

Original Article

Clinical Profile and Outcome of Young Patients with Extrahepatic Biliary Obstruction at A High-Volume Tertiary Care Centre in Northern India

Ravi Kant Thakur, Vinod Kumar Dixit, Sunit Kumar Shukla, Dawesh Prakash Yadav, Piyush Thakur, Tuhin Mitra

Department of Gastroenterology, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University.

Corresponding Author: Dr Vinod Kumar Dixit

Email: drvkdixitbhu@gmail.com

ABSTRACT

Background and Aim: The etiology of extrahepatic biliary obstruction (EHBO) ranges from benign disorders to pancreaticobiliary malignancy. We studied the demographic, clinical, laboratory, and endoscopic features of young patients with EHBO undergoing Endoscopic retrograde cholangiopancreatography (ERCP).

Methods: We retrospectively analyzed one-year data of ERCP procedures performed on adult patients under 40 years of age. The diagnosis was based on a clinical and radiological basis with histopathological confirmation.

Results: A total of 180 patients were included with a mean(\pm SD) age of 33.4(\pm 5.8, range: 15-40) years, and 67.8% being female. Benign (67.2%) findings included choledocholithiasis (57.8%), benign biliary stricture (9.44%, post cholecystectomy stricture 82.3%), and malignant (32.8%) causes were gallbladder carcinoma (24.4%), cholangiocarcinoma (4.4%), periampullary carcinoma (2.8%), pancreatic head carcinoma (1.1%). Clinical presentation included jaundice (66.1%), pain abdomen (59.4%), pruritis (26.1%), weight loss (19.4%), anorexia, fever, and cholangitis (24.44%). Mean bilirubin levels (16.9 \pm 6.8 vs 4.6 \pm 4.1 mg/dl) and alkaline phosphatase (1170 \pm 260.7 vs 439.3 \pm 362.7 IU/mL) were higher in malignant causes, in comparison to benign. Stone retrieval using balloon during ERCP was successful in 79% of cases. Large (>15 mm) or impacted stones or those with biliary stricture failed stone extraction. In gallbladder carcinoma, adequate endoscopic biliary drainage was achieved in 68% of patients. Endoscopic biliary drainage was achieved in 75%, 80%, and 50% cases of cholangiocarcinoma, periampullary carcinoma, and pancreatic head carcinoma, respectively.

Conclusion: Choledocholithiasis and gallbladder carcinoma are the most common benign and malignant causes of EHBO in young patients. The successful endoscopic therapeutic intervention could be achieved in most patients.

KEYWORDS: Extrahepatic biliary obstruction, Choledocholithiasis, Gallbladder carcinoma, Cholangitis.

Introduction

Extrahepatic biliary obstruction (EHBO) affects a significant proportion of the population worldwide. EHBO refers to obstruction of bile flow from the liver to the duodenum at the extrahepatic biliary system, which can originate within the duct or due to extrinsic compression from a broad spectrum of disorders.

Reports from the different parts of India have found choledocholithiasis, gallbladder carcinoma, carcinoma head of the pancreas and periampullary carcinoma to be the most frequent causes.¹⁻⁵ There is a lack of data for young patients (≤ 40 years of age) presenting with the biliary tract obstruction.

Materials and Methods

We retrospectively analyzed the hospital records of all patients at or below 40 years of age, who had undergone ERCP in Gastroenterology Department, Banaras Hindu University, Varanasi, Uttar Pradesh, India from July 2018 till June 2019.

Etiological diagnosis was based on clinical features and examination, blood investigations which included complete blood count (CBC), liver function test (LFT), kidney function test (KFT), prothrombin time (PT/INR), along with imaging with ultrasonography (USG) or contrast-enhanced computerized tomography (CECT), magnetic resonance imaging (MRI) or Magnetic resonance cholangiopancreatography (MRCP). When possible, all diagnoses were confirmed by histopathologically (image-guided FNAC, Brush cytology, Post-surgical histopathology).

Patients underwent ERCP for at least one of the following indications: Choledocholithiasis on imaging, EHBO with cholangitis and intractable pruritis, referral from oncology team before surgery or chemotherapy, or for stent placement across strictures.

Diagnosis of benign biliary stricture⁶ was based on history, clinical finding, serum markers, imaging studies (MRCP)^{7,8} and brush cytology. Malignant strictures were identified when definitive evidence of malignancy by serological markers, imaging, or tissue diagnosis whenever available.

Statistical analysis: Data was represented as a percentage for nominal data and mean \pm SD or range for continuous data. Continuous data were compared using unpaired t-test and discrete variables by χ^2 test or Fischer-exact test. A p-value <0.05 was considered as statistically significant.

The data was analyzed by using SPSS version-24.0 statistical software (Trial Version). The institutional ethics committee approved the research protocol and all participants had given written informed consent.

