

# Frequency of Cholestatic Liver Diseases in Zagazig University Hospitals, with Special Emphasize on Extrahepatic Causes

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## Background and study aim:

Extrahepatic cholestasis results from the mechanical obstruction of large bile ducts outside the liver or within the porta hepatis. The common etiologies of cholestasis have been reported to vary from one center to another. Our aim was to assess the frequency of cholestatic disorders in patients admitted to our department and try to identify the underlying extrahepatic causes aiming at improving the quality of management offered to this patients group.

**Patients and Methods:** In the present study, 506 cases admitted to our department were included. Sixty one of them met our inclusion criteria, of high serum alkaline phosphatase ( $ALP \geq 1.5$  times the upper limit of normal), high gamma glutamyl transferase ( $GGT \geq 3$  times the upper limit of normal) and ultrasonographic (US) features of extrahepatic cholestasis (dilated intra and/or extra-hepatic ducts) of whatever etiology. The selected patients underwent the following: Full history taking and thorough physical examination, complete blood picture, liver and kidney function tests and abdominal CT. Also, ERCP was performed whenever needed and the tumor markers, alpha feto-protein & (CA 19-9) were assessed in selected cases "when mass lesions were detected".

**Results:** The frequency of cholestatic liver diseases presented with elevated both ALP & GGT as described above, was %19.7 (100 of 506 patients). While the frequency of extrahepatic cholestasis was 12.1% with females accounting for 54.1% and males were 45.9% with mean ages  $\pm$  SD of  $51.1 \pm 11.7$  years. Benign causes of

surgical obstructive jaundice were more frequent than malignant ones (57.4% VS 42.6%). The most common cause was choledocholithiasis in 25/61 (40.9%), followed by cancer head of pancreas 9/61 (14.8%), peri-ampullary carcinoma 8/61 (13.11%), cholangiocarcinoma 5/61 (8.2%) and pancreatitis 4/61 (6.6%). Dark urine, clay stool and itching were more common in patients with malignant obstructive jaundice. There was a highly positive agreement between ALP and GGT with  $P < 0.01$ . The sensitivity of U/S, CT and ERCP in detection of CBD stones were 76%, 88% and 100% respectively. While in detection of cancer head of pancreas, it was 66.7%, 100% and 100% respectively. The predictive values of US compared to ERCP in detection of CBD stones was 100% positive and 85.7% negative, while the predictive value of US compared to ERCP in detection of cancer head of pancreas was 100% positive and 94.5% negative. The predictive values of CT compared to ERCP in detection of CBD stones was 100% positive and 92.3% negative, while the predictive value of CT compared to ERCP in detection of cancer head of pancreas was 100% positive.

**Conclusion:** We concluded that, the frequency of cholestatic liver diseases in our department was %19.7. Among them, extrahepatic causes had a frequency of 12.1% with choledocholithiasis as the commonest benign etiology, while cancer head of pancreas was the most frequently met with malignancy. ERCP is considered the gold standard modality in diagnosis and management of extrahepatic cholestasis.

## INTRODUCTION

Cholestasis is an impairment of bile formation and/or bile flow which may clinically present with fatigue, pruritus and, in its most overt form, jaundice [1]. Cholestatic jaundice is often accompanied by a broad spectrum of laboratory, clinical and histological abnormalities. Early

biochemical markers in asymptomatic patients include elevated serum alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) followed by conjugated hyperbilirubinemia at more advanced stages [2].

Cholestatic liver diseases are characterized by accumulation of hepatotoxic substances, mitochondrial dysfunction and impairment of liver antioxidant defenses. The storage of hydrophobic bile acids has been incriminated as the main cause of hepatotoxicity with alteration of some important cell functions, such as the mitochondrial energy production leading to development of oxidative damage [3].

