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Epidemiological and Clinical Insights into Pancreaticobiliary Malignancies: An Egyptian Tertiary Centre Study

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Abstract

Background: Pancreatic cancer and cholangiocarcinoma rank as exceptionally lethal cancers, typically diagnosed at advanced stages, leading to poor prognoses.

Aim of the work: This study aimed to investigate the clinical, epidemiological, laboratory, and diagnostic properties of pancreatic & biliary tract cancers in an Egyptian cohort.

Methods: This retrospective, observational study involved a cohort of 600 studied cases diagnosed with pancreatic or biliary tract cancers in a tertiary referral center. Comprehensive data were collected, including demographics, clinical presentations, laboratory investigations, imaging studies, tumor characteristics, and different therapeutic modalities.

Results: The mean age of the cases was 59 ± 9 years, with male predominance (67.3%) and a mean body mass index (kg/m²) of 24.5 ± 4.7. Pancreatic cancer (PC) distribution prevailed in the head (43.3%), 19% in the body, 12% in the pancreatic tail, and 22% in cholangiocarcinoma. A significant elevation in serum CA19-9 levels was observed in patients with metastatic tumors compared to those without metastasis (median levels: 656.20 vs. 130.10 U/mL, $p < 0.01$). Multivariate analysis revealed that older age (OR: 1.05, 95% CI: 1.01–1.09, $p < 0.01$), positive family history (OR: 2.47, 95% CI: 1.89–3.41, $p = 0.04$), and elevated serum CA19-9 levels (OR: 1.56, 95% CI: 1.21–2.46, $p = 0.03$) were significant predictors of advanced disease and poorer prognosis.

Conclusion: These findings emphasize the prognostic value of serum CA19-9 levels in assessing the severity of pancreatic & biliary tract cancers. Elevated CA19-9 levels are related to advanced disease & worse overall survival, highlighting the need for early detection and targeted therapeutic strategies to improve studied case results.

Keywords: Pancreaticobiliary Malignancies; Pancreatic Cancer; Cholangiocarcinoma; Gallbladder Cancer; Epidemiology; Egypt.

INTRODUCTION

Pancreaticobiliary malignancies present a significant challenge in oncology due to their high mortality rates and complex etiologies [1]. Pancreatic cancer, one of the most aggressive forms of cancer, ranks as the seventh leading reason for cancer-related deaths globally and is the third most common in the United States, according to GLOBOCAN 2020 [2]. The global burden of PC is significant, with approximately 495,773 new cases and 466,003 deaths reported in 2020 [3].

The incidence and mortality of PC increase with age, and the disease exhibits a slight male predominance [3]. In Egypt, PC accounts for 2.2 percent of all cancer incidences & 3.2 percent of cancer-related deaths, positioning it as the 11th most common cancer & the 8th leading reason for cancer mortality in the country [4].

Biliary tract cancers (BTC), encompassing intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma, distal cholangiocarcinoma, and gallbladder cancer, constitute the second most prevalent group of hepatobiliary cancers worldwide. The incidence and mortality of BTCs have risen markedly over the past three decades, underscoring the growing clinical importance of these malignancies [5].

In Egypt, gallbladder cancer represents 0.70% of all cancer incidences & 0.77% of cancer-related deaths, highlighting its significant yet often overlooked impact on public health [1].

The pathogenesis of PC is multifactorial, with cigarette smoking and family history emerging as prominent risk factors [6]. Similarly, BTCs are closely linked to chronic inflammatory conditions, including primary sclerosing cholangitis, chronic biliary tract infections, and viral hepatitis (HBV and HCV) [7]. Genetic predisposition and environmental influences further complicate the landscape of BTCs, necessitating a nuanced understanding of their development and progression [8].

