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POSITIVE PREDICTIVE VALUE OF RAISED SERUM ALKALINE PHOSPHATASE IN PREDICTING CHOLEDOCHOLITHIASIS, TAKING OPERATIVE FINDINGS AS THE GOLD STANDARD

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Abstract

Introduction:
Choledocholithiasis is an important medical condition linked to gallstone formation and can cause severe medical problems if not detected early enough. While liver function tests, especially ALP, are commonly used as initial screening tools, there are doubts about their diagnostic accuracy, especially where resources are limited.

Objective:
To evaluate the diagnostic utility, particularly the positive predictive value, of raised serum alkaline phosphatase in predicting choledocholithiasis using intraoperative findings as the gold standard.

Methods:
The present descriptive cross-sectional study was conducted in a tertiary care hospital during six months and included 139 patients of symptomatic gallstone disease who underwent laparoscopic cholecystectomy. The pre-operative serum levels of ALP were noted, and values higher than 400 IU/L were classified as high. Intraoperative findings were taken as the gold standard to detect the CBD stones. Various diagnostic indices such as sensitivity, specificity, PPV, NPV, and accuracy were obtained using a 2 × 2 contingency table. The Fisher's exact test was used to analyse the associations.

Results:
The average age of the respondents was 46.3 ± 14.9 years, with women accounting for 66.2% of the sample. The prevalence rate of CBD stones was 13.7%. An increase in ALP levels was noted in 96.4% of cases. The sensitivity level of ALP in diagnosing CBD stones was very high (89.5%, 95% CI: 66.9–98.7%), whereas the specificity level was extremely low (2.5%, 95% CI: 0.5–7.1%). The PPV and NPV were 12.7% (95% CI: 7.6–19.5%) and 60.0% (95% CI: 14.7–94.7%), respectively, giving an overall diagnostic accuracy of 14.4%. There was no significant relationship between elevated ALP levels and CBD stones (p = 0.138). However, subgroup analysis revealed that there was no significant relationship.

Conclusion:
Even though increased ALP shows high sensitivity, the fact that the method lacks specificity and predictive value makes it impossible to be used alone for the diagnosis of choledocholithiasis. This suggests the necessity to conduct diagnostics on the basis of a combination of various methods.

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Introduction:

Choledocholithiasis refers to the formation of stones in the common bile duct, a condition commonly observed in gallstone disease that can cause serious health problems, such as obstructive jaundice, cholangitis, and acute pancreatitis(1). Consequently, accurate detection of CBD stones before surgery is vital as it directly influences management decisions, including the necessity for further imaging tests and possible endoscopy procedures. In contemporary practice, there is a focus on selective patient selection, mainly due to the risks involved in ERCP, which, despite being a therapeutic modality, carries the risk of morbidity(1).

Diagnosis of suspected choledocholithiasis can be performed using the combined approach of physical examination, biochemical tests, and radiology(2). Transabdominal ultrasonography is commonly employed as a first-line diagnostic modality; nonetheless, ultrasonography does not have high sensitivity to detect CBD stones, especially when the stones are small or when there are only indirect findings, such as a dilated bile duct(3).

Newer imaging techniques, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS), are associated with high diagnostic accuracy and can be used for further investigations in selective patients. According to systematic reviews and meta-analyses, the diagnostic accuracy of MRCP and EUS is equal, which justifies using a risk-based strategy for investigation (2, 4). Despite these advances, selecting patients who require further evaluation remains a challenge in routine clinical practice.

Liver enzyme assays, such as those performed on hepatic functions, are widely used to raise suspicions of choledocholithiasis owing to their easy access and cost-effectiveness. Of special interest among them are ALP levels, which reflect both cholestasis and bile duct blockage. However, the raised ALP levels do not indicate choledocholithiasis per se, as there are other liver/biliary disorders associated with similar test results, which makes them less precise diagnostics. New studies have shown that liver function tests have a poor predictive value for CBD stones (5, 6). Moreover, the fact that even fluctuating biochemical liver enzyme concentrations provide very little added value in the risk stratification of patients has also been demonstrated (6). Such results suggest that the actual usefulness of biochemical tests remains ambiguous, especially when used independently. where access to advanced imaging modalities remains limited, and physicians often rely on readily available laboratory parameters.

