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# To Compare the Frequency of Choledocholithiasis in Symptomatic Cholelithiasis using Raised Gamma GT and Alkaline Phosphatase with MRCP

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## ABSTRACT

**Background:** Choledocholithiasis, the presence of gallstones within the common bile duct (CBD), is a significant complication of cholelithiasis (gallstones in the gallbladder). Raised levels of gamma-glutamyl transferase (Gamma GT) and alkaline phosphatase (ALP) are commonly used as biochemical markers to suspect choledocholithiasis in patients with symptomatic cholelithiasis. **Objective:** The goal of the present study was to evaluate the validity of GGT and ALP in identifying choledocholithiasis in the symptomatic cholelithiasis patients as compared with MRCP. **Study Design:** Cross sectional study. **Settings:** Department of General Surgery, Shaikh Zayed Hospital, Lahore and Allied Hospital, Faisalabad Pakistan. **Duration:** 12 months from 08/04/2020 to 07/04/2021. **Methods:** The present study involved 289 patients of both genders aged between 18-70 years diagnosed of cholelithiasis. These patients were assessed by routine liver function tests and choledocholithiasis was suspected on elevated serum alkaline phosphatase level (≥147 IU/L) and gamma glutamyl transferase level (≥48 IU/L). These patients underwent MRCP and diagnosis of CBD stones was confirmed which was considered as gold standard and results of elevated serum ALP and GGT levels were adjudicated accordingly as true or false and positive or negative. An informed written consent was acquired from every patient who was included in the study. **Results:** The mean age of the patients was 49.2±13.8 years. There was female predominance with male to female ratio of 1:2.8. The diagnosis of CBD stones was established in 56 (19.4%) patients on MRCP. The mean serum levels of ALP (203.84±65.22 vs. 94.07±44.62 IU/L; p-value<0.0001) and GGT (347.84±110.69 vs. 87.15±101.78 IU/L; p-value<0.0001) were significantly higher in patients with choledocholithiasis as compared to those without choledocholithiasis. A cut-off value of 147 IU/L for ALP had a sensitivity of 64.3%, specificity of 67.4% and diagnostic accuracy of 66.8% with positive and negative predictive values of 32.1% and 88.7% respectively. A cut-off value of 48 IU/L for GGT had sensitivity of 91.1%, specificity of 81.6% and diagnostic accuracy of 83.4% with positive and negative predictive values of 54.3% and 97.4% respectively. **Conclusion:** In the present study, a considerable proportion of patients with cholelithiasis also had choledocholithiasis that was associated with significantly higher mean serum levels of alkaline phosphatase and gamma glutamyl transferase which were found helpful in the diagnosis of CBD stones taking MRCP findings as gold standard and this along with widespread availability, radiation free nature and cheaper cost encourages the favored use of serum alkaline phosphatase and gamma glutamyl transferase in the non-invasive pre-operative diagnosis of choledocholithiasis in future practice.

***Keywords:*** *Cholelithiasis, Choledocholithiasis, Serum Alkaline Phosphatase, Gamma Glutamyl Transferase.*

## INTRODUCTION

Cholelithiasis is a common disease worldwide, with incidence of 5-25% of adult worldwide population.[1] 30% of these patients present with biliary colic in a period of 10 years. Incidence of common bile duct (CBD) stones in patients presenting with Cholelithiasis is 8-20%.[2]

Mostly CBD stones do not show any symptoms but they can cause pain and obstructive jaundice due to complete or partial obstruction. Complications associated with choledocholithiasis are cholecystitis, cholestatic syndrome, cholangitis, acute pancreatitis and hepatic abscess. Biliary obstruction can lead to biliary cirrhosis and subsequently lead to portal hypertension.[3]

A patient with gall stones presenting with jaundice, deranged liver function test and dilated CBD on USG, can be suspected to have choledocholithiasis. Pre-Operative diagnosis of common bile duct stones plays a crucial role in the management and to decrease the risk of retained stone in the CBD.[4,5]

Various imaging techniques and biochemical markers are used to diagnose the common bile duct stones. Specificity and sensitivity of MRCP in diagnosing the level and presence of CBD stones is 97% and 95% respectively.[6] But it causes increase economic burden on patient. The specificity and sensitivity of ERCP is 90% and 98% respectively.[7] But it is associated with grave complications like cholangitis, CBD or duodenal perforation and bleeding.