Accurately diagnosing and effectively managing these malignancies requires a comprehensive approach that integrates advanced imaging modalities and multidisciplinary treatment strategies. These malignancies are particularly concerning in Egypt, where unique epidemiological patterns and potential risk factors, like a high prevalence of hepatitis and parasitic infections like *Schistosoma* and *Fasciola*, may influence disease incidence and outcomes [1].

This research aims to delineate the epidemiological and clinical characteristics of pancreaticobiliary malignancies within an Egyptian cohort, thereby contributing to a broader understanding and improved management of these challenging diseases.

PATIENTS AND METHODS

Study Design:

This is a retrospective, observational research conducted at the National Liver Institute (NLI), Menoufia University, Egypt, to assess the epidemiological & clinical characteristics of studied cases diagnosed with pancreaticobiliary malignancies. The study period spans from the first of March 2022 to the end of February 2023.

Study Population: Patients included in this study are those diagnosed with pancreaticobiliary malignancies, including pancreatic cancer, cholangiocarcinoma, and gallbladder cancer, according to the National Comprehensive Cancer Network for hepatobiliary tumors [9] and the European Society for Medical Oncology Clinical Practice Guideline for diagnosis, treatment, and follow-up of pancreatic cancers [10].

The inclusion criteria were 1) Age 18 years or older, 2) Histopathological confirmed diagnosis of pancreaticobiliary malignancy, 3) Treated or evaluated at the specified tertiary care center.

Exclusion criteria included 1) Incomplete medical records, 2) Patient less than 18 or older than 70 years, 3) Patients with benign tumors, 4) Patients with either primary or secondary liver malignancies, 5) Refused to give a consent, 6) Studied cases who declined to take part in the research or drew consent.

Data Collection: Data had been collected retrospectively from the hospital's electronic medical records and patient charts. Collected data included:

1. **Demographic Information:** Age, gender, occupation, and geographic location.
2. **Clinical Characteristics:** Symptoms at presentation, duration of symptoms, and performance status.
3. **Risk Factors:** Presence of known risk factors such as chronic hepatitis, schistosomiasis, fascioliasis, alcohol use, smoking, family history of cancer, & diabetes mellitus.
4. **Laboratory investigations:** (a) Liver function tests: total & direct bilirubin, aspartate transaminase, alanine transaminase, alkaline phosphatase. (b) Tumor markers (CA19.9) & a complete blood count (red blood cells, platelets, & white blood cell count) are provided.
5. **Imaging:** Initially, conventional imaging methods were used to stage the studied cases.

Most studied cases had either antegrade or retrograde cholangiography, and nearly all underwent dynamic computed tomography scanning (5-7mm section). Selected visceral arterioportography & magnetic resonance imaging were occasionally used. It was advised against performing percutaneous needle biopsies because all of the studied cases seemed to have potentially treatable tumors. Surgery for resectable lesions usually involved a distal pancreatectomy, sometimes combined with a splenectomy.

6. **Treatment Data:** Types of treatment received, including surgical intervention, chemotherapy, radiotherapy, or palliative care.
7. **Outcomes:** Patient characteristics, Diagnostic measures, and Disease stage at diagnosis.

Ethical Considerations: The 1964 Helsinki Declaration & its subsequent revisions, as well as the ethical guidelines established by national & institutional research bodies, were adhered to throughout the study's conduct. The research was authorized by the Institutional

Review Board of Menoufia University, Egypt's National Liver Institute. Since the research was retrospective in nature, informed permission was not required, & studied case anonymity was upheld at all times.

Statistical Analysis: Clinical features, treatment modalities, and patient demographics were compiled using descriptive statistics. Depending on the distribution of the data, continuous variables were shown as means and standard deviations or as medians and interquartile ranges. Frequencies and percentages were used to summarize the categorical data. Survival analysis was performed using the Kaplan-Meier method, with overall survival & disease-free survival as the primary endpoints. Cox proportional hazards regression was used to identify factors related to survival outcomes. Statistical significance was defined as a p-value < 0.05.

