Alkaline Phosphatase: Reliability as a Predictor of Common Bile Duct Pathologies?

Shankarraman D, Singh KB, Mohanapriya T, Manuneethimaran T, Nitesh N, Ganesh P, Chandrasekharan A

1Resident, Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India; 2Professor and Head, Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India; 3Associate Professor, Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India; 4Assistant Professor, Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India; 5Professor and Head, Department of Medical Gastroenterology, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India; 6Professor, Department of Radiology and Imaging Sciences, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India.

ABSTRACT

Introduction: Choledocholithiasis is the presence of gall stones within the biliary tree which can lead to obstructive jaundice. Alkaline phosphatase, an enzyme secreted by the biliary canalicular cells, is reflective of bile obstruction.

Aims: This study aims to identify the dependability of Alkaline phosphatase in predicting choledocholithiasis by assessing sensitivity, specificity, predictive values, false positive and negative values.

Methodology: A retrospective, cross-sectional study carried out in Sri Ramachandra Institute of Higher Education and Research, Chennai. The sample size was calculated to be 162 based on the sensitivity (75%) and specificity (37%) of Alkaline phosphatase, using a precision of 10% and a confidence interval of 95%. 162 patients who had undergone Magnetic Resonance Cholangio-Pancreatogram (MRCP) from January to December 2019.

Results: Of 162 patients who had undergone MRCP, 72 (50.39 ± 16.487) had choledocholithiasis and 90 (49.92± 14.875) had other pathologies. Graphical representation of the ALP values revealed that the area under the curve in ROC was found to be 0.641. A clinical cut-off of ALP as >130IU/L had a sensitivity of 70.8% and specificity of 48%.

Conclusion: ALP having a low specificity, combined with a normal value in a significant number of patients can lead to a missed diagnosis of choledocholithiasis. The non-universal practice of intra-operative cholangiogram and MRCP adds to these numbers. Hence, more widespread use of MRCP without a selection bias based on ALP values is advocated for suspected choledocholithiasis or bile duct pathologies.

Key Words: Liver function tests, Alkaline phosphatase, Biliary pathologies, Obstructive jaundice, Choledocholithiasis, Magnetic resonance cholangiopancreatography
or the persistence of stones causing obstruction. Our study aims to identify the relation of one such cholestasis indicators, Alkaline Phosphatase with CBD stones by assessing sensitivity, specificity, predictive values and false negative and positive results.

**MATERIALS AND METHODS**

**Study design**
A cross-sectional retrospective study to assess the reliability of ALP was undertaken. Institutional Ethics Committee clearance was obtained and consent from the Departments of Medical Gastroenterology and Radiology were obtained. The sample size was calculated based on the formula below (figure 1).

![Figure 1: Sample size calculation formula.](image)

The sample size was calculated to be 162 based on the sensitivity (75%) and specificity (37%) of Alkaline phosphatase, using a precision of 10% and a confidence interval of 95%.

**Participants**
Eligibility criteria included all patients who had undergone Magnetic Resonance Cholangio-Pancreatogram (MRCP) in January 2019-December 2019. Exclusion criteria included Patients with non-hepatobiliary pathologies causing elevated ALP such as Bone diseases such as Osteomalacia, metastases, Paget’s disease, Hyperthyroidism, Hyperparathyroidism, Chronic renal failure, Pregnancy, Lymphoma. Amongst this, 162 patients (potentially eligible participants) were selected at random. These patients were identified from a registry containing detailed records of all patients who had undergone MRCP in the specified time frame. MRCP records and Liver Function Test results of these patients were retrieved from the hospital computer data systems retrospectively (figure 2).

![Figure 2: Patient selection protocol.](image)

**Test Methods**
MRCP was performed for all patients with Siemens MAGNETOM® MRI systems (1.5-Tesla)/SIGNATM GE Healthcare. All patients were imaged with a Torso array receive coil, rotating 90 degrees to eliminate wrap-around artifact. Sections of 5 mm thickness with 0 gap slices were taken from right dome of diaphragm to lower edge of liver. Sequences used include 3 plane Locator Breath Holding, Axial 2D FIESTA FATSAT, Coronal 2D FIESTA FATSAT, Axial T2 SSFSE Breath Holding, Coronal T2 SSFSE Breath Holding, 3D MRCP RTr ASSET, Axial DWI 800b, Axial Dual Echo FSPGR Breath Holding Asset, Thick slab MRCP ASSET, 3D MRCP RTr ASSET, Axial T2 SSFSE BH. A 3D reconstruction was performed by MIP post processing.