Associated risk of complications with ERCP is 5% to 10% and mortality rate is 0.02% to 0.5%.[7,8] Therefore it is important to consider biochemical markers initially to diagnose the CBD stones.[9]

Many enzymes are released in circulation due to shedding of hepatocyte plasma membrane such as gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), leucine amino peptidase and 5′ nucleotidase (5′NT). Various authors have explained the importance of gamma glutamyl transferase (GGT) over alkaline phosphatase (ALP). As ALP is released from various sites like bone and placenta other than its release from biliary canalicular membrane together with more specific enzyme such as GGT; regarding biochemical markers in predicting CBD stones GGT is more accurate than other serum markers.[10]

The usefulness of GGT can be attributed by the aspect that patients of choledocholithiasis who do not present with jaundice can have raised GGT values due to inflammatory edema which leads to obstruction. There GGT levels reflects the presence of CBD stone despite of normal bilirubin levels[11] 5′NT is also usually elevated in hepatobiliary disease usually with intrahepatic obstruction but its levels are not increased in infancy, childhood, pregnancy or osteoblastic disorders, so it is more specific than ALP. But studies show that GGT is more preferable than ALP and 5′NT in detecting CBD stones not only in patients presenting with biliary obstruction or jaundice but also in patients that presents without symptoms of biliary obstruction.[12]

## METHODS

It's a cross-sectional study conducted at General Surgery Department, Shaikh Zayed Hospital Federal PGMI Lahore and Department of Surgery Allied Hospitals, Faisalabad Pakistan. The Duration of study was 12 months from 08/04/2020 to 07/04/2021. Sample size of 289 patients was calculated by using 5% margin of error and 95% confidence level while taking frequency of choledocholithiasis as 25%.[14] Patients were enrolled through Non-Probability, Consecutive Sampling.

Admitted Patients of both male & female gender, patient age from 18 years & above and patients with cholelithiasis were included in the study.

Patient not willing to participate in study, patient with concomitant malignancy of biliary tract, patients with jaundice, known patient of choledocholithiasis and patient with bone disease were excluded from the study.

Approval from ethical review committee was taken before starting the study. 289 patients who satisfied the inclusion criteria of the study were selected. Prior to inclusion in to the study, written informed consent was taken from each patient. Patients' demographic details were gathered by filling a relevant preformed Proforma.

Peripheral venous blood sample of 3-5 mL was collected from each member. The blood sample was centrifuged for 10 min at 2000 r/min, and the supernatant was collected and stored in -80°C freezer.

The serum samples underwent biochemical measurement of GGT and serum alkaline phosphatase by using Beckman coulter kit. Finally, the optical density (OD) value of each sample was measured at 450 nm by an Absorbance Micro plate Reader (ELx800, Bio-Tek).

All the collected data was entered into and evaluated through SPSS version 20.

## RESULTS

The age of the patients ranged from 18 years to 70 years with a mean of 49.2±13.8 years. Majority (n=153, 52.9%) of the patients were aged between 30-50 years followed by more than 50 years (28.8%) and less than 30 years (18.3%). There were 77 (26.6%) male and 212 (73.4%) female patients with a male to female ratio of 1:2.8. The BMI of these patients ranged from 22.5 Kg/m$^2$ to 34.8

Kg/m² with a mean of 28.4±3.7 Kg/m². 100 (34.6%) patients were overweight and 122 (42.2%) patients were obese. Serum alkaline phosphatase level ranged from 40 IU/L to 281 IU/L with a mean of 115.34±65.61 IU/L while serum GGT level ranged from 34 IU/L to 475 IU/L with a mean of 137.67±146.08 IU/L as shown in Table 1.

