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Diabetes mellitus is associated with a higher rate of acute cholangitis among patients with common bile duct stones

A retrospective study

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Abstract

Common bile duct (CBD) stone is a commonly encountered disease that is associated with various clinical presentations ranging from the mild form of biliary colic to the severe complication of acute cholangitis. Recently, diabetes mellitus (DM) has been linked to the development of biliary diseases; however, no data regarding the association of DM with acute cholangitis development in the setting of CBD stone exist. The aim of the current study was to investigate whether DM represents a risk factor for acute cholangitis in patients with CBD stone. We performed a retrospective cross-sectional study from January 1, 2010 till June 1, 2020 of all patients presenting to Galilee Medical Center with various clinical presentations of documented CBD stone, including cholangitis, biliary pancreatitis, and biliary colic with abnormal liver enzymes. Overall, 687 patients were included in the final analysis. Among them, 101 patients (14.7%) had CBD stone associated with acute cholangitis (group A), as compared to 586 patients (85.3%) without acute cholangitis (group B). The average ages in groups A and B were 77.7 ± 13.6 and 62.5 ± 20.5 years, respectively ($P < .0001$). The prevalence of DM was significantly higher in group A as compared to group B (52.5% vs 36.3%, $P = .001$). On univariate analysis, age (odds ratio [OR] 1.05, $P < .0001$), male gender (OR 1.54, $P = .04$), and DM (OR 1.92, $P = .002$) were associated with acute cholangitis development, and on multivariate logistic regression analysis, the correlation was preserved for DM (OR 1.93, 95% confidence interval 1.26–2.96, $P = .002$). DM showed a significant association with acute cholangitis development among patients with CBD stone. Identification of bile duct stones in diabetic patients is of paramount importance since early diagnosis and treatment might prevent further life-threatening complications.

Abbreviations: CBD = common bile duct, CI = confidence interval, DM = diabetes mellitus, ERCP = endoscopic retrograde cholangiopancreatography, OR = odds ratio.

Keywords: CBD, cholangitis, diabetes mellitus, stone

1. Introduction

The prevalence of gallstone disease is high, reaching up to 10% to 15% in the general population,[1] with their prevalence increasing with increasing age.[2] Gallstones may remain asymptomatic or present with a wide range of clinical manifestations, ranging from mild biliary colic and elevated liver enzymes to severe and life-threatening complications including biliary pancreatitis and cholangitis. Of note, acute cholangitis should be identified and treated early since it might progress to sepsis and death.[2] To date, studies exploring risk factors that are associated with the development of acute cholangitis among patients with common bile duct (CBD) stones are lacking. Therefore, identification of factors that are correlated with severe clinical presentation is an unmet need, as clinical factors that predispose patients with bile duct stones to acute cholangitis are not completely understood.[3–5] Recently diabetes mellitus (DM) was reported to be associated with biliary diseases.[6,7] The aim of our study was to explore whether DM was associated with higher cholangitis rate among patients with CBD stone.

2. Study design

We reviewed and analyzed all patients' files, of adults over 18 years of age who were hospitalized at Galilee Medical Center from January 1, 2010 till June 1, 2020 with various clinical presentations of CBD stone disease (cholangitis, biliary pancreatitis, and biliary colic with abnormal liver enzymes who underwent endoscopic retrograde cholangiopancreatography [ERCP]) with documented CBD stone extraction. Exclusion criteria included patients suffering from concomitant diagnosis of

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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biliary malignancy and biliary strictures. The patient's files were reviewed for demographics, medical history, and laboratory data on admission.

All ERCP procedures were carried out via duodenoscope (Pentax-Japan), and performed by an experienced endoscopist over 20 years' experience comprising more than 5000 ERCP examinations in the field of advanced endoscopy. Patients were placed in the prone position and were sedated with intravenous midazolam, fentanyl, and propofol according to the decision of the anesthesiologist.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our institution's human research committee (NHR). Written informed consent was waived by the local ethics committee due to the retrospective non-interventional nature of the study.

2.1. Statistical analysis

Statistical comparison was performed between patients who presented with acute cholangitis secondary to CBD stone compared to patients who presented with CBD stone without cholangitis.

Continuous variables were reported as mean ± standard deviation and categorical variables were reported as frequencies (percentages). Univariate analysis and multivariate logistic regression analyses were performed to assess the association of the assessed parameters with acute cholangitis development by reporting the odds ratio (OR) and confidence interval (CI). A threshold for statistical significance was set at a P value $< .05$. All analyses were performed by an experienced statistician using the statistical analysis software SAS Vs 9.4 (Copyright (c) 2016 by SAS Institute Inc., Cary, NC).

