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CHOLANGIOCARCINOMA: CLINICAL AND LABORATORY TECHNIQUES WITH SPECIAL EMPHASIS ON IMAGING TECHNOLOGIES

Biljana Prgova Veljanova,[1,2] Sandra Dejanova,[1,2],Biljana Bozinovska,[1] Masa Kostova,[1,2]
Gordana Bozinovska-Beaka,[1,3],DimitarVeljanovski,[1,2], Martin Nedelkoski[4]
[1]PHI City General Hospital "8-mi Septemvri", North Macedonia,
[2]University Clinic of Radiology, Faculty of Medicine, Ss Cyril and Methodius University in Skopje, North Macedonia, [3]Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia,
[4]Clinical Hospital "Dr. Trifun Panovski", Bitola, North Macedonia

Abstract

Cholangiocarcinoma is a rare and highly aggressive malignancy of the biliary epithelium, marked by considerable anatomical heterogeneity and a largely nonspecific clinical presentation, factors that frequently contribute to delayed diagnosis. The purpose of this study was to examine the demographic, clinical, laboratory and imaging characteristics of patients with cholangiocarcinoma and to assess their relationship with imaging-based anatomical tumor classification.

This retrospective study included 40 adult patients with histopathologically confirmed cholangiocarcinoma diagnosed in General Hospital "8th September" in Skopje, Republic of North Macedonia, between January 2022 and December 2025. Clinical presentation, hepatobiliary laboratory parameters, and imaging findings obtained using contrast-enhanced computed tomography, and most often magnetic resonance imaging with magnetic resonance cholangiopancreatography were reviewed. Based on imaging findings, tumors were classified as intrahepatic, perihilar, or distal cholangiocarcinoma.

The study population demonstrated a male predominance (62.5%), with a mean age at diagnosis of approximately 68 years. Perihilar cholangiocarcinoma was the most commonly identified type (55%), followed by distal (27.5%) and intrahepatic tumors (17.5%). Jaundice and pruritus occurred exclusively in patients with extrahepatic disease, whereas all asymptomatic patients had intrahepatic tumors. Laboratory analysis revealed a marked cholestatic pattern in perihilar and distal cholangiocarcinoma, with substantially higher bilirubin, alkaline phosphatase, and gamma-glutamyl transferase levels compared with intrahepatic disease.

Overall, these findings highlight the importance of anatomical tumor classification and support the integrated use of imaging (MR and MRCP), clinical assessment, and laboratory data in the diagnostic evaluation of cholangiocarcinoma.

***Key words*:** Cholangiocarcinoma; Biliary tract neoplasms; Magnetic resonance cholangiopancreatography;

Introduction

Cholangiocarcinoma is a rare but highly aggressive malignant neoplasm arising from the epithelial cells of the intrahepatic and extrahepatic bile ducts. It represents the second most common primary malignancy of the liver after hepatocellular carcinoma and is associated with an unfavorable prognosis, high morbidity and mortality rates, and limited therapeutic options. The poor outcome is largely attributable to the insidious onset of disease, nonspecific clinical presentation, and delayed diagnosis, at a stage when curative treatment is rarely feasible. The incidence of cholangiocarcinoma increases with age, is slightly more common in men, and is most commonly diagnosed between the ages of 50 and 70 years.[1]

The pathogenesis of cholangiocarcinoma is closely linked to chronic inflammation of the biliary epithelium. Prolonged exposure to inflammatory mediators leads to repeated cycles of epithelial injury and regeneration, resulting in the accumulation of genetic and epigenetic alterations that promote malignant transformation. Chronic biliary inflammatory conditions, including primary sclerosing cholangitis, recurrent cholangitis, biliary strictures, and hepatolithiasis as well as chronic liver disease are recognized as major risk factors and constitute the central pathophysiological basis of the disease. Lifestyle, environmental, and metabolic factors, such as type 2 diabetes, obesity, alcohol consumption, and cigarette smoking also increase the risk of developing cholangiocarcinoma.[2]

Clinically, cholangiocarcinoma presents with largely nonspecific and variable symptoms, such as abdominal discomfort, fatigue, weight loss, pruritus, and intermittent or progressive jaundice, frequently resulting in significant diagnostic delay. Laboratory findings typically demonstrate a cholestatic biochemical profile, with elevated alkaline phosphatase, gamma-glutamyltransferase, and direct bilirubin levels, as well

as moderately increased transaminases. Tumor markers, particularly carbohydrate antigen 19-9 (CA 19-9), and in some cases carcinoembryonic antigen (CEA), may be elevated and serve as adjunctive diagnostic and prognostic indicators, although their specificity is limited.[3]

Cholangiocarcinoma is a heterogeneous entity and can be classified according to **a**natomical location, growth pattern, and extent of biliary involvement, all of which have important diagnostic and therapeutic implications.

