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**MINIREVIEWS**

- 1136 Spontaneous bacterial peritonitis due to carbapenemase-producing *Enterobacteriaceae*: Etiology and antibiotic treatment  
*Fiore M, Di Franco S, Alfieri A, Passavanti MB, Pace MC, Petrou S, Martora F, Leone S*
- 1148 Molecular heterogeneity in intrahepatic cholangiocarcinoma  
*Ahn KS, Kang KJ*
- 1158 Spectrum of esophageal motility disorders in patients with liver cirrhosis  
*Khalaf M, Castell D, Elias PS*
- 1168 Metabolic associated fatty liver disease: Addressing a new era in liver transplantation  
*Gill MG, Majumdar A*
- 1182 Liver injury in COVID-19: The hepatic aspect of the respiratory syndrome — what we know so far  
*Anirvan P, Bharali P, Gogoi M, Thuluvath PJ, Singh SP, Satapathy SK*

**ORIGINAL ARTICLE****Basic Study**

- 1198 Cyclin-dependent kinase inhibitors p21 and p27 function as critical regulators of liver regeneration following 90% hepatectomy in the rat  
*Moniaux N, Lacaze L, Gothland A, Deshayes A, Samuel D, Faivre J*
- 1211 Pivotal role of long non-coding ribonucleic acid-X-inactive specific transcript in regulating immune checkpoint programmed death ligand 1 through a shared pathway between miR-194-5p and miR-155-5p in hepatocellular carcinoma  
*Atwa SM, Handoussa H, Hosny KM, Odenthal M, El Tayebi HM*

**Case Control Study**

- 1228 Validation of genetic variants associated with metabolic dysfunction-associated fatty liver disease in an ethnic Chinese population  
*Lee GH, Phyo WW, Loo WM, Kwok R, Ahmed T, Shabbir A, So J, Koh CJ, Hartono JL, Muthiah M, Lim K, Tan PS, Lee YM, Lim SG, Dan YY*

**Retrospective Cohort Study**

- 1239 Comparison between hepatocellular carcinoma prognostic scores: A 10-year single-center experience and brief review of the current literature  
*Campigotto M, Giuffrè M, Colombo A, Visintin A, Aversano A, Budel M, Masutti F, Abazia C, Crocè LS*

**Retrospective Study**

- 1258 Effects of proprotein convertase subtilisin/kexin type-9 inhibitors on fatty liver  
*Shafiq M, Walmann T, Nutalapati V, Gibson C, Zafar Y*

- 1267 Timing of paracentesis and outcomes in hospitalized patients with decompensated cirrhosis  
*Tocia C, Dumitru A, Alexandrescu L, Popescu R, Dumitru E*
- 1276 Bioelectrical impedance vector analysis evaluates cellularity and hydration in cirrhotic patients  
*Fernandes SA, Leonhardt LR, da Silva DM, Alves FD, Marroni CA*
- 1289 Incidental biliary dilation in the era of the opiate epidemic: High prevalence of biliary dilation in opiate users evaluated in the Emergency Department  
*Barakat MT, Banerjee S*

**Clinical Trials Study**

- 1299 Effect of non-alcoholic beer, diet and exercise on endothelial function, nutrition and quality of life in patients with cirrhosis  
*Macias-Rodríguez RU, Ruiz-Margáin A, Román-Calleja BM, Espin-Nasser ME, Flores-García NC, Torre A, Galicia-Hernández G, Rios-Torres SL, Fernández-del-Rivero G, Orea-Tejeda A, Lozano-Cruz OA*

**Observational Study**

- 1314 HIPPOCRATES® project: A proof of concept of a collaborative program for hepatitis C virus micro-elimination in a prison setting  
*Gaspar R, Liberal R, Tavares J, Morgado R, Macedo G*

**Prospective Study**

- 1326 Subclinical proximal tubulopathy in hepatitis B: The roles of nucleot(s)ide analogue treatment and the hepatitis B virus  
*Brayette A, Essig M, Carrier P, Debette-Gratien M, Labrunie A, Alain S, Maynard M, Ganne-Carrié N, Nguyen-Khac E, Pinet P, De Ledinghen V, Renou C, Mathurin P, Vanlemmens C, Di Martino V, Gervais A, Foucher J, Isabelle FH, Vergniol J, Hourmand-Ollivier I, Cohen D, Duval X, Poynard T, Bardou M, Abergel A, Dao MT, Thévenot T, Hiriart JB, Canva V, Lassailly G, Aurières C, Boyer N, Thabut D, Bernard PH, Schnee M, Larrey D, Hanslik B, Hommel S, Jacques J, Loustaud-Ratti V*