This issue is particularly relevant in low- and middle-income settings, where access to advanced imaging modalities remains limited, and physicians often rely on readily available laboratory parameters. Here, serum ALP levels are assessed as routine preoperative investigations and do not add extra costs. Nonetheless, their predictive significance is affected by the population's incidence rates of the diseases under consideration, thus the need for assessment within selected populations using valid criteria.

Therefore, the present study was conducted to evaluate the diagnostic utility, particularly the positive predictive value, of raised serum alkaline phosphatase in predicting choledocholithiasis in patients with symptomatic gallstones, using intraoperative findings as the gold standard.

Methods:

The current study is a descriptive cross-sectional study, which was carried out over six months after the acceptance of the synopsis by the Department of General Surgery at Liaquat National Hospital, Karachi. The study population comprised a total of 139 patients suffering from symptomatic gallstone disease and undergoing surgery for laparoscopic cholecystectomy.

The inclusion criteria consisted of patients who had high serum levels of alkaline phosphatase (ALP) during an attack of symptomatic cholecystitis, those who suffered from gallstone pancreatitis, and those who showed abnormality in their liver function test results. The exclusion criteria consisted of patients suffering from any form of chronic liver disease, empyema gallbladder, or acute cholecystitis (characterized by peri-cholecystic fluid and gall bladder wall edema on ultrasound with clinical presentation offever21 00Fo and tachycardia; pulses I 00/minute).

The demographic characteristics of the subjects included baseline age and gender, which were

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collected. The serum alkaline phosphatase value was tested routinely pre-operatively, and if it exceeded 400 IU/L, the variable would be classified as elevated based on the operational definition provided. The operation done to all the participants was a laparoscopic cholecystectomy done by an experienced consultant surgeon with at least five years of post-fellowship practice. The intraoperative finding was noted and documented as a reference point for the choledocholithiasis condition.

Data were collected using a structured proforma and entered into SPSS version 21 for analysis. Quantitative variables such as age were summarized as mean ± standard deviation, while qualitative variables, including gender, diagnosis, raised ALP, and intraoperative detection of CBD stones, were presented as frequencies and percentages. Normality of age distribution was assessed using descriptive measures, including skewness and comparison of mean and median values.

To measure the diagnostic effectiveness of raised ALP, a 2 × 2 table was generated by taking raised ALP as an index test, while intraoperative confirmation of the presence of CBD stones served as a gold standard. The sensitivity, specificity, PPV, NPV, and overall diagnostic accuracy were manually calculated based on the standard formulas. Ninety-five percent confidence intervals for the values were estimated using exact binomial statistics.

Fisher's Exact Test was applied for the study of the relationship between increased ALP level and intraoperative finding of choledocholithiasis due to small cell sizes and violations of the chi-square test assumptions. Subgroup analysis was done concerning gender and type of clinical diagnosis to investigate effect modification. Statistical analysis was not done for those subgroups where all the variables were equal. Comparison of the age variable between the two groups was done using the independent samples t-test; if necessary, non-parametric tests were applied to corroborate.

Results:

A total of 139 patients were analysed. Mean age was 46.3 ± 14.9 years, with median age being 45 years (interquartile range: 20 years). Females constituted the majority at 92 out of 139 patients (66.2%), while males were 47 (33.8%). Prevalence of CBD stone during surgery was 13.7% (19 out of 139). Table 1 shows baseline demographics and characteristics.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Value
Age (years)	46.3 ± 14.9
Median (IQR)	45 (20)
Gender	
Male	47 (33.8%)
Female	92 (66.2%)
Diagnosis	
Acute calculus cholecystitis	63 (45.3%)
Biliary colic	32 (23.0%)
Chronic cholecystitis	22 (15.8%)
Gallstone pancreatitis	22 (15.8%)
Raised ALP (>400 IU/L)	134 (96.4%)
CBD stones (intraoperative)	19 (13.7%)

An elevation in serum ALP was found in 134 cases (96.4%). In terms of diagnostic utility, the sensitivity for elevated ALP was very high (89.5%; 95% CI: 66.9-98.7) but with an extremely low level of specificity (2.5%; 95% CI: 0.5-7.1). The positive predictive value was 12.7% (95% CI: 7.6-19.5), while the negative predictive value was 60.0% (95% CI: 14.7-94.7). The overall diagnostic accuracy was very low (14.4%).

