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Dynamic liver test patterns do not predict bile duct stones

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Abstract

Background Numerous models have been developed to predict choledocholithiasis. Recent work has shown that these algorithms perform suboptimally. Identification of clinical predictors with high positive and negative predictive value would minimize adverse events associated with unnecessary diagnostic endoscopic retrograde cholangiopancreatography (ERCP) while limiting the use of expensive tests including magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) for indeterminate cases.

Methods Consecutive unique inpatients who received their first ERCP at Los Angeles County Medical Center between January 2010 and November 2016 for suspected bile duct stones were reviewed. The primary outcome was the proportion of patients with specific combinations of liver enzyme patterns, transabdominal ultrasound, and clinical features who had stones confirmed on ERCP. As a secondary outcome, we assessed the performance of the American Society for Gastrointestinal Endoscopy (ASGE) risk stratification algorithm in our population.

Results Of the 604 included patients, bile duct stones were confirmed in 410 (67.9%). Detailed assessment of liver enzyme patterns alone and in combination with clinical features and imaging findings yielded no highly predictive algorithms. Additionally, the ASGE high-risk criterion had a positive predictive value of only 68% for stones. For the 236 patients for whom MRCP was performed, this imaging modality was shown to have highest predictive value for the presence of stones on ERCP.

Conclusion Exhaustive exploration of various threshold values and dynamic patterns of liver enzymes combined with clinical features and basic imaging findings did not reveal an algorithm to accurately predict the presence of stones on ERCP. The ASGE risk stratification criteria were also insensitive in our population. Though desirable, there may be no "perfect" combination of clinical features that correlate with persistent bile duct stones. MRCP or EUS may be considered to avoid unnecessary ERCP and associated complications.

Keywords Choledocholithiasis · Endoscopic retrograde cholangiopancreatography · Forecasting · Clinical enzyme tests · Gallstones · Cholestasis

Endoscopic retrograde cholangiopancreatography (ERCP) is the preferred treatment for choledocholithiasis. However, given the immediate proximity of the common bile duct (CBD) to the pancreatic duct, this invasive procedure carries significant risk of serious adverse events, including post-ERCP pancreatitis, post-sphincterotomy bleeding, cholangitis, and abdominal perforation [1–3]. In addition, a significant portion of CBD stones pass spontaneously. Thus, to avoid unnecessary procedural risks, there has been a keen interest in a test or a mathematical model to determine whether a suspected CBD stone has passed or remains in the bile duct.

Prior models have used a combination of cholestatic liver enzymes (alkaline phosphatase (ALKP), gamma-glutamyl transferase (GGT), and total bilirubin (T. Bili)), tests of parenchymal injury (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)), and abdominal ultrasound in patients with a contributory clinical history [4, 5]. Perhaps, the most frequently used risk stratification algorithm to determine which patients require more non-invasive testing prior to definitive diagnosis was developed by the American

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Society of Gastrointestinal Endoscopy (ASGE) [6]. However, recent studies have shown that this model, which integrates clinical presentation (i.e., cholangitis), transabdominal ultrasound findings, and T. Bili levels, has variable sensitivity (55–70%) and specificity (73–76%) for choledocholithiasis [7–9]. While > 50% of patients with high-risk criterion will have bile duct stones, contemporary biliary endoscopists desire a positive predictive value of > 85% to avoid the significant risk (and lack of benefit) of diagnostic ERCP [8, 9].

Magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) have very high sensitivity and specificity for bile duct stones, but they are expensive and not universally available [10, 11]. The aim of study was thus to use a combinatorial approach to determine whether liver enzyme fluctuations and specific cutoffs values in conjunction with imaging findings and clinical presentation predict the presence of stones on ERCP in hospitalized patients. We hypothesized that rising or fluctuating liver tests (increase-decrease-increase or decrease-increase-decrease) would predict completely or partially (e.g., ball-valving) obstructed CBD stones.

Methods

Patients

The target population of our study was unique hospitalized patients who underwent initial ERCP for suspicion of bile duct stones at Los Angeles County Medical Center from January 2010 and November 2016. Only the first admission and procedure were analyzed among patients who underwent ERCPs. Outpatients and those who had undergone a prior ERCP were not included. Patients whose primary indication was not stone disease (i.e., suspected bile leak, biliary obstruction due to stricture or malignancy, primary sclerosing cholangitis, and post liver transplant complications) were also not considered. Subjects were subsequently excluded if (1) admission abdominal ultrasound was not obtained; (2) patient had a history of cholecystectomy; (3) ERCP did not fully evaluate for the presence of stone disease via cholangiogram; (4) complete liver enzymes were not obtained on admission; (5) there was suspicion of ascending cholangitis as scored by the Tokyo criterion [12]; (6) age < 18 years; and (7) ERCP was performed more than 7 days after initial presentation to the hospital.

Approval for this study was obtained prior to development of the cohort by the USC Health Sciences Institutional Review Board (USC Health Sciences IRB # 10-00369). As the study did not involve an experimental intervention but development of a prospectively ascertained cohort of patients managed by standard clinical approaches, the requirement for informed consent was waived by the IRB.

Radiographic and clinical parameters

Clinical parameters of interest included age, gender, ethnicity, presentation (including the presence of pancreatitis), and imaging (primarily transabdominal ultrasound) results. Pertinent radiographic findings of interest included the presence of a CBD filling defect and the diameter of the CBD and intrahepatic bile duct (IHD). These data were prospectively entered in the research database, and any missing elements were retrospectively ascertained.

Static and dynamic liver tests models

T. Bili, AST, ALT, and ALKP, white blood cell (WBC), amylase, and lipase were recorded on each of the 3 days leading to ERCP. The biochemistries were used to define the following static and dynamic liver test patterns.

Liver test levels (static model)

T. Bili, ALKP, AST, and ALT were initially categorized based on the degrees of elevation (i.e., one, two, four, six, and eight times) above the upper limits of normal (ULN) as defined at the Los Angeles County Medical Center, which were 1 milligram per deciliter (mg/dL), 100 units per liter (U/L), 40 U/L, and 40 U/L, respectively. These lab values were further grouped based on whether they were the first or last set of three recorded values prior to ERCP. As a sensitivity analysis, we determined if patients exhibited an increase in any one of the four liver tests to one, two, four, six, and eight times above ULN.