3. Results

Overall, a total of 1461 patients were identified during the study period. Of them, 163 patients were excluded due to missing data and 611 patients excluded due to other diagnosis (Fig. 1), leaving 687 patients who were included in the study. Among them, 101 patients presented with acute cholangitis (14.7%, group A), and 586 patients presented with other clinical presentations of CBD stone (85.3%, group B). The average age in group A was 77.7 ± 13.6 years, as compared to 62.5 ± 20.5 years in group B ($P < .0001$). Male gender was more common in group A (52.5%) as compared to group B (41.6%), $P = .02$. Notably, patients in group A had a higher rate of DM as compared to group B (52.5% vs 36.3%, $P = .001$), while there was no difference in the rate of smoking (25.7% vs 24.9%, $P = .3$), chronic liver disease (3.9% vs 5.6%, $P = .2$), hemolytic anemia (0 vs 0.5, $P = .2$), and post-cholecystectomy status (26.7% vs 25.6, $P = .4$). The most common imaging modalities that were used to diagnose CBD stone before ERCP were ultrasound in 37.6% in group A, vs 30.2% in group B, followed by computed tomography in 29.7% in group A, vs 32.9% in group B. Additionally, the size of CBD stone in group A was 6.1 ± 3.2 mm, as compared to 5.9 ± 2.8 mm in group B ($P = .39$). Similarly, the size of CBD was 9.7 ± 4.1 mm in group A vs 9.6 ± 3.8 mm in group B ($P = .49$). Table 1 demonstrates the cohort baselines characteristics and laboratory findings at admission.

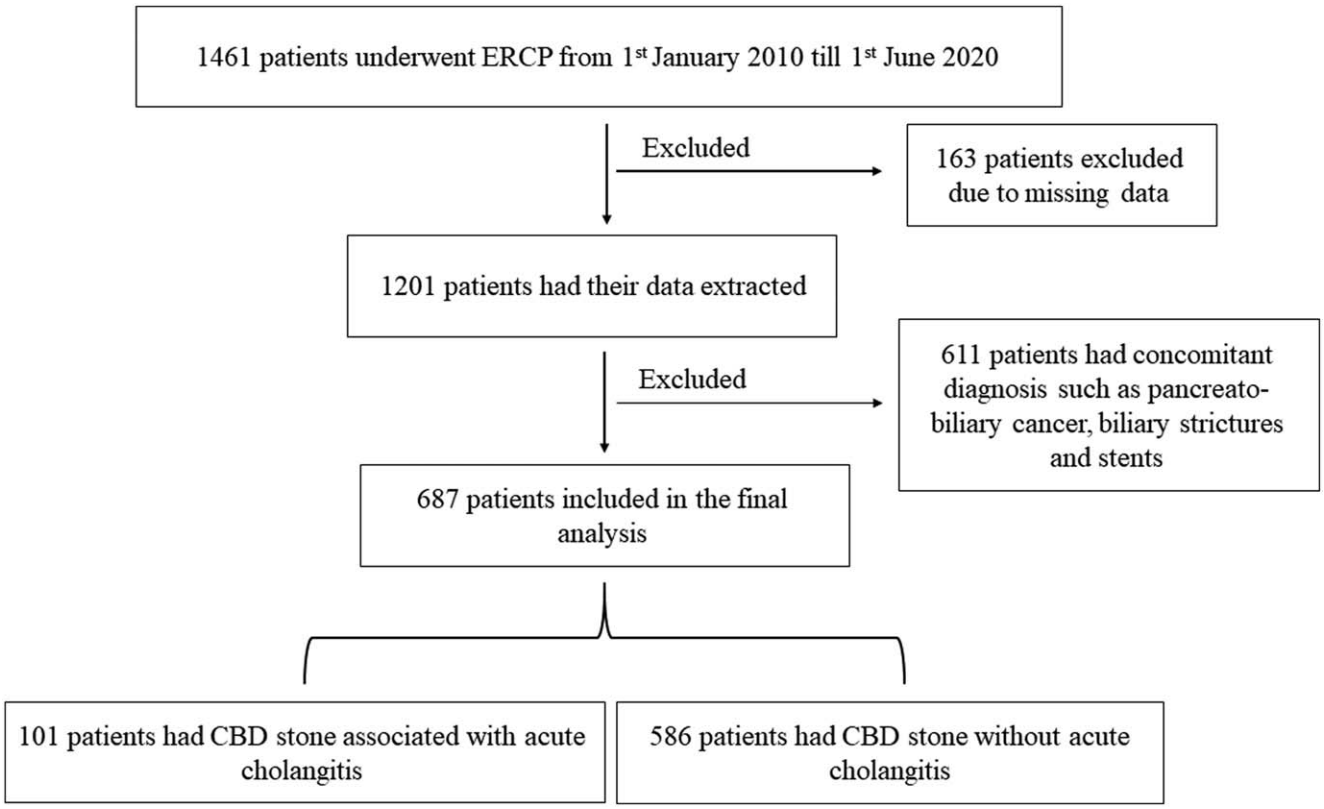

Figure 1. This figure demonstrates the flow chart of the study cohort.