Moreover, the absence of bile salts from the intestine can produce malabsorption, leading to steatorrhea and deficiencies of fat-soluble vitamins (particularly A, D and K). Vitamin K deficiency leads to prolonged prothrombin time. In long-standing cholestasis, concomitant vitamin D and Ca malabsorption can cause osteoporosis or osteomalacia [4].

Also in obstructive jaundice, increased intestinal permeability has been postulated to be a key factor contributing to bacterial and endotoxins translocation to mesenteric lymph nodes, portal circulation and the liver. A suppressed clearance capacity of Kupffer cells, the main hepatic macrophage population, attributed to accumulation of bile acids into the liver, permits the “spillover” of endotoxins from portal into systemic circulation, with consecutive release of pro-inflammatory cytokines, potentially leading to the development of the so called “gut derived sepsis” [3,22].

Nevertheless, the first critical step in approach to patients with cholestatic liver diseases, is to differentiate intra- and extra-hepatic cholestasis, bearing in mind that several intra-hepatic causes of cholestatic jaundice can mimic extra-hepatic obstruction to varying degree [1].

Jaundice due to biliary obstruction may be caused by a heterogeneous group of diseases that include both benign and malignant conditions. Benign causes include choledocholithiasis, primary sclerosing cholangitis, Mirrizi syndrome, post-operative biliary stricture, post inflammatory stricture, pancreatitis, choledochal cyst, recurrent pyogenic cholangitis, parasitic diseases, duodenal diverticulosis and AIDS cholangiopathy [5].

While malignant causes include cancer head of pancreas, carcinoma of the gall bladder, cholangiocarcinoma, carcinoma of the duodenum, ampullary tumors, hepatocellular carcinoma, lymphoma and metastatic tumors [6].

Extrahepatic cholestasis may be additionally subdivided into intraductal and extraductal.

Intraductal obstruction is caused by neoplasms, stone disease, biliary stricture, parasites, primary sclerosing cholangitis (PSC), AIDS-related cholangiopathy, and biliary tuberculosis. While extraductal obstruction is caused by external compression of the biliary ducts as that secondary to neoplasms, pancreatitis, or cystic duct stones with subsequent gallbladder distension [7].

In hepatic parenchymal diseases (e.g. cirrhosis), fibrosis may prevent the intrahepatic bile ducts dilatation, resulting in dilation confined to the extrahepatic bile ducts. The question then is whether the derangement of liver functions is related to the hepatic or extrahepatic etiology [8]. The common cause of obstructive jaundice have been reported to vary from one center to another.

Our aim was to assess the frequency of cholestatic disorders in patients admitted to our department and try to identify the underlying extrahepatic causes aiming at improving the quality of management offered to this patients group.

## PATIENTS AND METHODS

The present cross sectional study was conducted in Tropical Medicine Department, Zagazig university hospitals during the period from May 2012 to March 2013.

The study was conducted on 506 cases admitted serially to our department and accepted to participate in the present work. They were all subjected to:

- 1- Serum Bilirubin (total & direct), ALT, AST and ALP levels were assayed by (colorimetric assay RXL, Semiens, Germany).
- 2- Serum gamma glutamyl transferase level: (by colorimetric assay, Cobas, Roche, Germany). The inclusion criteria were high serum alkaline phosphatase level ( $\geq 1.5$  times the upper limit of normal), high gamma glutamyl transferase ( $\geq 3$  times the upper limit of normal) according to EASL [9].
- 3- Pelvi abdominal ultrasound by Ezzaoti-Mylab 20. ultrasonographic features of extrahepatic cholestasis included (dilated extra and/or intrahepatic ducts) of whatever cause.

All selected patients underwent the following:

- Full history taking and through physical examination.

- Assessment of body mass index (BMI) was conducted using the following formula:

$$\text{BMI} = \frac{\text{mass(kg)}}{(\text{height(m)})^2}$$

Body mass index (BMI) is defined as the individual's body mass divided by the square of their height with the value universally being given in units of kg/m<sup>2</sup>.