RESULTS

The mean age of the study population is 59 ± 9 years, with male predominance (67.3%). The mean BMI is 24.5 ± 4.7kg/m², with a notable proportion (27%) of the study population having a family history of similar malignancies. Patients were found to be anemics (Hg 10 ± 0.9 g/dL) with lymphopenia reflecting an immunosuppressive state. Liver function tests show elevated total bilirubin (8.5 ± 4.8 mg/dL), alkaline phosphatase (203.60 ± 167.89 mU/mL), ALT (92.41 ± 145.65 mU/mL), and AST (51.82 ± 68.15 mU/mL), which are indicative of hepatic involvement or dysfunction. The elevated CA19-9 levels (728 ± 672 U/mL) are consistent with pancreaticobiliary malignancies (table 1).

The distribution of comorbidities and diagnostic tools used provides a comprehensive overview of the patient profiles and the diagnostic approaches employed in this study (**Figures 1 & 2)**.

Pancreatic cancer is the most common, with the head of the pancreas being the predominant site (43.3%), followed by the body (18.2%) and tail (11.3%). Gall bladder cancer (2.3%) and cholangiocarcinoma (10% intrahepatic, 12% extrahepatic) are less common but still significant (**Table 2).**

The presence of strictures in 45% of cases indicates advanced disease in many patients. The stages at diagnosis show a significant proportion of metastatic disease (32%) & locally advanced disease (36%), emphasizing the late presentation. Tumor size (4 x 2.9 cm) is indicative of the advanced nature of the disease at diagnosis. A high percentage of studied cases are at advanced stages (III and IV) (50.7%), with a significant number exhibiting metastasis (46.7%) and lymph node involvement (79.3%). The treatment plans highlight a reliance on palliative care (65%), reflecting the advanced stages at diagnosis (**Table 3)**.

Univariable Models: Age, HCV status, family history, tumor site, total bilirubin, ALP, and CA19-9 levels are significantly associated with advanced disease. **Multivariable Models:** Age, family history, tumor site, total bilirubin, ALP, and CA19-9 levels remain significant, suggesting these are robust predictors of advanced disease (**Table 4).**

Significantly higher CA19-9 levels are observed in studied cases with metastatic tumors compared to those without metastasis, indicating its potential utility as a marker for metastatic disease (**Table 5)**.

Table (1): Characteristics of studied cases

Variables		N=600
Age	Mean± SD	59 ± 9
Sex (n,%)	Sex Male	404 (67.3%)
	Female	196 (32.7%)
BMI (kg/m^2)	Mean± SD	24.5 ± 4.7
Positive Family history (n,%)		27%
Hemoglobin (g/dl)	Mean± SD	10±0.9
Lymphocyte (× 103/µl)	Mean± SD	1.39 ± 0.58
Albumin (g/ml)	Mean± SD	3.3±0.3
Total bilirubin (mg/dl)	Mean± SD	8.5±4.8
Alkaline phosphatase (mU/mL)	Mean± SD	203.60 ± 167.89
ALT (mU/mL)	Mean± SD	92.41 ± 145.65
AST (mU/mL)	Mean± SD	51.82 ± 68.15
CA19-9 (U/ml)	Mean± SD	728±672

BMI: Body mass index. Hg: Hemoglobin. ALT: Alanine Aminotransferase. AST: Aspartate Aminotransferase. CA19-9: Cancer Antigen 19-9.

