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Clinical value of elevated gamma-glutamyltransferase and/or alkaline phosphatase in non-jaundiced symptomatic gallstone disease

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ABSTRACT

Aims: To evaluate the importance of elevated gamma-glutamyltransferase (GGT) and alkaline phosphatase (ALP) as predictor factors for choledocholithiasis in non-jaundiced symptomatic gallstone disease. Methods: This study was carried out in the Department of General Surgery, Zagazig University Hospitals in the period between February 2016 and February 2017. This study was carried out upon 20 patients diagnosed as symptomatic cholecystitis and met the inclusion criteria i.e., elevated GGT and/or ALP levels with normal bilirubin level and normal common bile duct (CBD) by ultrasonography. Results: We found that 20 diagnosed cases of symptomatic gallstone disease in the study and they were predominantly females (80%). In preoperative liver function tests, serum bilirubin was normal and ranged from 0.1–1 mg/dl. All cases had GGT level above 60 IU/L and ranged from 82–609 IU/L with mean standard deviation was (mean±SD: 298.3±184.08 IU/L). ALP level ranged from 57–520 IU/L with mean standard deviation was (mean±SD: 210.9±132.82 IU/L) and 30% of these cases had normal level (≤ 130 IU/L). Magnetic resonance cholangiopancreatography (MRCP) was done for all the cases of the study. 85% of the cases were normal and 15% of the cases were narrow. Statistically, there was highly significant difference decreasing in GGT and ALP levels among postoperative ($p < 0.001$). Conclusion: Gamma-glutamyltransferase (GGT) and alkaline phosphatase are sensitive but not specific to choledocholithiasis because of their multiple sources. The value of their estimation preoperatively is that their elevation increase the suspicious of CBD stone or pathology. Their elevation provokes the surgeon to assess the state of CBD by more accurate diagnostic tool as MRCP. Most of the cases (85%) with elevated GGT and/or ALP but with normal bilirubin and ultrasound findings of CBD had no stones at CBD at time of their evaluation. But the small sector (15%) had pathology indicated intervention by endoscopic retrograde cholangiopancreatography (ERCP) and if neglected before laparoscopic cholecystectomy, there would be morbidity on the patient.

Keywords: Gamma-glutamyltransferase, Alkaline phosphatase, Gallstones

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INTRODUCTION

The majority of patients with gallstones are asymptomatic. Acute cholecystitis occurs when the cystic duct becomes obstructed by a gallstone, leading to unresolving right upper quadrant pain, nausea, vomiting, anorexia, and fever [1]. Patients with gallstones undergo ultrasonography examination and hepatobiliary biochemical serum analysis (bilirubin, alkaline phosphatase, etc.) as routine preoperative screening for common bile duct (CBD) stones [2].

Alkaline phosphatase (ALP) is markedly elevated in persons with biliary obstruction. However, high levels of this enzyme are not specific to cholestasis. So, it should be associated with measuring gamma-glutamyltransferase (GGT) level. The GGT is used most commonly and is elevated in patients with diseases of the liver, biliary tract, and pancreas [3].

In numerous preoperative imaging investigations, endoscopic retrograde cholangiopancreatography (ERCP) showed the highest accuracy in the diagnosis of choledocholithiasis. As this approach is invasive and expensive, it is generally not a preferred option [4]. However, magnetic resonance cholangiopancreatography (MRCP) showed a high accuracy in the diagnosis of choledocholithiasis [5]. Its accuracy is comparable to that of ERCP, and its sensitivity and specificity were shown to reach 95% and 90%, respectively [6].

MATERIALS AND METHODS

This was a prospective study upon 20 patients who were admitted to the hospital as they had symptomatic gallstone disease with elevation in GGT and/or ALP, normal bilirubin, and normal CBD by ultrasonography. This study was conducted in the GIT surgical unit in the department of general surgery, Zagazig University Hospitals from February 2016 to February 2017. Routine preoperative laboratory investigations including GGT and ALP were done for all patients. Also imaging studies carried out for all patients include abdominal ultrasonography and MRCP. All patients admitted with symptomatic gallbladder stones for laparoscopic cholecystectomy will be included in the study and their ages between 20–67 years. Their laboratory investigations showed normal bilirubin, elevated GGT and/or ALP. Also, their imaging studies (abdominal ultrasonography) showed gallbladder stones with no stones or pathology in CBD.