Changes in liver tests (dynamic model)

Liver enzymes were further evaluated in a dynamic model examining ten different patters daily enzyme fluctuations. Based on the number of recorded lab values, there were a total of six different permutations: (1) single value; (2) two values, increasing or equal; (3) two values, decreasing; (4) three values, increasing or equal; (5) three values, decreased then increased; (6) three values, increased then decreased; and (7) three values, decreasing. As a sensitivity analysis, we also categorized patients with more than one recorded liver enzyme value into four additional simplified laboratory patterns: (1) decreasing; (2) increasing or equal; (3) decreased then increased; and (4) increased then decreased. The definition of increase or decrease was defined in two ways: (1) any absolute change and (2) at least 20% difference in sequential values.

American Society for Gastrointestinal Endoscopy (ASGE) criteria

The study population was also characterized into different risk groups for choledocholithiasis based on the ASGE criteria [6]. "Very strong" predictors included CBD stone on transabdominal ultrasound, T. Bili greater than 4 mg/dL, and ascending cholangitis. "Strong" predictors included CBD dilation greater than 6 mm on ultrasound and T. bili 1.8–4 mg/dL. "Moderate" predictors included abnormal ALKP, AST, or ALT, age greater than 55 years, and gallstone pancreatitis. High-risk patients were defined by those with any "very strong" predictor or both "strong" predictors. Low-risk patients were those without any of the above predictors. Intermediate risk patients included all those who did not fit into the above two categories.

Endoscopic retrograde cholangiopancreatography

ERCP findings were captured including the presence of CBD stone, sludge, stricture and dilation, as well as interventions performed including sphincterotomy, lithotripsy, stone removal, and bile duct stent placement. Stones were defined as concretions greater than 3 mm in size; those less than 3 mm were considered sludge.

Outcomes

Primary outcomes were the proportion of patients with each of the defined liver enzyme patterns combined with clinical features and imaging findings who had stones confirmed on ERCP. This was based on cholangiography findings combined with the yield of therapeutic maneuvers (i.e., material removed from duct). We also assessed the proportion of patients with each of the defined patterns who had either stones or sludge (stones/sludge) found on ERCP. We also aimed to determine the test of the 2010 ASGE criteria for our cohort.

Statistical analysis

All patient characteristics, imaging results, and ERCP findings were summarized by numerical count and percentages. We used a combinatorial approach assessing several hundred predictive models. We initially assessed the relationship between potential predictors (static (1×, 2×, 4×, 6×, 8× ULN) and dynamic liver tests (ten patterns), clinical features, and radiographic findings) and the finding of stones and stones/sludge on ERCP with univariate logistic regression model. Variables found to have statistically significant predictive values for stones at the level $p < 0.10$ were entered in a backwards stepwise regression model and remaining significant parameters at $p < 0.10$ were retained. For the subset analysis with the ASGE risk stratification, sensitivity and specificity of each risk category, along with their associated 95% confidence intervals (CI) determined using Clopper–Pearson confidence intervals, were calculated. All associations were distinguished between stones and stones/sludge. The significance level α for all hypothesis testing was 0.05. All statistical analyses were performed using Stata 15 (StataCorp LP, College Station, Texas).

Results

Patients

Between January 2010 and November 2016, 604 patients with native papilla who fulfilled inclusion criterion underwent ERCP for suspected bile duct stones (Fig. 1). In

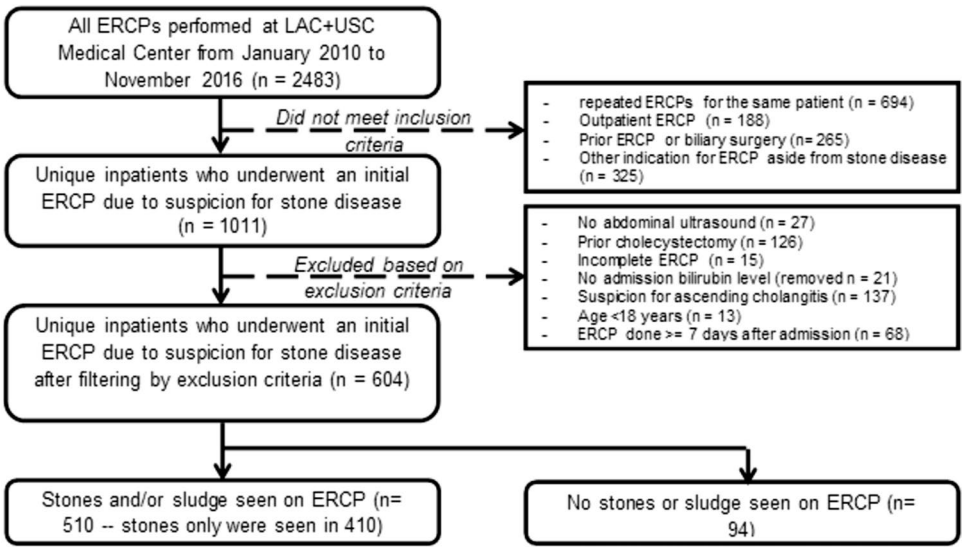

Fig. 1 Patient flow through the study

addition to the index procedures which were the focus of this analysis, these patients underwent 694 additional procedures for complex management or recurrent disease during the study period. Thus, the total number of procedures performed for the 604 patients between January 2010 and November 2016 was 1298. More than 70% of the included patients were female, 89.4% were of Hispanic ethnicity, and 82.5% were younger than 55 years of age (Table 1). 18% had pancreatitis on presentation. Abdominal ultrasound revealed CBD dilation in 72.5% and stones in 54%. MRCP was only obtained in 39.1% of patients and revealed CBD dilation in 82.1% and stones in 72.9%. ERCP confirmed CBD stones alone in 67.9% of patients, biliary sludge alone in 16.5%, and stones/sludge in 80.4%. Endoscopic sphincterotomy was performed in 95.5%, and CBD stents were placed in 20.7%.

Predictor of stones

Patient characteristics and imaging findings

Univariate analysis showed that age > 55 years and presence of pancreatitis were associated with a lower probability of detecting stones and stones/sludge on ERCP (Table 1). Ultrasound findings of stone but not intra- or extrahepatic dilation correlated with the presence of stones or stones/sludge. Identification of stones (Odds Ratio (OR) 6.73 [95% CI 3.50–12.92]) and stones/sludge (OR 7.72 [95% CI 3.80–15.65]) on MRCP was strongly correlated with stones on ERCP. There was no association between the number of days from admission to ERCP or the number of liver enzymes recorded and the findings of stones on ERCP.