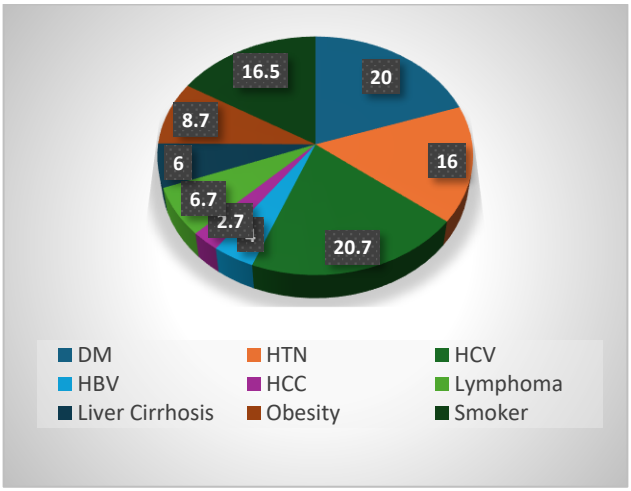

Figure (1): Distribution of studied cases according to comorbidities

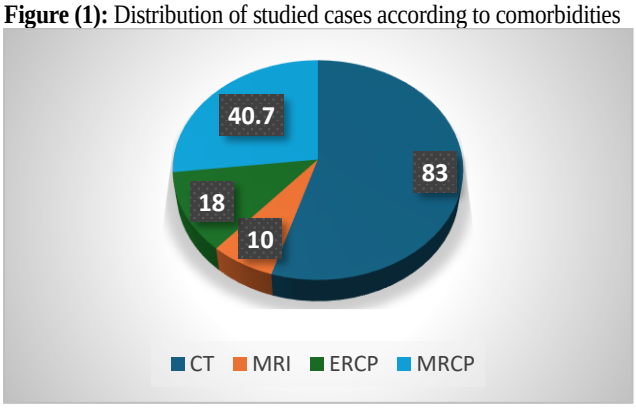

Figure (2): Distribution of studied cases according to diagnostic tools

Table (2): Site of tumors among studied cases (n=600)

Site of tumor		N=600 (n,%)
Pancreatic cancer	Head	263 (43.3%)
	Body	109 (18.2%)
	Tail	68 (11.3%)
Gall bladder cancer		14 (2.3%)
Cholangiocarcinoma	Intrahepatic	60 (10%)
	Extrahepatic	72 (12%)

Table (3): Tumor characteristics among studied cases (n=600)

	Tumor characteristics	N=600
	Stricture	45%
Stage of disease at diagnosis	**Local**	**42%**
	Locally advanced	**36%**
	Metastatic	**32%**
Size of tumor (cm) M± SD		4 x 2.9
Tumor stage	I	44 (7.3%)
	II	252 (42%)
	III	84 (14%)
	IV	220 (36.7%)
Metastasis		280 (46.7%)
LN involvement	N0	124 (20.7%)
	N1	216 (36%)
	N2	260 (43.3%)
Treatment plan:	Surgery+ adjuvant chemotherapy	35%
	Palliative	65%

Data is presented as frequency (%).

Table (4): Factors associated with advanced cases

	Univariable models		Multivariable model	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age (years)	1.78(0.89–1.49)	<0.01*	1.05(1.01–1.09)	<0.01*
DM	1.01(0.71–1.22)	0.45		
HCV	2.07(1.15–3.72)	0.02*	1.52(1.10–2.21)	0.14
Family history	3.17(1.57–4.21)	0.03*	2.47(1.89–3.41)	0.04*
Site of tumor	2.42(1.52–3.14)	<0.01*	1.89(1.14–2.11)	<0.01*
T. Bilirubin	1.98(0.89–1.49)	<0.01*	1.05(1.01–1.09)	<0.01*
ALP (mU/mL)	2.14(1.15–3.72)	0.02*	1.69(1.10–3.63)	0.04*
CA19-9 (U/ml)	1.57(1.41–2.56)	0.02*	1.56(1.21–2.46)	0.03*

DM: Diabetes Mellitus. HCV: Hepatitis C Virus. T. Bilirubin: Total Bilirubin. ALP: Alkaline Phosphatase. CA19-9: Cancer Antigen 19-9. OR (95% CI): Odds Ratio (95% Confidence Interval). *Statistically significant as p<0.05.

