Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i4.5617

CLINICAL, BIOCHEMICAL, RADIOLOGICAL AND ENDOSCOPIC PROFILE OF EXTRAHEPATIC BILIARY TRACT OBSTRUCTION IN TERTIARY CARE CENTRE OF NORTH INDIA

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ABSTRACT

Background: Extrahepatic biliary obstruction has a variety of benign and malignant causes. choledocholithiasis among benign causes whereas carcinoma of gall blader and carcinoma of head of pancreas & ampullary carcinoma are common among malignant causes. Initial treatment of cases of extrahepatic biliary obstruction depends on cause of the biliary obstruction and the clinical status of patients.

Aims and objective: To study the clinical, biochemical, radiological and endoscopic profile in EHBO patients

Material and Methods: The present study was a prospective observational study conducted in 100 patients with extrahepatic biliary obstruction admitted in M. M. Institute of Medical Sciences & Research, Mullana. Written informed consent was taken. The diagnosis of EHBO was based on clinical history, clinical findings, radiological and biochemical investigation. Detailed history was taken and relevant investigation were done which included CBC, LFT, PT/INR, USG abdomen, MRCP &/or CT Abdomen. ERCP was also done as indicated.

Result: The mean age of study participants was 50.68 years. 63% of cases were seen in females whereas 37% were seen in males. 77% of subjects had benign causes whereas 23% had malignancy. CBD Stone was the most common cause seen in benign causes whereas GB carcinoma was the most common cause of malignancy.

Conclusion: The present study shows that benign cause are more common for extrahepatic biliary obstruction than the malignant ones. Moreover, benign causes occur in younger individuals than malignant causes which occur in higher age groups. ERCP serves as both diagnostic and therapeutic procedure in both benign and malignant cases and helps to alleviate the symptoms of EHBO.

Keywords: Biliary obstruction, jaundice, choledocholithiasis, stricture

INTRODUCTION

Extra hepatic biliary obstruction is the blockage of biliary system outside the liver that obstruct the bile flow from liver into the second part of duodenum (1). An obstruction in biliary system leads to

cholestasis which can result in to serious complications like infections of biliary system, hepatic dysfunction, nutrient deficiencies and coagulopathy. (2)
Cholestasis due to extrahepatic biliary obstruction can cause jaundice abdominal pain, clay coloured stools, pruritus, and also manifest as abnormalities in blood liver enzymes such as variable increase in transaminases and alkaline phosphatase levels. (3) Choledocholithiasis is the most frequent causes of biliary obstruction and the most serious complication of this is the onset of cholangitis. (4)
There are two types of aetiologies for biliary obstruction: extrahepatic and intrahepatic. Extrahepatic biliary obstruction has a variety of benign and malignant causes. Among benign causes are choledocholithiasis, iatrogenic strictures following bile duct injury, primary sclerosing cholangitis and some congenital causes are like choledochal cysts and Mirizzi syndrome. (5)
Among malignant causes are carcinoma of gall blader, extrahepatic cholangiocarcinoma, carcinoma of head of pancreas, ampullary carcinoma and carcinoma of second part of duodenum. Some other uncommon causes of extrahepatic biliary obstruction are autoimmune cholangiopathy, HIV cholangiopathy and parasitic cholangiopathy (Clonorchis sinensis, Ascaris lumbricoides). (6)
Gallbladder stones prevalence are variable around the world , In India, it is approximately 4%, whereas it is 10% in the Western world. (7) The prevalence of gall bladder stone is more common in Northern Indians than Southern Indians (8). Common bile duct stones are found in between 10-15% of patients with gallstones but patient with CBD stones have gall stones in 80 to 90 % cases (9). Women are more likely than men to acquire gallstones, which increases their risk of choledocholithiasis. (10)
Initial treatment of cases of extrahepatic biliary obstruction depends on cause of the biliary obstruction and the clinical status of patients (11). Prognosis of biliary obstruction is strongly influenced by the cause. It can result in cholangitis and other life-threatening situations like multiple organ failure if untreated. With the help of medicinal, endoscopic and or surgical management most cases can be properly treated and totally recovered but obstruction due to malignant aetiology has a worse prognosis.(12) This study was undertaken to understand clinical, biochemical, radiological, and endoscopic profile of extrahepatic biliary tract obstruction in a tertiary care centre of North India.