Degree of liver enzyme elevation (static model)

The first of three recorded ALKP > 200 U/L (> 2× ULN) was associated with bile duct stones on univariate (OR 1.89 [95% CI 1.11–3.20]) and multivariate analyses (OR 2.10 [95% CI 1.22–3.60]) using the presence of pancreatitis as the co-dependent variable (Table 2; Appendix Table 5). However, ALKP > 200 U/L did not predict the combination of stones/sludge. The degree of ALKP elevation immediately prior to ERCP did not correlate in univariate or multivariate analysis (Appendix Table 6). No monotonic increase in odds of stone on ERCP with degree of enzyme abnormality was seen (i.e., Fourfold increase in ALKP was not more likely to have stones than twofold increase) (Table 2; Appendix Tables 5, 6). A twofold elevation in AST was associated with stones but not the combination of stones/sludge; there was also not the expected correlation with enzyme level and probability stones (Table 2; Appendix Tables 5, 6). Elevations in T. Bili and ALT were not associated with the presence of stone or stones/sludge.

In our sensitivity analysis assessing whether elevation in any of the four enzymes in each patient predicted stones, we did not see correlation for 1, 2, 4, or sixfold increases (Appendix Table 7). There was a modest increase in likelihood of stones if any of the enzymes were > eightfold ULN in the univariate (OR 2.27 [95% CI 1.06–4.83]) and multivariate (OR 2.83 [95% CI 1.31–6.07]) analyses in the first set of recorded labs.

Dynamic liver enzyme patterns (dynamic model)

In the univariate and multivariate analyses of the six different specific liver enzyme trends, there were no consistent patterns that predicated stones or stones/sludge when assessing for a 20% difference (Table 3; Appendix Table 8) or any difference (Appendix Table 9) among sequentially recorded liver test values. In particular, we did not see an increased risk for stones in those with increasing or alternating liver enzymes, the patterns we initially hypothesized to suggest obstructed CBD stones. Similar results were seen in our sensitivity analysis using four additional simplified liver enzyme trends (Appendix Table 10). The only significant trend was a lower odds of detecting CBD stones in patients with increasing or equal bilirubin values (multivariate OR 0.54 [95% CI 0.35–0.84]).

Performance of 2010 ASGE risk stratification criteria

Under the ASGE criteria, 82.3%, 17.4%, and 0.3% were considered high, intermediate, and low risk for choledocholithiasis (Table 4). There were no significant associations between ASGE risk stratification and the presence of stone or stone/sludge in our population. The sensitivity for stones on ERCP was 82.2% while the specificity was only 17.5% for the high-risk group. On the other hand, the sensitivity was only 17.3% while the specificity was 82.5% for the intermediate risk group. For findings of stones/sludge on ERCP, the sensitivities and specificities were 82.2% and 17.0% for the high-risk group and 17.5% and 83.0% for the intermediate risk group, respectively.

Adverse events in patients without stones or sludge

Among the 94 patients for whom there were no stones or sludge on ERCP, 3 developed post-ERCP pancreatitis, 1 cholangitis, and 1 severe hypotension due to sedation medications.

Discussion

ERCP has matured into a therapeutic procedure with the development of less invasive diagnostic tests including MRCP and EUS. While bile duct stones are the leading indication for ERCP, management decisions are challenging

Table 1 Univariate associations of patient characteristics and imaging findings with choledocholithiasis on ERCP

	Frequency	Stones		Stones/sludge	
		OR	95% CI	OR	95% CI
Demographics					
Male sex	162 (26.8%)	1.08	0.73–1.60	0.89	0.55–1.46
Non-Hispanic ethnicity	64 (10.6%)	1.14	0.64–2.00	0.99	0.49–2.03
Hispanic	540 (89.4%)				
Caucasian	19 (3.2%)				
Black	9 (1.5%)				
Asian	35 (5.8%)				
Other	1 (0.2%)				
Age > 55 years	106 (17.6%)	0.67	0.43–1.03	0.81	0.47–1.41
Age					
18–29	163 (27.0%)	1.00		1.00	
30–39	176 (29.1%)	0.86	0.53–1.38	0.76	0.40–1.44
40–49	112 (18.5%)	0.87	0.51–1.49	0.69	0.34–1.38
50–88	153 (25.3%)	0.58*	0.35–0.92	0.52*	0.28–0.97
Pancreatitis	109 (18.0%)	0.35*	0.22–0.53	0.34*	0.21–0.56
Ultrasound features					
Bile duct stone seen	326 (54.0%)	1.34	0.95–1.89	1.21	0.78–1.88
Bile duct stone or sludge seen	339 (56.1%)	1.27	0.90–1.80	1.21	0.78–1.88
CBD dilation > 6 mm[a]	437 (72.5%)	1.10	0.75–1.61	1.01	0.62–1.65
RIHD and/or LIHD dilation > 3 mm[b]	398 (66.6%)	1.03	0.71–1.48	0.61	0.37–1.01
MRCP features					
MRCP performed	236 (39.1%)	0.90	0.63–1.28	1.04	0.66–1.63
Bile duct stone seen	179 (75.9%)	6.73*	3.50–12.92	8.64*	3.98–18.73
Bile duct stone or sludge seen	188 (79.7%)	7.72*	3.80–15.65	8.97*	4.13–19.51
CBD dilatation > 6 mm[c]	192 (82.1%)	0.98	0.48–1.98	0.70	0.26–1.93
RIHD and/or LIHD dilation > 3 mm[d]	158 (70.9%)	1.12	0.60–2.05	0.56	0.23–1.36
Interval days from admission to ERCP					
0–1	82 (13.6%)	1.34	0.80–2.26	1.58	0.76–3.28
2	177 (29.3%)	1.11	0.76–1.62	0.97	0.60–1.57
3	143 (23.7%)	0.88	0.59–1.31	0.89	0.53–1.47
4–6	202 (33.4%)	0.88	0.59–1.31	0.89	0.53–1.47
Number of pre-ERCP measurements—bilirubin					
1	110 (18.2%)	1.40	0.88–2.23	1.82	0.93–3.54
2	209 (34.6%)	0.97	0.68–1.39	0.83	0.53–1.30
3	285 (47.2%)	0.85	0.60–1.19	0.88	0.56–1.36
ERCP features					
Bile duct stone seen	410 (67.9%)				
Bile duct stone or sludge seen	510 (84.4%)				
Bile duct stricture seen	30 (5.0%)				
Sphincterotomy performed	577 (95.5%)				
Bile duct stent placed	125 (20.7)				

*Statistically significant with $p < 0.05$

[a]Missing for $n = 1$ patient in whom an ultrasound was performed

[b]Missing for $n = 6$ patients in whom an ultrasound was performed

[c]Missing for $n = 2$ patients in whom an MRCP was performed

[d]Missing for $n = 13$ patients in whom an MRCP was performed

Table 2 Multivariate associations between different liver enzyme cutoffs and findings on ERCP

