Clinical Characteristics and Risk Factors of Different Types of Bile Duct Cancer in Upper Egypt

Ahlam M. Sapra[a], Mohammed Wahman[b], Mohammed Tag Eldeen Said [a], Ola Mohammed Fouad [a *], Mohamed Alsenbesy[a,c]

[a] Department of Internal Medicine, Faculty of Medicine, South Valley University, Qena, Egypt.
[b] Department of Medical Oncology, Faculty of Medicine, South Valley University, Qena, Egypt.
[c]Department of Internal Medicine, Faculty of Medicine and Medical Sciences (FMMS), Arabian Gulf University (AGU), Bahrain.

Abstract

Background: Cholangiocarcinoma (CCA) is a cancer that emerges from the biliary epithelium neoplastic transformation and has a steadily increasing incidence and prevalence. It is the 2nd most prevalent primary hepatic cancer, accounting for around 15% of cases and 3% of GITcancers.

Objectives: are to determine risk factors and prevalence for various forms of Cholangiocarcinoma (CCA).

Patients and methods: A prospective study was conducted at Qena university hospital on 62 patients with cholangiocarcinoma proved by imaging, cytological or pathological evidence. Complete full history was taken, then full clinical examination and laboratory study were done.

Result: Prevalence of distal cholangiocarcinoma was 56.5%, but hilar cholangiocarcinoma was 43.5% (n=27). A significant relation between gender and type of cholangiocarcinoma, where hilar type was more common among females P value= 0.02. Also, a significant relation between smoking and obesity and type of cholangiocarcinoma where distal type was more common among smokers and obese patients (P = 0.05 and P=0.03 respectively).

Conclusion:Gender variation, smoking and obesity are the most important risk factors of cholangiocarcinoma, with hilar type more common among females, distal type more common among smokers and obese patients. Distal cholangiocarcinoma is more prevalent than hilar cholangiocarcinoma (56.5% and 43.5% respectively).

Key words: Cholangiocarcinoma, upper Egypt, bile duct carcinoma.

Introduction

The second leading cause of cancer-related death worldwide is primary hepatic cancer. In most countries, hepatocellular carcinoma is the most common form of primary hepatic cancer, accounting for approximately 80% of cases **(Tohet al., 2019)**.

Cholangiocarcinoma (CCA) is the 2nd most common primary hepatic cancer, accounting for around 15% of cases and 3% of GITcancers. It has a broad geographic range due to exposure to multiple risk factors. Incidence of liver cancer has increased in many areas, according to some studies, but has decreased in some Asian countries **(Khan et al., 2019)**.

The biliary tree gives rise to a heterogenousgroup of cancers known as CCA. It is divided into three subtypes based on anatomic location: perihilar (60–70%), distal (20–30%), and intrahepatic (15–20%), which have similarities but also significant inter-tumor and intra-tumor variations that can influence pathogenesis and prognosis**(Khan et al., 2019)**.

TheUnion for International Cancer Control (UICC) and World Health Organization (WHO) currently classify cancers into only two groups based on their anatomic origin from the biliary tract **(Liao and Zhang, 2020)**:

1. Intrahepatic cholangiocarcinoma (ICC), which accounts for around 20% of all tumours; iCC emerges from the intrahepatic proximal biliary ducts **(Liao and Zhang, 2020)**.
2. Extrahepatic bile duct carcinoma (eBDC), which accounts for 80% of all cholangiocarcinomas; eBDC encompasses tumours that arise from the large hilar biliary ducts (Klatskin tumours) to extrahepatic biliary ducts located more distally, excluding ducts that emerge from ampulla of Vater. It can spread from liver hilum to perihilar intrahepatic parenchyma as a tumor at diagnosis time, making it difficult to pinpoint its origin **(Liao and Zhang, 2020).**

The majority of cholangiocarcinomas are adenocarcinomas that are well, moderately, or poorly differentiated, while other subtypes are histologically infrequent. Slow growth is a hallmark of these tumours, with locally infiltrating pattern. Desmoplastic stroma, immune response, angiogenesis, and fibrogenic mechanism are all characteristics of carcinogenesis. From 1979 to 2004, there was an increase in mortality rates, owing primarily to increasing incidence rates, especially among patients above the age of 65, who accounted for 72 percent of deaths related to cholangiocarcinoma in 2004. **(Nakanuma et al., 2010)**.