AIMS AND OBJECTIVES

1) To study Clinical and Biochemical profile in patients with EHBO.
2) To study Radiological and Endoscopic profile in patients with EHBO.

MATERIAL AND METHODS

This was a prospective observatioal study. The study was conducted in M. M. Institute of Medical Sciences & Research, Mullana. 100 consequential patients with extrahepatic biliary obstruction admitted in M. M. Hospital were considered for study. The patients were briefed about the nature of study, and written informed consent was obtained from them. The study was conducted between December 2021 to December 2022.

Study Design-Prospective observational study.

Sample size: Total of 100 cases, were included in the study.

Study Place: Outpatient / Inpatient department of Gastroenterology and Surgery in MM institute of medical sciences Mullana, Ambala during the period of Dec. 2021 to Dec. 2022.

Inclusion criteria

1. All patients diagnosed with EHBO on the basis of history taking clinical examination and radiological evidence of EHBO.
2. Age more than 18 years.
3. Patients who gave consent.

Exclusion criteria

i. Patients with jaundice due to causes other then EHBO e.g. haemolytic and hepatocellular jaundice etc.

ii. Patients who did not gave informed consent were excluded from the study.

Methodology

The diagnosis of EHBO was based on clinical history, clinical findings, radiological and biochemical investigation. Detailed history was taken and relevant investigation were done which included CBC, LFT, PT/INR, USG abdomen, MRCP &/or CT Abdomen. ERCP was also done as indicated. Other investigation including FNAC, CA19 -9, Brush cytology were done as indicated.

Statistical Analysis Plan

The analysis included profiling of patients on different demographic, clinical and laboratory, parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Categorical data was expressed as absolute number and percentage. Independent Student t – test was used for testing of mean between independent groups whereas Paired Student t – test was used for paired observation. Cross tables were generated, and Chi square test was used for testing of associations. P-value < 0.05 was considered statistically significant. All analysis was done using SPSS software, version 24.0.

RESULTS

The mean age of study participants was 50.68 + 13.81 years. Table 1 shows that maximum number of benign cases were seen in 51-60 years (26%) followed by 41-50 years (23.4%) and 31-40 years (23.4%) of age. Majority of malignant tumours (70%) were seen above 50 years. As the age advances, proportion of patients with malignant EHBO also increased. 63% of cases were seen in females whereas 37% were seen in males. More than two third cases of malignant cases (70%) were seen in females as compared to only 30% in males. In benign cases, 61% were seen in females while 39% were seen in males (Table 1).

Most common symptom in malignant cases (n=23) was jaundice (100%), clay coloured stool (73.9%), weight loss (69.6%), pruritus (60.9%), abdominal pain (30.4%), whereas majority of benign cases (n= 77) were presented with the complaint of abdominal pain (68.9%) and jaundice (58.4%). The most common comorbidity seen was hypertension in 10% of cases, cardiac disease in 5%, diabetes mellitus in 3%, CKD in 1% and hypothyroidism in 1%. The most common abdominal examination finding observed was abdominal tenderness in 51% of cases. Abdominal mass was seen in 34.8% of malignant cases (Table 1).

Table 1: Distribution of study participants according to demographic and clinical characteristics

Characteristics	Benign (n=77)		Malignant (n=23)		Total (n=100)	
	Freq (n)	Percent (%)	Freq (n)	Percent (%)	Freq (n)	Percent (%)
Age (years)						
< 31	6	7.8	0	0	6	6
31-40	18	23.4	2	8.7	20	20
41-50	18	23.4	5	21.7	23	23
51-60	20	26	8	34.8	28	28
>60	15	19.5	8	34.8	23	23
Gender						
Female	47	61	16	69.6	63	63
Male	30	39	7	30.4	37	37

