

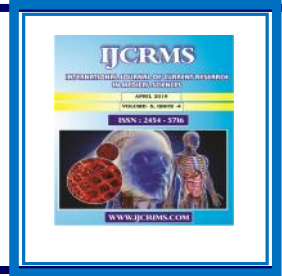


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## Biochemical Investigations vs Ultrasonography in Diagnosis of Bile Stones

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### Abstract

Gallbladder stones are an extremely common disorder and are usually asymptomatic. Some patients experience biliary colic, an intermittent and often severe pain in the epigastrium or right upper quadrant, and at times between the scapula because of temporary obstruction of the cystic duct with a gallstone. Ultrasonography, complete blood picture test and liver function tests are procedures of choice in suspected gallstones or biliary diseases. They are the most sensitive, specific, non-invasive and inexpensive tests for the detection of gallstones. Our main objective was to evaluate the relationship of ultrasonographic findings, hemolytic indices and liver function tests with gallstones. If the cystic duct obstruction persists, the gallbladder becomes inflamed and the patient develops cholecystitis, an acute inflammation and infection of the gallbladder. Gallbladder stones are an extremely common disorder and are usually asymptomatic. Some patients experience biliary colic, an intermittent and often severe pain in the epigastrium or right upper quadrant, and at times between the scapula because of temporary obstruction of the cystic duct with a gallstone. If the cystic duct obstruction persists, the gallbladder becomes inflamed and the patient develops cholecystitis, an acute inflammation and infection of the gallbladder. A **gallstone** is a stone formed within the gallbladder out of bile components.<sup>[4]</sup> The term **cholelithiasis** may refer to the presence of gallstones or to the diseases caused by gallstones.<sup>[5]</sup> Most people with gallstones (about 80%) never have symptoms.<sup>[13]</sup> When a gallstone blocks the bile duct, a cramp-like pain in the right upper part of the abdomen, known as biliary colic (gallbladder attack) can result.<sup>[4]</sup> This happens in 1–4% of those with gallstones each year.<sup>[14]</sup> Complications of gallstones may include inflammation of the gallbladder (cholecystitis), inflammation of the pancreas (pancreatitis), jaundice, and infection of a bile duct (cholangitis).<sup>[4][6]</sup> Symptoms of these complications may include pain of more than five hours duration, fever, yellowish skin, vomiting, dark urine, and pale stools.<sup>[2]</sup> The seriousness of disease can be estimated from combined information of clinical examination & specialized biochemical tests. Specialized enzymatic markers are helpful for proper follow-up as delay can be devastating. It can form a platform for malignant & cirrhotic changes of liver: Present study has been undertaken to avoid dreads by simple clinical enzyme study. Serum levels of 5'NT/ALP/AST/ALT/Bilirubin were estimated in sixty cases of clinically diagnosed cholecystitis against forty normal individuals. Purpose was to single out a parameter which is most significant & may help as an endoscope to Surgeon for timely intervention. The study differentiates 5'NT to be superior to ALP due to its specificity and Sensitivity. While elevated AST & ALT levels signify extent of hepatic cell damage, 5'NT specifically signifies the bile duct obstruction or cholestasis as well as hepatic cell damage.

**Keywords:** Cholelithiasis, cirrhotic changes, 5'NT/ALP/AST/ALT/Bilirubin, ultrasonographic findings.

## Introduction

Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts. Besides a high concentration of cholesterol, two other factors are important in causing gallstones. The first is how often and how well the gallbladder contracts; incomplete and infrequent emptying of the gallbladder may cause the bile to become overconcentrated and contribute to gallstone formation. The composition of gallstones is affected by age, diet and Sex.<sup>3</sup> In conclusion<sup>21</sup> On the basis of their composition, gallstones can be divided into the following types: cholesterol stones, pigment stones, and mixed stones.<sup>[3]</sup> An ideal classification system is yet to be defined.<sup>[3]</sup> The vast majority of patients with gallstones are asymptomatic. Symptomatic gallstones typically manifest with right upper quadrant abdominal pain, often accompanied by nausea and vomiting. The pain is often severe, may abate over several hours (biliary colic), or may progress to cholecystitis, with persistent pain and fever. On examination, there is pain to palpation in the right upper quadrant (Murphy's sign)<sup>14</sup>. The vast majority of patients with gallstones are asymptomatic. Symptomatic gallstones typically manifest with right upper quadrant abdominal pain, often accompanied by nausea and vomiting. The pain is often severe, may abate over several hours (biliary colic), or may progress to cholecystitis, with persistent pain and fever. On examination, there is pain to palpation in the right upper quadrant (Murphy's sign). **Cholesterol stones** vary from light yellow to dark green or brown or chalk white and are oval, usually solitary, between 2 and 3 cm long, each often having a tiny, dark, central spot. To be classified as such, they must be at least 80% cholesterol by weight (or 70%, according to the Japanese-classification system).<sup>[3]</sup> Between 35% and 90% of stones are cholesterol stones.<sup>[3]</sup> **Mixed (brown pigment stones)** typically contain 20–80% cholesterol (or 30–70%, according to the Japanese-classification system).<sup>[33]</sup> Other common constituents are calcium carbonate, palmitate phosphate, bilirubin and other bile pigments (calcium bilirubinate, calcium palmitate and calcium stearate). Because of their

