78.6%) had a laparoscopic approach. Compared to an open approach, patients with a laparoscopic cholecystectomy were more likely to be female, but other demographics were similar (Table 3). There was no significant difference in mortality (≤ 1.0% *vs* ≤ 3.8%, $P = 0.286$) but the LOS was longer and total hospital costs were greater in the open cholecystectomy group (14.5 d *vs* 8.9 d, $P = 0.009$; $43024 *vs* $23288, $P = 0.005$) (Supplementary Table 4). After adjusting for significant covariates, open route at surgery was associated with longer LOS (4.82 d, 95%CI: 0.82 d, 8.83 d, $P = 0.018$) and increased hospital costs ($18449, 95%CI: $5582, $31316, $P = 0.005$) (Table 4 and Supplementary Table 5). There were insufficient observations of mortality and post-operative complications to fit a multivariate model for these outcomes.

DISCUSSION

More patients with CF are reaching adulthood due to advances in CF care and CFTR modulators are increasingly used. With this, clinicians are likely to see an increasing prevalence of biliary disorders for which cholecystectomy will be considered as a definitive treatment. Therefore, it is important to clarify the safety of cholecystectomy. In this study, we used a nationally-representative database to evaluate the post-operative outcomes among adult patients with CF who undergo cholecystectomy. Importantly, we found that cholecystectomy had very low in-hospital mortality that was not significantly different from the general population. The surgical indications and approach were different between patients with and without CF. Open cholecystectomy was independently associated with longer LOS and greater hospital costs compared to laparoscopic approach. Finally, there is increased healthcare utilization among patients with CF compared to a propensity weighted cohort following laparoscopic cholecystectomy.

Our data shows a low mortality rate in a large and nationally representative cohort of CF patients, comparable to previous case series of cholecystectomy among CF patients. Aggregate data from case series show no deaths out of 12 patients who underwent laparoscopic surgery and 3/59 (5.1%) who underwent open cholecystectomy (although many of these surgeries were performed over 25 years ago)[6,8,10-12,15]. The previous case series also reported long lengths of stay after open cholecystectomy, up to 22 d in one series, partially due to prolonged pre- and post-operative intravenous antibiotics and frequent respiratory care[12]. Compared to these older studies, the current mean length of stay for laparoscopic cholecystectomy (8.9 d, standard error 0.71 d) is shorter. Similarly, CF patients experience longer LOS after sinus surgery compared to non-CF patients[24]. In one study using the American College of Surgeons' National Surgical Quality Improvement Program-Pediatric

Table 2 Univariate analysis of outcomes between propensity weighted cohort of patients with and without cystic fibrosis who underwent laparoscopic cholecystectomy in the Nationwide Inpatient Sample 2002-2014

	Without cystic fibrosis (*n* = 722)		With cystic fibrosis (*n* = 731)		
	n	**%**	***n***	**%**	***P* value**
Mortality[1]	≤ 10	≤ 1.39	≤ 10	≤ 1.37	0.662
Length of stay (mean ± SE)	5.18	0.33	9.36	0.89	< 0.001
Cost ($) (mean ± SE)	14103	842	25891	3859	0.003
Pulmonary complications	29	4.05	49	6.64	0.109
Surgical complications	16	2.27	33	4.48	0.094

[1]Where $n \leq 10$, the exact value is censored to protect patient privacy, per Nationwide Inpatient Sample regulation.

database, the authors suggested that the longer LOS was not due to complications but rather due to extended monitoring and intravenous antibiotics[24]. Our study shows this also appears to be true for cholecystectomy: Patients with CF have longer LOS than controls despite similar rates of post-operative complications.