**CASE REPORT**

- 1341 Safety and efficacy of sofosbuvir/velpatasvir/voxilaprevir in post-liver transplant patients with previous direct-acting antiviral failure: Six case reports  
*Higley C, Hsu CC, Smith C, Nadella S, Lalos AT*
- 1349 Successful hepatic resection for recurrent hepatocellular carcinoma after lenvatinib treatment: A case report  
*Yokoo H, Takahashi H, Hagiwara M, Iwata H, Imai K, Saito Y, Matsuno N, Furukawa H*
- 1358 Hepatitis E virus re-infection accelerates hepatocellular carcinoma development and relapse in a patient with liver cirrhosis: A case report and review of literature  
*Lin XN, Lin QX, Li SM, Xie KP, Hou J, Chen R*

**LETTER TO THE EDITOR**

- 1367 Autophagy related protein 9A increase in hepatitis B virus-associated hepatocellular carcinoma and the role in apoptosis  
*Kimkong I, Kunanopparat A*

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## Retrospective Study

# Incidental biliary dilation in the era of the opiate epidemic: High prevalence of biliary dilation in opiate users evaluated in the Emergency Department

Monique T Barakat, Subhas Banerjee

**ORCID number:** Monique T Barakat 0000-0003-2946-6325; Subhas Banerjee 0000-0003-2270-9742.

**Author contributions:** Barakat MT and Banerjee S were involved in conception and design of the study as well as collection, analysis and interpretation of the data in collaboration with the Stanford University Statistics Consulting Service; Barakat MT and Banerjee S were involved in drafting and critical revision of the article for important intellectual content; Banerjee S granted final approval of the article.

**Institutional review board**

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**Monique T Barakat**, Divisions of Adult and Pediatric Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA 94305, United States

**Subhas Banerjee**, Division of Gastroenterology and Hepatology, Stanford University Medical Center, Stanford, CA 94304, United States

**Corresponding author:** Subhas Banerjee, MD, Professor, Division of Gastroenterology and Hepatology, Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA 94304, United States. [subhas.banerjee@stanford.edu](mailto:subhas.banerjee@stanford.edu)

## Abstract

### BACKGROUND

Biliary dilation is frequently related to obstruction; however, non-obstructive factors such as age and previous cholecystectomy have also been reported. In the past two decades there has been a dramatic increase in opiate use/dependence and utilization of cross-sectional abdominal imaging, with increased detection of biliary dilation, particularly in patients who use opiates.

### AIM

To evaluate associations between opiate use, age, cholecystectomy status, ethnicity, gender, and body mass index utilizing our institution's integrated informatics platform.

### METHODS

One thousand six hundred and eighty-five patients (20% sample) presenting to our Emergency Department for all causes over a 5-year period (2011-2016) who had undergone cross-sectional abdominal imaging and had normal total bilirubin were included and analyzed.

### RESULTS

Common bile duct (CBD) diameter was significantly higher in opiate users compared to non-opiate users (8.67 mm vs 7.24 mm,  $P < 0.001$ ) and in patients with a history of cholecystectomy compared to those with an intact gallbladder (8.98 vs 6.72,  $P < 0.001$ ). For patients with an intact gallbladder who did not use opiates ( $n = 432$ ), increasing age did not predict CBD diameter ( $r^2 = 0.159$ ,  $P = 0.873$ ). Height weakly predicted CBD diameter ( $r^2 = 0.561$ ,  $P = 0.018$ ), but weight,

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body mass index, ethnicity and gender did not.

## CONCLUSION

Opiate use and a history of cholecystectomy are associated with CBD dilation in the absence of an obstructive process. Age alone is not associated with increased CBD diameter. These findings suggest that factors such as opiate use and history of cholecystectomy may underlie the previously-reported association of advancing age with increased CBD diameter. Further prospective study is warranted.