Table 1

Demographics, baseline characteristics, and laboratory tests at admission.

	Group A (n = 101)	Group B (n = 586)	*P* value
Age (yrs), mean ± SD	77.7 ± 13.6	62.5 ± 20.5	<.0001
Gender, N (%)			
• Male	53 (52.5)	244 (41.6)	.02
• Female	48 (47.5)	342 (58.4)	
CBD stone clinical presentation, N (%)			
• Acute cholangitis	101	0	–
• Biliary pancreatitis	0	34	–
• Biliary colic with abnormal cholestatic liver enzymes	0	552	–
Smoking, N (%)	26 (25.7)	146 (24.9)	.3
Diabetes mellitus, N (%)	53 (52.5)	213 (36.3)	.001
Chronic liver diseases, N (%)	4 (3.9)	33 (5.6)	.2
Hemolytic anemia, N (%)	0	3 (0.5)	.2
Status postcholecystectomy, N (%)	27 (26.7)	150 (25.6)	.4
Hepato-biliary malignancy, N	0	0	–
Previous ERCP, N	0	0	–
History of cholangitis or PSC, N	0	0	–
CBD stone size, mean ± SD (mm)	6.1 ± 3.2	5.9 ± 2.8	.39
CBD size, mean ± SD (mm)	9.7 ± 4.1	9.6 ± 3.8	.49
Hemoglobin, mean ± SD (g/dL)	11.9 ± 1.7	12.5 ± 1.9	.002
Neutrophils, mean ± SD ($\times 10^9$/L)	8.8 ± 6.7	5.6 ± 3.4	<.0001
Lymphocytes, mean ± SD ($\times 10^9$/L)	1.4 ± 0.8	1.6 ± 1.1	.05
Creatinine, mean ± SD (mg/dL)	1.02 ± 0.8	1.05 ± 2.3	.4
AST, mean ± SD (U/L)	115 ± 171.3	104.5 ± 124.6	.2
ALT, mean ± SD (U/L)	147.8 ± 204.1	172.3 ± 187.4	.1
ALP, mean ± SD (U/L)	286.3 ± 225	225.9 ± 186.9	.002
GGT, mean ± SD (U/L)	506.4 ± 409.7	453.8 ± 381.9	.1
Total bilirubin	8.7 ± 10	2.8 ± 6.4	.004
Albumin, mean ± SD (g/dL)	3.3 ± 0.5	3.6 ± 0.5	<.0001
C-reactive protein, mean ± SD (mg/dL)	106.8 ± 95.2	47.5 ± 65.3	<.0001
Neutrophil-to-lymphocyte ratio, mean ± SD	9.9 ± 12.8	5 ± 5.3	<.0001
Diagnosis of CBD stone prior to ERCP, N (%)			
• US	38 (37.6)	177 (30.2)	–
• CT	30 (29.7)	193 (32.9)	–
• EUS	23 (22.8)	181 (30.9)	–
• MRCP	8 (7.9)	19 (3.3)	–
• Imaging through PTBD	2 (2)	16 (2.7)	–

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CBD = common bile duct, CT = computed tomography, ERCP = endoscopic retrograde cholangiopancreatography, EUS = endoscopic ultrasound, GGT = gamma glutamyl transferase, MRCP = magnetic resonance cholangiopancreatography, PSC = primary sclerosing cholangitis, PTBD = percutaneous transhepatic biliary drainage, SD = standard deviation, US = ultrasound.

Table 2

Univariate and multivariate logistic analysis of parameters that are associated with acute cholangitis development.

Univariate analysis			
	OR	**95% CI**	***P* value**
Age	1.05	1.04–1.07	<.0001
Male gender	1.54	1.01–2.36	.04
Diabetes mellitus	1.92	1.26–2.94	.002
Smoking	1.05	0.65–1.71	.8
Chronic liver diseases	0.76	0.27–2.12	.6
Hemolytic anemia	0.82	0.03–25.29	.9
Status postcholecystectomy	0.66	0.67–1.72	.7
CBD dilation	0.85	0.50–1.43	.5
CBD stone size	0.98	0.86–1.21	.3
Multivariate logistic regression analysis			
	OR	**95% CI**	***P* value**
Diabetes mellitus	1.93	1.26–2.96	.002

CBD = common bile duct, CI = confidence interval, OR = odds ratio.