**Table 1: Baseline characteristics of study sample (n=289)**

| Characteristics | Study Sample |
|---|---|
| **Age (years)** | 49.2±13.8 |
| **<30 years** | 53 (18.3%) |
| **30-50 years** | 153 (52.9%) |
| **>50 years** | 83 (28.8%) |
| **Gender** | |
| **Male** | 77 (26.6%) |
| **Female** | 212 (73.4%) |
| **BMI (Kg/m²)** | 28.4±3.7 |
| **20-25 Kg/m²** | 67 (23.2%) |
| **25-30 Kg/m²** | 100 (34.6%) |
| **30-35 Kg/m²** | 122 (42.2%) |
| **Serum Alkaline Phosphatase (IU/L)** | 115.34±65.61 |
| **Serum GGT (IU/L)** | 137.67±146.08 |

The diagnosis of CBD stones was confirmed in 56 (19.4%) patients on MRCP. There was no statistically significant difference in the frequency of MRCP confirmed CBD stones across various subgroups based on age (p-value=0.876) and gender (p-value=0.518). However, the frequency of choledocholithiasis increased significantly with increasing BMI of the patient; 20-25 Kg/m² vs. 25-30 Kg/m² vs. 30-35 Kg/m² (11.9% vs. 16.0% vs. 26.2%; p-value=0.034) as shown in Table 2.

**Table 2: Comparison of choledocholithiasis across various Subgroups (n=289)**

| Subgroups | | n | Choledocholithiasis N (%) | P-value |
|---|---|---|---|---|
| **Age** | **<30 years** | 53 | 9 (17.0%) | 0.876 |
| | **30-50 years** | 153 | 30 (19.6%) | |
| | **>50 years** | 83 | 17 (20.5%) | |
| **Gender** | **Male** | 77 | 13 (16.9%) | 0.518 |
| | **Female** | 212 | 43 (20.3%) | |
| **BMI** | **20-25 Kg/m²** | 67 | 8 (11.9%) | 0.034* |
| | **25-30 Kg/m²** | 100 | 16 (16.0%) | |
| | **30-35 Kg/m²** | 122 | 32 (26.2%) | |

** Difference was statistically significant on chi-square test*

The mean serum levels of ALP (203.84±65.22 vs. 94.07±44.62 IU/L; p-value<0.0001) and GGT (347.84±110.69 vs. 87.15±101.78 IU/L; p-value<0.0001) were significantly higher in patients with choledocholithiasis as compared to those without choledocholithiasis as shown in Table 3.

**Table 3: Comparison of mean serum ALP and GGT between patients with versus without choledocholithiasis (n=289)**

| Parameter | Choledocholithiasis | | P-value |
|---|---|---|---|
| | Yes (n=56) | No (n=233) | |
| Serum ALP (IU/L) | 203.84±65.22 | 94.07±44.62 | <0.0001* |
| Serum GGT (IU/L) | 347.84±110.69 | 87.15±101.78 | <0.0001* |

** Difference was statistically significant on independent sample t-test*

Taking a cut-off value of 147 IU/L, CBD stones were suspected in 112 (38.8%) patients on ALP. Diagnosis of CBD stones was confirmed in 56 (19.4%) patients on MRCP. When cross tabulated the diagnosis of choledocholithiasis on ALP and MRCP, there were 36 true positive, 76 false positive, 20 false negative and 157 true negative cases which yielded a sensitivity of 64.3% and specificity of 67.4% with positive and negative predictive values of 32.1% and 88.7% respectively. The observed diagnostic accuracy was 66.8% as shown in Table 4. The area under curve was 0.872 (p-value<0.0001). The best cut-off value of ALP was predicted to be ≥170 IU/L which would give a sensitivity of 64.3% and specificity of 100.0%.

**Table 4: 2x2 table to calculate diagnostic performance of ALP in diagnosing choledocholithiasis (n=289)**

| Alkaline Phosphatase | MRCP | | Total |
|---|---|---|---|
| | Choledocholithiasis | No | |
| **Choledocholithiasis** | 36[a] | 76[c] | 112 |
| **No** | 20[b] | 157[d] | 177 |
| **Total** | 56 | 233 | 289 |