- Complete blood count, using sympx K x 21 cell counter (Roche diagnostics Mannheim, Germany).
- Tumor markers: cancer antigen (CA 19-9), normal levels <37 U/ml. [10] & Alpha fetoprotein (AFP): normal range 10-20 ng/ml, while a level 400 ng/ml is considered diagnostic for HCC in the presence of suggestive ultrasonography [11].
- Abdominal CT: Triphasic CT scanning of the liver was performed with CTi/Pro GE medical system and Toshiba X-Vision single slicer CT scanner.
- ECRP whenever needed for diagnosis and/or management of extrahepatic cholestasis.

#### Statistically analysis:

Data were checked, entered and analyzed using Epi-Info (2000) for data processing and statistics.

#### Descriptive statistics:

Data were expressed as numbers and percentages for qualitative variables and mean ± standard deviation for quantitative one.

#### Validity of a screening test:

**Sensitivity:** is the ability of the test to detect true positive cases =

$$\frac{\text{True positive}}{\text{True positive} + \text{False negative}}$$

**Specificity:** is the ability of the test to detect true negative cases =

$$\frac{\text{True negative}}{\text{True negative} + \text{False positive}}$$

**Positive predictive value:** is the probability of disease in a patient with positive test result =

$$\frac{\text{True positive}}{\text{True positive} + \text{False positive}}$$

**Negative predictive value:** is the probability of not having the disease in a subject with negative test result =

$$\frac{\text{True negative}}{\text{True negative} + \text{False negative}}$$

**Accuracy:** is the proportion of all test results both positive and negative that are correct =

$$\frac{\text{True positive} + \text{True negative}}{\text{True positive} + \text{True negative} + \text{False positive} + \text{False negative}}$$

## RESULTS

The frequency of cholestatic liver diseases was 19.7% (100 of 506 patients). While the extrahepatic cholestatic causes were detected in 61 out of 506 studied cases representing 12.1% being more in middle aged patients and more in females than males as shown in table (1).

**Table (1): Demographic data of cases with extrahepatic cholestasis.**

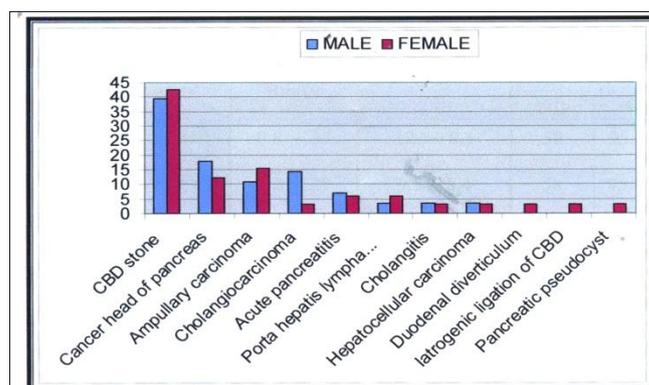
	Sex		Age	
	Male	Female	Range	Mean ± SD
NO	28	33	25 – 72	51.1 ± 11.7
%	45.9	54.1		
<b>Total NO = 61</b>				

The majority of patients in our study had benign causes for their obstructive jaundice (57.4%) with choledocholithiasis as the most common cause comprising 40.9 % of cases. While

malignant causes represented 42.6% of cases with cancer head of pancreas as the commonest malignancy detected, as shown table (2).

**Table (2): Frequency of causes of extrahepatic cholestasis.**

Etiology	NO	%
CBD stone	25	40.9%
Cancer head of pancreas	9	14.8%
Periampullary carcinoma	8	13.11%
Cholangiocarcinoma	5	8.2%
Acute pancreatitis	4	6.6%
Porta hepatis Lymphadenopathy	3	4.9%
Cholangitis	2	3.3%
Hepatocellular carcinoma	2	3.3%
Duodenal diverticulum	1	1.6%
Iatrogenic ligation of CBD	1	1.6%
Pancreatic pseudocyst	1	1.6%
Total	61	100%

**Fig. (1):** Relation between etiology of extrahepatic cholestasis and sex

The percentage of malignant extrahepatic cholestasis was higher in males (50%) than females (36.4%) as seen in Figure (1). Most of the patients with benign obstructive jaundice were younger in age as the percentage of benign

causes was the highest (85.7%) in the 20-40 years age group, while malignant causes were in elderly as the percentage of malignant causes was the highest (66.7%) in the age group of >60 years Table (3).