**Key Words:** Biliary dilation; Opiate; Narcotic; Endoscopic ultrasound; Endoscopic retrograde cholangiopancreatography; Bile duct

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**Core Tip:** What is current knowledge? Biliary dilation is often related to an obstructing process. Non-obstructive factors such as age and prior cholecystectomy have also been associated with biliary dilation. Rates of opiate use have dramatically increased within the United States over the past two decades. There has also been a dramatic increase in utilization of cross-sectional abdominal imaging over the past two decades. What is new here. Opiate use is associated with biliary dilation in the absence of an obstructive process. Increasing opiate use and increasing utilization of imaging are resulting in increased incidental detection of biliary dilation leading to increased referrals for endoscopic workup. Contrary to conventionally held views, our study indicates that age alone is not associated with increased bile duct diameter. Increasing probability of opiate use and cholecystectomy with advancing age may underlie the previously-reported association of advancing age with increased bile duct diameter. Height is weakly associated with increased bile duct diameter, consistent with an organ scaling effect.

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## INTRODUCTION

Bile duct dilation is commonly related to an obstructive process such as a stone, stricture or a mass. However, biliary dilation has also been associated with non-obstructive factors such as advanced age and previous cholecystectomy<sup>[1]</sup>. The role of other patient factors such as height, weight, body mass index (BMI), and substance use in modulating biliary dilation have not been well defined.

The opioid epidemic sweeping across the United States, has resulted in a 3-fold increase in opiate prescriptions since 1999. Approximately 255.2 million opioid prescriptions were reported in 2012, corresponding to a staggering 81.3 prescriptions per 100 United States residents<sup>[2,3]</sup>. Despite the high prevalence of opiate use in the United States, the impact of opiates on bile duct diameter remains under-studied. Data are limited to only a few case series, some of which suggest that opiate use may be associated with dilatation of the bile duct in the absence of biliary obstruction<sup>[4,5]</sup>. However, small sample size, and lack of controls have limited the generalizability of these observations<sup>[4-6]</sup>.

Additionally, perhaps in association with the ongoing national obesity epidemic, rates of cholecystectomy have increased over time, with over 900000 annual cholecystectomies currently performed in the United States<sup>[7]</sup>. Following cholecystectomy, it is widely accepted that the bile duct increases in diameter<sup>[1]</sup>. In 1894 Oddi postulated that the bile duct dilates following cholecystectomy so as to serve as a reservoir of bile—the pressure of which must then overcome the biliary sphincter pressure to enable bile to flow into the intestine<sup>[8]</sup>. Despite the longstanding

recognition of this phenomenon, systematic evaluations of the impact of cholecystectomy on bile duct diameter have only emerged over the past 5 years<sup>[9]</sup>. The extent to which other patient factors may modulate the occurrence and the degree of biliary dilation following cholecystectomy remains to be determined.

Studies of the impact of aging on bile duct diameter in adults are similarly limited. In children, bile duct diameter increases with advancing age in relative proportion to a child's growth curve<sup>[10]</sup>. In adults, some studies with limited sample sizes have suggested that common bile duct (CBD) diameter gradually increases with age in healthy adults<sup>[1,11,12]</sup>; however other studies have not demonstrated this trend<sup>[13]</sup>.

In parallel with the progressively aging population, the ongoing opiate and obesity epidemics, and the rising rates of cholecystectomy, utilization of cross-sectional abdominal imaging has more than tripled over the past two decades<sup>[14,15]</sup>. An unintended consequence of this escalating utilization of cross sectional imaging is detection of incidental biliary dilation<sup>[14]</sup>. At our tertiary care academic endoscopy unit, over the last decade, we have noted a 5-fold increase in referrals for endoscopic evaluation of incidentally detected biliary dilation with normal bilirubin in opiate users. Although the majority of these patients were referred for Endoscopic Retrograde Cholangiopancreatography (ERCP), we opted to perform endoscopic ultrasound (EUS) for these patients, as this is a lower risk procedure. However EUS has not revealed pancreatic or biliary pathology in the vast majority of these patients.

Given the escalating endoscopic burden of this important problem, it would be informative to determine when biliary dilation is within the range of expected variation given the clinical context and characteristics of the patient, and when biliary dilation is more pronounced than would be expected, implying obstructive pathology which warrants further diagnostic evaluation. We therefore undertook a formal, controlled study on over 1500 patients to evaluate factors such as opiate use, age, cholecystectomy status, gender, ethnicity, height, weight and BMI which might predict increased bile duct diameter in patients with normal liver function tests and no visualized obstructive process on cross-sectional imaging.