The ICC incidence rises with age, and its peak lies between 55 and 75 years old.ICC incidence is somewhat higher in males than females, resembling the other biliary tract cancers. **(Komuta et al., 2012)**

Surgical treatment is the best choice for all types, but it must take into account the presence of lymph nodes and vascular structures. Cholangiocarcinoma's highly desmoplastic pattern, substantial support from a rich tumor micro-environment, and extensive genetic heterogeneity, all led to its resistance. While surgery and liver transplantation are choices for some perihilar cholangiocarcinoma patients, 5-year survival rates still extremely poor **(Doherty et al., 2017)**. Gemcitabine and cisplatin are used in the treatment of inoperable cases. Intrahepatic cholangiocarcinoma is treated with locoregional therapies, but there is no definitive proof of efficacy. Cholangiocarcinoma biology understanding, the disease's oncogenic landscape, and its complex relationship with tumour microenvironment could produce more effective therapies and longer patient survival **(Sergi, 2020).**

Patients and methods

Study type and region

This prospective study was conducted at Internal Medicine Clinic in Qena university hospital.

Study population

This study was conducted on 62 patients presented with cholangiocarcinoma proved by imaging, cytological or pathological evidence from the outpatient clinic in Qena University hospital.

Sample size

We enrolled 62 patients with cholangiocarcinoma.

Inclusion criteria

- All patients presented with cholangiocarcinoma proved by imaging, cytological or pathological evidence, along the period of study from September 2019- august 2020; were included.

Exclusion criteria

Patients have any of the followings:

- Pancreatic cancer.
- Hepatocellular carcinoma.
- Ampulla of Vater cancer.

Study tools

From each patient the following data had been collected upon admission

i. Written consent before therapy

ii. Initial assessment:

Complete full history taking, including:

1. Age.
2. Gender.
3. History Of DM
4. History Of HCV
5. Special Habits of Medical Importance Like Smoking.
6. Family history of Git malignancies

iii. Full clinical examination.

iv. Investigations:

Laboratory study

- Liver profile: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, total bilirubin & direct bilirubin, prothrombin time and INR.
- Alpha-Feto protein (AFP), carbohydrate antigen [CA] 19-9, and carcino-embryogenic antigen [CEA].
- Renal function tests: serum creatinine.
- HCV Ab. & HBsAg (Hepatitis B surface antigen).

Time schedule of the study

Topic	Period
Preparatory phase	One month
Design of examination sheet	Two months
Review of literature	One month
Collection, organization, entering of data and statistical analysis	One year

Administrative and Ethical Design

- An Official permission was obtained from Faculty of Medicine, Qena University.
- An official permission was obtained from the internal medicine in Qena university hospital.
- Approval from ethical committee in the faculty of medicine (Institutional Research Board IRB).

Data management and Statistical Analysis

All data were collected, tabulated and statistically analysed using statistical package of special science SPSS version 23 (SPSS Inc. Chicago, IL, U.S.A) as follow:

1) Editing and coding.
2) Data entry in computer.
3) Quantitative data were stated as mean ± standard deviation (SD) for parametric data, median and range for non- parametric data.
4) Qualitative data were expressed as frequencies and percentage.
5) Data were handled using appropriate statistical tests of significance such as:
   a) Independent t-test and mann-whitney test were used to calculate difference between quantitative variables in two groups.
   b) Chi square test ($\chi 2$) was used to calculated difference between qualitative variables.
   c) All statistical comparison was two tailed with significance level of p-value $\leq$ 0.05 indicates significant, p-value <0.001 indicates highly significant difference while p-value > 0.05 indicates non-significant difference.
   d) Survival curve was carried out.

Results

This study was conducted on 62 patients presented with cholangiocarcinoma proved by imaging, cytological or pathological evidence from the outpatient clinic in Qena University hospital. Every patient underwent full history taking, full clinical examination, andlaboratory Investigation including: (ALT), aspartate aminotransferase (AST), serum albumin carbohydrate antigen [CA] 19-9, and carcino-embryogenic antigen [CEA]. Renal

function tests: serum creatinine. HCV Ab. & HBsAg (Hepatitis B surface antigen).