**Table (3):** Relation between malignant and non malignant causes of extrahepatic cholestasis and age

Age group		Malignant	Non malignant	Total	X <sup>2</sup>	P
20 -40 (adult)	NO	2	12	14	7.12	0.007
	%	14.3%	85.7%			
41-60 (middle)	NO	16	19	35	0.76	0.38
	%	45.7%	54.3%			
> 60 (elderly)	NO	8	4	12	18.87	0.001
	%	66.7%	33.3%			
<b>Total</b>		26	35	61		

Serum total and direct bilirubin levels were elevated in 95.1 % of cases with mean values of 12.5 and 9.3 respectively. There was a significant agreement between ALP and GGT, with P value <0.01, while serum transaminases were only

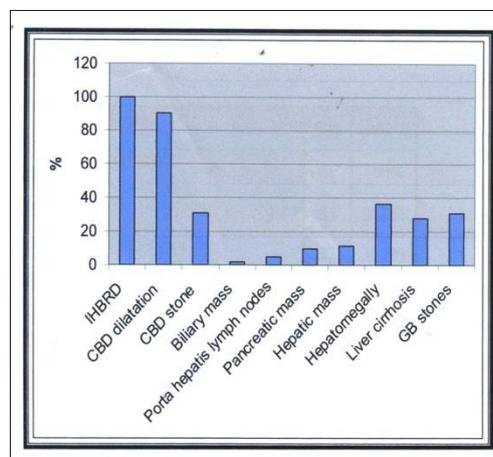
mildly elevated in 34.4% of cases. Regarding the clinical manifestations, 58 cases (95.1%) presented with jaundice. The percentage of dark urine, itching and clay stool in malignant cases were 92.3%, 73.1% and 53.8% respectively,

compared to 82.8%, 62.8% and 48.6% respectively, in non malignant conditions. Charcot's triad was more common in benign

conditions with a percentage of (40%) compared to (23.1%) in malignant cases.

**Table (4):** Frequency of clinical presentations of cases with extrahepatic cholestasis

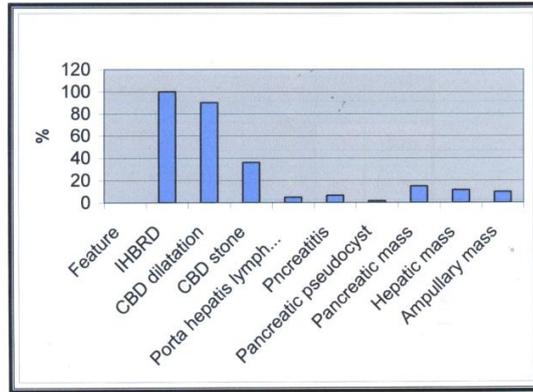
Clinical presentation	NO	%
Jaundice	58	95.1%
Dark urine	53	86.9%
Itching	41	67.2
Vomiting	37	60.7%
Clay stool	31	50.8%
Weight loss	25	41%
Hepatomegally	22	36.1%
Charcot triad	20	32.8%
Scratch marks	16	26.2%
Bleeding manifestation	10	16.4%
Palpable abdominal mass	5	8.1%
<b>Total</b>		<b>61</b>