TECHNIQUES

Those patients whose MRCP detected CBD pathology were managed by ERCP then after one week, laparoscopic cholecystectomy was performed and followed-up in surgery outpatient department. But those patients whose MRCP showed normal CBD were managed by laparoscopic cholecystectomy and followed-up in surgery outpatient department.

Endoscopic retrograde cholangiopancreatography (ERCP) technique

Under general anesthesia with endotracheal intubation, the endoscope was passed gently down through the mouth into the oropharynx then through esophagus into the stomach then advanced towards the pylorus. Gentle rotation and pressure was used to pass the endoscope through the pylorus into the proximal duodenum. Here, the patient was turned to prone position. Visualization of the papilla was done and selective cannulation of the common bile duct was performed. After an adequate sphincterotomy or papillary balloon dilatation, we used either ordinary balloon or basket extraction to retrieve the CBD stone and plastic stent was inserted (Figure 1). In case of CBD stricture, plastic stent was inserted.

Laparoscopic cholecystectomy technique

The patient is placed in a supine position. Under general anesthesia with endotracheal intubation, pneumoperitoneum was created by blind puncture with a Veress needle through a subumbilical incision using carbon dioxide. A four-port technique was used. Zero degree viewing laparoscope was used. The gallbladder fundus is grasped and retracted cranially towards the right shoulder. The cystic duct and the cystic artery were identified, clipped with tiny titanium clips and divided. Then the gallbladder was dissected away from the liver bed and removed through one of the ports (Figure 2 and Figure 3).

Figure 1: Common bile duct stone removal with a Dormia basket.

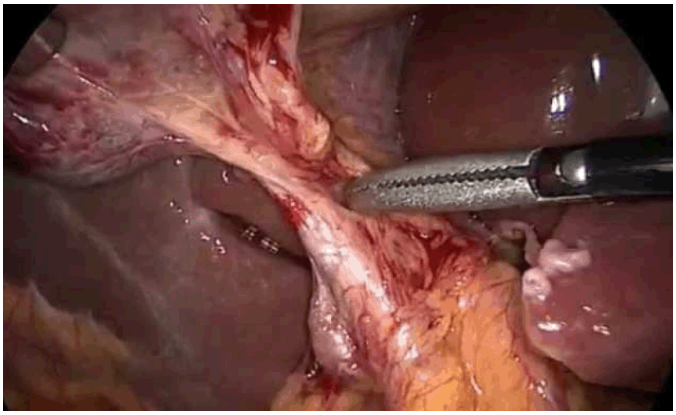

Figure 2: Cystic duct dissection.

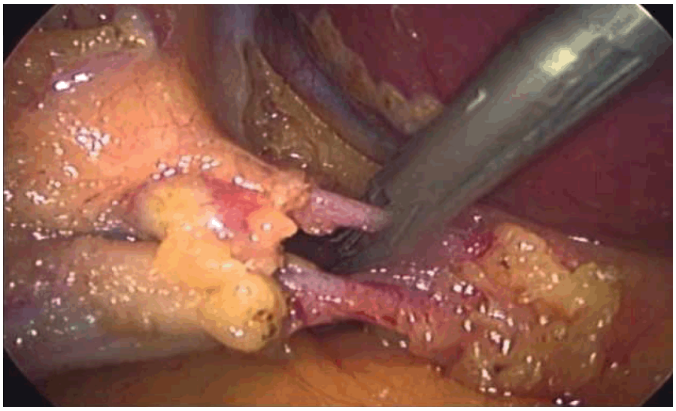

Figure 3: Clipping of cystic duct by titanium clips.