First set of labs	Frequency	Stones		Stones/sludge	
		OR	95% CI	OR	95% CI
T. Bili					
≥ 1 mg/dL	441 (73.0%)	0.81	0.48–1.36	0.49*	0.25–0.95
≥ 2 mg/dL	321 (54.1%)	1.10	0.68–1.80	0.88	0.45–1.71
≥ 4 mg/dL	171 (28.3%)	1.15	0.62–2.12	0.62	0.29–1.35
≥ 6 mg/dL	95 (15.7%)	0.86	0.44–1.70	0.89	0.35–2.29
≥ 8 mg/dL	44 (7.3%)	1.28	0.60–2.74	1.12	0.39–3.24
ALKP					
≥ 100 U/L	516 (85.4%)	1.80*	1.09–2.98	1.72	0.92–3.23
≥ 200 U/L	236 (39.1%)	2.10*	1.22–3.60	1.83	0.93–3.59
≥ 400 U/L	45 (7.5%)	2.43	0.96–6.16	2.49	2.74–8.39
≥ 600 U/L	15 (2.5%)	1.15	0.25–5.21	1.30	0.23–7.45
≥ 800 U/L	7 (1.2%)	1.97	0.35–11.09	0.68	0.12–3.94
AST					
≥ 40 U/L	535 (88.6%)	1.16	0.58–2.33	0.74	0.30–1.85
≥ 80 U/L	458 (75.8%)	1.29	0.69–2.39	0.96	0.41–2.27
≥ 160 U/L	326 (54.0%)	2.20*	1.11–4.39	1.23	0.49–3.12
≥ 240 U/L	227 (37.6%)	1.67	0.82–3.40	0.87	0.34–2.21
≥ 320 U/L	150 (24.8%)	1.46	0.79–2.68	1.07	0.46–2.49
ALT					
≥ 40 U/L	547 (90.6%)	1.26	0.56–2.82	0.79	0.29–2.16
≥ 80 U/L	499 (82.6%)	2.15	1.00–4.64	1.44	0.54–3.85
≥ 160 U/L	427 (70.7%)	1.19	0.56–2.50	1.14	0.43–3.03
≥ 240 U/L	360 (59.6%)	1.17	0.57–2.40	0.91	0.36–2.31
≥ 320 U/L	284 (47.0%)	1.96*	1.07–3.59	1.50	0.67–3.36

*Statistically significant with $p < 0.05$

Cofactors for multivariate analyses (Tables 2, 3) include significant patient characteristics from Table 1

given that these stones may spontaneously pass and obviate the need for these potentially morbid procedures. While a number of prediction algorithms have been proposed, they do not appear to have adequate sensitivity and specificity. We hypothesized that dynamic patterns of liver tests might improve predictive value. Assessment of this large cohort of patients with suspected bile duct stones indicates that dynamic patterns do not improve yield and further suggests that specific biochemical values, bile duct diameter, and the ASGE criteria do not predict choledocholithiasis.

Since the introduction of laparoscopic cholecystectomy, there have been numerous studies to define criteria that predict bile duct stones [4, 13–15]. These factors include hyperbilirubinemia, ductal dilation and/or stones on ultrasound, and age > 55 years. We hypothesized that dynamic patterns in liver tests might help to differentiate between persistent and passed bile duct stones. Specifically, we suspected that persistent rise might suggest a stone obstructed in the papilla and alternating patterns (increase–decrease–increase or decrease–increase–decrease) might suggest a stone ball-valve effect, whereby the liver enzymes increase when the stone obstructs and decreases as the stone releases from the CBD. Our analysis demonstrated that there is no correlation between alternating liver enzyme patterns with persistent stones whether we defined the patterns based on absolute values of liver tests or required a 20% change in values. The latter sensitivity measure was designed to account for lab errors and significant variations in liver enzymes which may occur in hospitalized subjects without hepatobiliary problems [16]. Our findings are contrary to prior case reports, which suggest that a transient rise and fall of liver tests may suggest persistent, ball-valving ductal stones [17, 18].

We also aimed to identify if other cutoffs of enzyme levels would be informative. Surprisingly, we did not see a linear or higher order correlation between enzyme levels and probabilities of stones. Only ALKP greater than two times ULN was predictive, and there was a modest increase in stone probability only if any one of the enzymes were markedly (eightfold) elevated. The lack of significant correlation among other liver function tests may be in part due to the high prevalence of liver disease in patients at the Los Angeles County Hospital. There were too few patients who had liver enzyme tests done prior to their hospitalization to compare their presentation labs to their baseline. However, a subset of those who have baseline labs already had AST and ALT in the 100's. We suspect that the somewhat worse performance of the ASGE criterion in our cohort may be explained by the presence of underlying liver test abnormalities in our population. Additionally, at our center, transabdominal ultrasound examinations are typically performed prior to admission in our Emergency Department while ERCP is frequently not available for one or several days given limited anesthesia support and other resources. As choledocholithiasis is a dynamic process in which stones may migrate out of the biliary tree, this delay likely diminished the performance characteristics of the diagnostic tests.

We also did not find a strong correlation between age, gender, and abdominal ultrasound findings and confirmation of bile duct stone. These results were contradictory to other studies, which suggested that older age (> 55 years) [4, 19] and female sex [20] were associated with bile duct stones. Similar to previous reports, however, transabdominal ultrasound had an overall low sensitivity in detecting CBD stones [21]. In addition, pancreatitis had a negative association with findings of CBD stones, which is congruent with multiple observations that ERCP detects stones in less than 20% of patient with acute biliary pancreatitis [22–24].

Our study has a number of strengths. The population had not undergone prior ERCP or biliary surgery, thus eliminating the possibilities that biochemical patterns could represent the occlusion of a bile duct stent or surgical anastomosis. Furthermore, the patient population was hospitalized from presentation until

Table 3 Multivariate associations between dynamic liver enzyme fluctuations with at least 20% difference and ERCP findings