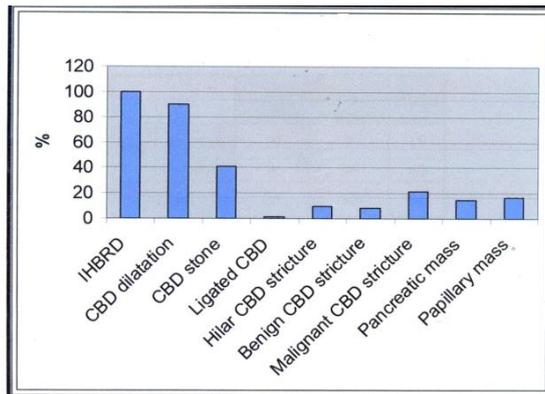
**Fig. (2):** Frequency of ultrasonographic features of extrahepatic cholestasis

According to imaging modalities ultrasound (U/S) was done to all cases. It picked dilated intrahepatic channels in 100% of patients of extrahepatic cholestasis and dilated CBD in 90.2% of them. CBD stones were detected in 31.1% while masses were detected in only 27.8% and most of the times, it was in the head of pancreas Figure (2). Abdominal computed tomography (CT) was done to all cases to confirm the diagnosis of (U/S) and/or to establish the cause of obstruction when U/S couldn't detect it. It picked dilated intrahepatic channels in 100% & dilated CBD in 90.2%, while CBD stones were detected in 36.1%.

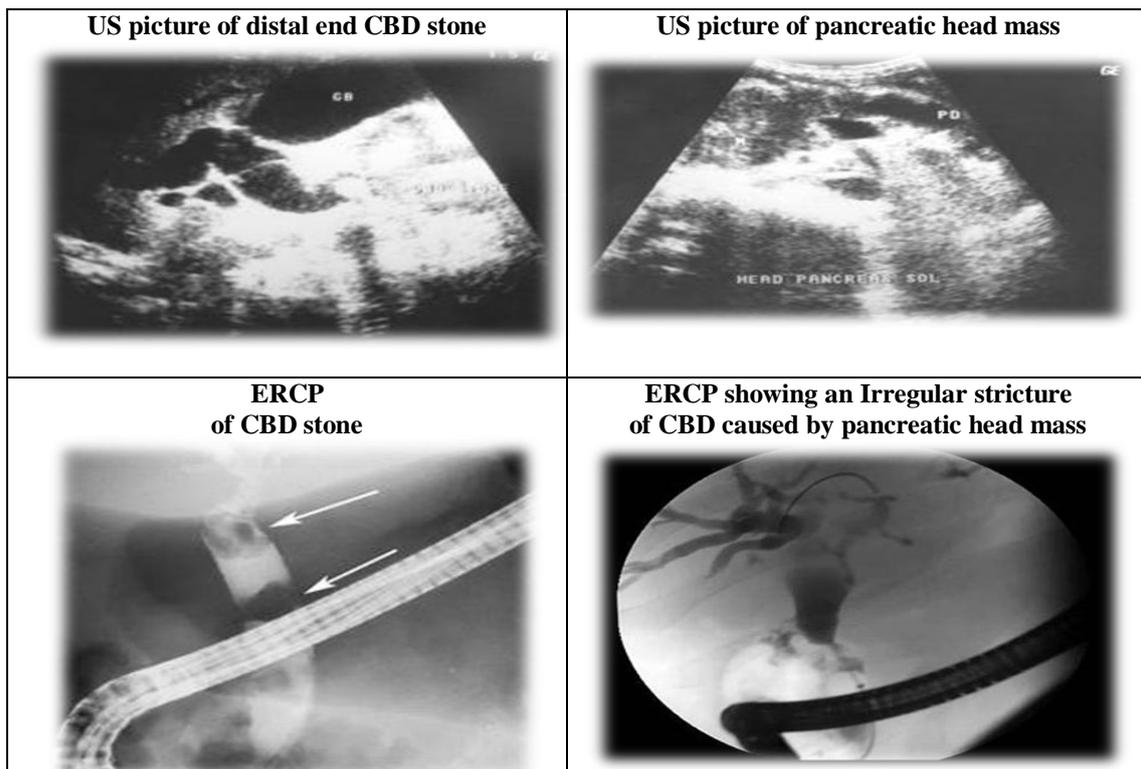
Masses were detected in 41% of cases Figure (3). Endoscopic retrograde cholangi-pancreatography (ERCP) was done to the cases which were not diagnosed by US or CT or as a therapeutic tool. It could detect all the 25 cases with CBD stones representing 40.9% of all cases with extrahepatic cholestasis. Cholangiocarcinoma was detected in 5 cases, in which 3 of them showed hilar CBD malignant stricture "Klatskin tumor" and 2 cases showed distal CBD stricture. Porta-hepatitis lymphadenopathy and HCC were demonstrated as either hilar or distal malignant CBD stricture (Figure 4).