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## MATERIALS AND METHODS

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We utilized an informatics platform, the Stanford Translational Research Integrated Database Environment (STRIDE) integrated standards-based platform<sup>[16]</sup>. This informatics resource consists of integrated components including a clinical data warehouse, which is based on the HL7 Reference Information Model, with clinical information on over 2 million pediatric and adult patients cared for at Stanford University Medical Center since 1995 and an application development framework for building research data management applications and initiating queries on the STRIDE platform<sup>[16]</sup>.

Utilizing this STRIDE informatics platform and a retrospective cohort study design, we evaluated a 20% sample of patients over 18 years of age presenting to our Emergency Department (ED) for all causes over a 5-year period (2011-2016). We identified patients who had undergone computed tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen with documentation of CBD diameter, and who had normal bilirubin with no evidence of biliary obstruction on imaging using our institutional informatics platform. Opiate use status is a mandatory question for all patients who are cared for in our ED. We extracted opiate use status responses from the electronic medical record (EMR) for all patients. Gallbladder status, age, gender, height, weight, BMI and ethnicity were also determined from the EMR.

Student's *t*-test was performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA). Reported *p*-values are 2-sided, and comparisons attained statistical significance at  $P < 0.05$ . Linear regression analysis was conducted using standard techniques and categorical age analysis was performed by comparison of decades. This study was approved by the Stanford University Institutional Review Board (Protocol No. 41605).

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## RESULTS

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This study included 1685 patients, 46% female and 54% male. There were 867 patients in the opiate user cohort and 818 in the non-opiate user cohort (mean age = 54.5 years *vs* 58.6 years,  $P = 0.20$ ). Gender did not predict CBD diameter ( $P = 0.12$ ). Stated ethnicity was only available for 56% of patients. For patients in whom ethnicity data

were available, ethnicity did not predict CBD diameter ( $P = 0.09$ ). Height and weight data were available for 86% of patients in this sample. Height weakly predicted CBD diameter ( $r^2 = 0.561$ ,  $P = 0.018$ ), but weight and body mass index did not ( $r^2 = 0.177$ ,  $P = 0.29$ ,  $r^2 = 0.210$ ,  $P = 0.21$ , respectively).

The mean CBD diameter was significantly higher in opiate users compared to non-opiate users (8.67 mm *vs* 7.24 mm,  $P < 0.001$ , **Table 1**). The mean CBD diameter was also significantly higher in patients with a history of cholecystectomy compared to those with an intact gallbladder (8.98 mm *vs* 6.72 mm,  $P < 0.001$ ). The lowest CBD diameter was evident in patients with an intact gallbladder who did not use opiates, with sequentially increasing diameters noted in patients with an intact gallbladder who used opiates, and in those with prior cholecystectomy who did not use opiates, with the largest mean CBD diameter observed in patients with a history of both cholecystectomy and opiate use (**Figure 1**). Gallbladder status appeared to modulate the effect of opiates on bile duct diameter. Among patients with an intact gallbladder, opiate users had a CBD diameter that was 43.5% greater than non-opiate users. In contrast, among patients with a history of cholecystectomy, opiate users had a CBD diameter that was only 6.5% greater than non-opiate users (**Table 1**, **Figure 1**). When 7 mm was used as the threshold for normal bile duct diameter in all patients regardless of age and cholecystectomy status, 72% of opiate using patients had biliary dilation, as compared with only 27% of non-opiate using patients (**Figure 2**).

Importantly, increasing age did not significantly correlate with CBD diameter upon analysis as a continuous variable ( $r^2 = 0.159$ ,  $P = 0.873$ ) or across age group categories ( $P = 0.217$ , **Figure 3**), for the population of patients with an intact gallbladder who did not use opiates ( $n = 432$ ). Increasing age weakly predicted ( $r^2 = 0.439$ ,  $P = 0.027$ ) increased CBD diameter in patients with a history of opiate use and/or a history of cholecystectomy ( $n = 1356$ ). When all patient cohorts were grouped for analysis, including opiate users and non-users, and patients with and without a history of cholecystectomy ( $n = 1685$ ), advancing age very weakly predicted ( $r^2 = 0.306$ ,  $P = 0.038$ ) increased CBD diameter when analyzed as a continuous variable and across age group categories (**Figure 3**).