Table (5): CA19-9 levels in studied cases with Metastatic & non-metastatic tumor

Metastasis	*N*	CA19-9 (U/mL)			Wilcoxon	
		Q_1	Q_2	Q_3	*Z*	*P*
Present	280	361.30	656.20	1780.00	-5.132	0.001
Absent	320	15.57	130.10	270.25		

DISCUSSION

The global burden of pancreaticobiliary malignancies (PBM) has surged recently [11, 12]. Despite Egypt's high prevalence of PBM risk factors like diabetes mellitus (DM), hepatitis C virus, & obesity, there are limited, precise estimates of these tumors. This research was conducted to pursue the characteristics of PBM in Egypt.

This study's demographic and clinical profiles align with existing research. The mean patient age was 59 ± 9 years, consistent with PBM typically occurring in the sixth and seventh decades. A male predominance was noted. There may be genetic and epigenetic differences that predispose men to pancreaticobiliary cancers. Research has shown that men may have different expressions of genes associated with cell cycle regulation, DNA repair, and apoptosis, which could lead to a higher likelihood of cancer development when exposed to risk factors [13].

Differences in immune function and inflammation regulation between men and women, potentially influenced by both genetic and hormonal factors, might make males more prone to cancers of the pancreas and bile ducts [14].

Estrogen is also believed to have protective effects against certain cancers, including pancreatic and biliary cancers. Studies have shown that it reduces inflammation and oxidative stress in cells, both of which are mechanisms involved in cancer development. Lower estrogen levels in males may contribute to an increased susceptibility to cellular changes that lead to malignancies in the pancreas and bile ducts [15].

In agreement with our results, Abdelwahed et al. reported a mean age of 61.16 years [1]. Also, **Van Dongen *et al.*** stated a median age of 72 in a similar cohort [16].

Risk factors among PBM patients in this study included 20% with DM, 16% with hypertension (HTN), 20.7% with HCV, 4% with hepatitis B virus, 2.7% with hepatocellular carcinoma, 6.7% with lymphoma, 6% with liver cirrhosis, 8.7% with obesity, and 16.5% smokers. These figures suggest a broader reflection of the Egyptian population's health. Previous studies by Aggarwal et al. (2012) found that forty percent of pancreatic cancer studied cases had DM [17], while Ren et al. showed a 1.4-fold increased risk of bile duct cancer (BTC) in diabetics [18].

Berrington et al.'s meta-analysis indicated a 1.19-fold higher relative risk for pancreatic cancer in obese individuals [19]. Further, Genkinger et al. and Bosetti et al. emphasized the increased risk of pancreatic cancer related to obesity & smoking [20]. The finding suggests a significant genetic predisposition that 26.7% of the patients had a positive family history, supporting regular screening for PBM within families [5]. The advanced-stage disease was prevalent at diagnosis, reflecting the challenges noted by **Halbrook** because of the asymptomatic nature of early PBM & the lack of effective early detection methods [21]. This underscores the need for robust early detection strategies.

Elevated CA19-9 levels observed in this study are consistent with another research confirming CA19-9 as a crucial biomarker for PBM. CA19-9 is commonly elevated in pancreaticobiliary cancers due to its overexpression in response to malignant changes in these tissues [14].

In pancreaticobiliary cancer, particularly pancreatic ductal adenocarcinoma, and cholangiocarcinoma, cancer cells frequently exhibit mutations and alterations in glycosylation pathways that lead to the overproduction and release of CA19-9 into the bloodstream [22]. This elevation primarily occurs because malignant transformation in pancreaticobiliary cells increases cellular turnover, dysregulates glycoprotein synthesis, and triggers

inflammatory processes that enhance the expression of CA19-9 [23].