Trends: (with at least 20% difference)	Frequency	Stones		Stones/sludge	
		OR	95% CI	OR	95% CI
T. Bili					
Single value	110 (18.2%)	1.00		1.00	
Two values, increasing (or equal)	148 (24.5%)	0.59	0.34–1.03	0.48	0.23–1.03
Two values, decreasing	61 (10.1%)	1.41	0.65–3.04	0.69	0.26–1.85
Three values, increasing (or equal)	160 (26.5%)	0.59	0.35–1.02	0.58	0.27–1.24
Three values, decreased then increased	15 (2.5%)	2.84	0.59–13.79	1.87	0.22–16.03
Three values, increased then decreased	24 (4.0%)	0.99	0.37–2.64	0.78	0.22–*2.78
Three values, decreasing	86 (14.2%)	0.96	0.51–1.84	0.58	0.25–1.35
ALKP					
Single value	110 (18.2%)	1.00		1.00	
Two values, increasing (or equal)	191 (31.6%)	0.69	0.41–1.18	0.49	0.24–1.02
Two values, decreasing	19 (3.2%)	1.87	0.50–7.00	1.93	0.23–16.09
Three values, increasing (or equal)	260 (43.1%)	0.71	0.43–1.17	0.62	0.30–1.26
Three values, decreased then increased	2 (0.3%)	NA	NA	NA	NA
Three values, increased then decreased	0 (0.0%)	NA	NA	NA	NA
Three values, decreasing	22 (3.6%)	1.56	0.53–4.58	0.59	0.17–1.99
AST					
Single value	112 (18.6%)	1.00		1.00	
Two values, increasing (or equal)	94 (15.6%)	0.61	0.33–1.14	0.50	0.22–1.15
Two values, decreasing	123 (20.4%)	0.78	0.43–1.40	0.49	0.23–1.08
Three values, increasing (or equal)	95 (15.8%)	0.50*	0.27–0.91	0.67	0.29–1.58
Three values, decreased then increased	17 (2.8%)	0.45	0.15–1.33	0.19*	0.06–0.61
Three values, increased then decreased	19 (3.2%)	1.50	0.44–5.04	1.11	0.22–5.61
Three values, decreasing	143 (23.7%)	0.84	0.47–1.48	0.70	0.32–1.54
ALT					
Single value	110 (18.2%)	1.00		1.00	
Two values, increasing (or equal)	124 (20.5%)	0.67	0.38–1.19	0.52	0.23–1.14
Two values, decreasing	86 (14.2%)	0.87	0.46–1.66	0.55	0.24–1.30
Three values, increasing (or equal)	139 (23.0%)	0.62	0.35–1.08	0.59	0.27–1.28
Three values, decreased then increased	7 (1.2%)	0.22	0.05–1.06	0.12*	0.02–0.60
Three values, increased then decreased	13 (2.2%)	1.51	0.37–6.12	1.72	0.20–14.93
Three values, decreasing	125 (20.7%)	0.98	0.54–1.76	0.70	0.31–1.57

Cofactors for multivariate analyses include significant patient characteristics from Table 1

*Statistically significant with $p < 0.05$

determination of whether or not there was a bile duct stone, allowing a rich characterization of the associated clinical and biochemical features. Specifically, we were able to determine biochemical variations up to 3 days prior to ERCP.

An important limitation is that ERCP was used as the gold standard for the presence and absence of stones. As ERCP is reserved at our center for those with higher probability of stones, our findings may only be applied to those at high or intermediate probability of stones and not those at average risk. Nevertheless, our results agree with other published studies which have used a combination of ERCP, EUS, MRCP [7–9], or ERCP alone [25, 26] that there is an overall low sensitivity and specificity of the 2010 ASGE criteria in predicting the presence of stones on ERCP.

Additionally, gastroenterologists are typically asked to determine whether ERCP is required in precisely this population with intermediate and high risk. An algorithm to better predict persistent stones is most needed in this cohort. In our series, nearly 20% of patients underwent ERCP for suspected choledocholithiasis had neither stones nor sludge and 16.6% had only sludge, which has less definite clinical significance. Furthermore, a number of inpatients who were found to have no stones or sludge on ERCP developed procedure-related complications, emphasizing the need for better prediction models.

In this study, an exhaustive assessment of numerous combinations of clinical predictors, ultrasound findings, dynamic, and static liver tests revealed no "perfect test."

Table 4 Associations between ASGE predictors and ERCP findings

	High-risk criterion[a]	Intermediate-risk criterion	Low-risk criterion
Stones			
Frequency	497 (82.3%)	105 (17.4%)	2 (0.3%)
OR (95% CI)	0.98 (0.63–1.54)	0.99 (0.63–1.55)	NA
Sensitivity	82.20 (78.14–85.78)	17.32 (13.78–21.33)	NA
Specificity	17.53 (12.45–23.62)	82.47 (76.38–87.55)	NA
PPV	67.81 (66.06–69.51)	67.62 (59.02–75.17)	NA
NPV	31.78 (24.35–40.26)	32.06 (30.38–33.80)	NA
Stones/sludge			
OR (95% CI)	0.94 (0.53–1.69)	1.04 (0.58–1.85)	NA
Sensitivity	82.16 (78.55–85.38)	17.45 (14.26–21.03)	NA
Specificity	17.02 (10.05–26.16)	82.98 (73.84–89.95)	NA
PPV	84.31 (82.94–85.59)	84.76 (77.41–90.03)	NA
NPV	14.95 (9.78–22.19)	15.63 (14.36–16.99)	NA

[a]Per 2010 ASGE Guidelines [6]

Our findings combined with the knowledge that abnormal liver tests and biliary dilation may result from many different causes suggest that the asymptote for in clinical predictors may have been reached and a diagnostic ERCP rate of 15–20% may be the best achievable using these inexpensive tests. Though the study was designed to determine whether dynamic liver enzyme patterns in combination with clinical factors and abdominal ultrasound could predict bile duct stones, by far, the strongest predictors of choledocholithiasis in our cohort were positive findings on MRCP.

Existing literature demonstrated utility in MRCP in excluding choledocholithiasis in intermediate- to high-risk patients [27]. EUS has also been shown to decrease the requirement for ERCP and post-ERCP complications in randomized trials of EUS prior to ERCP in indeterminate cases [28]. As MRCP and EUS become more universally available they will likely be performed in a greater proportion of patients with risk for choledocholithiasis.

Author contributions CYY, NR, JB: concept and design. CYY, NR, NJ, JB: acquisition of data. CYY, NR, JB: statistical analysis and interpretation of data. CYY, NR, NJ, JC, JVD, RS, JB: drafting and revision of manuscript.

Compliance with ethical standards

Disclosures Drs. Chung Yao Yu, Nitzan Roth, Niraj Jani, Jaehoon Cho, Jacques Van Dam, Rick Selby, and James Buxbaum have no conflicts of interest or financial ties to disclose.

Appendix

See Tables 5, 6, 7, 8, 9, and 10.