Imaging assessed the size of the liver, presence of focal lesions and dilatation of intrahepatic biliary radicles. The gall bladder size, wall thickness, presence of calculi if any, size of calculi and presence of any pericholecystic fluid was noted. The biliary tree was assessed for the presence or absence of filling defects within the right and left hepatic ducts, common hepatic ducts, cystic ducts, common bile ducts. The pancreatic size, texture and ducts were noted. In completion, the duodenum, spleen, and kidneys were also visualised.

The diagnosis of choledocholithiasis was made based on the presence of filling defects within the biliary tree. Common bile duct and common hepatic duct diameters were measured. CBD diameter was defined as per age-appropriate criteria: “Decade of life +1” – e.g. for a 30-year-old patient, normal CBD diameter was taken as 3+1 = 4mm. The MRCP reports were categorised into those with choledocholithiasis and those without – i.e. any other diagnosis such as pancreatitis, cholangiocarcinoma, pancreatic neoplasms etc.
Analysis
LFT reports of all patients were collected and ALP values were correlated with the MRCP findings and diagnosis. 2x2 contingency table was created and results assessed. A Chi-square test was used to assess independent variables. The Receiver Operating Curve was plotted for the significance of ALP. Statistical analysis was performed using SPSS Statistics version 16.

RESULTS
Of the total 162 patients, 72 were those with choledocholithiasis and 90 were those with other diagnoses – e.g. pancreatitis, cholangiocarcinoma, gall bladder carcinoma, pseudocyst of pancreas etc (Figure 3 – Sample size and data collection pathway).

Figure 3: Sample size and data collection pathway.

The data was computerised and analysed. The Receiver Operating Curve was plotted using the ALP levels of all patients. The area under the curve was found to be 0.641 (significant if area is >0.70) (figure 4 and Table 1). This indicated that ALP had low reliability in predicting choledocholithiasis.

Table 1: Receiver Operating Curve Area depicting Standard Error and Asymptotic Confidence Interval of 95%

| Area Under the Curve | Test Result Variable(s): ALP |
|----------------------|-------------------------------|
| Area                | Std. Errors | Asymptotic Sig.b | Asymptotic 95% Confidence Interval |
|                     |             |                  | Lower Bound | Upper Bound       |
| 0.641               | 0.045       | 0.003            | 0.552       | 0.729             |

The test result variable(s): ALP has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption Null hypothesis: true area = 0.5

The mean age of those with choledocholithiasis was found to be 50.39 with SD ± 16.487. The mean age of those without choledocholithiasis was 49.92 with SD ± 14.875 (Figure 5 and Table 2). The Chi-square test performed revealed no significant relation with age.

Figure 5: Mean Age of those with and without choledocholithiasis.

Table 2: Mean Age and Standard deviation of those with Choledocholithiasis and those without Choledocholithiasis

| Age                | Mean       | Standard Deviation | Standard Error Mean |
|--------------------|------------|--------------------|---------------------|
| Choledocholithiasis| 50.39      | 16.487             | 1.943               |
| Non-choledocholithiasis | 49.92 | 14.875             | 1.568               |

Gender distribution was as follows: The total number of females were 59 and males were 103. Amongst the 59 women, 32(54.7%) had choledocholithiasis and among the males, 40(38.8%) had choledocholithiasis (Table 3 and Figure 6).
Table 3: Gender distribution data

| Diagnosis                  | Females | Males | Total |
|----------------------------|---------|-------|-------|
| Choledocholithiasis        | 32      | 40    | 72    |
| Percentage within diagnosis| 44.4%   | 55.6% | 100%  |
| Percentage within gender   | 54.2%   | 38.8% | 44.4% |
| Non-Choledocholithiasis    | 27      | 63    | 90    |
| Percentage within diagnosis| 30%     | 70%   | 100%  |
| Percentage within gender   | 45.8%   | 61.2% | 55.6% |

Percentage of breakdown:
- Choledocholithiasis: 44.4%
- Non-Choledocholithiasis: 55.6%
- Total: 100%

Table 4: 2x2 contingency table for Alkaline Phosphatase (ALP) values of those with Choledocholithiasis and without Non-Choledocholithiasis

| ALP value | Cholelithiasis | Non-cholelithiasis | Total |
|-----------|----------------|--------------------|-------|
| >130 IU/L | 51 (True Positives) | 39 (FALSE POSITIVES) | 90    |
| PPV 56.7% | 70.8% | % of FP 44.3% | 100   |
| <130 IU/L | 21 (False Negatives) | 49 (True Negatives) | 70    |
| 30% | 55.7% | % of FN 29.2% | 100%  |

Total:
- 72
- 88
- 160
- 45%
- 55%
- 100%

*2 of the 90 patients with diagnoses other than choledocholithiasis had not undergone LFT.