Clinical Symptoms						
Abdominal Pain	53	68.8	7	30.4	60	60
Fever	14	18.2	6	26.1	20	20
Jaundice	45	58.4	23	100	68	68
Pruritus	9	11.7	14	60.9	23	23
Clay coloured Stool	3	3.9	17	73.9	20	20
Weight Loss	0	0	16	69.6	16	16
Clinical Signs						
Temperature Raised	11	14.3	7	30.4	18	18
Pallor	6	7.8	7	30.4	13	13
Clubbing	0	0	1	4.3	1	1
Lymphadenopathy	0	0	6	26.1	6	6
Per abdominal examination						
Normal	34	44.2	7	30.4	41	41
Abdominal Mass	0	0	8	34.8	3	3
Abdominal Tenderness	43	55.8	8	34.8	51	51

Table 2 shows the distribution of mean values of blood parameters. It was observed that the mean haemoglobin level was lower in malignant cases (10.67 ±1.8gm%) as compared to benign cases (12.42 ±1.4gm%) and mean TLC level was higher in malignant cases (10±1.88 x 1000 /ml) as compared to benign case (7.79±3.5 x 1000 /ml). It was also seen that serum bilirubin, ALP levels, SGOT and SGPT all were on higher side in malignant cases as compared to benign cases. It was observed that the mean serum creatinine level was higher in malignant cases as compared to benign cases.

Table 2: Distribution of study participants according to biochemical and laboratory parameters

Blood parameters	**Benign (n=77)**		**Malignant (n=23)**		**p-value**
	Mean	**SD**	**Mean**	**SD**	
Hb	12.42	1.46	10.67	1.88	<0.001
TLC	7.79	3.53	10	4.56	0.016
Neutrophil	65.99	10.52	72.04	10.79	0.018
Platelet	3.18	0.88	3.28	1.16	0.668
Serum bilirubin	4.37	2.8	13.06	5.04	<0.001
Direct	2.98	2.18	10.12	4.24	<0.001
Indirect	1.38	0.86	3.01	1.44	<0.001
Alkaline phosphatase	269.35	141.5	605.65	190.82	<0.001
SGOT	51.05	35.98	109.09	55.01	<0.001
SGPT	57.69	48.34	107.43	50.95	<0.001
Total protein	6.51	0.86	5.77	1.41	0.003
serum albumin	3.88	0.61	3.06	0.66	<0.001
PT/INR	1.09	0.26	1.43	0.25	<0.001
Blood urea	27.34	13.8	35.3	13.24	0.016
Serum creatinine	0.92	0.34	1.25	0.47	<0.001

Serum Sodium	134.58	7.78	133.87	7.19	0.695
Serum Potassium	3.86	0.53	4.05	0.63	0.14

Out of 44 cases of CBD stone found on USG, 36.3% of subjects had isolated CBD Stone whereas 63.6% subjects had CBD Stone in association with gall stones. On USG, 59.1% of subjects had CBD Stone in distal CBD, 34.1% subjects had CBD Stone in middle segment and 6.8% subjects had CBD Stone in proximal part of CBD (Table 3).

Table 3: Distribution of study participants according to characteristics on USG

Site of Stone	**Frequency (n=44)**	**Percentage (%)**
CBD Stone	16	36.3
CBD Stone & GB Stone	28	63.6
Site of Stone in CBD		
Proximal	3	6.8
Mid	15	34.1
Distal	26	59.1

Whereas on MRCP 60 subjects had biliary stone of which 67% of subjects had stone size of <1 cm while 33% of subjects had stone size of >1 cm. Out of these 60 cases of biliary stone, 58.3% of subjects had single stone while 41.7% of subjects had multiple stones (Table 4). On MRCP, intrahepatic biliary radicles dilatation was seen in 95% cases of EHBO of which 100% malignant cases had IHBRD.