**Fig. (4):** Frequency of CT features of extrahepatic cholestasis



**Fig. (5):** ERCP features of cases with extrahepatic cholestasis



**Table (5):** Relation between BMI and sex in cases with GB stones

		BMI											
		>25				25 – 30				> 30			
Sex		Male		Female		Male		Female		Male		Female	
		No	%	No	%	No	%	No	%	No	%	No	%
GB stone	-ve	1	100	-	0	20	87	14	63.6	3	60	4	44.4
	+ve	-	0	1	100	3	13	8	36.4	2	40	5	55.6
X2		-				3.311				0.311			
P		-				0.069				0.577			

As shown in (Table 5) there was an increased percentage of females with BMI more than 30 in patients with GB stones, though it was non significant as P value was  $> 0.05$ . Regarding the group with BMI  $< 25$ , there were only 2 patients (which was not sufficient for statistical analysis).

The sensitivity of U/S, CT and ERCP in detection of CBD stones was 76%, 88% and 100% respectively, whereas their sensitivity in detection of cancer head of pancreas was 66.7%, 100% and 100% respectively. While the predictive values of US compared to ERCP in detection of CBD stones was 100% positive and 85.7% negative, and the predictive value of US compared to ERCP in detection of cancer head of pancreas was 100% positive and 94.5% negative. The predictive values of CT compared to ERCP in detection of CBD stones was 100% positive and 92.3% negative, while the predictive value of CT compared to ERCP in detection of cancer head of pancreas was 100% positive.

## DISCUSSION

Among the many functions of the liver, production of bile is the most distinctive and liver specific. Adults produce approximately 500 ml of bile per day which is an aqueous solution containing bile salts, cholesterol proteins, bilirubin conjugates and others [5].

Cholestasis is caused by obstruction within the liver (intrahepatic) or outside the liver (extra-hepatic). Intrahepatic cholestasis is characterized by widespread blockage of small ducts or by disorders, such as hepatitis, that impair the body's ability to eliminate bile. Extra-hepatic cholestasis results from the mechanical obstruction to large bile ducts outside the liver or within the porta hepatis [6].

This cross sectional study was performed to assess the frequency of cholestatic liver diseases and identify the frequency of extrahepatic causes as a health problem in our department. It was found that 61 out of 506 cases admitted to our tropical department had extraheaptic cholestasis representing 12.1%. The high frequency of extraheaptic cholestasis in our study could be attributed to performing this study on a defined population, with high prevalence of chronic liver diseases and cirrhosis which increased the risk of gall bladder and common bile duct stones as noted by Marrelli [7] who studied the prevalence of calcular cholecystitis in Egyptian patients with chronic liver disease and found that chronic hepatitis C virus (HCV) infection is considered an important risk factor for the development of gallstone disease in those patients.

The lower incidence of obstructive jaundice in other studies as that reported by Khalili and Wilson [8] who reported its prevalence to be only 5 cases per 1000 people could be due to differences in the study group, as they assessed their incidence through a large scale study conducted on the general population. Also, the increased incidence of hepatocellular carcinoma in cases admitted to our department, could have contributed to the increased frequency in our study. The extra- hepatic cholestasis was more common among middle aged patients with a mean age of 51 years and a range of 25-72 years. This is in agreement with Bektas [9] who found almost similar results.