Table 5 Univariate associations between the first set of liver enzyme values and ERCP findings

First set of labs	Stones		Stones/sludge	
	OR	95% CI	OR	95% CI
T. Bili				
≥ 1 mg/dL	0.70	0.43–1.16	0.43*	0.22–0.81
≥ 2 mg/dL	0.97	0.60–1.55	0.76	0.40–1.46
≥ 4 mg/dL	1.16	0.63–2.12	0.64	0.30–1.37
≥ 6 mg/dL	0.81	0.42–1.58	0.83	0.33–2.10
≥ 8 mg/dL	1.18	0.56–2.48	1.03	0.36–2.93
ALKP				
≥ 100 U/L	1.55	0.95–2.55	1.46	0.79–2.69
≥ 200 U/L	1.89*	1.11–3.20	1.63	0.84–3.17
≥ 400 U/L	1.69	0.70–4.11	1.67	0.52–5.40
≥ 600 U/L	0.73	0.17–3.09	0.77	0.14–4.15
≥ 800 U/L	1.81	0.33–9.86	0.64	0.11–3.59
AST				
≥ 40 U/L	0.84	0.43–1.65	0.53	0.22–1.28
≥ 80 U/L	1.14	0.62–2.09	0.84	0.36–1.96
≥ 160 U/L	1.78	0.91–3.48	0.99	0.40–2.47
≥ 240 U/L	1.42	0.71–2.85	0.74	0.29–1.85
≥ 320 U/L	1.21	0.66–2.20	0.87	0.38–2.01
ALT				
≥ 40 U/L	1.15	0.52–2.54	0.71	0.26–1.93
≥ 80 U/L	1.43	0.69–2.97	0.94	0.36–2.41
≥ 160 U/L	0.93	0.45–1.92	0.86	0.33–2.22
≥ 240 U/L	1.08	0.53–2.19	0.83	0.33–2.08
≥ 320 U/L	1.66	0.92–3.01	1.25	0.57–2.76

*Statistically significant with $p < 0.05$

Table 6 Univariate and multivariate associations between the last set of liver enzyme values and ERCP findings

Last set of labs	Frequency	Univariate				Multivariate			
		Stones		Stones/sludge		Stones		Stones/sludge	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
T. Bili									
≥ 1 mg/dL	422 (69.9%)	0.81	0.49–1.34	0.47*	0.26–0.87	0.94	0.56–1.58	0.54	0.29–1.02
≥ 2 mg/dL	307 (50.8%)	0.83	0.51–1.33	1.13	0.57–2.23	0.91	0.56–1.48	1.27	0.64–2.53
≥ 4 mg/dL	166 (27.5%)	0.54*	0.31–0.94	0.46*	0.24–0.91	0.56*	0.32–0.98	0.49*	0.25–0.97
≥ 6 mg/dL	86 (14.2%)	1.00	0.48–2.10	1.88	0.54–6.58	1.06	0.50–2.25	2.03	0.57–7.18
≥ 8 mg/dL	44 (7.3%)	1.07	0.51–2.23	0.92	0.35–2.41	1.15	0.54–2.45	0.99	0.37–2.64
ALKP									
≥ 100 U/L	511 (84.6%)	1.38	0.84–2.24	1.32	0.72–2.43	1.54	0.94–2.54	1.51	0.81–2.81
≥ 200 U/L	231 (38.3%)	1.58	0.94–2.68	1.62	0.83–3.16	1.74*	1.02–2.98	1.80	0.91–3.57
≥ 400 U/L	45 (7.5%)	1.14	0.48–2.74	1.44	0.44–4.67	1.47	0.59–3.65	1.95	0.58–6.55
≥ 600 U/L	17 (2.8%)	0.84	0.27–2.63	0.6	0.17–2.13	1.03	0.32–3.31	0.74	0.20–2.74
≥ 800 U/L	3 (0.5%)	1.26	0.11–14.44	0.48	0.04–5.59	1.12	0.10–12.80	0.41	0.04–4.80
AST									
≥ 40 U/L	516 (85.4%)	1.22	0.68–2.16	1.06	0.52–2.17	1.62	0.89–2.96	1.44	0.68–3.05
≥ 80 U/L	395 (65.4%)	1.42	0.82–2.45	1.37	0.68–2.76	1.54	0.88–2.69	1.50	0.74–3.05
≥ 160 U/L	230 (38.1%)	1.25	0.69–2.27	1.15	0.54–2.44	1.30	0.71–2.37	1.19	0.56–2.55
≥ 240 U/L	125 (20.7%)	1.31	0.63–2.73	1.67	0.61–4.57	1.45	0.69–3.07	1.88	0.67–5.26
≥ 320 U/L	74 (12.3%)	1.42	0.73–2.74	1.27	0.55–2.94	1.55	0.79–3.03	1.40	0.59–3.28
ALT									
≥ 40 U/L	550 (91.1%)	1.22	0.54–2.75	0.65	0.24–1.77	1.53	0.67–3.52	0.83	0.30–2.30
≥ 80 U/L	498 (82.5%)	0.72	0.36–1.45	0.71	0.28–1.77	0.97	0.47–2.01	1.01	0.39–2.61
≥ 160 U/L	412 (68.2%)	1.09	0.54–2.20	0.90	0.36–2.30	1.33	0.65–2.73	1.14	0.44–2.96
≥ 240 U/L	319 (52.8%)	1.49	0.72–3.09	1.25	0.47–3.33	1.73	0.83–3.62	1.48	0.55–3.99
≥ 320 U/L	229 (37.9%)	1.31	0.70–2.46	1.07	0.46–2.48	1.49	0.79–2.82	1.24	0.53–2.90

Cofactors for multivariate analyses include significant patient characteristics from Table 1

*Statistically significant with $p < 0.05$

Table 7 Association of combined liver enzyme patterns with ERCP findings

Liver enzyme patterns	Frequency	Stones		Stones/sludge	
		OR	95% CI	OR	95% CI
Univariate association					
Any LFT (first set of labs)					
≥ 1× ULN	574 (95.0%)	1.70	0.66–4.33	0.98	0.29–3.32
≥ 2× ULN	527 (87.3%)	1.80	0.73–4.43	0.85	0.27–2.73
≥ 4× ULN	469 (77.7%)	1.51	0.63–3.59	1.04	0.33–3.30
≥ 6× ULN	401 (66.4%)	1.4	0.60–3.28	0.72	0.24–2.16
≥ 8× ULN	323 (53.5%)	2.27*	1.06–4.83	1.34	0.49–3.69
Any LFT (last set of labs)					
≥ 1× ULN	574 (95.0%)	1.72	0.68–4.37	0.67	0.21–2.12
≥ 2× ULN	522 (86.4%)	1.35	0.57–3.22	0.91	0.29–2.82
≥ 4× ULN	450 (74.5%)	1.24	0.54–2.84	1.09	0.36–3.31
≥ 6× ULN	353 (58.4%)	1.66	0.71–3.84	1.16	0.38–3.53
≥ 8× ULN	258 (42.7%)	1.98	0.91–4.27	1.27	0.46–3.55
Multivariate association					
Any LFT (first set of labs)					
≥ 1× ULN	574 (95.0%)	1.93	0.75–4.97	1.14	0.33–3.93
≥ 2× ULN	527 (87.3%)	2.54	1.01–6.41	1.26	0.38–4.14
≥ 4× ULN	469 (77.7%)	2.23	0.91–5.46	1.64	0.50–5.39
≥ 6× ULN	401 (66.4%)	1.68	0.71–3.96	0.89	0.29–2.71
≥ 8× ULN	323 (53.5%)	2.83*	1.31–6.07	1.73	0.62–4.83
Any LFT (last set of labs)					
≥ 1× ULN	574 (95.0%)	2.17	0.84–5.59	0.86	0.26–2.78
≥ 2× ULN	522 (86.4%)	1.78	0.74–4.29	1.26	0.40–3.99
≥ 4× ULN	450 (74.5%)	1.68	0.72–3.92	1.59	0.51–4.93
≥ 6× ULN	353 (58.4%)	2.11	0.90–4.94	1.54	0.50–4.79
≥ 8× ULN	258 (42.7%)	2.36*	1.09–5.14	1.58	0.56–4.43

