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Total bilirubin trend as a predictor of common bile duct stones in acute cholecystitis and symptomatic cholelithiasis

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ABSTRACT

Background: We hypothesized that trends in total bilirubin in the context of cholecystitis and symptomatic cholelithiasis could be used to guide testing for the presence of common bile duct stones (CBDS).
Methods: A review of adult patients with acute cholecystitis or biliary colic with elevated total bilirubin and at least two levels drawn prior to procedural intervention was performed. Trends of total bilirubin and other serum makers were examined to predict the presence of CBDS.
Results: The total bilirubin level at presentation, average over 24 h and average over 48 h (3.74 mg/dl vs. 2.29 mg/dl, $p = 0.005$; 3.72 mg/dl vs. 2.40 mg/dl, $p = 0.009$; 2.41 mg/dl vs. 1.47 mg/dl, $p < 0.001$) respectively, were all higher in those with CBDS. However, prediction was not improved by following levels over time.
Conclusion: Patients presenting with elevated serum bilirubin, should undergo immediate imaging or procedural intervention rather than obtaining follow-up bilirubin levels.

Introduction

Gallstone disease is common in Western countries, with an incidence of approximately 10–20% in the adult population, and of those, 2–4% become symptomatic from cholelithiasis annually.[1,2] It is estimated that 3–33% of all patients with symptomatic cholelithiasis may harbor concomitant common bile duct stones (CBDS),[2–5] and 4–20% will have CBDS at the time of cholecystectomy.[3] If left undiagnosed and untreated, CBDS carry additional morbidity, potentially causing common bile duct (CBD) obstruction leading to cholangitis or, pancreatitis.

Historically, intraoperative cholangiogram (IOC) was performed routinely during open cholecystectomy for diagnosis, and common bile duct exploration for management of CBDS.[3] However, with the advent of laparoscopic surgery, IOC is no longer performed routinely, and not all surgeons are skilled in advanced laparoscopic techniques required for laparoscopic common bile duct exploration.[3] This has made the need for accurate pre-operative diagnosis of choledocholithiasis important.

Imaging modalities used in the diagnosis of CBDS include abdominal ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and IOC. Abdominal ultrasound, while non-invasive and relatively inexpensive, is unreliable for diagnosis of CBDS, with a sensitivity of 25–63%.[3,6] ERCP is the gold standard for diagnosis of CBDS due to its high sensitivity, specificity, and accuracy.[7] However, routine pre-operative ERCP is low yield and carries associated risks given to its invasive nature.[8–10] MRCP and EUS are also highly sensitive and specific for diagnosis of CBDS,[7,9,11] however EUS is also invasive with risk and MRCP may not be immediately available and is slightly higher cost.

Patients who present with acute cholecystitis often present with elevated bilirubin, raising the suspicion for CBDS. Use of bilirubin and other biochemical markers for pre-operative diagnosis of CBDS has been widely studied,[2,3,5,8,9,12–17] with most researchers examining the role of biochemical markers at the time of patient presentation. When patients present in off hours, follow-up imaging and procedures are often delayed for purely administrative reasons leading to repeat laboratory values being obtained. When this occurs, clinical decisions may be made based on the trend of the biochemical markers. However, few investigators have studied biochemical marker trends over the first several hours of hospitalization to guide further treatment or diagnostic testing. We

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Abbreviations

CBDS	Common bile duct stones
IOC	Intraoperative cholangiogram
ERCP	endoscopic retrograde cholangiopancreatography
MRCP	magnetic resonance cholangiopancreatography
EUS	endoscopic ultrasound
ROC	receiver-operator characteristic
WBCs	white blood cell count

hypothesized that trends in total bilirubin in the context of acute cholecystitis and symptomatic cholelithiasis could be used to more accurately define the probability of the presence of CBDS and therefore guide further diagnostic testing, including ERCP, EUS, MRCP and/or IOC.