calcium content, they are often radiographically visible. They typically arise secondary to infection of the biliary tract which results in the release of  $\beta$ -glucuronidase (by injured hepatocytes and bacteria) which hydrolyzes bilirubin glucuronides and increases the amount of unconjugated bilirubin in bile. Between 4% and 20% of stones are mixed.<sup>[3]</sup> Gallstones can vary in size and shape from as small as a grain of sand to as large as a golf ball.<sup>[3, 4]</sup> The gallbladder may contain a single large stone or many smaller ones. Pseudoliths, sometimes referred to as sludge, are thick secretions that may be present within the gallbladder, either alone or in conjunction with fully formed gallstones<sup>14</sup>.

**Bilirubin ("pigment", "black pigment") stones** are small, dark (often appearing black), and usually numerous. They are composed primarily of bilirubin (insoluble bilirubin pigment polymer) and calcium (calcium phosphate) salts that are found in bile. They contain less than 20% of cholesterol (or 30%, according to the Japanese-classification system).<sup>[3]</sup> Between 2% and 30% of stones are bilirubin stones.<sup>[7]</sup> Diagnosis and therapy of gallstones aim to provide current recommendations on the following issues: Prevention of gallstones, Diagnosis of gallbladder stones, Medical therapy of gallbladder stones, Surgical therapy of gallbladder stones, Diagnosis of bile duct stones, Endoscopic and surgical therapy of bile duct stones, Diagnosis and therapy of intrahepatic stones, Therapy of gallstones during pregnancy<sup>11</sup>. Most gallstones are composed primarily of cholesterol, with smaller amounts of mucus, calcium bilirubinate, and protein. Pigment stones, a result of hemolysis, are less common and are made primarily of calcium bilirubinate. Symptoms occur with gallstones when the gallbladder contracts, often after a meal, resulting in occlusion of the cystic duct with a stone that produces symptoms, typically pain. The vast majority of patients with gallstones are asymptomatic. Symptomatic gallstones typically manifest with right upper quadrant abdominal pain, often accompanied by nausea and vomiting<sup>10</sup>. The pain is often severe, may abate over several hours (biliary colic), or may progress

to cholecystitis, with persistent pain and fever. On examination, there is pain to palpation in the right upper quadrant (Murphy's sign). The vast majority of patients with gallstones are asymptomatic. Symptomatic gallstones typically manifest with right upper quadrant abdominal pain, often

accompanied by nausea and vomiting. The pain is often severe, may abate over several hours (biliary colic), or may progress to cholecystitis, with persistent pain and fever. On examination, there is pain to palpation in the right upper quadrant (Murphy's sign).

**Table-1 Age wise breakup of patients**

Age	No. of study group	Percentage	Control group no.	Percentage
38-50	33	33	11	25
50-60	23	23	23	24
60-65	44	44	44	44
>65	10	17	17	25

**Table-2 Analysis of various groups**

Category wise	Total	Males	Percentage	Females	Percentage
Cholecystitis	100	45	45	55	55
Control	40	20	50	20	50



**Biliary sludge found with gallstones. There is borderline thickening of the gallbladder wall**



**A normal gallbladder on ultrasound with bowel peristalsis creating the false appearance of stones**

**Table-3 Analysis of various biochemical parameters in control group**

Group	Range	Mean+SD
5'NTIU/L	2-8	5.0+1.68
ALP KA U/L	3-10	6.42+2.19
AST IU/L	4-12	7.55+2.37
ALT/L	5-12	9.15+2.42
Bilirubin	0.4-0.8	0.57+0.66