*[a]True Positive = 36, [c]False Positive = 76, [b]False Negative = 20, [d]True Negative = 157*

| Statistic | Formula | Value |
|---|---|---|
| **Sensitivity** | $\frac{a}{a+b}$ | 64.3% |
| **Specificity** | $\frac{d}{c+d}$ | 67.4% |
| **Accuracy** | $\frac{a+d}{a+b+c+d}$ | 66.8% |
| **Disease prevalence** | $\frac{a+b}{a+b+c+d}$ | 19.4% |
| **Positive Predictive Value** | $\frac{a}{a+c}$ | 32.1% |
| **Negative Predictive Value** | $\frac{d}{b+d}$ | 88.7% |

Taking a cut-off value of 48 IU/L, CBD stones were suspected in 94 (32.5%) patients on GGT. Diagnosis of choledocholithiasis was confirmed in 56 (19.4%) patients on MRCP. When cross tabulated the diagnosis of choledocholithiasis on GGT and MRCP, there were 51 true positive, 43 false positive, 5 false negative and 190 true negative cases which yielded a sensitivity of 91.1% and specificity of 81.6% with positive and negative

predictive values of 54.3% and 97.4% respectively. The observed diagnostic accuracy was 83.4% as shown in Table 5. The area under curve was 0.934 (p-value<0.0001). The best cut-off value of GGT was predicted to be ≥293 IU/L which would give a sensitivity of 87.5% and specificity of 92.3%.

**Table 5: 2x2 table to calculate diagnostic performance of GGT in diagnosing choledocholithiasis (n=289)**

| Gamma Glutamyl Transferase | MRCP | | Total |
|---|---|---|---|
| | Choledocholithiasis | No | |
| Choledocholithiasis | 51[a] | 43[c] | 94 |
| No | 5[b] | 190[d] | 195 |
| Total | 56 | 233 | 289 |

[a]True Positive = 51, [c]False Positive = 43, [b]False Negative = 5, [d]True Negative = 190

| Statistic | Formula | Value |
|---|---|---|
| Sensitivity | $\frac{a}{a+b}$ | 91.1% |
| Specificity | $\frac{d}{c+d}$ | 81.6% |
| Accuracy | $\frac{a+d}{a+b+c+d}$ | 83.4% |
| Disease prevalence | $\frac{a+b}{a+b+c+d}$ | 19.4% |
| Positive Predictive Value | $\frac{a}{a+c}$ | 54.3% |
| Negative Predictive Value | $\frac{d}{b+d}$ | 97.4% |

## DISCUSSION

Gallstone disease is one of the most prevalent gastrointestinal diseases and affects approximately 10-15% of the adult population.[1,2] Women are at greater risk for cholelithiasis, especially if they are overweight, over forty years of age, or have children.[2] Stones in the common bile duct are seen in patients with gallbladder stones in up to 20% of cases.[1] However, the coexistence of stones in the CBD in a patient with gallbladder stones is not always obvious from the history or the preoperative investigations of the patient, yet this coexistence of stones in the CBD complicate the management of gallbladder stones and are important determinants of prognosis. In patients undergoing surgery for gallbladder stones on elective lists, the surgeon must choose whether or not to look for CBD stones.[3,4] Also the extent of this look up for CBD stones is variable and depends upon the risk of finding a CBD stone from case to case. In cases where a surgeon suspects stones in the CBD either from pre-operative workup or during surgery, an intraoperative cholangiogram is performed, but this is not sensitive nor specific to clearly help the surgeon and the interpretation of its results is highly difficult and variable.[4,5] Therefore CBD exploration requires pre-operative planning which in turn requires accurate pre-operative diagnosis of choledocholithiasis. Magnetic resonance cholangiopancreatography (MRCP) is the current gold standard investigation but it cannot be performed in each and every suspected case due to time and cost restraints.[6] Recent studies claimed raised serum ALP and GGT levels in patients with gallbladder stones to be predictive of associated stones in the common bile duct.[5,14] However, there was disagreement in the existing published literature. Moreover, no such published material was found in local population that compelled the present study.

The goal of the present study was to evaluate the validity of GGT and ALP in identifying choledocholithiasis in the symptomatic cholelithiasis patients as compared with MRCP.

In the current study, the mean age of the subjects with gallbladder stones was 49.2±13.8 years.

