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Original article

Prospective Analysis of Malignant Biliary Stricture Diagnosis: Experience from a Tertiary-Care Hospital

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Abstract

Introduction: Malignant biliary strictures represent a persistent diagnostic challenge that requires a coordinated multidisciplinary approach to achieve histopathological confirmation. The limited sensitivity of commonly used diagnostic modalities may delay definitive diagnosis and increase healthcare expenditures. **Methods:** A prospective study was conducted at a tertiary-care hospital in Panama involving patients with malignant biliary strictures (MBS) who underwent drainage via endoscopic retrograde cholangiopancreatography (ERCP). Patients were followed for 12 months, during which all therapeutic and diagnostic procedures, time to histological confirmation, and associated costs were documented. A ROC-curve analysis was performed to determine optimal cutoff values for predictive variables associated with MBS. **Results: A** total of 147 patients with MBS were included, with distal strictures being the most frequent presentation (74%). Pancreatic cancer was the leading underlying malignancy (46.2%), followed by cholangiocarcinoma (36.7%). Cholangiocarcinoma exhibited a notably high proportion of unconfirmed histopathological diagnoses (39%) and incurred the greatest diagnostic costs, with an estimated mean expenditure of USD 12,000. In ROC analyses, the cutoffs associated with malignancy were total bilirubin >8.9 mg/dL, stricture length >1.5 cm, and CA 19-9 >35 U/mL. **Conclusion:** Elevated total bilirubin levels, longer stricture length, and higher CA 19-9 concentrations emerged as predictive factors for MBS. Conventional ERCP-based diagnostic techniques, including brush cytology and biopsy, demonstrated limited diagnostic accuracy, necessitating the use of alternative methods, repeated procedures, and consequently higher costs. Standardizing diagnostic protocols that prioritize more sensitive and specific modalities is essential to enhance diagnostic efficiency and improve care for patients with suspected MBS.

Keywords

Bile ducts, stricture, cholangiocarcinoma, endoscopic retrograde cholangiopancreatography.

INTRODUCTION

Biliary strictures may arise from benign or malignant causes. Diagnosing malignant biliary strictures (MBS) is complex and requires a multidisciplinary approach, which entails high associated costs[1,2]. Histopathological confirmation is essential to define the most appropriate treatment and to establish patient prognosis[3–6].

The diagnosis of biliary strictures is based on clinical suspicion and imaging studies that guide the acquisition of histological samples[1,3,7]. Although endoscopic retrograde cholangiopancreatography (ERCP) has traditionally been the primary diagnostic method, endoscopic ultrasound (EUS) has redefined its role, particularly in pancreatic cancer and complex biliary drainage[8–10]. Brush cytology during ERCP has low sensitivity but high specificity for the diagnosis of

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cholangiocarcinoma[1,11–14]. Advanced techniques such as cholangioscopy improve diagnostic sensitivity, and interventional radiology becomes relevant when advanced endoscopic options are limited or unavailable[3,15].

In resource-limited settings, a stepwise approach is frequently used, in which advanced diagnostic techniques for MBS are mainly reserved for cases in which conventional methods, such as ERCP and brush cytology, are insufficient[16–19]. However, evidence regarding the effectiveness of this approach in both the short and long term is scarce. In this study, we describe the experience of a tertiary-care hospital in Panama with the implementation of a stepwise approach for diagnosing patients with suspected MBS.

PATIENTS AND METHODS

We conducted a prospective study that included patients with a diagnosis of MBS referred to the Department of Gastroenterology of Complejo Hospitalario Metropolitano de Panamá who underwent biliary drainage by ERCP between June 2021 and June 2023. The study received approval from the institutional bioethics committee. We followed patients who underwent ERCP for 12 months, during which we documented therapeutic and diagnostic procedures, time to histological diagnosis, associated diagnostic costs (including procedures performed), and patient mortality.

All participants in this study were required to have a verified diagnosis of malignant disease. We confirmed the presence of cancer through histopathological samples obtained by various procedures, including ERCP, EUS, computed tomography (CT)-guided biopsy, endoscopy, and surgery. When histology could not be obtained or yielded inconclusive results, we also considered a strong suspicion based on the patient's clinical presentation, CT findings, and ERCP results.

We excluded patients younger than 18 years, patients without an indication for ERCP, and patients with a prior histopathological diagnosis. We categorized patients according to the type of neoplasm causing MBS: pancreatic cancer, cholangiocarcinoma, gallbladder cancer, ampullary cancer, metastases, and lymphoma. We also divided the data into two groups based on stricture location: distal strictures, located below the junction of the cystic duct and the bile duct, and hilar strictures, located above this junction.