The majority of our patients had benign obstructive jaundice (57.4%) while malignant causes comprised (42.6%) which was in agreement with many other authors[10,11,12,13] who documented that the percentage of benign to malignant causes were about 60% - 40%.

Cholelithiasis was the most common cause among various causes of extrahepatic cholestasis in our study with a percentage of 40.9%. Similar results were demonstrated by Khurram et al. [14] who stated that cholelithiasis caused 35% of cases, being also the most common etiology of obstructive jaundice in their study. Moreover, in our study, patients with BMI >30 showed increased percentage of GB stones (55.6%), while in those with BMI (25-30), the percentage was (36.4%). Obesity and high dietary cholesterol could lead to increased biliary cholesterol secretion and decreased bile acid synthesis and pool which assist in cholesterol gall stone formation [21].

In our work extrahepatic cholestasis was more common in females (54.1%), which was usually benign in nature (60.6%) and common bile duct stone (CBD) obstruction as the most common cause in them (42.2%). This may be due to the higher prevalence of cholelithiasis in females. Women are at greater risk of developing gall bladder cholesterol stones, which could be attributed to their estrogen levels. Many studies as Everson [17] have shown that, female steroid hormones can significantly alter hepatobiliary physiology. As the gall bladder volume increases during pregnancy or by the prolonged use of contraceptive pills and its emptying is delayed as well. Moreover, the biliary cholesterol content was increased and the bile acid metabolism was altered by the previous conditions.

Other benign causes in our study were acute pancreatitis (6.6%), cholangitis (3.3%), duodenal diverticulum, pancreatic pseudocyst and iatrogenic common bile duct (CBD) ligation with a percentage of (1.6%) for each of them. This was not in agreement with Absi et al [18] who found Ascariasis and Hydatid disease of the biliary tract to be important benign causes of extrahepatic cholestasis, this difference could be attributed to the fact that their study was conducted in Saudi Arabia where high prevalence of these parasitic infections is present.

The percentage of pancreatitis and its complications as causes of extra-hepatic cholestasis, were higher in other studies done in USA and Europe by Granger and Remick, and Banks [19,20]. This could be explained by the high alcohol consumption in these countries predisposing to chronic pancreatitis.

The percentage of malignant extrahepatic cholestasis was higher in males (50%) than females (36.4%), being mainly cancer head of

pancreas with reported incidence of 17.9%. This is in agreement with Kiran and Pokola [21] who also found malignant obstructive jaundice to be more in males than females. Cancer head of pancreas had higher incidence with more mortality in males than females. This may be due to increased frequency of tobacco use in males which is considered a risk factor for that malignancy [22]. Similar observations were obtained by Syed et al. [10] and Khurram et al. [14] who found that the commonest causes of benign and malignant obstructive jaundice were cholelithiasis and cancer head of pancreas respectively.

Other malignant causes in our study included, ampullary carcinoma (13.11%), cholangiocarcinoma (8.2%), porta hepatis lymphadenopathy (4.9%) and hepatocellular carcinoma (3.3%). The results of Zarin et al. [23], was found to be similar to ours regarding malignant causes other than cancer head of pancreas.

Regarding the clinical manifestations, 58 cases (95.1%) presented with jaundice. The other three cases were one patient diagnosed as ampullary carcinoma which is usually manifested by intermittent jaundice. Way [24] postulated that, the intermittent jaundice demonstrated in patients with ampullary carcinoma is attributed to tumor necrosis allowing passage of bile with transient relief of symptoms. While, the other two cases were manifested mainly with itching and upper abdominal pain. They were both diagnosed as CBD stone induced obstruction. Flores et al [25] mentioned that, CBD stones can lead to intermittent jaundice due to the ball and valve action induced by the stone at the lower end of CBD leading to partial and intermittent obstruction.