*Statistically significant with $p < 0.05$

Table 8 Univariate association between liver enzyme trends with at least a 20% difference and ERCP findings

Trends (with at least 20% difference)	Stones		Stones/sludge	
	OR	95% CI	OR	95% CI
T. Bili				
Single value	1.00		1.00	
Two values, increasing (or equal)	0.59	0.34–1.01	0.48	0.23–1.00
Two values, decreasing	1.47	0.68–3.13	0.74	0.28–1.94
Three values, increasing (or equal)	0.57*	0.33–0.96	0.55	0.26–1.16
Three values, decreased then increased	2.33	0.49–10.94	1.56	0.19–12.99
Three values, increased then decreased	0.72	0.28–1.85	0.56	0.16–1.92
Three values, decreasing	0.87	0.47–1.64	0.53	0.23–1.21
ALKP				
Single value	1.00		1.00	
Two values, increasing (or equal)	0.69	0.41–1.17	0.50	0.24–1.02
Two values, decreasing	1.91	0.52–7.03	2.00	0.24–16.46
Three values, increasing (or equal)	0.66	0.41–1.09	0.58	0.28–1.17
Three values, decreased then increased	NA	NA	NA	NA
Three values, increased then decreased	NA	NA	NA	NA
Three values, decreasing	0.95	0.34–2.67	0.38	0.12–1.22
AST				
Single value	1.00		1.00	
Two values, increasing (or equal)	0.65	0.35–1.18	0.53	0.23–1.21
Two values, decreasing	0.75	0.42–1.32	0.47	0.22–1.02
Three values, increasing (or equal)	0.48*	0.26–0.86	0.63	0.27–1.46
Three values, decreased then increased	0.48	0.17–1.37	0.20*	0.06–0.65
Three values, increased then decreased	1.25	0.38–4.08	0.93	0.19–4.55
Three values, decreasing	0.73	0.42–1.26	0.60	0.28–1.30
ALT				
Single value	1.00		1.00	
Two values, increasing (or equal)	0.70	0.40–1.23	0.54	0.25–1.19
Two values, decreasing	0.83	0.44–1.54	0.53	0.23–1.21
Three values, increasing (or equal)	0.60	0.35–1.03	0.56	0.26–1.21
Three values, decreased then increased	0.27	0.06–1.27	0.15*	0.03–0.85
Three values, increased then decreased	1.19	0.31–4.64	1.33	0.16–11.25
Three values, decreasing	0.82	0.46–1.45	0.58	0.27–1.28

NA due to only 0 or 2 datapoints available

*Statistically significant with $p < 0.05$

Table 9 Univariate and multivariate associations between liver enzyme trends with absolute differences and ERCP findings

Trends (with any absolute difference)	Frequency	Univariate				Multivariate			
		Stones		Stones/sludge		Stones		Stones/sludge	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
T. Bili									
Single value	110 (18.2%)	1.00		1.00		1.00		1.00	
Two values, increasing (or equal)	96 (15.9%)	0.52*	0.29–0.94	0.45	0.20–1.00	0.53*	0.29–0.96	0.46	0.20–1.03
Two values, decreasing	113 (18.7%)	1.04	0.57–1.89	0.63	0.28–1.41	1.02	0.56–1.88	0.61	0.27–1.38
Three values, increasing (or equal)	85 (14.1%)	0.56	0.30–1.04	0.62	0.26–1.45	0.56	0.30–1.05	0.62	0.26–1.48
Three values, decreased then increased	47 (7.8%)	0.76	0.36–1.61	0.63	0.23–1.75	0.79	0.37–1.69	0.66	0.23–1.84
Three values, increased then decreased	59 (9.8%)	0.60	0.30–1.18	0.48	0.20–1.20	0.76	0.37–1.54	0.62	0.25–1.58
Three values, decreasing	94 (15.6%)	0.89	0.47–1.64	0.54	0.24–1.23	1.00	0.53–1.87	0.61	0.26–1.40
ALKP									
Single value	110 (18.2%)	1.00		1.00		1.00		1.00	
Two values, increasing (or equal)	59 (9.8%)	0.64	0.33–1.28	0.54	0.22–1.37	0.60	0.30–1.20	0.50	0.20–1.27
Two values, decreasing	151 (25.0%)	0.79	0.46–1.37	0.53	0.25–1.13	0.81	0.47–1.42	0.55	0.26–1.17
Three values, increasing (or equal)	58 (9.6%)	0.51*	0.26–0.99	0.35*	0.15–0.83	0.53	0.26–1.04	0.36*	0.15–0.87
Three values, decreased then increased	85 (14.1%)	0.81	0.43–1.52	0.75	0.31–1.82	0.81	0.43–1.54	0.75	0.30–1.84
Three values, increased then decreased	52 (8.6%)	0.81	0.39–1.66	0.71	0.26–1.96	0.94	0.45–1.98	0.85	0.30–2.38
Three values, decreasing	89 (14.7%)	0.67	0.36–1.23	0.55	0.24–1.26	0.80	0.43–1.51	0.67	0.29–1.58
AST									
Single value	112 (18.6%)	1.00		1.00		1.00		1.00	
Two values, increasing (or equal)	48 (8.0%)	0.51	0.25–1.04	0.41	0.16–1.05	0.47*	0.23–0.98	0.38*	0.15–0.97
Two values, decreasing	169 (28.0%)	0.77	0.45–1.32	0.53	0.25–1.10	0.79	0.46–1.38	0.54	0.26–1.14
Three values, increasing (or equal)	30 (5.0%)	0.50	0.21–1.17	0.54	0.17–1.71	0.590	0.25–1.41	0.67	0.21–2.15
Three values, decreased then increased	49 (8.1%)	0.57	0.28–1.18	0.48	0.19–1.56	0.54	0.26–1.13	0.45	0.17–1.19
Three values, increased then decreased	43 (7.1%)	1.26	0.54–2.95	1.45	0.38–5.48	1.28	0.54–3.03	1.47	0.39–5.63
Three values, decreasing	152 (25.2%)	0.57*	0.33–0.98	0.50	0.24–1.07	0.66	0.38–1.15	0.60	0.28–1.28
ALT									
Single value	110 (18.2%)	1.00		1.00		1.00		1.00	
Two values, increasing (or equal)	59 (9.8%)	0.60	0.31–1.18	0.71	0.27–1.87	0.55	0.28–1.09	0.64	0.24–1.71
Two values, decreasing	151 (25.0%)	0.82	0.47–1.41	0.49	0.23–1.03	0.85	0.48–1.48	0.50	0.24–1.07
Three values, increasing (or equal)	34 (5.6%)	0.45	0.20–1.01	0.43	0.15–1.21	0.48	0.21–1.08	0.46	0.16–1.32
Three values, decreased then increased	44 (7.3%)	0.69	0.33–1.47	0.59	0.21–1.63	0.72	0.33–1.56	0.62	0.22–1.73
Three values, increased then decreased	48 (8.0%)	1.07	0.49–2.34	0.96	0.31–2.92	1.15	0.52–2.54	1.02	0.33–3.16
Three values, decreasing	158 (26.2%)	0.67	0.39–1.15	0.52	0.24–1.09	0.76	0.44–1.31	0.59	0.28–1.26