Figure 6: Graphical representation of gender distribution of those with and without choledocholithiasis.

Of the total 162 patients, 72 had choledocholithiasis. Out of the 72, 51 patients had raised ALP beyond 130 IU/L and 21 patients (30%) had a normal ALP value (<130IU/L). The sensitivity of ALP was calculated as 70.8% and Specificity was 55.7%. A Positive predictive value of 56.7% and a negative predictive value of 70% was observed. The percentage of false positives was 44.3% whereas the percentage of false negatives was 29.2% (Table 4).

Table 4: 2x2 contingency table for Alkaline Phosphatase (ALP) values of those with Choledocholithiasis and without Non-Choledocholithiasis

DISCUSSION

Liver function tests are the preliminary serum markers done in all patients with suspected hepato-biliary pathologies. Alkaline phosphatase is thought to be specific for ductal pathologies as one of its main sources is the cells lining the biliary canaliculi. Although Gamma-glutamyl transpeptidase and 5’nucleotidase are also specific for cholestasis. Our study focussed only on routine LFT parameters as GGT is not routinely done. The observed pattern in obstruction is increased in serum bilirubin, alkaline phosphatase and elevated ALT, AST with a cholestatic pattern.

Anciaux et al.² demonstrated that serum ALP and γ-GT were elevated within the 1st 3 days in 100% of patients with biliary obstruction, whereas aminotransferase levels were elevated in up to 88% of patients, with a mean of 102 to 150 IU/L for AST and ALT; “In our experience, the absence of any biological abnormality during the three days following the onset of symptoms made the diagnosis of choledocholithiasis quite improbable.”

In a study carried out by H C van Santvoort et al.³, to determine which radiological or serological parameters best predicted CBD stones, they reported that “raised ALP (OR: 3.16, p=0.006) on admission blood tests was a superior indicator to ALT (OR: 2.30, p=0.187) and bilirubin (OR: 0.89, p=0.637) for CBD stones although all had low sensitivity”; “In univariate analysis, the only parameters significantly associated with CBD stones were GGT and alkaline phosphatase.”
The positive predictive value of elevated liver tests is poor because deranged liver function can indicate a variety of other pathologies as well. Hence it was understood so far that, normal levels help in excluding choledocholithiasis. The need for further imaging is assessed based on clinical progression, which subjectively varies from each patient to the other and biochemical indicators of cholestasis such as raised bilirubin, ALP or GGT.

In our study, 21 out of 72 patients with MRCP detected choledocholithiasis had a normal alkaline phosphatase. This accounts for 30% of patients who would have had a missed diagnosis is reliant on the above criteria. The percentage of false negatives was 29.2% with a positive predictive value of 56.7% and a negative predictive value of 70%. Our study highlights the percentage of patients who would be left with a missed diagnosis in the event of the use of selective MRCP based on ALP as the predictive parameter. The consequences of a missed diagnosis are wide-ranging such as the conversion of laparoscopic procedure to open, the need for further post-operative re-intervention such as ERCP or second surgery, postcholecystectomy syndrome, increased morbidity, prolonged hospital stay and increased financial burden.

Hence, it is imperative to identify the presence or absence of common bile duct stones as it dictates the line of management for the surgeon. Common bile duct stones can be easily missed on routine ultrasonography, and hence require further imaging studies. This depends on the choice of the surgeon: some prefer MRCP, others utilise EUS and some go ahead with an intra-operative cholangiogram. ERCP has been the preferred modality as it can be therapeutic as well as diagnostic of choledocholithiasis for many decades; although MRCP is non-invasive, whereas EUS is less invasive than ERCP. The choice of investigation and further management is dictated by the individual clinical settings. The availability of endoscopic services, feasibility, and cost-effectiveness also determine the role of ERCP and EUS.

EUS is thought to be the choice to identify biliary sludge, smaller stones (<6mm) and in those with a nondilated common bile duct and it is an option for patients for whom MRCP is contraindicated (e.g. pacemaker, claustrophobia, gadolinium allergy). However, the limiting factors may be the lack of availability of endoscopic services, skilled endoscopists and operator dependency producing subjective results.

