ORIGINAL ARTICLE

Positive Predictive Value of Raised Serum Alkaline Phosphatase in Predicting Choledocholithiasis taking Operative Findings as Gold Standard

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ABSTRACT

Aim: To determine the positive predictive value of raised serum alkaline phosphatase in predicting choledocholithiasis in patients with cholelithiasis taking operative findings as gold standard.
Design: It was a cross sectional survey.
Study Settings: The present study was carried at Surgical Unit-I of Sir Ganga Ram Hospital, Lahore over 6 months from Jan 2018 to June 2018.
Methods: The study involved 139 patients of both genders aged between 20-70 years diagnosed of cholelithiasis and suspected of choledocholithiasis on raised serum alkaline phosphatase level (≥400 IU/L). These patients underwent open cholecystectomy with CBD exploration and diagnosis of choledocholithiasis was confirmed operatively which was taken as gold standard and results of raised serum alkaline phosphatase level were judged accordingly as true positive or false positive. An informed consent was taken from each patient.
Results: The mean age of the patients was 44.1±12.7 years. Majority (52.5%) of the patients were aged between 30-50 years followed by >50 years (26.6%) and <30 years (20.9%). There were 37(26.6%) male and 102 (73.4%) female patients with a male to female ratio of 1:2.8. Diagnosis of choledocholithiasis was confirmed in 125 (89.9%) patients on operative findings. Thus there were 125 true positive and 14 false positive cases which yielded a positive predictive value of 89.9% for raised serum alkaline phosphatase level (≥400 IU/L) in the diagnosis of choledocholithiasis taking operative findings as gold standard.
Conclusion: Raised serum alkaline phosphatase level (cut-off value ≥400 IU/L) was found to have a high positive predictive value of 89.9% in the diagnosis of choledocholithiasis taking operative findings as gold standard which along with routine access, radiation free nature and cheaper cost advocates its preferred use
Keywords: Cholelithiasis, Choledocholithiasis, Serum Alkaline Phosphatase

INTRODUCTION

Eleven to 21% of patients with cholelithiasis also have concomitant common bile duct (CBD) stones at the time of surgery. They may pass on to duodenum, remain asymptomatic or may cause obstructive jaundice or symptoms like acute cholecystitis[1]. Cholecystectomy is the treatment of choice in patients with cholelithiasis but an asymptomatic CBD stone is often missed in such patients which may later become symptomatic leading to secondary surgical intervention and patient dissatisfaction[2]. A right upper quadrant trans-abdominal ultrasound (US) is the most appropriate initial imaging study in most patients with complaints of right upper quadrant pain or suspected cholelithiasis. The clue for CBD stone on ultrasound is the dilatation of proximal portion which is however not always true. Thus a fraction of CBD stones are routinely missed. Abdominal CT has a sensitivity of 86% (vs. 82% for US) and a specificity of 98% (vs. 98% for US) for the diagnosis of choledocholithiasis[3]. But not every patient can be subjected to CT due to radiation exposure and time and cost restraints. Therefore there has always been a quest to identify high risk patients who can be subjected to an abdominal CT[2,3].

Alkaline phosphatase (ALP), a plasma membrane-bound glycoprotein, belongs to a large family of dimeric enzymes, usually confined to the cell surface. The activity of bone- and liver-alkaline phosphatases in serum has been used widely in routine diagnosis. The normal serum level of alkaline phosphatase ranges from 20 to 140IU/L. The alkaline phosphatase enzyme is a principal serum analyte and an elevated level in serum is linked with the presence of liver, bone and other diseases[4]. Tozatti et al. (2015) reported the positive predictive value (PPV) of raised serum alkaline phosphatase level (≥400IU/L) to be 90% in predicting choledocholithiasis in Brazilian patients with cholelithiasis[5]. Isherwood et al. (2014) using a cut-off value of ≥400IU/L for serum alkaline phosphatase level reported the positive predictive value of 51.7% among British such patients[6]. Videhult et al[7] (2011) and Zare et al[8] (2011) reported the positive predictive value of raised serum alkaline phosphatase to be 42% and 18% among Swedish and Iranian such patients respectively taking a cut-off value of ≥150 mg/dl for serum alkaline phosphatase while Notash et al.[9] (2008) reported much lower PPV of 12.5% among Iranian such patients (cut-off not given).