Cofactors for multivariate analyses include significant patient characteristics from Table 1

*Statistically significant with $p < 0.05$

Table 10 Association of simplified liver enzyme trends with ERCP findings

	Frequency	Univariate				Multivariate			
		Stones		Stones/sludge		Stones		Stones/sludge	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Trends (with any absolute difference)									
T. Bili									
Decreasing	207 (41.9%)	1.00		1.00		1.00		1.00	
Increasing or equal	181 (36.6%)	0.56*	0.36–0.86	0.88	0.52–1.51	0.54*	0.35–0.84	0.86	0.50–1.48
Decreased then increased	47 (9.5%)	0.79	0.40–1.57	1.08	0.45–2.63	0.78	0.39–1.57	1.08	0.44–2.67
Increased then decreased	59 (11.9%)	0.62	0.34–1.15	0.83	0.39–1.76	0.75	0.40–1.42	1.07	0.49–2.33
ALKP									
Decreasing	240 (48.6%)	1.00		1.00		1.00		1.00	
Increasing or equal	117 (23.7%)	0.77	0.49–1.22	0.80	0.46–1.40	0.69	0.43–1.11	0.70	0.39–1.24
Decreased then increased	85 (17.2%)	1.09	0.64–1.86	1.39	0.68–2.84	1.00	0.58–1.73	1.25	0.60–2.59
Increased then decreased	52 (10.5%)	1.08	0.57–2.07	1.32	0.56–3.14	1.16	0.60–2.26	1.46	0.60–3.53
AST									
Decreasing	321 (65.4%)	1.00		1.00		1.00		1.00	
Increasing or equal	78 (15.9%)	0.76	0.46–1.26	0.89	0.47–1.67	0.71	0.42–1.19	0.82	0.43–1.56
Decreased then increased	49 (10.0%)	0.86	0.46–1.61	0.94	0.43–2.05	0.75	0.40–1.42	0.79	0.35–1.75
Increased then decreased	43 (8.8%)	1.89	0.87–4.08	2.82	0.84–9.43	1.76	0.80–3.86	2.58	0.76–8.77
ALT									
Decreasing	309 (62.6%)	1.00		1.00		1.00		1.00	
Increasing or equal	93 (18.8%)	0.73	0.46–1.19	1.15	0.62–2.15	0.65	0.40–1.06	1.00	0.53–1.90
Decreased then increased	44 (8.9%)	0.94	0.48–1.83	1.17	0.50–2.76	0.90	0.45–1.78	1.12	0.47–2.70
Increased then decreased	48 (9.7%)	1.46	0.73–2.92	1.90	0.72–5.02	1.44	0.71–2.92	1.88	0.70–5.04
Trends (with at least 20% difference)									
T. Bili									
Decreasing	147 (29.8%)	1.00		1.00		1.00		1.00	
Increasing or equal	308 (62.4%)	0.54*	0.35–0.84	0.85	0.50–1.45	0.53*	0.34–0.83	0.86	0.50–1.48
Decreased then increased	15 (3.0%)	2.19	0.47–10.14	2.60	0.33–20.72	2.56	0.54–12.27	3.13	0.38–25.74
Increased then decreased	24 (4.9%)	0.67	0.27–1.70	0.93	0.29–2.96	0.89	0.34–2.34	1.32	0.40–4.40
ALKP									
Decreasing	41 (8.3%)	1.00		1.00		1.00		1.00	
Increasing or equal	451 (91.3%)	0.53	0.25–1.14	0.83	0.34–2.05	0.42*	0.19–0.93	0.65	0.26–1.65
Decreased then increased	2 (0.4%)	NA	NA	NA	NA	NA	NA	NA	NA
Increased then decreased	0 (0.0%)	NA	NA	NA	NA	NA	NA	NA	NA
AST									
Decreasing	266 (54.2%)	1.00		1.00		1.00		1.00	
Increasing or equal	189 (38.5%)	0.75	0.51–1.12	1.08	0.65–1.79	0.68	0.45–1.02	0.96	0.57–1.62
Decreased then increased	17 (3.5%)	0.65	0.24–1.76	0.37	0.13–1.06	0.56	0.20–1.55	0.30*	0.10–0.89
Increased then decreased	19 (3.9%)	1.70	0.55–5.28	1.73	0.39–7.76	1.84	0.58–5.89	1.89	0.41–8.74
ALT									
Decreasing	211 (42.7%)	1.00		1.00		1.00		1.00	
Increasing or equal	263 (53.2%)	0.78	0.53–1.15	0.99	0.61–1.61	0.69	0.46–1.03	0.85	0.51–1.41
Decreased then increased	7 (1.4%)	0.33	0.07–1.50	0.27	0.06–1.24	0.24	0.05–1.11	0.18*	0.04–0.83
Increased then decreased	13 (2.6%)	1.45	0.39–5.45	2.39	0.30–18.95	1.62	0.41–6.32	2.75	0.33–22.61

NA due to only 0 or 2 datapoints available

*Statistically significant with $p < 0.05$

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