## DISCUSSION

Prescription and illicit use of opiates has increased dramatically over the last 2 decades, with the emergence and escalation of a nationwide opiate epidemic<sup>[2,3]</sup>. The number of cholecystectomies performed annually in the United States has increased by more than 20%<sup>[7]</sup>, and utilization of abdominal imaging has also increased approximately 3-fold over the same time period<sup>[14]</sup>. Age has previously been considered a factor associated with biliary dilation<sup>[1,11,13]</sup> and the proportion of the United States population aged over 65 has progressively increased and is projected to continue increasing. We therefore sought to evaluate the impact of each of these parameters on biliary dilation. It has been our impression that these concurrent phenomena have led to the increasing incidental detection of bile duct dilation in patients, which in turn is driving increased utilization of invasive, expensive and potentially risky endoscopic procedures. In our own practice we have noted a 5-fold increase in referrals for EUS and ERCP over the past decade, for patients with biliary dilation and a normal total bilirubin. Over 60% of these referrals in 2018 had concurrent opiate use. A few small previous case series have suggested that opiate use may be associated with biliary dilation; however, small sample size, study populations focused on opiate-dependent patients, confounding variables and lack of controls have limited the generalizability of these observations<sup>[4-6]</sup>.

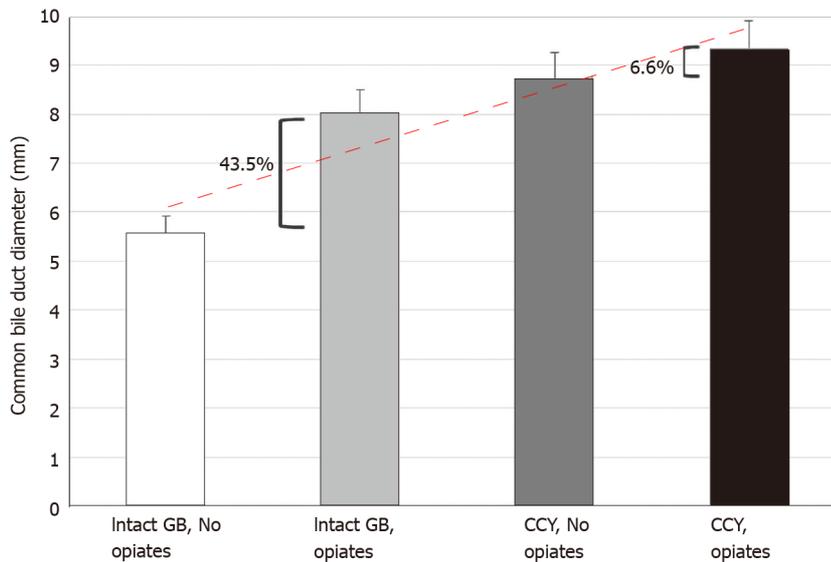
Our study, the largest conducted to date evaluating the association between opiate use and bile duct diameter, demonstrates that opiate use is a modulating factor associated with biliary dilation in the setting of a normal bilirubin. Patients who have both undergone cholecystectomy and use opiates have the largest CBD diameters overall. The impact of opiate use on CBD dilation is most striking in patients with an intact gallbladder. The opiate impact is muted in patients who have undergone cholecystectomy, perhaps related to a ceiling effect, given the significant pre-existing dilatory effect of cholecystectomy on the bile duct. We find that height is positively correlated with CBD diameter, consistent with an organ scaling effect. Our data indicate that patient weight, BMI, ethnicity and gender are not correlated with bile duct diameter.

Age has long been held to modulate bile duct diameter – this conventional wisdom is commonly asserted in radiology and gastroenterology textbooks. A standard