Thus in the light of this evidence, raised serum alkaline phosphatase level can be used to predict choledocholithiasis in patients presenting with cholelithiasis which will enable pre-operative preparation and per-operative exploration of common bile duct to improve the patient outcome. Serum alkaline phosphatase level is acquired during routine pre-operative work of patients before general anaesthesia as a part of liver function tests (LFTs) and doesn't need special hardware or extra cost. However, the positive predictive value of raised serum ALP varied in the existing literature, possibly owing to variable cut-off values used among studies. Also as the positive predictive value varies with the prevalence of disease and there was no such local published material, the objective of

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the present study was to repeat this trial and further endorse the results with a hope that the results of the present study may provide a cost-effective tool for the identification of suspected patients of choledocholithiasis in future practice.

MATERIAL AND METHODS

It was a cross-sectional survey carried at Surgical Unit-I of Sir Ganga Ram Hospital Lahore over 6 months from Jan 2018 to June 2018. Sample size of 139 cases was calculated with 95% confidence level and 5% margin of error while taking expected percentage of positive predictive value of raised serum alkaline phosphatase (≥400IU/L) to be 90% in the diagnosis of choledocholithiasis taking operative findings as gold standard[5]. Patients of both genders with ages in the range of 18-70 years presenting with cholelithiasis with raised serum alkaline phosphatase level (≥400IU/L) that subsequently underwent open cholecystectomy were included in this study. Cholelithiasis was suspected in patients presenting with off & on pain in right hypochondrium for ≥6 weeks and was confirmed upon ultrasound evidence of stones in the gall bladder (echoic shadow). Patients with chronic liver disease (characterized by cirrhosis of liver on ultrasound, clinical jaundice, episodes of hematemesis, positive for HbsAg or Anti HCV), empyema gallbladder (characterized by distended gall bladder on ultrasound with fever, tachycardia and guarding in right hypochondrium) and acute cholecystitis (characterized by peri-cholecystic fluid and gall bladder wall oedema on ultrasound with clinical presentation of fever≥100F^{o} and tachycardia; pulse≥100/minute) were excluded. All the patients had serum alkaline phosphatase level estimation and raised serum alkaline phosphatase level (≥400IU/L) was taken as predictive of choledocholithiasis. All these patients underwent open cholecystectomy where the diagnosis of choledocholithiasis was confirmed. All the labs were acquired from the same (hospital) lab and all the surgeries were performed by a single surgical team to minimize bias. Confounding variables were dealt by careful exclusion criteria. Numerical variables like age and serum alkaline phosphatase level have been presented by mean±sd while categorical variables i.e., gender and choledocholithiasis on operative findings have been presented by frequency and percentage. Positive predictive value of raised serum alkaline phosphatase has been presented as percentage.

RESULTS

The age of the patients ranged from 20 years to 70 years with a mean of 44.1±12.7 years. Majority (n=73, 52.5%) of the patients were aged between 30-50 years followed by >50 years (26.6%) and <30 years (20.9%). There were 37 (26.6%) male and 102 (73.4%) female patients with a male to female ratio of 1:2.8. Duration of symptoms ranged from 6 weeks to 19 weeks with a mean of 12.8±3.9 weeks while the serum alkaline phosphatase level ranged from 402 IU/L to 780 IU/L with a mean of 599.2±110.8 IU/L as shown in Table 1. Diagnosis of choledocholithiasis was confirmed in 125(89.9%) patients on operative findings as shown in Table 2. Thus there were 125 true positive and 14 false positive cases which yielded a positive predictive value of 89.9% for raised serum alkaline phosphatase level (≥400 IU/L) in the diagnosis of choledocholithiasis taking operative findings as gold standard as shown in Table 2. There was no statistically significant difference in the positive predictive value of raised serum alkaline phosphatase across various subgroups based on patient's age, gender and duration of symptoms.

Table 1: Demographic characteristics of study participants

Characteristics	**Study sample**
Age (years)	44.1±12.7
• <30 years	29 (20.9%)
• 30-50 years	73 (52.5%)
• >50 years	37 (26.6%)
Gender	
Male	37 (26.6%)
Female	102 (73.4%)
Duration of Symptoms (weeks)	12.8±3.9
• 6-12 weeks	62 (44.6%)
13-19 weeks	77 (55.4%)
Serum Alkaline Phosphatase (IU/L)	599.2±110.8

Table 2: Diagnosis of choledocholithiasis on operative findings

Choledocholithiasis	**Frequency(n)**	**%age**
Yes (Tru +ve)	125	89.9
No(False +ve)	14	10.1
Total	139	100.0