According to anatomical location, cholangiocarcinoma is divided into:

- Intrahepatic cholangiocarcinoma, which typically presents as a mass-forming lesion within the hepatic parenchyma, often associated with peripheral bile duct dilatation;
- Perihilar cholangiocarcinoma (Klatskin tumor), the most common type, arising at the hepatic duct confluence and predominantly manifesting as biliary strictures;
- Distal extrahepatic cholangiocarcinoma, involving the distal common bile duct and frequently causing proximal biliary dilatation;

Based on growth pattern, cholangiocarcinoma can be classified as :

- mass-forming;
- periductal infiltrating;
- intraductal growing type;

each demonstrating distinct imaging features on cross-sectional imaging and MRCP.

Perihilar cholangiocarcinoma is the most commonly encountered type, accounting for approximately 50% of cases. Distal (40%) and intrahepatic cholangiocarcinoma (10%) are less common.

Radiological imaging plays a central role in the diagnosis of cholangiocarcinoma. Ultrasound is often used as the initial imaging modality and may reveal bile duct dilatation or a hepatic mass. Cross-sectional imaging with contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) provides more detailed evaluation, allowing assessment of tumor location, extent, staging and vascular involvement.[4]

Magnetic resonance cholangiopancreatography (MRCP) has emerged as the imaging modality of choice for the noninvasive evaluation of the biliary tree. MRCP provides high-resolution visualization of the bile ducts, allowing precise detection and characterization of strictures, interruptions, and ductal dilatation, as well as assessment of the length and extent of tumor infiltration.

Unlike invasive techniques, MRCP enables comprehensive anatomical assessment without ionizing radiation or potentially nephrotoxic contrast agents. The advantages and disadvantages of each imaging modality are summarized in Table 1.

In clinical practice, a multimodal imaging approach allows for a more accurate diagnosis, staging, and treatment planning as the combined use of these modalities provides a more comprehensive assessment than any individual technique alone.

Table 1: Imaging modalities used in evaluation of cholangiocarcinoma

Feature	CT	MRI	MRCP
Imaging principle	X-ray–based cross-sectional imaging, contrast enchansed	Multiplanar T1/T2, DWI, contrast-enhanced sequences	Heavily T2-weighted sequences for fluid-sensitive biliary imaging
Visualization of bile ducts	Indirect; based on contrast enhancement and secondary dilatation	Indirect; enhanced when combined with MRCP	Direct, high-resolution visualization of the biliary tree
Detection of biliary strictures	Moderate sensitivity, subtle strictures may be missed	High sensitivity with contrast and diffusion imaging	High sensitivity and specificity for detection and characterization
Tumor morphology	Good for mass-forming tumors; limited for infiltrative disease	Excellent soft-tissue contrast for mass-forming and infiltrative tumors	Superior delineation of periductal and intraductal growth
Longitudinal tumor extent	Limited accuracy, especially in perihilar tumors	Good assessment; improved with MRCP	Superior assessment of stricture length and ductal involvement
Anatomical classification	Limited biliary mapping	Accurate when integrated with MRCP	Optimal for anatomical classification and ductal mapping

Vascular involvement	Excellent arterial and venous assessment	Good to excellent with contrast-enhanced sequences	Limited alone
Nodal/metastatic disease	Good detection of nodal and distant metastases	Good sensitivity, particularly for liver lesions	Limited; complementary role
Benign vs malignant strictures	Limited specificity	Improved differentiation with diffusion and contrast	High confidence based on ductal morphology
Contrast / radiation	Iodinated contrast; radiation exposure	Gadolinium contrast; no radiation	No contrast required; no radiation
Primary clinical role	Staging, resectability, vascular invasion	Local tumor characterization and staging	Biliary mapping and diagnostic classification

The aim of this study was to characterize the demographic, clinical, and laboratory features of cholangiocarcinoma and to relate them to imaging-based anatomical tumor classification.