Materials and methods

A single institution retrospective review of patients who presented to the Emergency Department from January 1, 2010 through December 31, 2015 with the diagnosis of acute cholecystitis, choledocholithiasis, or biliary colic was performed. The electronic medical record was searched for all patients with a primary discharge diagnosis of cholelithiasis, choledocholithiasis, or biliary colic. We included adult patients with an elevated total bilirubin and at least two levels drawn prior to any procedural intervention. Patients with gallstone pancreatitis, ascending cholangitis, or elevated total bilirubin secondary to malignancy, biliary stricture or other chronic disease resulting in elevated bilirubin were excluded.

We assessed trends in total bilirubin as well as multiple other serum markers including white blood cell count (WBCs), platelet count, alkaline phosphatase (AP), aspartate transaminase (AST), and alanine transaminase (ALT). Trends in bilirubin were plotted over time as were the other serum laboratory values. Absolute laboratory values as well as the trends in laboratory values over 48 h were examined. Specific emphasis on the rate of change immediately after admission was examined for all values and summary statistics were computed. To assess whether changes in bilirubin may have been due to systemic inflammation or obstruction by CBDS, concomitant changes in other laboratory values including WBCs, platelets, AP, AST and ALT were examined. These indicators marked each change as simultaneous increase, simultaneous decrease, or an opposite trend between bilirubin and the other serum marker.

Statistical analysis was performed using the *t*-test and logistic regression to determine if the trend of the total bilirubin level could predict the presence of common bile duct stones. Sensitivities and specificities were calculated as were areas under the receiver-operating characteristic (ROC) curve to assess the various tests. All analysis was carried out using R version 3.2.1 with the ggplot2 and pROC packages installed.

Results

Over the study period 1481 patients were discharged with the diagnosis of cholelithiasis, choledocholithiasis or biliary colic. Of these, 98 patients were noted to have an elevated total bilirubin level at presentation to the Emergency department, which was not secondary to malignancy or other chronic illness. Seven patients were excluded because their primary diagnosis was either cholangitis or gallstone pancreatitis. An additional 30 patients had only one drawn total bilirubin level prior intervention, and therefore were also excluded. The remaining 59 patients were included in the analysis.

The mean age was 61.2, 57.6% were female, and the mean BMI was 28.95 (Table 1). The average LOS for all patients was 6.27 days, and was longer in patients with CBDS (7.11 days) compared with patients without CBDS (4.9 days). The average total bilirubin level at presentation was higher in patients with CBDS. The average total bilirubin level over the first 24 and 48 h was higher for those with CBDS (Table 2). Average total bilirubin level over 1.168 was 90% sensitive for CBDS (Tables 3 and 4). Bilirubin was more predictive of the presence of CBDS the longer it was monitored with increasing area under the ROC curve. Bilirubin trends, however, were not

Table 1
Patient demographics and baseline characteristics.

	Patients with CBDS (n = 38)	Patients without CBDS (n = 21)	All patients (n = 59)
Age	62.32 (range 17–95)	59.23 (range 20–89)	61.2 (range 17–95)
Gender (% female)	60.5	52.3	57.6
BMI (kg/m^2)	28.68	29.44	28.95
Race/Ethnicity (%)			
White/Caucasian	64.1	61.9	64.4
Hispanic	15.7	14.3	15.3
Black/African American	10.5	19.0	13.5
Average Total bilirubin at admission	3.74	2.29	3.27
Average alkaline phosphatase at admission	274.8	182.1	241.8
CBD diameter on ultrasound (mm)	7.6	6.6	7.3
Average Length of Stay	7.11	4.9	6.27

CBDS – common bile duct stones; BMI = body mass index.

Table 2
Average total bilirubin level at various time points for patients with and without CBDS.