Results

During the study period, a total of 1148 patients underwent ERCP, of whom 180 patients were ≤ 40 years of age.

The mean age of patients was 33.38 ± 5.8 years, and most of them were females (67.78%). Choledocholithiasis (F=67.3%), benign biliary stricture (F=76.47%), and gall bladder carcinoma (GBC, F=72.73%) were seen predominantly in females. Periampullary carcinoma (M=60%) preferentially affected males. Pancreatic head carcinoma and cholangiocarcinoma was equally distributed between males and females. The youngest patient with GBC was 25 years of age.

Benign causes were seen in 67.2%, which included choledocholithiasis as the most prevalent cause (n=104, 57.8%) followed by benign biliary stricture in 17(9.4%). (**Table 1**) The latter was caused by prior cholecystectomy in 14 patients, portal biliopathy in 2 patients, and chronic pancreatitis in 1 patient. Malignant etiologies included GBC (n=44, 24.4%), cholangiocarcinoma (hilar cholangiocarcinoma in 6, and distal cholangiocarcinoma in 2 patients), periampullary carcinoma (5 patient) and pancreatic head carcinoma (2 patient).

The patients presented clinically with jaundice (66.1%), pain abdomen (59.44%), itching (26.11%), weight loss (19.44%, only in malignant EHBO), anorexia, and vomiting. (**Table 2**) Charcot's cholangitis triad was present in only 68.18% of patients with cholangitis, fever being most consistent symptom present in all patients.

The mean hemoglobin concentration was higher in benign (12.0 ± 1.8 gm/dl) as compared to malignant causes (10.92 ± 1.67 gm/dl). In patients with cholangitis, total leukocyte count was elevated in 95.54%, and

Table 1: Aetiological spectrum along with age and sex distribution of EHBO cases undergoing ERCP.

Cause of EHBO	Number (%)	AGE (years) = mean ± SD	Gender
Choledocholithiasis	104(57.8%)	32.40 ± 6.05	F(70), M(34)
Benign biliary stricture †	17(9.44%)	30.59 ± 5.88	F(13) , M(4)
GB carcinoma	44(24.44%)	35.79 ± 4.46	F(32), M(12)
PACA	5(2.78%)	36 ± 3.24	F(2), M(3)
Pancreatic head carcinoma	2(1.10%)	37.5 ± 3.53	F(1), M(1)
cholangiocarcinoma	8(4.44%)	36.13 ± 4.97	F(4), M(4)
Total	180(100%)	33.38 ± 5.8	F(122), M(58)

†Benign biliary stricture included post Cholecystectomy 14(82.35%), portal biliopathy 2 (11.76%), chronic pancreatitis 1 (5.88%)

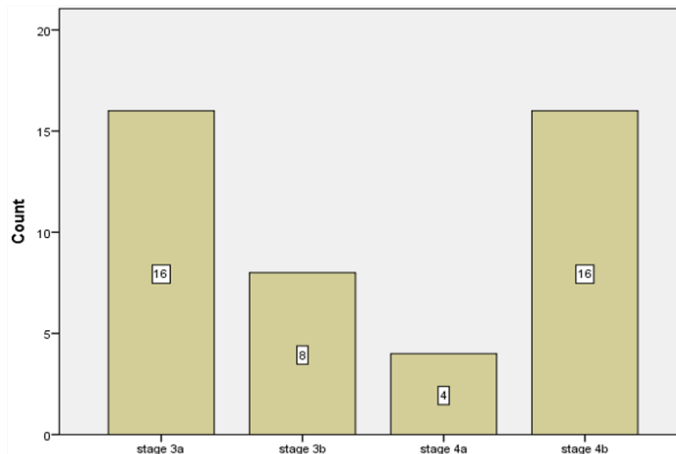
Table 2: Clinical presentation of patients with EHBO undergoing ERCP.

Symptom	Benign (N=121)	Malignant (N=59)	P value
Jaundice	60 (49.6%)	59 (100%)	<0.001*
Pain Abdomen	92 (76.03%)	15 (25.4%)	<0.001*
Itching	15 (12.39%)	32 (54.23%)	<0.001*
Cholangitis	26 (21.49%)	18 (30.51%)	0.201
Weight loss	0%	35 (59%)	<0.001*
Fever	26/44 (21.49%)	18 (30.51%)	0.201

differential count in showed markedly elevated neutrophilic count in all these patients. Renal dysfunction was seen in 8(18.18%) patients with cholangitis. Mean bilirubin (16.9 mg/dl ± 6.8 versus 4.6 mg/dl ± 4.1) and alkaline phosphatase (1170.98 U/L ± 260.73 versus 439.34 ± 362.73) were higher in malignant as compared to benign causes. (Table 3)

On imaging studies GBC patients had liver (segment IV, V) infiltration (36.36%), liver metastasis (18.18%), left adrenal metastasis (2.72%), loco-regional lymphadenopathy (40.91%), gastric outlet obstruction (4.55%) and ascites (9.09%). All GBC cases referred for endoscopic biliary drainage had advanced disease (stage 3 and 4) (figure 1).