Materials and methods

This study was designed as a retrospective analysis based on review of medical records and included patients diagnosed with cholangiocarcinoma at a single public health care center in Skopje, Republic of North Macedonia, over a four-year period from January 2022 to December 2025.[5]

A total of 40 adult patients with a confirmed diagnosis of cholangiocarcinoma were included in the study. Eligibility criteria comprised age ≥18 years and histopathological confirmation of cholangiocarcinoma obtained through biopsy or surgical specimens within the time frame included in the study. Patients with incomplete diagnostic documentation or biliary obstruction caused by non-biliary primary malignancies were excluded from the analysis.

Initial evaluation in most patients began with abdominal ultrasonography, performed either as part of routine clinical assessment or in response to symptoms suggestive of hepatobiliary disease. Based on ultrasonographic findings and clinical suspicion, patients were referred to gastroenterology specialists and subsequently underwent cross-sectional imaging for further diagnostic evaluation. Definitive imaging assessment was performed using contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP). Four patients underwent contrast-enhanced abdominal CT only, while the remaining 36 patients underwent MRI with MRCP; several of these patients also had CT examinations prior to MRI. Ultrasonography findings were not systematically analyzed, as a proportion of the examinations were performed outside the study institution and complete imaging data were not uniformly available.[6]

Contrast-enhanced abdominal CT examinations were performed using a standardized multiphase protocol following intravenous administration of iodinated contrast material, typically including arterial, and portal venous phases. This approach enabled evaluation of tumor morphology, vascular involvement, regional lymphadenopathy, and the presence and level of biliary obstruction. MRI examinations were conducted using a dedicated hepatobiliary protocol that included T1-weighted and T2-weighted sequences, diffusion-weighted imaging, and dynamic contrast-enhanced sequences after gadolinium administration. MRCP was performed using heavily T2-weighted sequences to allow detailed, noninvasive visualization of the intrahepatic and extrahepatic bile ducts, facilitating precise localization of biliary strictures and tumor extent. According to imaging findings tumors were classified into intrahepatic, perihilar (Klatskin tumors), or distal cholangiocarcinoma, based on their anatomical location within the biliary tree.[7]

Demographic data, including age and sex, risk factors, clinical presentation at the time of diagnosis, as well as laboratory findings were retrospectively extracted from medical records, admission notes, and clinician reports. Of all available laboratory parameters, only those reflecting the hepatobiliary function were analyzed, including serum bilirubin, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). All laboratory analyses were performed in the hospital's central laboratory using standardized methods, and results were recorded in conventional units. All collected data underwent statistical analysis, and the results are presented as numbers and percentages for categorical variables and as median values with ranges for continuous variables.[8]

The study was conducted in accordance with the principles of the Declaration of Helsinki. Owing to the retrospective design and the use of anonymized medical record data, informed consent was waived.

Results

A total of 40 patients diagnosed with cholangiocarcinoma at a single public health care center in Skopje, Republic of North Macedonia in a period of 4 years were included in this study. 25 (62,5%) of them were men and 15 (37.5%) women. Age at the time of diagnosis ranged from 40 to 80 years, with a mean age of approximately 68 years. Most patients were diagnosed after the age of 60, with 16 patients (40 %) in the 60 to70-year age group and 11 patients (27.5%) aged between 70 and 80 years. Patients aged 50 to 60 years accounted for 9 cases (22.5%), while only 4 patients (10 %) were younger than 50 years (Table 2).

Table 2: Age distribution of patients

Patient's age	40-50	50-60	60-70	70-80	Total
Number of patients	4 (10%)	9 (22.5%)	16 (40%)	11 (27.5%)	40

Based on imaging classification, perihilar cholangiocarcinoma was the most frequently identified type, observed in 22 patients (55 %). Distal cholangiocarcinoma was diagnosed in 11 patients (27.5%), while intrahepatic cholangiocarcinoma was less common, occurring in 7 patients (17.5%). This distribution was consistent across all age groups, with perihilar tumors representing the majority of cases in each decade

(Table 3, Chart 1).