We informed all patients before discharging for follow-up at surgery outpatient department after two weeks, one month and three months.

RESULTS

In this study, the age of the patients ranged from 20–67 years with mean age of 42.6±14.77 years and median 46.5 years. Regarding sex, it shows highly proportion in female sex (80%). Gamma-glutamyltransferase level is elevated in all cases of the study, However, ALP level is elevated in 70% of the cases only (Table 1). About the liver condition of the cases included in the study, There were 20% of the cases had enlarged liver and 50% had bright fatty liver. Also all cases had no intrahepatic biliary radicle dilatation (IHBRD). Fifty percent of the cases had thick wall gallbladder. Also 80% of the cases had multiple stones and 30% had stones smaller than 4 mm in size (Table 2). Eighty-five percent of the cases were normal by MRCP and managed by laparoscopic cholecystectomy.

Only one case (5%) had short smooth narrowing at distal part of CBD detected by MRCP (Figure 4) and was managed by ERCP which required stenting only, and two cases (10%) had small stone in CBD detected by MRCP (Figure 5) and was managed by ERCP for stone extraction and stenting. Then laparoscopic cholecystectomy was done for those three cases after one weak (Table 3). Forty-seven of the cases managed by cholecystectomy had straight forward operation. While in 12% of the cases, there were acute inflammation and edema in gallbladder during operation and 41% had wide cystic duct which required clipping by large sized clips.

The operation time ranged from 30–90 min with mean 43 min.

There were decreasing in GGT and ALP levels in postoperative comparing to preoperative. Also, all cases showed normal levels of (GGT level ≤ 60 IU/L and ALP level ≤ 130 IU/L) (Table 4). Statistically, there was highly significant difference decreasing in GGT and ALP levels among post-operative ($p < 0.001$). While there was no statistical significance difference between cases preoperative and postoperative in the level of bilirubin. All cases needed two weeks for ALP to return to normal. While in GGT, 90% of the cases needed two weeks and 10% needed one month to return to normal level of GGT (Table 5).

Table 1: Laboratory findings preoperative among the studied group

Variable		Number of patients
Total Bilirubin (mg/dL)	X±SD	0.41±0.21
	Median	0.40
	Range	(0.1–1)
GGT (IU/L)	X±SD	298.3±184.08
	Median	252
	Range	(82–609)
	≤ 60 N (%)	0 (0%)
	> 60 N (%)	20 (100%)
ALP (IU/L)	X±SD	210.9±132.82
	Median	168
	Range	(57–520)
	≤ 130 N (%)	6 (30%)
	> 130 N (%)	14 (70%)

GGT: Gamma-glutamyltransferase (N: 8–60)
ALP: Alkaline phosphatase (N:40–130)
X±SD: Mean±Standard deviation
IU/L: International unit per litre

Table 2: Gallbladder condition among the studied group by ultrasonography

Variable		Number of patients
Wall	Normal	10 (50%)
	Thick	10 (50%)
Number of stones	Single	4 (20%)
	Multiple	16 (80%)
Size of stones	< 4 mm	6 (30%)
	> 4 mm	14 (70%)

Table 3: Magnetic resonance cholangiopancreatography results and decisions among the studied group

Variable		Number of patients
MRCP	Normal	17 (85%)
	Short smooth narrowing at distal part of CBD	1 (5%)
	Small stone in CBD	2 (10%)
Decision	Laparoscopic cholecystectomy	17 (85%)
	ERCP and stenting then laparoscopic cholecystectomy	1 (5%)
	ERCP, stone extraction and stenting then laparoscopic cholecystectomy	2 (10%)

MRCP: Magnetic resonance cholangiopancreatography, CBD: Common bile duct, ERCP: Endoscopic retrograde cholangiopancreatography