We witnessed that most (n=153, 52.9%) of the subjects were aged between 30-50 years trailed by more than 50 years (28.8%) and less than 30 years (18.3%). Our finding matches with that of Ghazanfor et al.[17] (2017) who stated comparable frequency of under 30 years (21.5%), 30-50 years (52.0%) and more than 50 years (26.5%) age groups in individuals presenting with CBD stones at Holy Family Hospital Rawalpindi.

In the current study, we noticed female predominance in patients with gallstones with male to female ratio of 1:2.8. Ghazanfor et al.[17] described similar female prevalence with male to female ratio of 1:2.8 among such cases at Holy Family Hospital.

The mean serum levels of ALP (203.84±65.22 vs. 94.07±44.62 IU/L; p-value<0.0001) and GGT (347.84±110.69 vs. 87.15±101.78 IU/L; p-value<0.0001) were considerably higher in patients with choledocholithiasis as compared to those without choledocholithiasis. Our results are in line with those of Peng et al.[14] (2005) who also described similar significantly higher mean levels of ALP (189 vs. 95 IU/L; p-value<0.001) and GGT (347 vs. 87 IU/L; p-value<0.001) in British patients with choledocholithiasis as compared to those without choledocholithiasis. Tozatti et al.[5] also reported similar significantly higher mean levels of ALP (202±238.1 vs. 92±67.9 IU/L; p-value=0.002) and GGT (452±561.4 vs. 105±184.3 IU/L; p-value=0.013) in Brazilian patients with versus without choledocholithiasis.

We observed that a cut-off value of 147 IU/L for ALP had a sensitivity of 64.3%, specificity of 67.4% and diagnostic accuracy of 66.8% with positive and negative predictive values of 32.1% and 88.7% respectively in the diagnosis of CBD stones.

Tozatti et al.[5] (2015) on the other hand reported higher sensitivity of 78.0% and much higher specificity of 99.0% in Brazil.

We observed that a cut-off value of 48 IU/L for GGT had sensitivity of 91.1%, specificity of 81.6% and diagnostic accuracy of 83.4% with positive and negative predictive values of 54.3% and 97.4% respectively in the diagnosis of CBD stones. Comparable results have also been reported by Peng et al.[14] (2005) who reported its sensitivity to be 86.0% and specificity to be 74.5%. Our results are also comparable to those of Tozatti et al.[5] (2015) who described similar sensitivity (93.0%) but much lower specificity (63.0%) for raised serum GGT in the differential diagnosis of choledocholithiasis. Again a possible explanation for this conflict among studies can be the variable cut-off values taken by the authors for the diagnosis of choledocholithiasis. It is also evident from the fact that our ROC curve predicted a sensitivity of 87.5% and specificity of 92.3% for GGT if a cut-off value of ≥293 IU/L is taken for analysis.

The strengths of the present study were its large sample size of 289 cases. We also followed strict exclusion criteria and stratified the results for various affect modifiers. A very strong limitation to the present study was that it was a single center experience and didn't consider laboratory errors in the assessment of serum levels of alkaline phosphatase and gamma glutamyl transferase. Moreover, other markers of liver function like bilirubin, AST and ALT were not considered which have also been proposed for non-invasive diagnosis of choledocholithiasis. Such a study would further help in the non-invasive pre-operative diagnosis of choledocholithiasis and is highly recommended in future research.

## CONCLUSION

In the present study, a considerable proportion of patients with cholelithiasis also had choledocholithiasis that was associated with significantly higher mean serum levels of alkaline phosphatase and gamma glutamyl transferase which were found helpful in the diagnosis of CBD stones taking MRCP findings as gold standard and this along with widespread availability, radiation free nature and cheaper cost encourages the favored use of serum alkaline phosphatase and gamma glutamyl transferase in the non-invasive pre-operative diagnosis of choledocholithiasis in future practice.

## LIMITATIONS

Single Center study is the limitations.

## SUGGESTIONS / RECOMMENDATIONS

In the diagnosis of choledocholithiasis, it is suggested that use of serum alkaline phosphatase with GGT along with MRCP is useful and cheaper as non invasive pre-operative diagnosis.

## CONFLICT OF INTEREST / DISCLOSURE

None.

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