Table 3: Cholangiocarcinoma types distribution in different age groups

Patient's age	**Cholangiocarcinoma types**			**Total**
	Perihilar	**Distal**	**Intrahepatic**	
40-50 yo	2	1	1	4
50-60 yo	5	3	1	9
60-70 yo	9	4	3	16
70-80 yo	6	3	2	11
Total	22	11	7	40

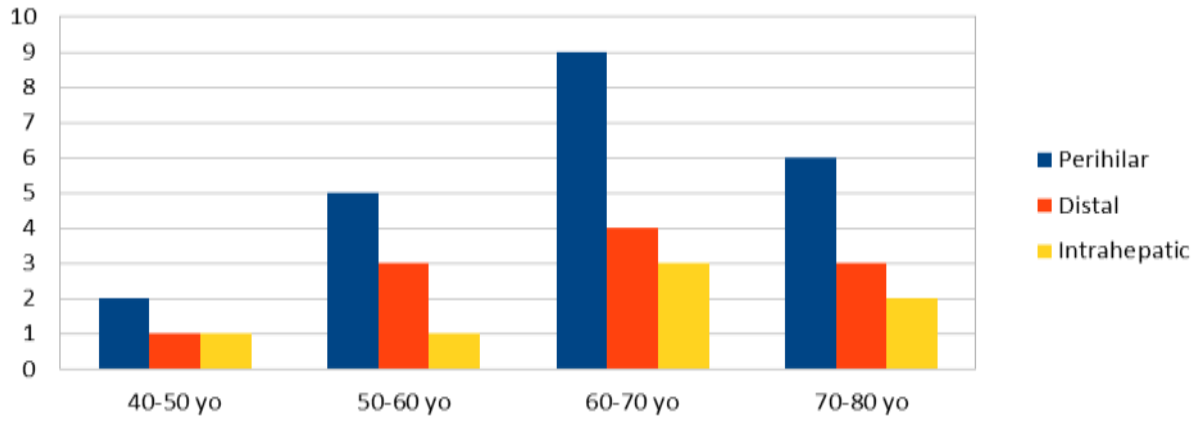


Chart 1: Cholangiocarcinoma types distribution in different age groups

Imaging findings

In all patients, tumor localization and anatomical classification were established using contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging with magnetic resonance cholan-

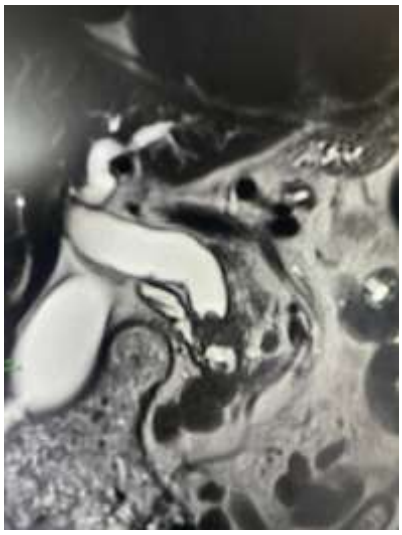
giopancreatography (MRI/MRCP). MRI with MRCP represented the primary imaging modality in 36 patients (90%), while in 4 patients (10%) the diagnosis was based exclusively on contrast-enhanced CT.

Perihilar cholangiocarcinoma most commonly appeared as irregular biliary strictures at the level of the hepatic duct confluence, associated with marked dilatation of the intrahepatic bile ducts. In several cases, a periductal infiltrating growth pattern was observed without a clearly defined mass lesion.[9]

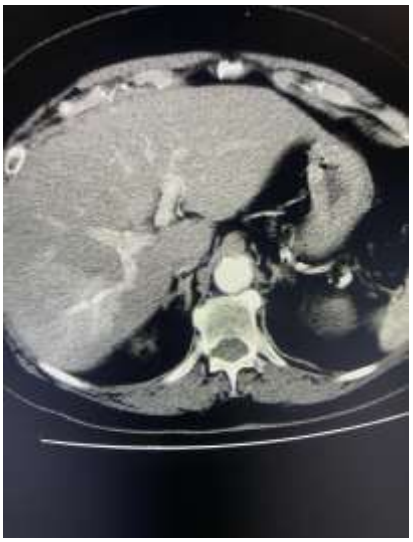
Distal cholangiocarcinoma was typically visualized as a short-segment stricture of the distal common bile duct, frequently accompanied by upstream biliary dilatation and, in some cases, gallbladder enlargement.