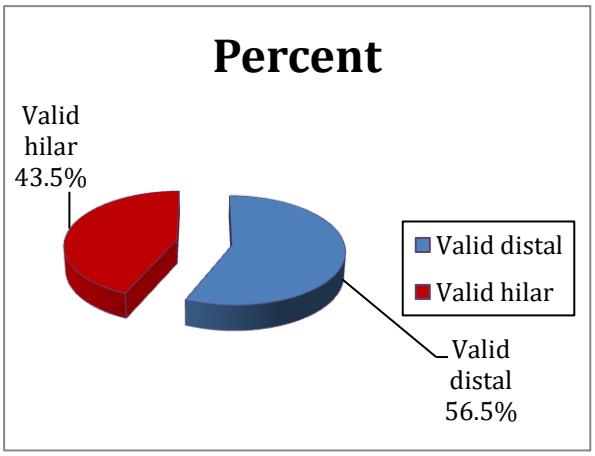

Fig.1. Percent of types of cholangiocarcinoma in the studied groups.

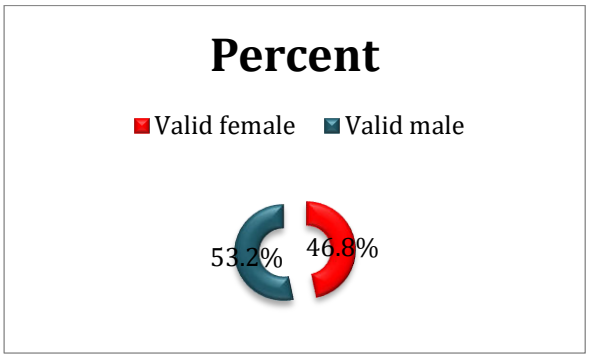

Fig.2. Percent of male and female in the studied groups

Table 1. Basic information of the studied groups

Variable	Number (percent)
DM	24 (38.7%)
HTN	13(21%)
Smoking	30 (48.3%)
Liver cirrhosis	11 (17.7%)
HBV	2 (3.2%)
HCV	18 (29%)
Obesity	53 (85.4%)
Family history of GIT malignancies	16 (25.8%)

Table 2. Basic information of the studied groups

Variable	Median
Age	62(35-82)
ALP	447(126-2134)
AST	57(16-624)
ALT	65(19-457)
S.Cr	1.1(0.4-2.6)
CA 19-9	150(5.5-16584.0)

This study aimed to determine Clinical characteristics and risk factors of different types of Cholangiocarcinoma in Upper Egypt. Prevalence of distal cholangiocarcinoma is 56.5%, but hilar cholangiocarcinoma was 43.5% (n=27) (**Figure 1**), 53.2 %(n=35) of cases where male while 46.8% where females (**Figure 2**), their ages where between 35 and 82 years. **Table 1** and **Table 2** show basic information of the studied groups.

Table 3 shows that a significant relation between gender and type of cholangiocarcinoma, where hilar type is more common among females p value= 0.02.

There was a significant relation between smoking and type of cholangiocarcinoma where distal type is more common among smokers P value = 0.05.

There was a statistically significant relation between obesity and type of cholangiocarcinoma, where distal type was more common among obese patient, P value= 0.03.

Table 4 shows thatthere was no significant relationship between cholangiocarcinoma and Age, ALP, AST, ALT and CA 19-9

Discussion

The prevalence and incidence ofcholangiocarcinomaare increasing progressively. The majority of cholangiocarcinomas develop de novo, with no known risk factors. However,primary sclerosing cholangitis, bacterial infections, hepatolithiasis, biliary-duct cysts, and toxins are all known risk factors for CC. hepatitis B

virus (HBV),hepatitis C virus (HCV), Inflammatory bowel disease (IBD), diabetes, obesity, cirrhosis, smoking, alcohol, and host genetic polymorphisms are all less well-known possible risk factors **(Zheng et al,. 2017)**.

Above risk factors cause biliary epithelium chronic inflammation in addition to partial bile obstruction. These two factors are thought to be the background (chronic inflammation) that favours the development of cancer **(Petrick et al., 2018)**.

Surgical radical resection is the only treatment that is effective but, it is applicable in only less than 40% of CCA patients, as CCA is frequently diagnosed at end stage. This is due to the silent pattern of CCA in the most of CCA patients, and symptoms only appear at end stages. Also, lack of accurate biomarkers necessary for screening purpose contribute to late diagnosis. Many bile and serum biomarkers have been proposed recently for CCA diagnosis but they still under evaluationrelating their effect on early diagnosis poor **(Doherty et al., 2017)**.