In patients with choledocholithiasis, 75% also had cholelithiasis. Multiple common bile duct calculi (≥2) were found in 37.5% of patients. (Table 4) Complete biliary clearance was achieved in 82 (78.85%) patients. Reasons for failure of biliary clearance with balloon sweeping were large stones >15 mm in size (n=17/104, 16.35%), associated biliary stricture (n=2/104, 1.92%), impacted stones in (n=2/104, 1.92%) and altered anatomy

**Figure 1: Stage at presentation of gallbladder carcinoma patients (N=44).**

in (n=1/104, 0.96%) patients. (Table 4) Those with failure of biliary clearance were sent for surgical intervention after biliary drainage with stent in situ.

Bismuth type 1, type 2 and type 3 of benign biliary strictures were seen in 70.59%, 17.65%, and 11.76%, respectively. (Table 5) Successful biliary stenting was achieved in only 52.9% patients, and the reason for failure

Table 3: Laboratory investigations of patients with EHBO undergoing ERCP.

Laboratory parameter	Benign aetiology (N=121)	Malignant aetiology (N=59)	P value
Haemoglobin (gm/dl) (mean ± SD)	12.04 ± 1.79	10.92 ± 1.67	<0.001*
Elevated TLC (>11000)	25/121 (20.66%)	17/121 (28.81%)	0.261
TLC cells/mm ³ (mean ± SD)	8761.27 ± 4843.75	11636.31 ± 7304.61	<0.002*
Total Bilirubin in mg/dl (mean ± SD) †	4.6 ± 4.1	16.9 mg/dl ± 6.8	<0.001*
Direct bilirubin in mg/dl (mean ± SD)	3.16 ± 3.08	12.48 ± 4.97	<0.001*
ALP in U/L (mean ± SD)	439.34 U/L ± 362.73	1170.98 U/L ± 260.73	<0.001*
Total protein (gm/dl)	8.02 ± 0.55	7.80 ± 0.73	0.030*
Albumin (gm/dl)	4.02 ± 0.47	3.78 ± 0.50	0.002*
Deranged RFT (serum Creatinine >1.5)*	5/121 (4.13%)	3/59 (5.08%)	0.520

*Statistically significant.

Table 4: ERCP findings in EHBO patients (N=104) with choledocholithiasis.

No of calculi (N=104)	1 = 65 (62.5%) ≥ 2 = 39 (37.5%)
Cholelithiasis	78/104 (75%)
Cannulation achieved	Yes = 103 (99.04%) No† = 1 (0.96%)
Complete Biliary clearance	Yes = 82 (78.85%) No = 22 (21.15%)
Reason for failure of stone extraction by balloon	Large stones (>15 mm in 17/104 = 16.35%) Associated biliary stricture in 2/104 (1.92%) Impacted stones in 2/104 (1.92%) Altered anatomy in 1/104 (0.96%) †

†Patient had altered anatomy (choledochoenterostomy)

was tight stricture, not allowing guidewire passage across the stricture.

Cholangiography in GBC showed a perihilar stricture of predominantly Bismuth type 2 (n=12, 27.27%) and type 1 (20.45%). (Table 6) Thirteen patients had direct infiltration of CBD not extending up to hila, and three patients had lymph nodes compressing biliary radicles. Adequate endoscopic biliary drainage was achieved in 30/44(68.18%), while 31.82% required percutaneous transhepatic biliary drainage (PTBD) after the failed ERCP, which was successful in all patients.

Table 5: ERCP findings in patients with benign biliary stricture (N=17) undergoing ERCP.

Type of stricture (Bismuth classification)	Type 1 = 12 (70.59%) Type 2 = 3 (17.65%) Type 3 = 2 (11.76%)
Successful biliary stenting	Yes = 9 (52.94%) No = 7 (47.06%)
Reason for failure of procedure	Tight biliary stricture

The failure of endoscopic biliary drainage was due to tight biliary stricture (12 patients) and gastric outlet obstruction (2 patients). (Table 6) Adequate endoscopic biliary drainage was achieved in 75%, 80%, and 50% cases of cholangiocarcinoma, periampullary carcinoma, and pancreatic head carcinoma, respectively. Types of hilar cholangiocarcinoma stricture seen were type 2, type 3a, type 4 in 3, 1, and 2 patients, respectively.