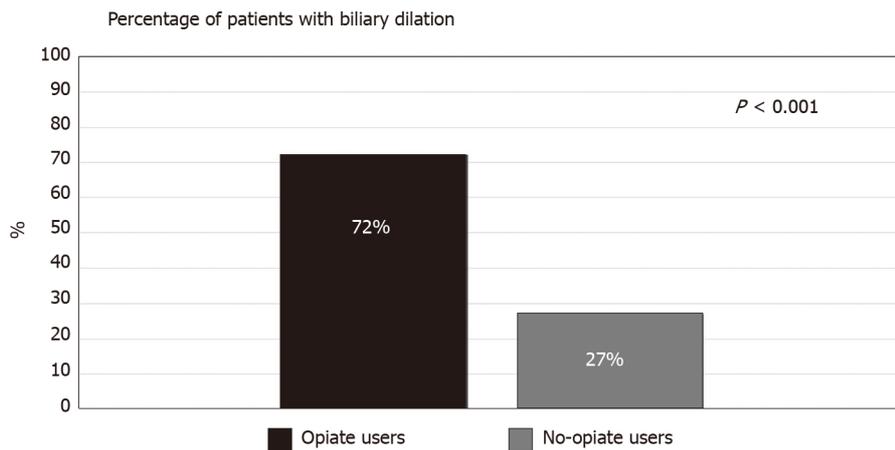
**Table 1 Common bile duct diameter varies with opiate use and cholecystectomy status**

Cholecystectomy status	Non opiate users, mean (SD) CBD diameter in mm	Opiate users, mean (SD) CBD diameter in mm	P value
All patients	7.24 (2.28), n = 818	8.67 (1.89), n = 867	P < 0.001
Gallbladder intact (n = 814)	5.58 (1.38), n = 432	8.01 (1.83), n = 382	P < 0.001
Gallbladder absent (n = 871)	8.72 (1.86), n = 386	9.30 (1.72), n = 485	P < 0.001

SD: Standard deviation; CBD: Common bile duct.



**Figure 1 Common bile duct diameter varies with gallbladder and opiate use status.** Bar graph depicting mean common bile duct (CBD) diameter for groups categorized by gallbladder status and opiate use. The lowest CBD diameter is seen in patients with an intact gallbladder who did not use opiates, with sequentially increasing diameters noted in patients with an intact gallbladder who used opiates, and in those with prior cholecystectomy who did not use opiates, with the largest mean CBD diameter observed in patients with a history of both cholecystectomy. Trendline (red) depicts this trend, error bars depict standard deviation. Calipers indicate percentage change between the means of indicated categories. GB: Gallbladder; CCY: Cholecystectomy.



**Figure 2 Percentage of patients with biliary dilation.** Bar graph depicting proportion of all patients, regardless of age and cholecystectomy status, with biliary dilation when 7 mm was used as the threshold for normal bile duct diameter. With this threshold of normal bile duct diameter, 72% of opiate using patients had biliary dilation, as compared with only 27% of non-opiate using patients.

radiology textbook, for example, indicates that an estimate of normal bile duct diameter at a given age may be roughly derived from considering a 4 mm bile duct diameter normal at age 40, and assuming a 1 mm increase in bile duct diameter for each subsequent decade of life<sup>[17]</sup>. The proposed association between age and CBD diameter was supported by a few limited studies conducted over 25 years ago, which concluded that CBD diameter is age-dependent<sup>[18-20]</sup>. However, a subsequent small prospective study did not demonstrate this association between age and bile duct diameter<sup>[13]</sup>. Our large study has not demonstrated an independent role for age in modulating CBD diameter in the absence of a history of cholecystectomy or opiate use. Our data suggest for the first time that other factors which modulate CBD diameter (cholecystectomy, opiate use) may account for the assertions in previous studies regarding increasing bile duct diameter with age. Further prospective study of this association is warranted.

Workup of incidentally detected biliary dilation in opiate users reflects yet another previously-unrecognized cost of the opiate epidemic. In recent years, cross-sectional imaging of the abdomen has supplanted abdominal radiography as the most frequently reimbursed abdominal imaging study<sup>[15]</sup>. Integrated health care systems and Medicare data demonstrate that for every 100 Medicare beneficiaries, over 50 CT scans, 50 abdominal ultrasounds and 15 abdominal MRIs are performed annually<sup>[21,22]</sup>. A subset of these patients undergo this imaging for evaluation of non-specific abdominal pain for which they may be prescribed opiates and may potentially then develop associated biliary dilation. Incidental findings from these imaging studies may then result in a cascade of healthcare expenses related to additional studies, diagnostic workup, procedures and ongoing surveillance, each with associated patient anxiety and the potential for adverse events<sup>[14]</sup>.