	Admission		24 h		48 h	
CBDS present	Yes	No	Yes	No	Yes	No
Tbili	3.74	2.28	3.72	2.41	2.41	1.47
WBC	11.58	10.35	9.55	8.74	9.29	7.04
Alkaline Phosphatase	273.68	181.86	245.32	187.79	227.4	171.8
AST	274.11	215	206.86	238.32	108.8	180.08
ALT	312.95	224.43	289.26	272.8	246.45	125

Table 3
Sensitivity of total bilirubin level at time points.

Time point	Best Combined Sensitivity/Specificity	90% Sensitivity	Area Under ROC curve
Initial Tbili	90%/45%	1.103	0.6924
Mean Tbili over 24hr	57%/74%	1.161	0.6892
Mean Tbili over 48hr	86%/55%	1.168	0.7400

Tbili – serum total bilirubin.

Table 4
Total bilirubin trends.

Measure of bilirubin trend	AUC	95% CI
Presenting bilirubin	0.692	0.556–0.829
Rate of change after first bilirubin	0.551	0.392–0.705
Maximum bilirubin in 24 h	0.726	0.592–0.859
Maximum bilirubin in 48 h	0.712	0.577–0.847
Average bilirubin in 24 h	0.689	0.545–0.834
Average bilirubin in 48 h	0.740	0.545–0.834

AUC – Area under receiver-operating characteristic curve.

predictive of CBDS. There were no discernible patterns in bilirubin trends for patients with and without CBDS (Fig. 1).

Trends in other biochemical markers were not predictive of the presence of CBDS. However, when trends in other biochemical markers were examined simultaneously with total bilirubin, there were several statistically significant trends. When the white blood cell counts trended opposite bilirubin, or the ALT trended in the same direction as bilirubin, there was an increased probability of CBDS. The simultaneous trend for AST and AP were not significant and there was no evident relationship for platelets (Table 5).

Methods of diagnosis for CBDS included ERCP, MRCP, and IOC. Overall 37 patients underwent ERCP, and stones were identified and extracted in 27 of those patients. Thirty-five patients underwent MRCP, and stones were identified in 20 patients. There were 12 patients who underwent both MRCP and ERCP pre-operative where stones were identified. There were also 6 patients who underwent intraoperative cholangiogram, and stones were identified in 5 patients. One of those patients also had pre-operative MRCP where stones were visualized (Table 6).

Ultimately, 36 patients underwent cholecystectomy, and of those, 23 had CBDS diagnosed by one of the modalities described above. Eleven patients were treated with placement of a percutaneous cholecystostomy tube, and of those five had CBDS. There was only one mortality in a patient without CBDS.

Discussion

Cholelithiasis is relatively common in adults in the United States, and presents with symptoms in 2–4% of patients.[1,17] Concomitant CBDS are seen in up to 33% of patients with symptomatic gallstones,[7,10,16,18,19] and carry significant morbidity when left untreated.[4,18] Indentifying patients at highest risk for concomitant CBDS has the potential to reduce the need for expensive, invasive or time-consuming imaging modalities while minimizing the risk of failure to diagnose CBDS.

Our study evaluated the use of biochemical marker trends in the context of cholecystitis and cholelithiasis to determine if subsequent measures of serum bilirubin improve the ability to predict the presence of CBDS. We found that in patients with acute cholecystitis and symptomatic cholelithiasis, an elevated total