Table 3. Comparison of qualitative data of the studied groups according to type of cholangiocarcinoma

Variable		Distal (n=35)	Hilar (n=27)	P
Gender	**Female**	12(34.3%)	17(63%)	0.02*
	Male	23(65.7%)	10(37%)	
Locality	**Rural**	20(57.1%)	12(30%)	0.4
	Urban	15(42.9%)	28(70%)	
DM	**Yes**	12(34.3%)	12(44.4%)	0.5
	No	23(65.7%)	15(55.6%)	
HTN	**Yes**	8(22.9%)	5(18.5%)	0.5
	No	27(77.1%)	22(81.5%)	
Smoking	**Yes**	20(57.1%)	10 (37%)	0.05*
	No	15(42.9%)	17 (63%)	
Liver cirrhosis	**yes**	4(12.1%)	7(28%)	0.2
	No	29(87.9%)	18(72%)	
HBV	**Yes**	0(0%)	2(7.8%)	0.1
	No	35(100%)	25(92.6%)	
HCV	**Yes**	9(25.7%)	9(33.3%)	0.5
	No	26(74.3%)	18(66.7%)	
Obesity	**Yes**	33(94.3%)	20(74.1%)	0.03*
	No	2(5.7%)	7(25.9%)	
Family history of GIT malignancies	**Yes**	12(34.3%)	16(59.3%)	0.8
	No	23(65.7%)	11(40.7%)	

* Chi-square test was used to compare proportions between groups.

* Statistically significant at < 0.05

Table 4. Comparison of continuous data of the studied groups according to type of cholangiocarcinoma

Variable	Distal	Hilar	P
Age (years) mean rank	29.8	33.7	0.38
ALP mean rank	29.6	32.2	0.5
AST mean rank	32.9	28.5	0.33
ALT mean rank	32.9	28.5	0.33
S.Cr	30.2	31.9	0.7
CA 19-9 mean rank	32.3	30.4	0.6

* Mann—Whitney test.

* Statistically significant at < 0.05

Gad et al. (2020) found that mortality and incidence and of cholangiocarcinoma were 10.295 and 11.977. Both mortality and incidence were higher in males, Asians, and individuals more than 65 years old.

In our results there was a significant relation between smoking and type of cholangiocarcinoma where distal type is more common among smokers p value = 0.05.

Cigarette smoking has been investigated as a risk factor for CCA. A meta-analysis of case-control studies was done in 2012 showed borderline evidence of relationship between smoking and intrahepatic cholangiocarcinoma (OR 1.31, 95% CI 0.95-1.82). However, high level of heterogeneity existed among the included studies **(Palmer and Patel, 2012**). Several studies reported a positive relationship between smoking and intrahepatic cholangiocarcinoma recently (HR = 1.47, 95% CI 1.07-2.02 and OR = 1.46, 95% CI 1.28-1.66 respectively) **(Petrick et al., 2018).**Eleven case-control meta-analysis studies informed an increased risk for extrahepatic cholangiocarcinoma in smokers, in comparison with non-smokers (summary RR = 1.23; 95% C 1.01-1.50) **(Ye et al., 2013).**

Different results are obtained by **Burak et al. (2004)** studywhere it did not consider smoking as a risk factor, while **Berquist et al. (1998)** case-control study reported a significant relationship (ten patients vs. zero patients, p <0.0004). There are no conclusive data confirmed that smoking and/or alcohol can elevate the risk of cholangiocarcinoma in primary sclerosing cholangitis patients.

In our current study there was no significant relation between hepatitis B virus (HBV), Hepatitis C virus (HCV) and liver cirrhosis and cholangiocarcinoma type.**Zhou et al. (2019)**, a study conducted in China,showed a similar resultsrelating extrahepatic cholangiocarcinomarisk factors. Hepatitis B virus infection prevalence was not significantly different betweencontrolsand cases.

Several case-control studies that investigated the relation between viral hepatitis and cholangiocarcinoma, showed similar results. A case-control study in Korea**(Shin et al., 1996),** compared 41 cases of cholangiocarcinoma with 406 non-cancer controls, reported that there was no significant relation between HCV or HBV seropositivity and cholangiocarcinoma. While another Korean case-control study **(Lee et al., 2008)**,that compared 622 cases of intrahepatic cholangiocarcinoma with 2,488 controls, showed a significant relation between intrahepatic cholangiocarcinoma and HBV in addition to cirrhosis regardless of its cause. There was no significant relationship between intrahepatic cholangiocarcinoma and HCV seropositivity.