In this era of escalating health care costs, our study indicates that the detection on imaging of incidental bile duct dilation without a visualized obstructing process in known opiate users with normal liver function tests may not require expensive and potentially risky endoscopic evaluation. However, the complexity of the problem of incidentally detected biliary dilation must also be acknowledged. The rising rates of Non Alcoholic Fatty Liver Disease (NAFLD) and increased rates of statin utilization in the United States population result in associated liver function tests (LFT) abnormalities in up to 20% of NAFLD patients<sup>[23-25]</sup> and around 3% of statin users<sup>[26,27]</sup>. LFT abnormalities in these and in similar scenarios will impact the workup of patients referred for workup of incidental biliary dilation.

Additionally, valid concerns of referring and consulting physicians should be acknowledged. Sensitivity for detection of pancreatic adenocarcinoma, ranges from 76%-96% for CT<sup>[28-35]</sup> and from 83%-93.5% for MRI<sup>[30-35]</sup>, with higher sensitivity corresponding with larger masses<sup>[31,33,35]</sup>. Additionally, in 5.4%-18.4% of patients with pancreatic malignancy, the lesion is isoattenuating relative to the background pancreas, with smaller lesions more likely to be isoattenuating<sup>[36-39]</sup>. Furthermore, cholangiocarcinoma, another concerning potential etiology of biliary obstruction and resultant dilation, often does not present as a mass on cross-sectional imaging and may be only partially occlusive, with incipient obstruction resulting in biliary dilation before significant LFT abnormalities develop<sup>[40-42]</sup>. Taken together, these limitations of cross sectional imaging, and the implicit potential for missed malignant lesions, prompt referring physicians to request additional evaluation for patients with incidental biliary dilation and biliary specialists to proceed with additional endoscopic evaluation.

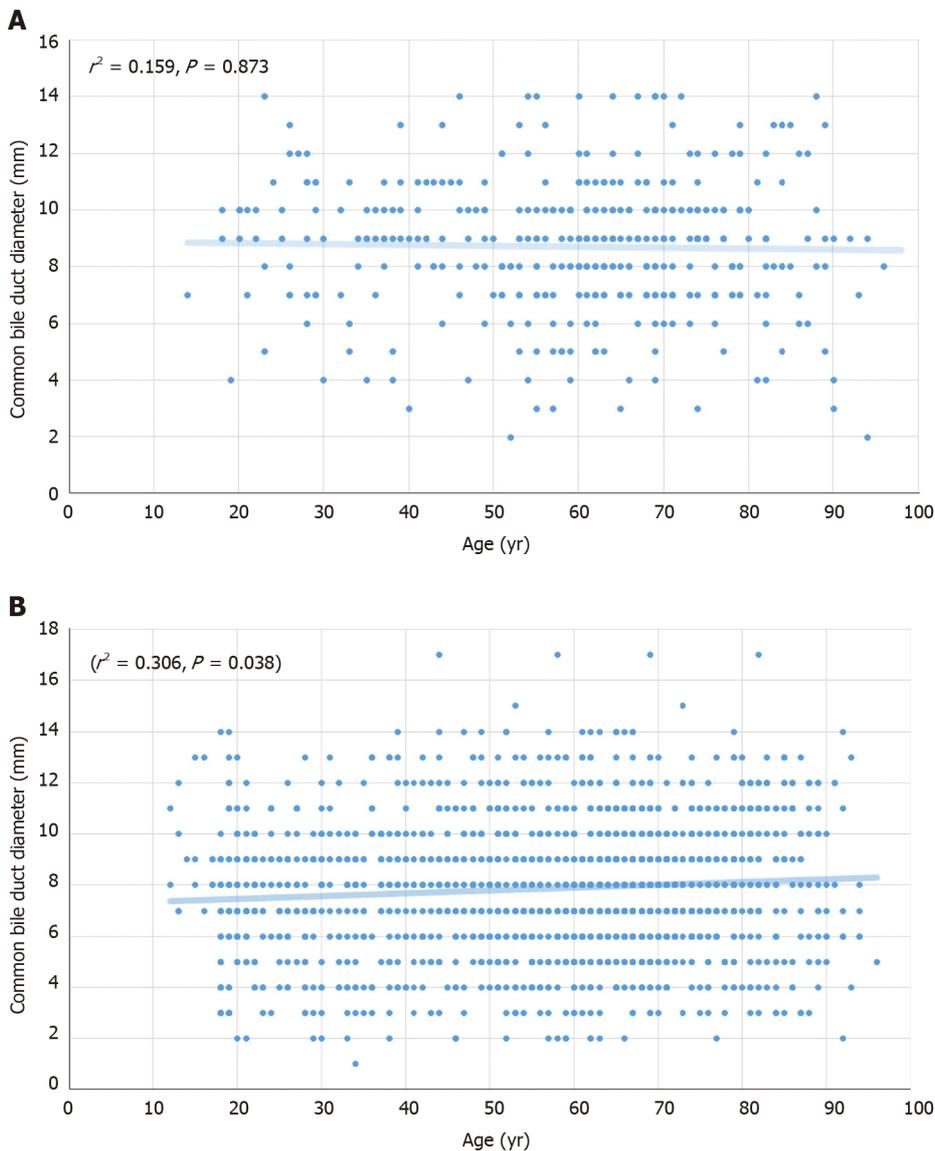
Limitations of this study include its retrospective nature, reliance on data from the electronic medical record and reliance on reports from multiple radiologists for documentation of bile duct diameter. However, the large sample size should neutralize these effects. Due to limitations in opiate type, duration and use pattern details included within the electronic medical record, it was not possible to associate these parameters with CBD diameter. Prospective study of these phenomena would be informative to construct recommendations for when endoscopic evaluation of biliary dilation is most appropriate in the setting of these study limitations.