The percentage of dark urine, itching and clay stool in malignant cases were 92.3%, 73.1% and 53.8% respectively, compared to 82.8%, 62.8% and 48.6% respectively, in non malignant conditions. Charcot's triad was more common in benign conditions with a percentage of (40%) compared to (23.1%) in malignant cases. Sharma and Ahuja [26] said that dark urine and clay stool were more common in malignant obstructive jaundice while Charcot's triad was a more frequent presentation in benign conditions.

In selected cases in our study with extrahepatic cholestasis, the frequency of gall bladder (GB) stones was higher among cirrhotic patients (52.9%) than non cirrhotics (22.7%) with a

significant relation between them. The pathophysiologic mechanisms responsible for induction of GB stones in cirrhotic patients may be related to altered bile pigments secretion, increased estrogen levels and/or abnormal gallbladder motility in cirrhosis [27]. The abnormal bile secretion in patients with liver cirrhosis may also be due to diminished liver reserve, damaged bile ductules, increased GB wall thickness caused by hyperemia and edema as well as decreased contractility with impaired emptying which could further contribute to gall stone formation [28].

In our study, there was a positive agreement between both GGT and ALP. This indicates that both markers together should be used for confirmation of cholestasis. The same finding was previously confirmed by [29].

According to imaging modalities ultrasound (U/S) was done to all cases. It picked dilated intrahepatic channels in 100% of patients of extrahepatic cholestasis and dilated CBD in 90.2% of them. CBD stones were detected in 31.1% while masses were detected in only 27.8% and most of the times, it was in the head of pancreas. The diagnostic accuracy of ultrasound was also studied by Akhtar and Mufti [30] and was close to our results as it was shown to be 85%.

Abdominal computed tomography (CT) was done to all cases to confirm the diagnosis of (U/S) and/or to establish the cause of obstruction when U/S couldn't detect it. It picked dilated intrahepatic channels in 100% & dilated CBD in 90.2%, while CBD stones were detected in 36.1%. Masses were detected in 41%. It was superior to ultrasound in detection and localization of masses. It could detect 6 out of 8 cases with ampullary masses and all the 9 cases with pancreatic masses compared to zero and 6 cases respectively detected by ultrasound. CT could also detect the 4 cases with acute pancreatitis while U/S couldn't detect any of them. The higher efficacy of CT in diagnosis and staging of tumors causing obstructive jaundice has also been reported by Pasanen, et al. [31].

Endoscopic retrograde cholangiopancreatography (ERCP) was done to the cases which were not diagnosed by US or CT or as a therapeutic tool. It could detect all the 25 cases with CBD stones representing 40.9% of all cases with extrahepatic cholestasis. Cholangiocarcinoma was detected in 5 cases, in which 3 of them

showed hilar CBD malignant stricture "Klatskin tumor" and 2 cases showed distal CBD stricture. Porta-hepatis lymphadenopathy and HCC were demonstrated as either hilar or distal malignant CBD stricture.

The sensitivity of US, CT and ERCP in detection of the various causes of extrahepatic obstruction was 76%, 88% and 100% respectively. These findings are broadly in agreement with studies done at various other centers for CT [31] and ERCP [32].

We can conclude that, the frequency of cholestatic liver diseases was 19.7%, among them; extrahepatic causes comprised 12.1% in our department. Ultrasonography is considered the best primary non invasive diagnostic modality for extrahepatic cholestasis. While CT scans has more accuracy in detection of biliary and pancreatic masses and ERCP, is considered the gold standard modality in diagnosis and treatment of extrahepatic cholestasis with excellent accuracy in identification of the cause.

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**Conflicts of interest:** The authors declare no conflict of interest.

**Ethical approval:** Informed consent was obtained from all participants, and the study was approved by the Ethical committee of Faculty of Medicine, Zagazig University.

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