PPV 89.9%

DISCUSSION

Since choledocholithiasis is responsible for much of the serious morbidity of gallstone disease, the detection and elimination of stones within the common bile duct are major objectives of biliary surgery[10]. Various strategies can be used to achieve these goals. For example, exploration of the common bile duct might be recommended for all patients undergoing cholecystectomy. However, since most diagnostic and therapeutic measures are costly to the patient and increased surgical effort cannot necessarily be equated with better care, most surgeons resort to selective exploration based upon several specific indications[10,11]. In an appreciable proportion of patients, choledochostomy for suspected calculi is fraught with complications such as stricture of the common bile duct, external or internal biliary fistulae and "post-cholecystectomy syndrome."[12] In addition, common duct stones retained after choledochostomy present problems, and operative mortality may reach significant proportions[10]. The preoperative diagnosis of common bile duct stones is therefore important but as every surgeon knows, can be most difficult, even in the presence of certain well-known signs[1,2,10,11]. Recent studies claimed raised serum alkaline phosphatase in patients with cholelithiasis to be predictive of associated choledocholithiasis[5-9]. However, there was controversy in the existing literature over its positive predictive value[5-9]. Moreover, there was no such local published material which necessitated the present study.

The objective of this study was to determine the positive predictive value of raised serum alkaline phosphatase in predicting choledocholithiasis in patients with cholelithiasis taking operative findings as gold standard.

In the present study, the mean age of the patients was 44.1±12.7 years. Naz et al[13] (2016) reported similar

mean age of 44.5±11.3 years in patients presenting with choledocholithiasis at Civil Hospital Karachi while Hussain et al[14] (2016) reported it to be 44.2±12.3 years among such patients presenting at Lady Reading Hospital, Peshawar. A similar mean age of 42±8.9 year has been reported by Gupta et al[15] in Indian patients with choledocholithiasis while Pradhan et al.[16] (2016) observed it to be 44.1±14.3 years in Bangladesh. A comparable mean age of 44±9.8 years has been reported by Videhult et al[7] (2011) in Swedish such patients.

We observed that majority (52.5%) of the patients were aged between 30-50 years followed by >50 years (26.6%) and <30 years (20.9%). Our observation is in line with that of Ghazanfor et al[17] (2017) who reported similar frequency of <30 years (21.5%), 30-50 years (52.0%) and >50 years (26.5%) age groups in patients presenting with choledocholithiasis at Holy Family Hospital Rawalpindi.

In the present study, there were 37 (26.6%) male and 102 (73.4%) female patients with a male to female ratio of 1:2.8. Ghazanfor et al.[17] reported similar female predominance with male to female ratio of 1:2.7 among such patients at Holy Family Hospital Rawalpindi while Sattar et al.[18] (2007) reported it to be 1:2.7 at Jinnah Postgraduate Medical Centre, Karachi. A similar female predominance among Indian such patients has been reported by Rai et al.[19] and Gupta et al.[15] who reported a male to female ratio of 1:2.8 and 1:2.3 respectively.

We observed that raised serum alkaline phosphatase level had a positive predictive value of 89.9% in the diagnosis of choledocholithiasis taking operative findings as gold standard. Our results are in line with those of Tozatti et al[5] (2015) who also reported the positive predictive value (PPV) of raised serum alkaline phosphatase level (>400IU/L) to be 90% in predicting choledocholithiasis in Brazilian patients with cholelithiasis.

The present study is first of its kind in local population and has found that the raised serum alkaline phosphatase level (cut-off value ≥400 IU/L) has a high positive predictive value of 89.9% in the diagnosis of choledocholithiasis taking operative findings as gold standard which along with routine access, radiation free nature and cheaper cost advocates its preferred use in future practice. Thus in future, patients with cholelithiasis and raised serum alkaline phosphatase level upon admission should be taken as high risk for choledocholithiasis

In the present study, we also noted that the positive predictive value of raised serum alkaline phosphatase was higher in patients with shorter duration of symptoms; 6-12 weeks vs. 13-19 weeks (93.5% vs. 87.0%) which may be due to the fact that alkaline phosphatase is released from cells lining the common bile duct due to injury resulting from impacted stones which increases with the passage of time as the inflammation and fibrosis results while the stone may have passed into the intestine. Keeping in view this finding, patients with acute onset of symptoms and raised serum alkaline phosphatase should be considered at higher risk and those with prolonged history should be subjected to abdominal CT to further confirm the results.

CONCLUSION

Raised serum alkaline phosphatase level (cut-off value ≥400 IU/L) was found to have a high positive predictive value of 89.9% in the diagnosis of choledocholithiasis taking operative findings as gold standard which along with routine access, radiation free nature and cheaper cost advocates its preferred use in future practice.

Disclosure of conflict of interest: None

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