Intrahepatic cholangiocarcinoma predominantly presented as a mass-forming lesion within the hepatic parenchyma, often associated with peripheral bile duct dilatation. These lesions frequently demonstrated heterogeneous contrast enhancement and diffusion restriction on diffusion-weighted imaging sequences.[10]

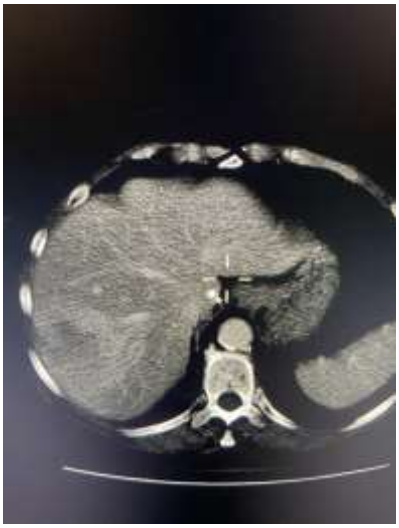
MRCP allowed accurate delineation of biliary anatomy, precise assessment of stricture length and extent, and reliable differentiation between intrahepatic, perihilar, and distal tumor locations, particularly in patients with perihilar disease.



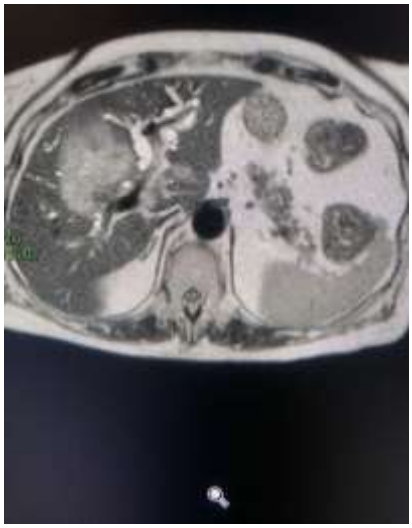
Picture 1. MRCP distal cholangiocarcinoma



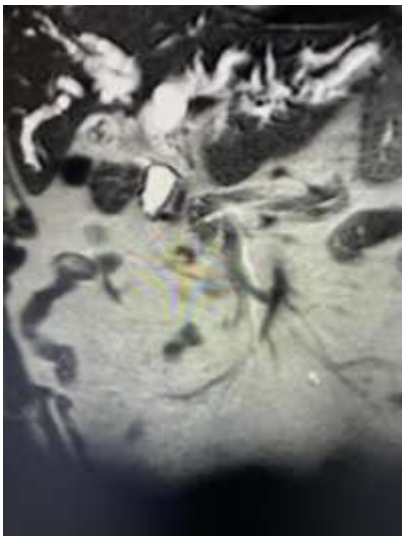
Picture 2. CT intrahepatic cholangiocarcinoma



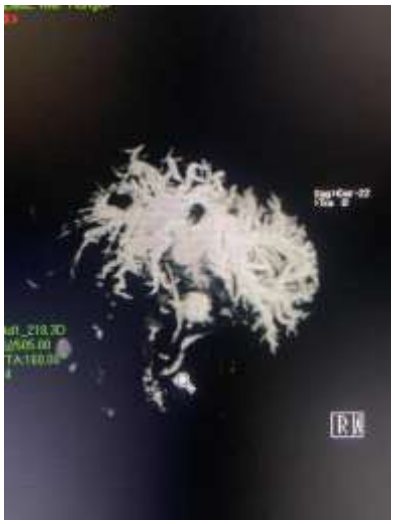
Picture 3. CT intrahepatic cholangiocarcinoma



Picture 4. MR intrahepatic cholangiocarcinoma



Picture 5. MR prihilar cholangiocarcinoma



Picture 6. MRCP perihilar cholangiocarcinoma

Clinical presentation varied and showed a clear relationship with the type of cholangiocarcinoma. Jaundice was present in 24 patients (60 %) and was observed only in patients with perihilar or distal cholangiocarcinoma. Another symptom appearing exclusively in patients with the extrahepatic types was pruritus, detected in 19 patients (47.5%). Nausea and vomiting were the most commonly reported symptoms overall, occurring in 28 patients (70%). Right upper quadrant abdominal pain was less frequent, reported in 7 patients (17.5%). In addition, nonspecific symptoms were commonly noted, including weight loss in 18 patients (45%), abdominal discomfort in 14 patients (35%), and fatigue in 12 patients (30%). Four patients (10%) were asymptomatic at the time of diagnosis and each of them had a cholangiocarcinoma that was classified as intrahepatic on imaging (Table 4).