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Table 2: Diagnostic Performance of Raised Serum ALP

Parameter	Value (%)	95% Confidence Interval
Sensitivity	89.5	66.9–98.7
Specificity	2.5	0.5–7.1
Positive Predictive Value (PPV)	12.7	7.6–19.5
Negative Predictive Value (NPV)	60.0	14.7–94.7
Accuracy	14.4	9.0–21.3

No statistical significance was noted between elevated ALP levels and the presence of CBD stone during surgery (exact Fisher test, p=0.138) (Table 3). Gender-wise analysis showed that no significance was obtained among women (p=0.108) and men (p=1.000), indicating no effect modification by gender.

Table 3: Association Between Raised ALP and CBD Stones

Raised ALP	CBD Stones Present	CBD Stones Absent	Total
Yes	17 (12.7%)	117 (87.3%)	134
No	2 (40.0%)	3 (60.0%)	5
Total	19	120	139

Stratified analysis by clinical diagnosis demonstrated no significant association in patients with biliary colic (p = 1.000), while statistical testing could not be performed in acute and chronic cholecystitis due to a lack of variability in ALP levels. A statistically significant association was observed in patients with gallstone pancreatitis (p = 0.043) (Table 4).

Table 4: Stratified Analysis by Diagnosis

Diagnosis	p-value	Remarks
Acute calculus cholecystitis	Not applicable	ALP constant
Biliary colic	1.000	Not significant
Chronic cholecystitis	Not applicable	No variability
Gallstone pancreatitis	0.043	Significant

Discussion:

In the current research, the predictive value of elevated serum levels of alkaline phosphatase (ALP) for choledocholithiasis was assessed by comparing it with intraoperative results considered as the gold standard in individuals with symptomatic gallstones. This study demonstrates that although the sensitivity of elevated ALP is very high, its specificity and positive predictive value are considerably poor.

The high sensitivity found in this study conforms to the underlying mechanism in the formation of biliary obstruction, in which cholestasis results in increased synthesis and excretion of ALP by the biliary cells (5). Nevertheless, the extremely low specificity is explained by the fact that ALP levels may be elevated in various hepatobiliary disorders not related to bile duct stones. These results are similar to the findings in other recent studies investigating the diagnostic utility of liver function tests, in which ALP and other enzymes revealed poor discrimination power when applied individually(7).

These results are in line with current data showing that liver enzyme assays, when applied independently, demonstrate poor accuracy in predicting common bile duct calculi (3, 6). Modern research shows that biochemical indices alone cannot be used effectively to differentiate patients and must be considered alongside clinical manifestations and imaging results (8, 9). Additionally, there is modern data supporting the idea that variations in liver enzymes over time also fail to increase the diagnostic value above that of known risk factors. The discrepancy in predictive power between studies can be explained by varying prevalence rates, patient populations, and thresholds for abnormal results(10, 11).

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In the current investigation, there was no significant relation found between elevated ALP levels and the identification of CBD stones during surgery. The result was similar for both genders, implying that the discriminatory power of ALP is not affected by gender. A significant correlation was seen in gallstone-induced pancreatitis patients; however, this may be attributed to the common factor of bile duct obstruction rather than diagnostic accuracy. In such conditions, obstruction, either temporary or permanent, could increase ALP regardless of whether CBD stones were still present at the time of surgery (12).

Clinically, these findings suggest there are several implications resulting from these research findings. Although serum ALP is a convenient method, which is inexpensive, easily performed, and accessible in many healthcare facilities, especially in resource-constrained settings, it lacks high specificity and a low predictive value for its application as a standalone tool in the process of diagnosis. The obtained data confirm existing clinical guidelines, according to which the use of ALP should be combined with clinical examination, laboratory parameters, and more complicated diagnostic methods, such as MRCP or EUS. Such conclusions can be applied to resource-limited settings, where advanced diagnostic methods are less available, thus contributing to further diagnostic challenges and different approaches in management (2, 8, 13)

Limitations:

This study has several limitations. The prevalence rate for elevated levels of ALP in the patient sample was relatively high, leading to imbalance and low specificity, as well as to wide confidence intervals in some cases. Moreover, the number of patients who had normal levels of ALP is too low, making it difficult to carry out subgroup analysis. This study focused only on one indicator of liver function without including other liver test results. In addition, the study was conducted by a single centre and used non-probability sampling.

Conclusion:

However, despite the limitations, this study contributes immensely to providing local evidence of the test characteristics of ALP among patients suffering from symptomatic gallstones. The employment of surgical diagnosis as the criterion for establishing true diagnoses is a source of increased reliability of the conclusions drawn in this work. Further studies should be directed towards the creation and validation of combined prediction models.

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