Post-operative pulmonary decompensation and infection has been reported in previous case series, with an overall incidence of 7.0% (5/71) that is similar to our study[6,8,10-13,15]. To mitigate this risk, chest physiotherapy and antibiotics were used pre- and post-operatively. One group targeted pre-operative pulmonary function tests at the "highest level attained in the past 2 years, or until a prolonged period of therapy reaches a plateau of improvement" for elective surgery[10]. Increased pulmonary complications after open cholecystectomy may be attributed to derangements in respiratory mechanics due to the surgical incision near the diaphragm and increased post-operative pain[25]. Accordingly, laparoscopic cholecystectomy is recommended over open cholecystectomy for subjects with chronic pulmonary comorbidities to minimize risks of post-operative complications[25,26]. These data suggest that optimal outcomes are attained by elective laparoscopic intervention, and further study may be required to determine the best approach for pre- and post-operative pulmonary optimization among patients with CF.

While the incidence of post-cholecystectomy pulmonary complications has been described, the risk of surgical complications including soft tissue infections, perforation during surgery and need for recurrent surgery in CF compared to the general population has not been previously reported. We demonstrate an increased risk of surgical complications in patients with CF compared to the general population in the survey weighted cohort, and an increased risk with open compared to laparoscopic cholecystectomy among patients with CF. In the propensity weighted analysis, we found no significant difference in the rate of surgical complications. Patients with CF have an increased risk of infections with drug resistant bacteria, which may place this population at higher risk of infection after surgical intervention as these organisms may not be treated by routine pre-operative antibiotics[27].

Our study has several limitations inherent to the use of a large database, such as the potential for coding errors. Additionally, we cannot account for characteristics that are not included in the NIS which may influence outcomes, such as medication use, nutritional status, and baseline pulmonary function, nor can we evaluate survival beyond the inpatient period. Lastly, there may be selection bias, as only patients with acceptable surgical risk would have undergone cholecystectomy. Due to these limitations, "causality" cannot be inferred from large database analyses. However, in the absence of a prospectively collected surgical registry among patients with CF, the NIS remains an excellent data source due to its large number of observations and sophisticated sampling design. The NIS included 1239 inpatient cholecystectomies among patients with CF which greatly outnumbers the 71 cases reported in the literature to date. Additionally the NIS represents national demographics so the reported outcomes are likely to be generalizable to similar CF patients encountered in clinical practice. Finally, the volume of cholecystectomy in the control population allowed for a propensity weighted analysis to approximate a randomized trial, which could not be reasonably accomplished outside of a large database.

Table 3 Comparison of characteristics between subjects with cystic fibrosis who underwent open compared to laparoscopic cholecystectomy from 2002 to 2014

	Laparoscopic CCY (*n* = 973)		Open CCY (*n* = 266)		
	n	**%**	***n***	**%**	***P* value**
Patient and hospital characteristics					
Age (mean ± SE)	30.78	0.86	33.11	1.95	0.272
Gender					0.005
Male	330	33.92	145	54.60	
Female	643	66.08	121	45.40	
Race					0.911
White	718	90.92	199	90.93	
Black	≤ 10	≤ 1.03	≤ 10	≤ 3.76	
Hispanic	29	3.65	≤ 10	≤ 3.76	
Other	33	4.13	≤ 10	≤ 3.76	
Income quartile					0.110
First	210	23.22	60	23.86	
Second	221	24.47	100	39.95	
Third	264	29.20	48	19.34	
Fourth	209	23.11	42	16.85	
Primary payer					0.265
Medicare	221	22.73	34	12.86	
Medicaid	177	18.23	37	14.07	
Private insurance	482	49.56	164	61.69	
Other	92	9.47	30	11.38	
Elixhauser co-morbidity score					0.311
< 3	778	79.93	196	73.81	
≥ 3	195	20.07	70	26.19	
Chronic respiratory failure	24	2.50	0	0.00	-
Hospital bed size					0.244
Small	71	7.29	19	7.21	
Medium	219	22.58	87	33.34	
Large	679	70.13	155	59.45	
Hospital location/teaching status					0.476
Rural	53	5.45	≤ 10	≤ 3.76	
Urban non-teaching	193	19.94	59	22.67	
Urban teaching	723	74.61	197	75.56	
Hospital region					0.812
Northeast	167	17.15	43	16.12	
Midwest	258	26.53	76	28.73	
South	378	38.85	88	33.27	
West	170	17.47	58	21.88	
Indication for cholecystectomy[1]					
Acute cholecystitis	527	54.17	69	26.07	