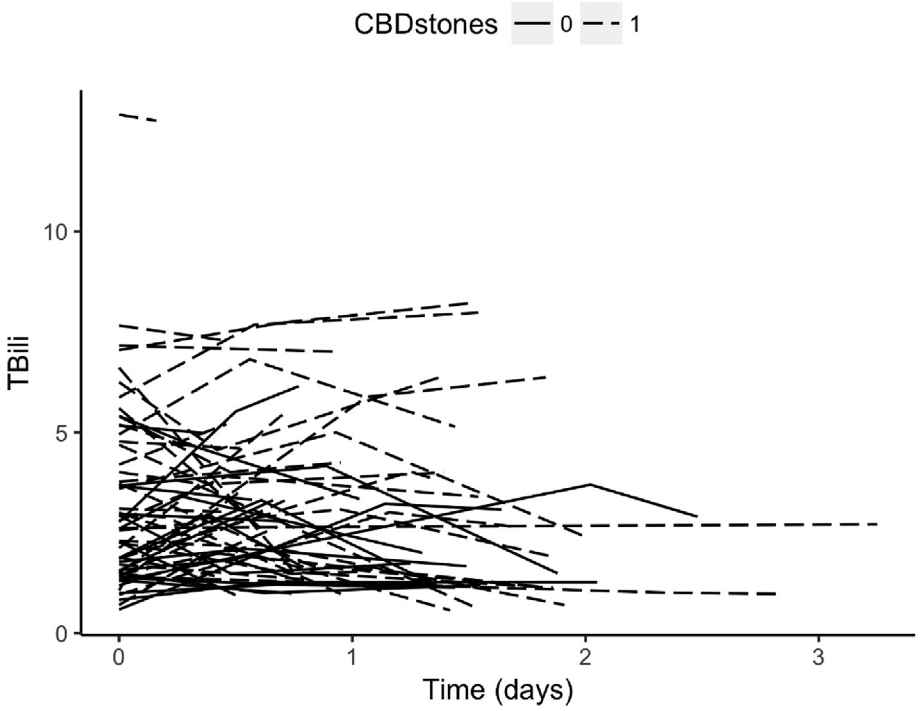

Fig. 1. Plot depicting total bilirubin trends for individual patients. Solid line represents patients without CBDS, and dashed line represents patients with CBDS.

Table 5
Simultaneous trends for other markers compared to bilirubin.

	Choledocholithiasis	No Choledocholithiasis	p-value and OR for opposite trend
Bilirubin up/WBC down	9	9	0.035
Bilirubin up/WBC up	9	3	3.84 (1.24–11.87)
Bilirubin down/WBC up	2	4	
Bilirubin down/WBC down	17	5	
Bilirubin up/Platelets down	13	10	1.0
Bilirubin up/Platelets up	5	1	0.89 (0.30–2.65)
Bilirubin down/Platelets up	3	1	
Bilirubin down/Platelets down	17	8	
Bilirubin up/AST down	11	2	0.251
Bilirubin up/AST up	7	10	0.36 (0.09–1.47)
Bilirubin down/AST up	1	1	
Bilirubin down/AST down	19	8	
Bilirubin up/ALT down	9	1	0.011
Bilirubin up/ALT up	9	11	0.10 (0.01–0.80)
Bilirubin down/ALT up	4	0	
Bilirubin down/ALT down	16	9	
Bilirubin up/Alk Phos down	12	2	0.35
Bilirubin up/Alk Phos up	6	9	0.20 (0.02–1.02)
Bilirubin down/Alk Phos up	2	0	
Bilirubin down/Alk Phos down	18	9	

ALT – alanine aminotransferase, AST – aspartate aminotransferase, Alk Phos – alkaline phosphatase.

Table 6
Methods of CBDS diagnosis.

Method of CBCS diagnosis	Number	Percent
ERCP	27	51.9
MRCP	20	38.4
IOC	5	9.6
ERCP and MRCP	12	23.1
MRCP and IOC	1	1.9

bilirubin at the time of presentation is suggestive of the presence of CBDS. This is a finding previously reported by several other authors.[1–3,8,11–13,18] We also found that persistent elevation over time becomes more predictive, with increased area under the curve. The improvement in predictive ability with bilirubin over time, however, was minimal and not statistically significant. Maximum bilirubin within 48 h of admission was the best predictor of CBDS however there was not a statistically significant advantage for this measure over the initial presenting bilirubin. As demonstrated in Fig. 1, of the 30 patients with rising bilirubin over the first 48 h only 18 (60%) were found to have CBDS. The slope of the increase in total bilirubin in patients where CBDS were present was generally steeper in patients with CBDS, however this was not statistically significant. Following bilirubin or any other single measure over time should not be a strategy for improving the probability of predicting CBDS even in the setting where delays to imaging or procedures are otherwise unavoidable.