3.1. Univariate and multivariate analyses of parameters associated with acute cholangitis

On univariate analysis, 3 parameters were significantly associated with acute cholangitis development: age (OR 1.05, 95% CI 1.04–1.07, $P < .0001$), male gender (OR 1.54, 95% CI 1.01–2.36, $P = .04$), and DM (OR 1.92, 95% CI 1.26–2.94, $P = .002$). However, the other assessed parameters were not associated with acute cholangitis, including smoking (OR 1.05, $P = .8$), chronic liver diseases (OR 0.76, $P = .6$), hemolytic anemia (OR 0.82, $P = .9$), and post-cholecystectomy status (OR 0.66, $P = .7$). On multivariate logistic regression analysis, DM remained a statistically significant correlator with the development of acute cholangitis (OR 1.93, 95% CI 1.26–2.96, $P = .002$) (Table 2).

4. Discussion

Approximately 1.5% of the general population suffers from CBD stone, and the prevalence increases with age.[8] In fact, CBD stone

spectrum of clinical presentations ranges from mild disease including biliary colic and abnormal liver enzymes to the more severe and life-threatening diseases, including pancreatitis, cholangitis, and sepsis, which can deteriorate and lead to death. In our study, and for the first time, we identified that DM significantly correlated with acute cholangitis among patients with CBD stone on univariate and multivariate analysis with OR of 1.93 (95% CI 1.26–2.96). Few studies have addressed the association of DM with biliary diseases. Ludvigsson et al[9] reported that the association of primary sclerosing cholangitis with DM. A recent study demonstrated that DM was associated with reduced risk of cholangiocarcinoma among patients with biliary tract diseases.[7] Moreover, previous studies have reported the association of DM with cholelithiasis[10] and with biliary stones.[11,12] The suggested underlying mechanism for this association is related to several key factors important in the process of stone formation, including lithogenic bile that is supersaturated with cholesterol, particularly in subjects with dyslipidemia and after initiation of insulin therapy.[13] After an extensive literature search, we could identify only 1 study by Yeom et al[14] demonstrating several independent risk factors for acute cholangitis caused by CBD stone among 181 investigated patients, including chronic smoking (OR 9.86, $P=.008$), advanced age >70 years (OR 8.9, $P=.002$), impacted CBD stone (OR 34.12, $P=.01$), and gallstone (OR 4.74, $P=.016$), while DM was not associated with development of acute cholangitis ($P=.7$).

To the best of our knowledge, this is the first report demonstrating the association of DM with acute cholangitis among patients with CBD stone. The proposed underlying pathophysiology is still unclear; however, 2 hypothesis may explain this association, the first one is impaired gallbladder emptying due to autonomic neuropathy of hyperglycemia,[15] and the second one is impaired cholecystokinin secretion in the jejunum and reduced sensitivity to cholecystokinin in DM.[16] Both mechanisms lead to hypo-contractility of the gallbladder which leads to stasis of biliary contents including stones if present, subsequently leading to bacterial overgrowth and infection. Of note, the CBD has few unorganized smooth muscle fibers, and it was demonstrated previously by Scatliff et al[17] who were unable to visualize any coordinated motor function in the human bile duct, and later confirmed by Hauge and Mark[18] who showed that the CBD is a passive conduit without evidence of peristaltic contractions using multiple pressure lumen catheter in dogs. These make the above-mentioned hypotheses more relevant in explaining the underlying relation of DM with cholangitis, as bile exflow from the CBD is dependent on normal gallbladder contractility. Thus, gallbladder hypo-motility leads to reduction in bile flow through the CBD and subsequently to CBD bile stasis and infection.

Our study has a few limitations: importantly is the retrospective nature of data collection which might limit the value of the results, another that it is a single center study; however, the strengths are the relatively large number of patients included, and that all patients had confirmed CBD stone as all of them underwent ERCP with definite stone extraction.

In conclusion: we showed that DM might be a possible predisposing risk factor for the development of acute cholangitis among patients with CBD stone. This association might be related in part to DM related autonomic dysfunction that may lead to impaired gallbladder contractility and subsequent biliary stasis and infection within the gallbladder and bile ducts. Further multicenter prospective studies are needed to confirm our findings and explore the underlying mechanisms behind this association.

Author contributions

Tawfik Khoury and Wisam Sbeit contributed to study design and conception and contributed to data collection, analysis, and interpretation. Tawfik Khoury and Wisam Sbeit wrote the draft of the manuscript and approved the final version to be published.
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