MRCP, although non-invasive, has not been standardised as the investigation of choice due to high cost, reliability on patient co-operation for optimal results. We are trying to highlight the need for standardised use of MRCP as the diagnostic modality for all patients of clinically suspected choledocholithiasis to reduce the consequences of a missed diagnosis.

**CONCLUSION**

Alkaline phosphatase, a biochemical indicator of cholestasis, is poorly reliable in predicting common bile duct pathologies. According to our results, the sensitivity (70.8%) and specificity are both low (55.7%) with the area under the Receiver Operating Curve was plotted with ALP levels of all patients as 0.641 (<0.70- insignificant). A normal Alkaline Phosphatase value in a patient with suspected choledocholithiasis does not rule out the presence of a common bile duct stone.

The lack of non-universal practice of biliary ductal imaging modalities highlights the increased likelihood of missed diagnosis and morbid complications. All patients with suspected CBD stones should be subjected to a pre-operative MRCP to identify the presence of CBD stones. Alkaline phosphatase should not be the sole biochemical indicator to dictate the selective use of MRCP.

Declarations:

**Ethics approval:** Sri Ramachandra Institute of Higher Education and Research, Institutional Ethics Committee Clearance: REF: CSP-MED/20/0CT/62/114

**Consent for Publication:** Not applicable

**Competing Interests:** The authors declare that they have no competing interests.

**Availability of data and materials:** References provided, not applicable otherwise.

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**Author’s contributions:**

DS was responsible for data collection. KBS was in charge of reviewing the manuscript. TM conceived the idea of the study and reviewed the manuscript. TM and NN were responsible for multiple revisions of the drafted manuscripts.

All authors have approved the final submitted version and have agreed with both to be personally accountable for the author’s contributions and to ensure that questions related to the accuracy or integrity of any part of the work, are appropriately investigated, resolved, and the resolution documented in the literature.

The manuscript is in accordance with STARD 2015 Guidelines.

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Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116

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Department of Medical Gastroenterology, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116

Department of Radiology and Imaging Sciences, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116

Abbreviations
ALP- Alkaline phosphatase
ALT – Alanine amino-transferase
AST- Aspartate amino-transferase
CBD- Common Bile duct
CHD- Common hepatic duct
ERCP- Endoscopic retrograde cholangio-pancreatogram
MRCP – Magnetic resonance cholangiopancreatogram
NPV- Negative predictive value
PPV- Positive predictive value
ROC- Receiver operating characteristic curve

REFERENCES
1. Barlow AD, Haqq J, McCormack D, Metcalfe MS, Dennison AR, Garcea G. The role of magnetic resonance cholangiopancreatography in the management of acute gallstone pancreatitis. Ann R Coll Surg Engl. 2013 Oct;95(7):503–6.
2. Anciaux ML, Pelletier G, Attali P, Meduri B, Liguory C, Etienne JP. Prospective study of clinical and biochemical features of symptomatic cholelithiasis. Dig Dis Sci. 1986 May 1;31(5):449–53.
3. Van Santvoort HC, Bakker OJ, Besselink MG, Bollen TL, Fischer K, Nieuwenhuijs VB, et al. Prediction of common bile duct stones in the earliest stages of acute biliary pancreatitis. Endoscopy. 2011 Jan;43(1):8–13.
4. Qiu Y, Yang Z, Li Z, Zhang W, Xue D. Is preoperative MRCP necessary for patients with gallstones? An analysis of the factors related to the missed diagnosis of choledocholithiasis by preoperative ultrasound. BMC Gastroenterol. 2015 Nov 14;15:158.
5. Isherwood J, Garcea G, Williams R, Metcalfe M, Dennison AR. Serology and ultrasound for the diagnosis of choledocholithiasis. Ann R Coll Surg Engl. 2014 Apr;96(3):224–8.
6. Zarea M, Kargar S, Akhondi M, Mirshamsi MH. Role of liver function enzymes in the diagnosis of choledocholithiasis in biliary colic patients. Acta Med Iran. 2011;49(10):663–6.
7. Zidi S, Prat F, Le Guen O, Rondeau Y, Rocher L, Fritsch J, et al. Use of magnetic resonance cholangiography in the diagnosis of choledocholithiasis: prospective comparison with a reference imaging method. Gut. 1999 Jan;44(1):118–22.
8. Karakan T, Cindoruk M, Alagozlu H, Ergun M, Dumlu S, Unal S. EUS versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a prospective randomized trial. Gastrointest Endosc. 2009 Feb 1;69(2):244–52.