Table 4. Clinical presentation

Symptoms	**Number of patients**
Nausea and vomiting	28 (70%)
Jaundice	24 (60%)
Pruritus	19 (47.5%)
RUQ abdominal pain	7 (17.5%)
Weight loss	18 (45%)
Abdominal discomfort	14 (35%)
Fatigue	12 (30%)
Asymptomatic	4 (10%)

Laboratory findings were consistent with imaging features of biliary obstruction, particularly in patients with perihilar and distal tumors. Median total bilirubin levels were highest in perihilar cholangiocarcinoma (186.9 μmol/L; range 38.4–501.2), followed by distal cholangiocarcinoma (171.3 μmol/L; range 29.7–428.6). Patients with intrahepatic cholangiocarcinoma demonstrated lower median total bilirubin levels (83.5 μmol/L; range 9.8–232.1). Direct bilirubin levels showed a similar distribution. Marked elevations in alkaline phosphatase and gamma-glutamyl transferase were observed across all tumor types, with the highest median values seen in perihilar disease. Transaminase levels were moderately elevated in all groups, with slightly higher median AST and ALT values noted in patients with intrahepatic cholangiocarcinoma (Table 5).

Table 5. Laboratory findings in patients diagnosed with cholangiocarcinoma

Parameter	Type of cholangiocarcinoma		
	Perihilar	Distal	Intrahepatic
Total bilirubin (μmol/L)	**186.9** (38.4-501.2)	**171.3** (29.7-428.6)	**83.5** (9.8-232.1)
Direct bilirubin (μmol/L)	**141.8** (22.6-356.4)	**127.9** (18.9-319.5)	**51.2** (3.9-168.4)
Indirect bilirubin (μmol/L)	**45.1** (7.4-161.8)	**43.4** (6.1-112.7)	**32.3** (4.2-91.6)
ALP (U/L)	**612.4** (182-1420)	**548.2** (160-1210)	**389.7** (132-820)
GGT (U/L)	**748.6** (128-2050)	**692.3** (110-1780)	**502.4** (95-1140)
AST (U/L)	**102.8** (34-315)	**91.6** (32-256)	**118.9** (40-340)
ALT (U/L)	**94.1** (29-284)	**85.4** (30-250)	**109.6** (35-310)

Several pre-existing conditions associated with cholangiocarcinoma were identified in the study population. Chronic biliary inflammation was the most frequently documented condition, present in 18 patients (45 %). Gallstone disease was identified in 9 patients (22.5%), while chronic hepatitis was reported in 4 patients (10 %).

Discussion

Cholangiocarcinoma remains a heterogeneous and clinically challenging malignancy, with marked variability in anatomical distribution, clinical presentation, and laboratory characteristics. In this single-center study, we aimed to provide a focused overview of cholangiocarcinoma characteristics in a population of 40 patients and offers an opportunity to compare local findings with those reported in the literature.[11]

In this cohort, males comprised 62.5% of the patients, producing a male-to-female ratio of 5:3 (1,6:1), which is consistent with prior reports demonstrating a male predominance in cholangiocarcinoma across diverse populations. Large epidemiological studies from Europe and North America have demonstrated male-to-female ratios ranging from approximately 1.2:1 to 1.7:1, suggesting a modest but reproducible sex-related difference in incidence (Tyson and El-Serag, 2011; Bridgewater et al., 2014). Similar sex distributions have also been noted in population-based Asian cohorts, despite regional differences in underlying risk factors (Banales et al., 2020).[12]

The mean age at diagnosis in our study, approximately 68 years, further supports existing evidence that cholangiocarcinoma is predominantly a disease of older adults. Several large series have reported median ages at diagnosis between 65 and 72 years, with the majority of cases occurring after the sixth decade of life (Razumilava and Gores, 2014; Alabraba et al., 2019; StatPearls Publishing, 2024).[13]

