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

Shankarraman D,[1*] Singh KB,[2] Mohanapriya T,[3] Manuneethimaran T,[3] Nitesh N,[4] Ganesh P,[5] Chandrasekharan A[6]

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

INTRODUCTION

Choledocholithiasis is one of the most common pathologies affecting the bile duct system. It is defined by the presence of gall stones within the biliary tree. These may be primarily formed within the tree or can be secondarily present having slipped out of the gall bladder. It can cause bile outflow obstruction. Obstructive jaundice that develops can further lead to complications such as hepatitis, cholangitis and pancreatitis. Timely intervention is the dictum. The obstruction leads to failure of drainage of bile via the extra-hepatic ductal system, leading to increased serum conjugated and total bilirubin. Deposition of bile salts in the dermis of the skin, as well as release of endogenous opioids, are thought to be the causes of pruritus. Failure of bile drainage into the intestine leads to a lack of stercobilin component in the stools producing clay-coloured stools. These cardinal symptoms offer a clinical diagnosis of obstructive jaundice.

The presence of obstruction can cause derangement of liver function test (LFT) parameters. Serum bilirubin, alkaline phosphatase, Gamma-glutamyl transpeptidase and 5'-nucleotidase are used in the assessment of biliary obstruction. Serial evaluation of LFT can hint at the spontaneous passage

Corresponding Author:
Debashri Shankarraman, Resident, Department of General Surgery, Sri Ramachandra Institute of Higher Education and Research, Chennai – 600116, India; Email: debashri.shankar@gmail.com

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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).

Estimating the Sensitivity of a new test

Assumption

- The variable must be a categorical.

Formula

$$n = \frac{z^2_{1-\frac{\alpha}{2}} p(1-p)}{d^2}$$

Where,

p : Sensitivity of the new test

d : precision

$Z_{1-\alpha/2}$: Desired Confidence level

Figure 1: Sample size calculation formula.

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%.[1]

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).

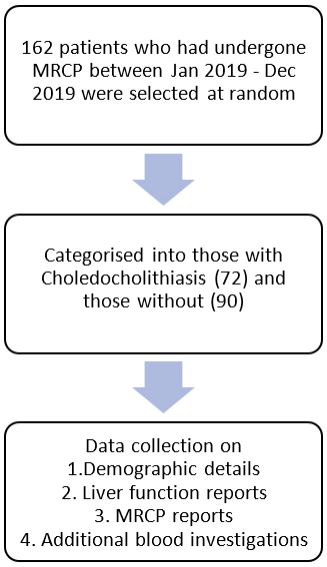

Figure 2: Patient selection protocol.

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).

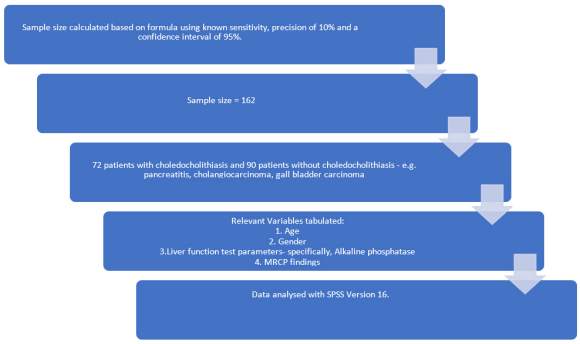

Figure 3: Sample size and data collection pathway.

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.

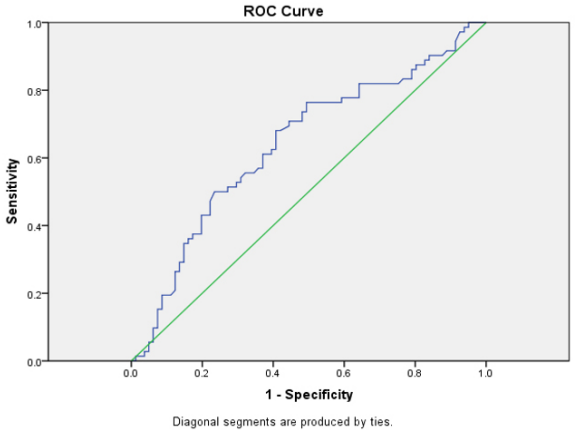

Figure 4: Receiver Operating Curve was plotted with ALP levels of all patients. The area under the curve was found to be 0.641 (<0.70- insignificant).

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 assumptionNull 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.

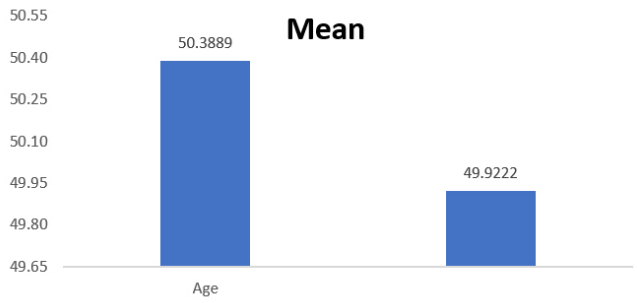

Figure 5: Mean Age of those with and without choledocholithiasis.

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

	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%
TOTAL	59	103	162
	36.4%	63.6%	100%
	100%	100%	100%

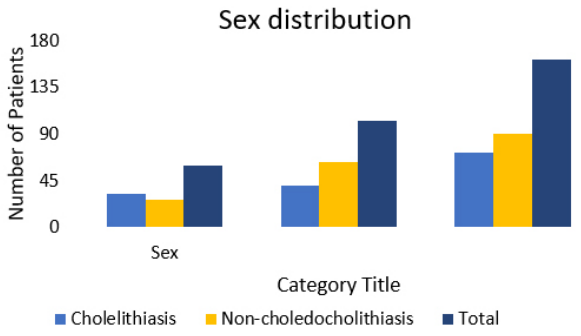

Figure 6: Graphical representation of gender distribution of those with and without choledocholithiasis.

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

	Choledocholithiasis	Non-choledocholithiasis	Total
ALP value >130IU/L	51 (True Positives)	39 (FALSE POSITIVES)	90
	PPV 56.7%	43.3%	100
	70.8%	% of FP 44.3%	
ALP value <130IU/L	21 (False Negatives)	49 (True Negatives)	70
	30%	NPV 70%	100%
	% of FN 29.2%	55.7%	
Total	72	88	160
	45%	55%	100%

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

30% (21) of all patients with choledocholithiasis showed a normal ALP – a significant number of patients in whom the diagnosis can be missed if relying only on ALP to show evidence of biliary obstruction. Of the 21, 12 were male and 9 were female. The mean age was found to be 53.619. Concurrent Cholelithiasis was present in 13 of the cases. 4 had features of calculous cholecystitis. Adenomyomatosis of the gall bladder was present in 2 patients. Concurrent pancreatic calculus was present in 1 patient. An anatomical variant of the biliary tree with hepatomegaly was observed in 1 case. 2 cases showed MRI features of acute pancreatitis. Serum amylase was elevated more than 80u/l in 7 patients whereas 6 out of 21 had lipase elevated more than 60u/l. CBD and CHD Diameter was measured and matched with age-appropriate standard diameters as "Decade of age +1". CBD was dilated in 17 out of the 21 patients. Total bilirubin was elevated as >1.20mg/dl in 9 out of 21. Clinically evident jaundice (>3mg/dl) was present only in 1 patient. SGOT and SGPT (normal <50u/l) were elevated only in 4 out of 21 patients. All 21 of them underwent ERCP with common bile duct stenting.

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.[4,8] 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.[5,6] 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).[7,8] 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.

Funding: Not applicable

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 concordance with STARD 2015 Guidelines.

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

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

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