## Observation

The study was carried out on diagnosed, pre-operative and symptomatic patients of cholelithiasis. Diagnosis was based upon history, physical examination and ultrasound examination. Abdominal ultrasound was performed by expert sonologists who had experience of more than 5 years. All Ultrasounds were performed and all diagnoses were made. Informed written consent was taken from every patient. Exclusion criteria were patients of gallbladder and pancreatic carcinoma, emergency operations, patients having age <12 years and non-cooperative patients, who refused to give written consent for participation in the study. No age proportion was considered and patients were selected randomly, without considering gender. Tests on complete blood count and liver function tests were carried out. Complete blood count was done including WBC, RBC, RBC morphology, Hematocrit, Neutrophil count, lymphocyte count, basophil count, and blood urea nitrogen and serum creatinine. **LIVER FUNCTION TESTS** include total **BILIRUBIN, SGPT AND ALKALINE PHOSPHATASE, GGT, 5'NT**. Normal range for blood urea nitrogen is 7–20 mg/dL. Normal range for alkaline phosphatase is 30 to 136 IU/L, for total bilirubin is 0.1–1.0 mg/dL and for SGPT is 7 to 56 IU/L. Any value above or below normal was considered as abnormal finding. Sample size was calculated by using Open-epi sample size calculator, prevalence (p) = 35% d = 5% and

confidence interval (C.I) 95% = 350. Study was approved by Ethical Review committee of Medical College. All the data was entered and analyzed through SPSS 19. Mean and standard deviation were used for continuous data and percentage and frequency were calculated for categorical data. All the percentages and frequencies were calculated by considering n=100

## Results:

100 patients were identified with acute cholecystitis. (Females n=57, 57.0%). Mean (range) age was 59.3yrs (18-94). 17 (12.1%) had choledocholithiasis. Mean bilirubin 2.7mg/dL (range 0.1-8.8; reference range 2.1-2.9), GGT 204.6U/L (range 7-1448; reference range 5-39), AST 89.3U/ L (range 9-684; reference range 13-35) and ALP 148.7 (range 35-658; reference range 42- 98) 5'Nucleotidase (2-5 IU/L). Bilirubin was elevated in 20 patients (14.3%), GGT in 100 (71.4%), AST in 57 (40.7%) and ALP in 69 (49.3%) 5'NT (34.8%). Table 1 shows the comparison of LFTs for the 2 groups. Table 2 shows the comparison proportions of elevated results in the 2 groups. Sensitivity and specificity for the diagnosis of choledocholithiasis for bilirubin were 47.0% and 90.2%, for GGT 100% & 32.5%, for AST 70.6% & 63.4% and for ALP 76.5% and 5'NT 54.5% respectively. Factor analysis showed that elevation of all 5 liver enzymes is predictive of choledocholithiasis.

**Table-4 Statistical Analysis of Serum 5'NT, ALP, AST, ALT, Bilirubin in control and study Group**

Group	Number of patients	5'NT (iu/l) Mean+SD	ALP (kau/l) Mean+SD	AST (iu/l) Mean+SD	ALT iu/l Mean+SD	Serum bilirubin mg% Mean+SD	Significance
Control	(40)	5.0+1.69	12.219+2.19	7.55+2.37	9.15+2.42	0.57+0.66	'P'
Cholecystitis with cholelithiasis	27	17.03+11.59	18.0+8.5	18.03+8.85	37.12+7.37	24-26	P< 0.01
Acute cholecystitis	22	7.32+1.2	11.19+2.3	13.54+13	20+3.43	0.01MG%	P< 0.01
Chronic cholecystitis	10	9.34+4.65	12.23+4.54	18.48+4.56	14.7+5.8	0.01MG%	P< 0.01
Study Group	100	12+2.3	14+2.2	10.76+4.87	19.87+5.9	2.98_0.50	P< 0.01



**A 1.9 cm gallstone impacted in the neck of the gallbladder and leading to cholecystitis as seen on ultrasound. There is 4 mm gall bladder wall thickening**

## Discussion

Gallstones are seen in all age groups but the incidence increases with every age, most prevalent in 4th and 5th decade of life<sup>[5, 8]</sup>. Incidence was found to be much more in, fat, fertile, females of forty years age group. Our findings were also consistent with past studies<sup>17</sup>. Reason for this increment is well understood now and it is due to elevated estrogen levels, which increase cholesterol excretion in bile by causing its super saturation with cholesterol<sup>[4]</sup>. In the present study stones can be either single or multiple. Gallstones are of three varieties; most commonly they are composed of cholesterol followed by pigment and mixed stones [4]. Majority of newly formed gallstones remains asymptomatic following rapid weight loss, the risk of both uncomplicated and complicated gallstone disease and cholecystectomy is still increased and is 3-fold greater in very-low-calorie than in low-calorie diets [139]. Appropriate fat content (at least 7 g/day) in very-low-calorie diets might improve gallbladder motility and decrease the risk of symptomatic gallstones, as shown in recent controlled studies [3, 9]. Patients undergoing rapid weight loss are more likely to become symptomatic for gallstones, with incidence reaching 28% to 71% after gastric bypass. It was indicated clearly in ultrasonographic findings that non alcoholic fatty liver had a significant association with gallstones; our findings were consistent with findings of the past studies [9]. This confirms the fact that due to fatty liver there is accumulation of lipids, specifically triglycerides in the hepatocytes, which triggers inflammatory responses that prompt the leakage of liver enzymes into the blood stream. Due to the fatty liver, gall bladder doesn't empty normally, thus causing bile