If, however, the bilirubin is trended for other reasons, the mean bilirubin over the first 48 h or the maximum value in the first 24 h may be the best measure to predict CBDS. Additional findings of discrepant changes in total bilirubin and WBC count or concordant changes in total bilirubin with either ALT or AP add additional support to the diagnosis of CBDS.

The pathophysiology underlying our findings are not clear and likely multifactorial. Worsening inflammatory changes of the gallbladder may lead to increased bilirubin without the presence of a CBDS. Similarly, passage of a gallstone and relief of CBD obstruction may not result in rapid reduction in bilirubin levels. A third possibility is the presence of a CBDS that intermittently obstructs the flow of bile. We did however identify trends in multiple combined markers that may help to predict CBDS in these patients.

Because imaging studies with adequate sensitivity and specificity to identify CBDS are often invasive, unavailable or delay care, many clinicians have investigated biochemical markers to help guide their decision making.[2,3,5,8,9,12–17] The goal of serum markers is to minimize the use of additional imaging while maximizing yield when imaging tests are performed. However, despite numerous studies evaluating the use of biochemical markers to assist in the diagnosis of CBDS, no consensus has been reached. Some studies found that GGT elevation was especially useful in evaluation for CBDS,[3,8,11,13,14] while others found that elevated alkaline phosphatase was suggestive of CBDS.[3,4,6,7,11–16] Other studies found that total bilirubin level at admission was an independent predictor of stone.[1,3,6–8,11,13] Some authors concluded that biochemical markers alone were insufficient to predict stones, and suggest that a combination of radiographic studies and biochemical markers should be used to drive decision making.[1,6,11,15,16,18] Our findings are similar to prior findings that very high bilirubin levels, over 4.5 mg/dl, are predictive of CBDS however following a trend with these or lower values of bilirubin is of little benefit.

There are several limitations that must be addressed with this study. Most importantly is the retrospective nature and the incumbent selection bias. Patients who present with acute cholecystitis or biliary colic may be managed according to various algorithms, each likely affecting how imaging was chosen and when, if any, follow-up lab testing was performed. Similarly, because there was no protocol in place for management of these patients, each decision for imaging and lab testing was at the discretion of multiple physicians. Time of day at presentation may have also affected imaging studies chosen and whether follow-up testing was performed. Only total bilirubin data were analyzed as this was the lab value most commonly followed. Bilirubin was often only fractioned on the first set of laboratory values performed and therefore we were unable to assess direct bilirubin and this may have demonstrated different results. Including both biliary colic and acute cholecystitis may have also hidden significant findings, however splitting the cohort into two data sets would have reduced the

number of subjects and may have also obscured significant findings. We were also unable to choose a reference imaging study as various studies were used to assess the presence of CBDS. Each of these tests carries its own sensitivity and specificity further complicating analysis of the data. Despite these limitations, this study did follow what is likely standard clinical practice, including its variations, and failed to identify any clear patterns in bilirubin that may identify the presence of CBDS.

Conclusions

An elevated total bilirubin level at the time of presentation with acute cholecystitis or biliary colic is suggestive of a common bile duct stone, and persistent elevation becomes slightly more predictive. However, the small improvements in predictive capability do not warrant delaying surgical intervention or further imaging to obtain additional labs in patients who present with an elevated total bilirubin. Following trends simultaneously in multiple serum markers may prove valuable and our preliminary findings should be evaluated in larger groups of patients.

Author contributions

Study conception (KS, DG), acquisition of data (DG), statistical analysis (KS), manuscript preparation (DG, KS, KD).

Disclosures

No author has a conflict of interest to report.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.amjsurg.2018.06.011.

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