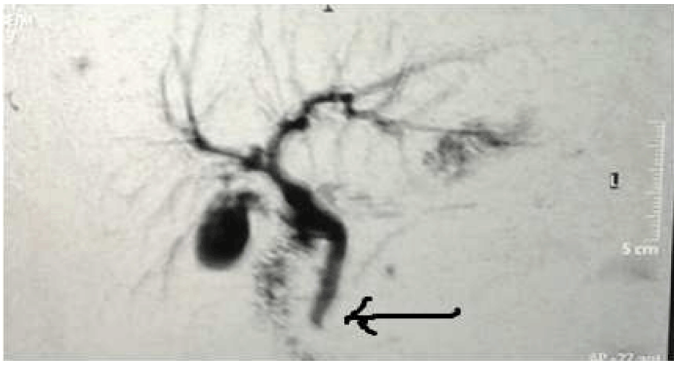

Figure 4: Magnetic resonance cholangiopancreatography showing smooth narrowing at distal part of common bile duct.

Figure 5: Magnetic resonance cholangiopancreatography showing small stone at common bile duct.

Table 4: Comparison between laboratory findings preoperative and postoperative among the studied group

Variable		Preoperative (n = 20)	Postoperative (n = 20)	Paired Wilicoxon	p-value
GGT (IU/L)	X±SD	298.3±184.08	36.35±14.62		< 0.001 (HS)
	Median	252	37.5	3.92	
	Range	(82–609)	(11–60)		
ALP (IU/L)	X±SD	210.9±132.82	94.3±19.59		< 0.001 (HS)
	Median	168	90	3.47	
	Range	(57–520)	(70–130)		
Bilirubin (mg/dL)	X±SD	0.41±0.21	0.35±0.11	0.97	0.33 (NS)
	Median	0.40	0.35		
	Range	0.1–1	0.1–0.8		

GGT: Gamma-glutamyltransferase (N:8–60)
ALP: Alkaline phosphatase (N:40–130)
IU/L: International unit/litre
HS: Highly significance ($p < 0.001$)
X±SD: Mean±Standard deviation

Table 5: Time needed for GGT and ALP to return to normal level among the studied group

Variable	Time	Number of patients
Alkaline phosphatase (IU/L)	2 Weeks	20 (100%)
Gamma-glutamyltransferase (IU/L)	2 Weeks	18 (90%)
	1 Month	2 (10%)

All cases, either managed by cholecystectomy or ERCP followed by cholecystectomy, had no abnormality detected by clinical examination at the follow up i.e., no pain, no fever and even no jaundice.

DISCUSSION

Common bile duct stones assessment by biochemical testing of liver enzymes is a common clinical practice with a high sensitivity [7]. When a stone becomes impacted in the CBD, obstructive jaundice results. Bile stasis triggers release of liver enzymes e.g., serum ALP and GGT [8]. Thus, this study was to evaluate the clinical value of elevated GGT and ALP as predictor factors for choledocholithiasis in non-jaundiced symptomatic gallstone disease. In our study, the age of adult population ranged from 20–67 years; median age was 46.5 years with a mean age of 42.6±14.77 years. Regarding the patient sex; there was higher frequency of gallstone in females (80%). That was in agreement with the study done by Reshetnyak et al. that revealed gallstone is more common in women than in men [9].

In our study, preoperative liver function tests results for all patients showed normal serum bilirubin which ranged from 0.1–1 mg/dl. And also, 100% of the cases had GGT serum level above 60 IU/L and ranged from 82–609 IU/L. Peng et al. found that the serum level of GGT was more than 90 IU/l is considered being high risk to have stone in common bile duct [10].

In a study, Fikry et al. found that serum levels of GGT were elevated in patients with acute and chronic calcular cholecystitis with the highest level was 130 IU/L without elevation in serum level of bilirubin [11]. If the serum ALP is persistently elevated for a long period of time, it suggests prolonged cholestasis [12]. In our study, the serum ALP level was elevated in patients ranged from 57–520 IU/L and 30% of the cases had normal level (≤ 130 IU/L).