accumulation which precipitate gallstones. Interestingly, it was found in our study that 3.5% patients of gallstones were also associated with Splenomegaly which has not been previously reported. Long list of investigations, makes the diagnostic pathway complex and expensive but good clinical history has been worked out as the best predictor of gallstones<sup>8</sup>. Abnormal liver function tests were most common in patients with gallstones. Raised 5'Nucleotidase has emerged as the most reliable predictor of gallstones after ultrasonography which was consistent with the findings indicated in the past<sup>[2, 5]</sup>. In our study, subjects were predominantly females and increase in the level of alkaline phosphatase might be due to increased bone turn over or simultaneous formation of osteoid in these females<sup>[2, 6]</sup>. Bilirubin also represented one of the indicators of gallstones but not as reliable as Alkaline phosphatase. It seems to be raised in 13.6% patients which was consistent with past studies<sup>[2, 3]</sup>. Actually serum bilirubin is important in predicting postoperative/preoperative procedural outcomes. The degree of hyperbilirubinemia reflects the degree of liver dysfunction affecting both nutrition and reticuloendothelial cells<sup>[1]</sup>. Occurrence of gallstones was positively correlated with rise in SGPT levels. Our findings correlate with findings of past studies but frequency was found to be much higher as compared to the past<sup>[3]</sup>. It may be due to the fact that the study was published in 1994 and this reflects the change in trends of biochemical parameters. Our findings highlight the fact that due to gallstone disease liver is inflamed and damaged which simultaneously causes rise in hepatic enzymes in blood. Principal finding of our study was the massive increment in blood urea nitrogen and it was increased in approximately 42% patients which were very high.<sup>[5]</sup>



Literature concerning the relationship between gallstones and blood urea nitrogen is scarce and it was the first research which indicates the positive and significant relationship. Further researches will be necessary to figure out a better understanding of this relationship. Fall in hemoglobin level in more than half of the subjects. It may possibly be due to the fact that bilirubin is the main constituent in the formation of gallstones. It is mainly formed by the breakdown of hemoglobin, which leads to low levels of hemoglobin in patients of gallstones.

## Conclusion

Gallstones represent a significant burden for health care systems. **Ultrasonography, complete blood picture test and liver function tests** are procedures of choice in suspected gallstones or biliary diseases. They are the most sensitive, specific, non-invasive and inexpensive tests for the detection of gallstones. Our main objective was to evaluate the relationship of ultrasonographic findings, hemolytic indices and liver function tests with gallstones. The risk of gallstones may be decreased by maintaining a healthy weight with exercise and a healthy diet.<sup>[2]</sup> If there are no symptoms, treatment is usually not needed.<sup>[2]</sup> Physical activity appears to protect against gallstone formation<sup>[6,8]</sup> and to cut the risk of symptomatic stones by about 30%. In those who are having gallbladder attacks, surgery to remove the gallbladder is typically recommended.<sup>[2]</sup> This can be carried out either through several small incisions or through a single larger incision, usually under general anesthesia.<sup>[2]</sup> In rare cases when surgery is not possible, medication can be used to dissolve the stones or lithotripsy to break them down.<sup>[7]</sup> Regular vitamin C supplementation or regular use of vitamin C-enriched diet might have a protective effect on gallstone formation. In fact, cholesterol conversion to bile acids requires 7 - hydroxylation and an appropriate content of vitamin C in the hepatocyte<sup>[8]</sup>. In humans, vitamin C deficiency might therefore increase the risk of cholesterol gallstone formation. Conflicting results are available on the protective effect of statins alone or with UDCA on gallstone disease. The use of statins was evaluated in two

population-based case-control studies. A decreased risk of gallstone disease and cholecystectomy emerged with regular use of statins<sup>[3]</sup>. The beneficial effect of fish oil (n-3) polyunsaturated fatty acids on biliary crystallization was confirmed in a randomized double-blind placebo-controlled trial in obese women during rapid weight loss with a hypocaloric diet (1200 kcal/day), and compared with UDCA (1200 mg/day). To sum up, achievement in study of pathogenesis and physiology of gallstone diseases has allowed expanding indication for therapeutic treatment of gall bladder diseases and reducing the number of patients who undergo surgical treatment. From a public health point of view, it is not only important to study the background of gallstone formation but also explore demographic and biochemical markers related to the development of gallstones. If we are able to predict the contributing factors, then we can also prevent it by controlling those factors.

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