In the present series, perihilar cholangiocarcinoma was the most frequently identified type, accounting for 55% of cases, followed by distal (27.5%) and intrahepatic tumors (17.5%). This anatomical distribution closely parallels that observed in multiple Western clinical series, where perihilar tumors typically represent 50–60% of all cholangiocarcinomas (DeOliveira et al., 2007; StatPearls Publishing, 2024). Despite recent epidemiological data demonstrating a rising incidence of intrahepatic cholangiocarcinoma, particularly in high-income countries, perihilar disease continues to be the most

common type in many hospital-based cohorts (Saha et al., 2016).[14]

In our study, perihilar cholangiocarcinoma predominated across all age groups. This pattern differs from findings reported by Reddy et al. 2023, in which younger patients demonstrated a higher relative frequency of intrahepatic cholangiocarcinoma. However, the small number of younger patients in our study limits meaningful comparison, and this discrepancy is likely influenced by sample size and referral patterns rather than reflecting a true difference in disease distribution.

Clinical presentation in our cohort showed a strong relationship with tumor location, a finding that is well established in the literature. Jaundice and pruritus were observed exclusively in patients with perihilar or distal cholangiocarcinoma, reflecting the cholestatic nature of extrahepatic tumors. Previous studies have outlined jaundice as the most common presenting symptom in extrahepatic cholangiocarcinoma, occurring in up to 80% of patients, whereas it is significantly less frequent in intrahepatic disease (DeOliveira et al., 2007; Rizvi and Gores, 2013).[15]

In our study, all the patients who were asymptomatic at the time of diagnosis had intrahepatic disease. This finding is in keeping with prior reports indicating that intrahepatic cholangiocarcinoma is commonly clinically silent, meaning it presents without symptoms or with vague, nonspecific clinical manifestations in the early stages of disease, often being incidentally detected (Endo et al. 2008, Rizvi and Gores, 2013).

Laboratory findings in this study were characteristic of cholestatic liver injury, particularly in patients with perihilar and distal tumors. Median total and direct bilirubin levels were markedly elevated in these groups, reflecting mechanical biliary obstruction, whereas patients with intrahepatic cholangiocarcinoma exhibited substantially lower bilirubin levels. Similar biochemical patterns have been described in comparative analyses, where extrahepatic cholangiocarcinoma is associated with pronounced hyperbilirubinemia, while intrahepatic tumors may present with near-normal bilirubin values until late in the disease course (Blechacz and Gores, 2008; Alabraba et al., 2019). Mild to moderate elevations in transaminases were noted in all groups, with slightly higher median AST and ALT levels in intrahepatic cholangiocarcinoma. This pattern has been attributed to greater involvement of hepatic parenchyma in intrahepatic tumors and has been observed in earlier clinicopathological studies (Endo et al., 2008).

Regarding the risk factors, we have noted chronic biliary inflammation in 45 % of the patients and gallstones were identified in nearly a quarter of the patients. These observations support the central role of chronic inflammation in cholangiocarcinogenesis, a concept that has been extensively documented in the literature. While the independent contribution of gallstones remains debated, chronic mechanical and inflammatory injury to the biliary epithelium has been proposed as a potential mechanistic link (Tyson and El-Serag, 2011; StatPearls Publishing, 2024).

Conclusion

This single-center study demonstrates a clear correlation between cholangiocarcinoma subtype and the demographic, clinical, and biochemical characteristics of the disease, closely mirroring patterns reported in the international literature. Our findings highlight the importance of anatomical tumor classification in predicting clinical presentation and laboratory abnormalities in patients with cholangiocarcinoma. Despite the modest sample size, the consistency of our results with those from larger, multicenter studies supports the external validity of our observations.Importantly, our results underscore the central role of magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography (MRCP) in the diagnostic evaluation of cholangiocarcinoma. MRI/MRCP enabled accurate noninvasive visualization of the biliary tree, precise anatomical tumor classification, and reliable assessment of the extent of biliary involvement, particularly in perihilar disease. This comprehensive anatomical mapping is essential for early diagnosis, appropriate staging, and treatment planning.Early and accurate diagnosis remains a critical determinant of therapeutic options and prognosis in cholangiocarcinoma. Given the nonspecific nature of early symptoms and the frequent diagnostic delay—especially in intrahepatic disease—heightened clinical awareness is essential. Prompt evaluation of patients presenting with jaundice, pruritus, unexplained cholestasis, or persistent constitutional symptoms, combined with timely MRI/MRCP assessment, should be prioritized, as earlier diagnosis may facilitate timely intervention and improve clinical outcomes.

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