Discussion

This study in a young population (≤ 40 years of age) was done primarily to understand the spectrum, clinical features, and the usefulness of ERCP as a therapeutic or palliative modality in EHBO. In our study, choledocholithiasis and GBC were the most prevalent causes of EHBO. Despite having a younger study population, pancreaticobiliary malignancy was responsible for one-third cases of EHBO. Few studies available from India have investigated the

Table 6: ERCP finding in EHBO cases with gallbladder carcinoma.

Type of stricture in patient with high biliary stricture (Bismuth corlette classification) N=28 (63.64%)	Type 1 = 9 (32.14%) Type 2 = 12 (42.86%) Type 3 = 3 (10.71%) Type 4 = 4 (14.29%)
Direct infiltration of CBD not extending upto hila	13/44 (29.55%)
Nodes compressing biliary radicles	3/44 (6.82%)
Adequate biliary drainage achieved	Yes = 30/44 (68.18%), No = 14/44 (31.82%)
Reason for failure of endoscopic biliary drainage (N=14) †	Tight stricture = 12 (85.71%) Gastric outlet obstruction = 2 (14.29%)

†All patients sent for PTBD achieved adequate biliary drainage.

spectrum of EHBO but did not analyze the younger population separately.

In a large prospective study from AIIMS, Delhi¹, malignant causes were more common than benign (75.3% vs. 24.7%), and GBC (28.7%) and choledocholithiasis (12.4%) were the most common malignant and benign causes, respectively. Madhu *et al.*² observed malignant and benign causes in 63.3% and 36.6%. Verma *et al.*³ from Meerut studied 110 patients, reporting malignancy in 62.7% and benign causes in 37.2%. In their population, carcinoma head of the pancreas (33.6%) was the most common malignancy. In another study from North India, GBC was the most frequent malignant cause of EHBO⁹. Selvasekaran *et al.*¹⁰ reported that malignant causes (70%) were more common than the benign cause (30%) with periampullary carcinoma (34%) being the commonest malignancy.

All the above-mentioned studies found malignancy to be the commonest cause of EHBO; however, benign causes were predominant in our study, possibly because we studied only younger individuals, and the incidence of malignancy increases with age. A recent survey by Upadhyay *et al.*⁵ in 287 patients reported similar findings to our study (choledocholithiasis (67.9%) followed by malignant stricture (18.12%)). GBC was the most frequent malignant cause of EHBO in most of these studies, like the present study.

Most cases of EHBO were females (67.8%) like those reported by Upadhyay *et al.*⁵ (57.7%) and Madhu *et al.*² (65.6%). Choledocholithiasis (F=67.3%), GBC (F=72.73%) and benign biliary stricture (F=76.47%) was predominantly seen in females comparable to global

trends^{5,11,12}. Periampullary carcinoma (60%) had male preponderance like other studies^{3,13}.

The most common presenting symptoms were jaundice and pain abdomen, which have been reported in 66-88% and 51 to 66% of cases from different parts of the country.^{3,5} All malignant cases had jaundice at presentation as they were referred primarily for ERCP for biliary drainage. A clinically palpable hard lump was present in 56.8% cases with GBC, and this should be examined routinely with the caveat in mind that its absence doesn't rule out underlying malignancy.

The mean bilirubin and ALP levels were higher in malignant EHBO cases than benign cases, and the mean bilirubin level in choledocholithiasis (3.83 mg/dL) was like previous studies¹⁴. Thus, higher bilirubin levels could be an indicator of malignant pathology in patients with obstructive jaundice. Complete Charcot's triad may not be present in all patients with cholangitis, and fever or new-onset organ dysfunction in an appropriate clinical setting demands further evaluation. Elevated TLC with a neutrophilic predominance and renal dysfunction could help in identifying patients with cholangitis. GBC patients presented in an advanced stage of the disease, as is common throughout the country, and is associated with poor prognosis.⁹

Among patients with choledocholithiasis, single calculus was present in 62%, and ERCP achieved biliary clearance in 78.85%, comparable to a previous report by Upadhyay *et al.*⁵ Reasons for balloon method failure were large stones (≥ 15 mm), presence of biliary stricture, impacted calculi, and modified anatomy. Biliary stenting for benign biliary stricture was successful in 52.94%

cases, and failure was due to tight biliary stricture. Adequate endoscopic biliary drainage was achieved in 68.2% case of GBC, while the rest required percutaneous transhepatic biliary drainage (PTBD). Causes of failure in malignant cases were tight biliary stricture and gastroduodenal infiltration.

Conclusion

The present study highlights that benign causes, especially CBD stones, predominate in case of extra-hepatic biliary obstruction in younger patients under 40 years of age, and endoscopic therapy is rewarding. Also, malignancy (especially gallbladder carcinoma) contributes to a significant proportion of these cases, even among younger patients. Malignant EHBO cases present with advanced disease and endoscopic palliation is required for mitigating symptoms. Endoscopic palliative therapy has excellent results in most of these patients, and PTBD remains a reasonable alternative.

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