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## CONCLUSION

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In conclusion, our data indicate that opiate use is associated with bile duct dilation in the absence of an obstructive process. We confirm that a history of prior cholecystectomy is associated with increased CBD diameter. We demonstrate that, in adult populations, height positively correlates with CBD diameter. Finally, we



**Figure 3 Overall (all groups combined), age weakly predicts common bile duct diameter, suggesting that cholecystectomy status and opiate use may be more common in older individuals and this may be driving previously-described associations between age and biliary dilation.** A: Advancing age weakly predicts increased CBD diameter in all patient groups combined; B: Age is not predictive of CBD diameter in patients with an intact gallbladder who do not use opiates.

demonstrate that advancing age does not independently predict a larger CBD diameter in our analysis, and previously-reported associations of advancing age with larger CBD diameter may be attributable instead to other variables such as cholecystectomy and opiate use. Our data suggest that incidentally detected biliary dilation without a visualized obstructive process in the setting of normal bilirubin in known opiate users may not require expensive and potentially risky endoscopic evaluation.

## ARTICLE HIGHLIGHTS

### Research background

Bile duct dilation is often related to an obstructive process such as a stone, stricture or a mass. The role of other patient factors such as height, weight, body mass index, and substance use in modulating biliary dilation have not been well defined.

### Research motivation

In the past two decades, both opiate use/dependence and utilization of cross-sectional

abdominal imaging have sharply increased. We have noted an increase in referrals to our academic tertiary care medical center for incidentally detected biliary dilation, particularly in patients who use opiates.

### Research objectives

Our goal was to evaluate associations between opiate use, age, cholecystectomy status, ethnicity, gender, and body mass index to understand how these factors may be related to biliary dilation.

### Research methods

We evaluated associations between opiate use, age, cholecystectomy status, ethnicity, gender, and body mass index utilizing our institution's integrated informatics platform. We evaluated 1685 Emergency Department patients (a 20% sample from 2011-2016) who had undergone cross-sectional abdominal imaging and had normal total bilirubin.

### Research results

Diameter of the common bile duct was significantly higher in opiate users compared to non-opiate users (8.67 mm *vs* 7.24 mm,  $P < 0.001$ ) and in patients with a history of cholecystectomy compared to those with an intact gallbladder (8.98 *vs* 6.72,  $P < 0.001$ ). For patients with an intact gallbladder who did not use opiates ( $n = 432$ ), increasing age did not predict common bile duct (CBD) diameter ( $r^2 = 0.159$ ,  $P = 0.873$ ).

### Research conclusions

A history of cholecystectomy and opiate use are associated with common bile duct dilation in the absence of an obstructive process. Age alone does not appear to be associated with increased common bile duct diameter.

### Research perspectives

These findings suggest that factors such as opiate use and history of cholecystectomy may underlie the previously-reported association of advancing age with increased CBD diameter. Future prospective study would be desirable to expand upon these findings.

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