Table 4: Distribution of study participants according to characteristics on MRCP

Stone Size	**Frequency (n=60)**	**Percentage (%)**
< 1 cm	40	66.7
> 1 cm	20	33.3
Number of Stone		
Single	35	58.3
Multiple	25	41.7

Based on endoscopy in benign cases, 77.9% subjects had biliary stones, 11.7% had CBD stricture, 6.5% had sludge, 2.6% had Mirrizi Syndrome and 1.3% had Pancreatic Divisum (Table 5). According to final diagnosis established, out of 77 benign cases, 77.9% had CBD Stone, 11.7% had CBD Stricture, 6.5% had CBD Sludge, 2.6% had Mirrizi Syndrome and 1.3% Pancreatic Divisum whereas out of 23 malignant cases, 39.1% had Gall Bladder Carcinoma, 34.8% had Periampullary Carcinoma, 17.4% had Cholangiocarcinoma and 8.7% CBD Stricture (Table 5). Endoscopically stent was placed in CBD in 97.4% of benign cases and 73.9% of malignant cases. Among benign cases, endoscopic CBD clearance was complete in 78.5% and partial in 12.3% while in 9.2% no clearance could be achieved endoscopically.

Table 5: Distribution of study participants according to Final Diagnosis of EHBO

Benign Disorders (n=77)	**Frequency (n)**	**Percentage (%)**
CBD STONE	60	77.9
CBD STRICTURE	9	11.7
CBD SLUDGE	5	6.5
MIRRIZI SYNDROME	2	2.6
PANCREATIC DIVISUM	1	1.3
Malignant Disorders (n=23)		

GALL BLADDER CARCINOMA	9	39.1
PERIAMPULLARY CA	8	34.8
CHOLANGIOCARCINOMA	4	17.4
CBD STRICTURE	2	8.7

DISCUSSION

In the present study majority patients were in the age group of 51–60 years in both benign (26%) and malignant (28%) cases of EHBO, the mean age was 49.6 ± 13.9 years in benign and 56.6 ± 11.5 years in malignant cases respectively, overall mean age were 50.68 ± 13.8 years. Mean age was higher in malignant cases as compared to benign cases. This coincide with Upadhyay et al (13) where mean age for benign and malignant cause were 48.2 years and 56.8 years respectively and over all mean age was 50 years.(32) In another study conducted by Sharma et al (14) on malignant cases of EHBO the mean age was 58 years.

In our study, majority of cases were females both in benign (61%) and malignant (63%) cases and overall percentage of female was 63 %. This was similar to other studies from India and other country such as Ethiopia, Tanzania, Italy, and the USA.(15–18). Mabula et al. (15) conducted a study in Ethiopia, in which 60.9% cases of EHBO were females similar to our study results. In our study the male to female ratio was 1:1.7. This coincides with Mabula et al. (15) study which reported male to female ratio of 1:1.6. Also Madhu et al. (19) reported that majority of EHBO cases (67.8%) were females.

In our study the benign cases of EHBO were 77% out of these CBD stones (77.9%) was most common benign cause followed by CBD stricture (11.7%), CBD sludge 6.5 %, Mirrizi syndrome 2.3 %, pancreatic divisum 1.3 % while malignant causes were 23% out of malignant causes of which GB carcinoma (39.1%) was most common malignant cause followed by periampullary carcinoma 34.8 %, cholangiocarcinoma 17.4 % and malignant CBD stricture 8.7 %.

In this study, women (63%) were more likely to have biliary blockage than men (37%). This was similar to other studies from Ethiopia, Tanzania, Italy, and the USA.(15–18) Due to hepatic hypersecretion, estrogen increases the biliary cholesterol's supersaturation, which promotes the crystallization of cholesterol monohydrate. Gallbladder contraction is inhibited by progesterone, which also promotes bile stasis and lessens the gallbladder's reaction to cholecystokinin. Similar to global trends choledocholithiasis, Ca GB, and benign biliary stricture were most frequently observed in females (13,20,21). Similar to earlier studies periampullary carcinoma (60%) seemed to be more common in men. (22,23)

Overall CBD stone was most common cause (60%) of EHBO in our study. This is similar to study by Thakur et al (24) in which (CBD stone (67.2%) and benign CBD stricture were most frequent benign causes and GB carcinoma was the most common malignant cause. Gall bladder carcinoma was the most frequent malignant aetiology of EHBO according to a study from North India by Vijay et al (25). A recent survey by Upadhyay et al. (13) also showed similar results, stone was most common cause (67.9%) of EHBO and carcinoma of gall bladder found in (40.4%) cases of malignant causes. Study from India and Sweden by Anand S et al and Pitiakoudis M. et al showed that CBD stone was the common cause of bile duct obstruction in young patients (2,26).