Liver cirrhosis,Hepatitis B virus and hepatitis C virus, have been suggested to be risk factors for cholangiocarcinoma. **Tobersenson et al. (2007)** examined the pathology of more than 1000 explanted livers, and showed that there was biliary duct dysplasia, a precursor of cholangiocarcinoma, in about 2% of the explanted livers. The affected livers belonged to cirrhotic patients caused byalcohol, HCV, or both.

Many studies from USshowed that there was a relationship between HCV and/or

liver cirrhosis and increased risk of intrahepatic cholangiocarcinoma.**Shaib et al. (2007),** a case-control study conducted in the M.D. Anderson Cancer Centre, compared 83 patients with intrahepatic cholangiocarcinoma and 163 with extrahepatic cholangiocarcinomato 236 controls. Hepatitis C virus was a significant risk factor for intrahepatic cholangiocarcinoma. Liver cirrhosis was not investigated separately, but 80% of the patients with hepatitis C virus were cirrhotic. For extrahepatic cholangiocarcinoma, neither HBV nor HCV had a significant association. Regarding extrahepatic cholangiocarcinoma, nonspecific liver cirrhosis was a risk factor, but hepatitis C virus infection had no significant association**(Welzel et al., 2008)**.

In our current study there was no significant relation between diabetes and type of cholangiocarcinoma. A population-based study conducted in Denmark showed the similar results that there was no significant relationship between diabetes and intrahepatic cholangiocarcinoma**(Welzel et al., 2008)**. Several other studies could not show a significant relationship between cholangiocarcinoma and diabetes **(Zhou et al., 2008).**

A large case-control study from the UK which is population-based, **(Grainge et al., 2009)** reported a significant relationship between cholangiocarcinoma and diabetes**.** Data on diabetes, as acholangiocarcinoma risk factor, especially intrahepatic type, are indicative of a modest relationship, but is not consistent.

In our study, there was asignificant relation between obesity and type of cholangiocarcinoma, where distal type was more common among obese patients. The obesity role in cholangiocarcinoma development is controversial and there are too limited data to make any reliable conclusions **(Khan et al., 2019).** However, three case-control studies meta-analysis studies showed a pooled OR = 1.56 (95% CI 1.26-1.94) for intrahepatic cholangiocarcinoma**(Palmer and Patel, 2012)**. A positive relationship between obesity and cholangiocarcinomahas been reported in another meta-analysis including five case-control and five cohort studies and where, a comparison to normal weight subjects was done, a pooled OR = 1.52 (95% CI 1.13-1.89) was reported in obese people. However, the analysis was not graded according to tumour anatomy**(Li et al., 2014)**. These results agree with the current concepts that consider obesity as a risk factor for several types of cancer. Obesity could elevate the risk of many types ofcancers, including cholangiocarcinoma, by affecting the levels of adiponectin,leptin, and pro-inflammatory cytokines **(Khan et al., 2019).**

There are limited dates on obesity. Two case-control studies, which were population-based, showed that obesity is a weak significant risk factor for cholangiocarcinoma. In **Grainge et al. (2009)** study, a BMI ≥ 30 was associated with cholangiocarcinoma significantly.**Welzel et al. (2007)** study conducted in US, showed a significant relationship between intrahepatic cholangiocarcinoma and obesity, not between extrahepatic cholangiocarcinoma and obesity. However, **Welzel et al. (2008)** study, which was population-based, conducted in Danish, showed no significant relationship between intrahepatic cholangiocarcinoma and obesity. The available data on obesity are too limited to make any reliable conclusions.

In our study there were no significant relationship between cholangiocarcinoma and ALP, AST, ALT and CA 19-9.

Different results were obtained from**Zhang et al. (2017)** where ALP, AST and ALT had a significant association with cholangiocarcinoma and patient outcome.

Similar results were obtained by **Aktas et al. (2019)** where CA19-9 had nosignificant associationwith cholangiocarcinoma.

Conclusion

A number of risk factors for developing cholangiocarcinoma have been identified, whereas gender variation, smoking and obesity are the most important, with hilar type more common among females, distal type more common among smokers and obese patients. Distal cholangiocarcinoma is more prevalent than hilar cholangiocarcinoma (56.5% and 43.5% respectively).

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