Chronic cholecystitis	84	8.61	14	5.28
Gallstone disease without cholecystitis	285	29.25	45	16.82
Biliary dyskinesia[2]	58	5.95	≤ 10	≤ 3.76
Other	20	2.02	133	50.18

[1]Hierarchy model.
[2]Where $n \leq 10$, the exact value is censored to protect patient privacy, per Nationwide Inpatient Sample regulation. CCY: Cholecystectomy.

Table 4 Multivariate comparison of post-operative outcomes between subjects with cystic fibrosis who underwent open compared to laparoscopic cholecystectomy from 2002 to 2014

	Length of stay			Hospitalization cost		
	Days	95%CI	*P* value	$	95%CI	*P* value
Open cholecystectomy	4.82	(0.82, 8.83)	0.018	18449	(5582, 31316)	0.005
Elixhauser co-morbidity score ≥ 3	8.35	(4.28, 12.43)	< 0.001	28344	(10548, 46141)	0.002
Hospital location/teaching status			< 0.001			< 0.001
Rural	-5.88	(-11.53, -0.24)		-13801	(-22490, -5111)	
Urban non-teaching	-3.69	(-5.71, -1.68)		-13709	(-20684, -6734)	
Urban teaching	Ref.			Ref.		

Adjusted for significant covariates.

CONCLUSION

Cholecystectomy among adult patients with CF did not carry an increased risk of in-hospital mortality compared to controls. Length of stay and hospital costs are higher in patients with CF and there is a higher risk of post-operative surgical complications and a tendency to develop more pulmonary complications, although this risk of complications is no longer seen when demographic and health variables are taken into account. A laparoscopic approach is safer and reduces healthcare utilization compared to an open approach in adults with CF. These results should inform the discussion between clinicians and patients with CF when cholecystectomy is considered.

ARTICLE HIGHLIGHTS

Research background

Symptomatic biliary disorders are common in cystic fibrosis (CF) and may become more common now that patients with CF are living longer. Biliary disorders are often managed with cholecystectomy but this surgery carries high risk of morbidity and mortality among adults with CF. However, the reported rate of complications is based on older studies, and may not represent modern surgical outcomes.

Research motivation

Currently, there is insufficient data examining the safety of cholecystectomy among adults with CF using modern surgical techniques.

Research objectives

To investigate the outcomes of inpatient cholecystectomy among adults with and without CF.

Research methods

The Nationwide Inpatient Sample was used to collect data on inpatient cholecystectomies between 2002 and 2014. Subjects without CF were matched 1:1 to subjects with CF, accounting for over 20 variables including age, sex, and comorbidities.

Research results

Among patients with CF, 1239 cholecystectomies were performed during the study period. Open cholecystectomy was independently associated with an $18449 increase in hospital costs (P = 0.005) and a 4.8 d longer length of stay (P = 0.018) compared to laparoscopic cholecystectomy. The mortality rate among patients with CF was < 0.81%, which was similar to the mortality rate among patients without CF (P = 0.719). Similarly, there was no significant difference in mortality or post-operative surgical complications (4.5% *vs* 2.3%, P = 0.094) or pulmonary complications (6.6% *vs* 4.1%, P = 0.109) after laparoscopic cholecystectomy between patients with and without CF in the propensity weighted analysis.

Research conclusions

With modern anesthesia and surgical techniques, cholecystectomy is equally safe for patients with and without CF.

Research perspectives

Cholecystectomy may be increasingly considered for the management of biliary symptoms among adults with CF. Future research will need to clarify if there are unique indications for cholecystectomy among patients with CF.

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