However, in contrast to our study, malignant causes were more prevalent than benign causes (75.3% vs. 24.7%) in a prospective study from AIIMS, Delhi (27), with GBC (28.7%) and CBD stone (12.4%) being the most common malignant and benign causes, respectively. In 63.3% and 36.6% of cases, respectively, Madhu et al. (19) found malignant and benign causes. In a study by Verma et al. (22) showed that most common carcinoma was pancreatic head carcinoma (33.6%). According to Selvasekaran et al. (28), periampullary carcinoma (34%) was the most prevalent malignancy.

In the present study subjects above 50 years, malignancy was more common (70%). Singh et al. (29) and Shukla et al. (16) made similar observations.

Based on above discussion, it seems that causes of EHBO depend on age of subjects and geographical location of patients.

The two most common malignant causes of EHBO, accounting for 39.1% and 34.8%, respectively, were gall bladder carcinomas and pancreatic head tumors. This was also noted by Borkman et al. (30), Mabula et al. (15), and Olatoke et al.(11) in Sweden, Tanzania, and Nigeria, respectively.

Patients with EHBO typically presented with abdominal pain (60%) and jaundice (68.1%) in our study. The results of other studies by Mabula et al. and Engida Abebe et al. corroborated this (15). Jaundice and abdominal discomfort were the most prevalent presenting symptoms, occurring in 66-88% and 51–66% of cases, respectively.(13,22)

In our study most common clinical symptom in benign causes was abdominal pain found in 68.8% of patients followed by jaundice in 58.4%, fever 18.2 %, clay coloured stool in 3.9 %, pruritus 11.7%. And no weight loss found in any benign case.

In malignant cases most common clinical finding was jaundice found in 100 % cases other clinical findings are clay coloured stool 73.9 %, weight loss in 69.9 % pruritus 60.9 %, abdominal pain 30.4% and fever 26.1 %.

Clinical presentation of our study is similar to a study by Thakur et al (24) which was conducted in IMS BHU and showed abdominal pain as the most common clinical finding in benign cases (76%). Other findings in benign cases were jaundice (49.6%) and pruritus (12%) but in malignant cases jaundice was seen in 100 % cases, other symptoms were weight loss (59%), itching (54%) and pain abdomen (25.4%).

A study conducted by Upadhyay et al (13) showed that abdominal pain (76.9%) was most common clinical finding in benign cases, other findings in benign case were jaundice (33.8%), fever (12%) and pruritus (9.7%). In malignant cases jaundice (96.1%) was the most common clinical finding followed by pruritus (53.8%), abdominal pain (48%) and fever (23%).

In our study biochemical derangement occurred mainly in liver function tests. Serum bilirubin and alkaline phosphatase were raised both in benign and malignant cases of EHBO but higher levels were observed in malignant cases in comparison to benign cases, mean value of bilirubin in benign and malignant cases were 4.3±2.8 mg/ml and 13±5.0 mg /ml ±respectively, mean value of alkaline phosphatase in benign and malignant cases were 269 ±141.5 IU/ml and 605 ±190.8 IU/ml respectively.

Above findings correlate with the findings of Upadhyay et al (13) and Thakur et al (24) in which serum bilirubin and alkaline phosphatase levels were raised and higher levels were seen in malignant case then benign cases similar to the present study.

In a study performed by Thakur et al (24) mean bilirubin level was 4.6 mg/ml in benign cases and 16.9 mg/ml in malignant cases, mean alkaline phosphatase level was 439.3 IU/ml in benign and 1170 IU/ml in malignant cases, in this study higher level of alkaline phosphatase may be due to large sample size of this study. In another study by Upadhyay et al (13) showed that mean value of serum bilirubin was 3.4 mg/ml in benign cases and 11 mg/ml in malignant cases similar to our study. A study conducted by Hyatt et al (39) also reported that bilirubin and alkaline phosphatase levels are raised both in benign and malignant case, but higher levels seen in malignant cases.