Chronic inflammation associated with pancreatico-biliary malignancies also stimulates the upregulation of adhesion molecules and signaling pathways, such as those involving cytokines and tumor growth factors, which further promote the production of CA19-9 by cancerous cells. Additionally, since CA19-9 can be produced by inflamed non-malignant tissue, inflammatory conditions like pancreatitis and cholangitis can also contribute to elevated CA19-9 levels, even in the absence of cancer [24]. However, in malignant settings, the continuous release of CA19-9 by tumor cells and compromised excretion due to biliary obstruction lead to persistently high serum CA19-9 levels, making it a valuable but nonspecific biomarker for detecting and monitoring pancreaticobiliary cancer progression and treatment response [25].

Marrelli *et al.* validated its correlation with tumor burden and stage [26]. Nonetheless, the potential for false positives, particularly in benign conditions, should be acknowledged.

Laboratory findings indicated significant liver dysfunction at presentation, suggesting poor outcomes and highlighting the necessity for earlier detection. Tumor characteristics revealed a predominance in the head of the pancreas (43.3%), with lymph node involvement (N1 and N2) in 79.3% of cases, reinforcing the aggressive nature of these cancers. Significant liver dysfunction at presentation in pancreaticobiliary cancer is often attributed to the aggressive nature of the disease, which frequently leads to biliary obstruction and subsequent cholestasis. In cases of pancreatic cancer, such as those presenting with decompensated chronic liver disease, the malignancy can remain occult until advanced stages, complicating diagnosis and treatment [27].

Elevated bilirubin levels and liver dysfunction are common, as seen in patients undergoing chemotherapy, where drug-induced liver failure can exacerbate pre-existing conditions [28].

In addition, the presence of jaundice is a critical indicator of advanced disease, correlating with tumor spread and poor prognosis, as evidenced by studies on ampullary carcinoma. The interplay between hepatic dysfunction and tumor characteristics underscores the need for vigilant monitoring and early intervention to improve patient outcomes [29].

Independent predictors of advanced PBM included older age, HCV, positive family history, pancreatic tail tumors, intrahepatic biliary tumors, elevated total bilirubin, alkaline phosphatase (ALP), and CA19-9 levels. These factors are crucial for patient stratification and the potential for more aggressive treatment, including early chemo-therapy or clinical trials. Similarly, the study of Dell'Aquila et al. signified CA19-9 as the most extensively researched prognostic biomarker, yet its predictive value remains uncertain. Meanwhile, various clinical, histological, & molecular biomarkers are gaining attention in prognostic & predictive contexts [30].

Treatment approaches in this study showed that 64.7% of patients received palliative chemotherapy, while 35.3% underwent surgery with adjuvant chemotherapy. The frequent discovery of metastases during surgery underscores the critical need for early integration of palliative care to support both patients and their families.

Being conducted in a single tertiary center in Egypt, the study's findings may not be generalizable to other regions or healthcare settings, limiting its broader applicability. Moreover, the study's retrospective nature could introduce biases related to data collection, such as incomplete patient records or inconsistencies in diagnostic criteria over time. However, this study is privileged and has many strengths. Firstly, it provides a thorough analysis of the demographic and clinical characteristics of PBM in an Egyptian population, offering valuable insights into the specific features of these cancers in a region with high-risk factors. Secondly, by examining the prevalence of risk factors like diabetes, HCV, & obesity, the study enhances understanding of the association between these conditions and PBM, which could inform targeted prevention strategies. Thirdly, the study identifies independent predictors of advanced disease, such as elevated CA19-9, HCV, and positive family history, which could aid in patient stratification and the development of tailored treatment protocols. Lastly, the findings have direct clinical relevance, particularly in terms of improving early detection strategies, enhancing the use of biomarkers like CA19-9, and informing the design of treatment plans that consider the high prevalence of advanced-stage diagnosis.

Conclusion This study contributes significant epidemiological and clinical insights into PBM in Egypt, highlighting the urgency for improved early detection, the clinical relevance of CA19-9, and the necessity for individualized treatment strategies. Research should continue to validate biomarkers like CA19-9 and develop early detection methods to enhance patient outcomes in these challenging malignancies.

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