Fikry et al. found that serum ALP was elevated in patients with acute calcular cholecystitis with the highest level up to 250 IU/L [11]. And also, this correlated with a study done by Thapa et al. stated that, the serum level of ALP was raised in patients with acute cholecystitis by 1.69+0.118 fold [13].

In the present study, 20% of the patients had enlarged liver and 50% had bright fatty liver discovered by preoperative ultrasonography. All patients had no IHBRD. These findings were in agreement with that study of Gupta et al. [7]. Also, 50% of the cases had thick wall gallbladder. And 80% of the cases had multiple stones and 30% had stones smaller than 4 mm in size. That also was in agreement with the study of Gupta et al. [7].

An MRCP is a reliable and non-invasive procedure for detecting or excluding the presence of CBD stones [14]. It also has the potential to reduce the number of invasive preoperative diagnostic procedures [15].

All our cases with the inclusion criteria underwent MRCP preoperatively and 85% of the results of MRCP were negative for CBD stones or tumor i.e., there were no obstruction in CBD. One case (5%) had smooth narrowing at distal part of CBD and also two cases (10%) had small stone in CBD. Based upon our MRCP results, the patients with normal CBD (85%) were managed by laparoscopic cholecystectomy without any need for ERCP preoperatively and the other three cases (15%) underwent ERCP. Between the three cases managed by ERCP, two cases had stone extraction and stenting and one case showed narrowing at distal CBD which required stenting only. After one weak from ERCP, laparoscopic cholecystectomy was done for those three cases.

This was in agreement with the study of Dalton et al. which showed that 80% of their results of MRCP were normal CBD and 20% had small stones in CBD and so the same decisions of our study were taken in the cases of their study [14].

In our study 41% of cases had wide cystic duct which required clipping by large sized clips. These findings were nearly in agreement with the study of Dalton et al. which revealed that 53% of his cases had wide cystic duct [14].

In our study, the average time needed for cholecystectomy operation ranged from 30–90 min with mean 43 min, while the mean time needed in the study of Dalton et al. was 39 min [14]. In the study, we found highly significant difference decreasing in GGT and ALP levels among postoperative ($p < 0.001$) which was consistent with past studies of Habib et al. and Zare et al. [16, 17].

All cases of the study needed two weeks for ALP to return to normal. While 90% of the cases needed two weeks and 10% needed one month to return to normal level of GGT and these findings were in agreement with the study of Zare et al. [17]. There was no statistical significance difference in bilirubin level among patients before and after surgery ($p > 0.33$). These findings were in accordance with the study done by Wong et al. [18].

CONCLUSION

Gamma-glutamyltransferase and alkaline phosphatase are sensitive but not specific to choledocholithiasis because of their multiple sources. The value of their estimation preoperatively is that their elevation increase the suspicious of common bile duct (CBD) stone or pathology. Their elevation provokes the surgeon to assess the state of CBD by more accurate diagnostic tool as magnetic resonance cholangiopancreatography (MRCP). Most of cases (85%) with elevated GGT and/or ALP but with normal bilirubin and ultrasound findings of CBD had no stones at CBD at time of evaluation. But the small sector (15%) had pathology indicated intervention by ERCP and if neglected before laparoscopic cholecystectomy, there would be morbidity on the patient. All patients with non-jaundiced symptomatic gallstone disease and

normal CBD by ultrasonography with elevation in GGT and/or ALP must be managed by either doing MRCP as a mandatory investigation preoperatively or undergoing intra-operative cholangiogram during laparoscopic cholecystectomy to avoid missing CBD stone or pathology necessitate post-operative intervention by endoscopic retrograde cholangiopancreatography (ERCP) or open surgery.

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Author Contributions

Muhammad Ali Baghdadi – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Ali Helmi El-Shewy – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Zaki Muhammad Allam – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Amr Ahmed Ibrahim – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Gamal Muhammad Osman – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Abd-Elrahman Mostafa Metwalli – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Waleed Ahmed Abd-Elhady – Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Tamer Mahmoud El-shahidy – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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