Canto et al (31) also observed similar results. Therefore, in patients with obstructive jaundice, greater bilirubin levels may be a sign of malignant disease. All individuals with cholangitis may not have the whole Charcot's triad, so any patient who exhibits fever or newly apparent organ dysfunction in a clinical environment calls for more testing. Renal failure and elevated TLC with a neutrophil predominance may help to identify patients with cholangitis.

Based on above discussion, it seems that higher levels of bilirubin and alkaline phosphatase were indicator of malignant causes.

In the present study mean Hb level observed was 12.4±1.4 mg/dl in benign cases and 10.6±1.8 mg/dl in malignant cases (p-value <0.001). Antony Prabakar et al (32) conducted an study on EHBO cases, in which mean Hb level observed was 10.5 mg/dl in benign cases and 9.5 mg/dl in malignant cases similar to our study.

Mean TLC count in our study was 7.79±3.5 x1000 cc/ml in benign cases and 10 ±4.5 x 1000 cc/ml in malignant cases. A study conducted by Thakur et al (24) showed TLC count in his study was 8.7x

1000 cc /ml in benign cases 11.6 x 1000 cc/mm in malignant cases. Renal failure and elevated TLC with a neutrophil predominance may help to identify patients with cholangitis. (25)
In our study IHBRD on abdominal ultrasound was found 95% cases whereas IHBRD on MRCP was found in 98% of cases. Kushwah et al (33) reported IHBRD in 98% of cases on abdominal USG and 100 % on MRCP. Our study results are also supported by Balde et al (34).
In the present study abdominal USG detected CBD stone in 44 cases out of 60 cases of CBD stone so sensitivity of USG was 73.3% whereas the sensitivity of MRCP was 100% for CBD stone. A study conducted by Kushwah et al (33) showed sensitivity for CBD stone was 77.7 and on MRCP was 88.8.
In our study Gall bladder stones were seen in 73.3% cases of CBD stones. This finding is supported by Thakur et al (24) in which gall bladder stone was found in 75% cases of CBD stone.
In our study CBD stone size of <1 cm was seen in 66.7% of cases and >1 cm found in 33.3 % cases. This finding is similar to a study by Upadhyay et al (13), in which CBD stone size less than 1 cm were found in 66.1 % cases and more than one cm were found in 33.9% cases.
In our study, on ERCP single CBD stone was found in 58.3% of cases and multiple CBD stone was found in 41.7% of cases. Upadhyay et al (13) reported single stone in 53.8% and multiple stone in 46.2 % cases of CBD stone similar to our study results. Thus, prevalence of single CBD stone is higher as compared to multiple CBD stone.
In the present study with ERCP complete clearance was done in 78.5% of cases, partial clearance in 12.3% and no clearance in 9.2% of cases. Thakur et al (24) reported that complete CBD clearance was done in 78.81% and no CBD clearance was done in 22.15% cases similar to our study. Another study conducted by Upadhyay et al (13) showed complete clearance was done in 70.7 % of case, partial in 9.23% cases and no clearance in 20% of cases.
The majority of patients showed progressive, and continuous jaundice, along with significant weight loss, mostly in the malignant group, according to the study's findings. Other reports of comparable findings in sub-Saharan Africa were also published. (11,15,30) The majority of patients in the USA, UK, Sweden, and India presented with intermittent jaundice, presumably because choledocholithiasis was the most common ethology of EHBO.(15,16) The variation in observations depend on variations in exposure and etiological spectrum from one geographic region to another.

Conclusion

The present study shows that benign causes are more common for extrahepatic biliary obstruction than the malignant ones. Moreover, benign causes occur in younger individuals than malignant causes which occur in higher age groups. CBD stones predominate in cases of extra-hepatic biliary blockage, and endoscopic therapy is effective. Additionally, malignancy particularly gallbladder carcinoma and periampullary carcinoma contributes to a sizeable number of these cases. Malignant EHBO instances exhibit advanced disease, necessitating endoscopic palliation to reduce symptoms. In the majority of these patients, endoscopic therapy has outstanding results, MRCP is effective and useful tool for the diagnosis of EHBO as compared to ultrasonography. ERCP serves as both diagnostic and therapeutic procedure in both benign and malignant cases and helps to alleviate the symptoms of EHBO.

Source(s) of support: Nil
Conflicting Interest: Nothing to Disclose

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