Study Variables and Definitions

A gastroenterologist established the diagnosis of malignant biliary stricture using the diagnostic resources available at the institution during patient evaluation. We calculated time to diagnosis as the interval from the patient's first related medical encounter to histopathological confirmation of the diagnosis. We recorded histopathological results, including brush cytology (see the Brush Cytology section), and biochemical parameters such as baseline total bilirubin (BTI_0), alkaline phosphatase (IU/L), albumin (mg/dL), aspartate aminotransferase (AST) (U/L), alanine aminotransferase (ALT) (U/L), and carbohydrate antigen 19-9 (CA 19-9) (U/mL).

For comparative purposes in ROC models, we included patients with benign biliary strictures, defined by the following criteria: absence of an identifiable mass on CT, transabdominal ultrasound, EUS, or magnetic resonance imaging (MRI); absence of distant metastases on imaging studies; no recent (<3 months) history of traumatic or iatrogenic bile duct injury; negative tissue sampling; and no evidence of a tumor mass during a follow-up period of at least 12 months.

For our cost analysis, we carefully documented all procedures performed for each patient. These included endoscopic interventions, imaging studies, interventional radiology approaches, and other relevant procedures (stent placement). We did not collect data on length of hospitalization or on medications used during the treatment process. We assumed that consumables required for ERCP were constant for both plastic stent (PS) placement and uncovered self-expanding metal stent (uSEMS) placement, with the exception of the stents themselves. We determined costs associated with ERCP, percutaneous biopsies performed by interventional radiology, and diagnostic imaging studies based on standardized prices established in Panama by insurance providers for these medical procedures.

Brush Cytology

We used the same ERCP protocols for cytological sample collection in all cases. Under fluoroscopic guidance, we placed a guidewire into the bile duct and advanced it across the stricture. We then introduced a double-lumen cytology brush with a metal guidewire (manufactured by Boston Scientific, Natick, MA, USA; and Cook Medical, Winston-Salem, NC, USA) into the stricture and performed at least eight brush passes. We used two methods: in the first, we employed the cytology brush directly; in the second, we removed the brush head and immersed it in a preservative solution. In addition, we prepared smears and stained them after cytocentrifugation at 1,500 revolutions per minute (rpm) for 5 minutes. To obtain the final cytological diagnosis, we fixed smears and cell pellets in 95% ethanol and stained them using the Papanicolaou method. We classified samples as showing no abnormal cells (benign), atypical cells, suspicious cells, or malignant cells. We considered both suspicious and malignant cells as confirmatory of malignant disease.

Statistical Analysis

We performed the statistical analysis using Stata/SE 16.0 (StataCorp, 4905 Lakeway Dr, College Station, TX, USA). We applied the Kolmogorov-Smirnov test to assess the normality of continuous data and found that our data did not follow a normal distribution.

We summarized continuous variables using the median and interquartile range, and we expressed quantitative variables as percentages. We used the Mann-Whitney test to analyze unpaired continuous variables and the chi-square test to assess differences between qualitative variables. We considered results statistically significant at a two-tailed *p* value <0.05.

We constructed receiver operating characteristic (ROC) curves to determine optimal cutoff values for factors significantly associated with malignant biliary strictures compared with benign biliary strictures, using the trade-off between sensitivity and specificity on the ROC curves. We estimated the accuracy of MBS prediction using the area under the ROC curve (AUC)[19]. Our analysis included laboratory parameters (BTI_0, ALT, AST, alkaline phosphatase, CA 19-9), age, and stricture length. We also generated ROC curves to evaluate our diagnostic performance and accuracy using brush cytology.

RESULTS

We included 147 patients with a diagnosis of malignant biliary stricture (MBS) and 22 patients with benign biliary strictures. Of the MBS cases, 74% were classified as distal strictures and 26% as hilar strictures (p <0.005). Notably, obstructive jaundice was the predominant indication for medical evaluation, observed in 87.7% of patients. Pancreatic cancer was the most prevalent neoplasm (46.2%), followed by cholangiocarcinoma (36.7%) (**Table 1**).

Table 1. Characteristics of patients with malignant biliary strictures according to stricture location

Variable	Total	Distal Stricture (n = 109)	Hilar Stricture (n = 38)	*p*-Value
Age (years)	70.5 (RIC: 60-78)	72 (RIC: 61-79)	66 (RIC: 55-73)	**0.03**
Sex				
- Male	69 (46.9%)	49 (44.9%)	20 (52.6%)	0.414
- Female	78 (53.1%)	60 (55.1%)	18 (47.4%)	
Suspicious clinical presentation				
- Obstructive jaundice	129 (87.7)	99 (91.7%)	30 (76.9%)	0.432
- Choledocholithiasis	2 (1.4%)	1 (0.9%)	1 (2.6%)	
- Cholangitis	15 (10.2%)	8 (7.4%)	7 (17.9)	
- Liver mass	1 (0.7%)	0	1 (2.6%)	
Diagnosis				
- Pancreatic cancer	68 (46.3%)	64 (58.7%)	4 (10.5%)	**0.031**
- Cholangiocarcinoma	54 (36.7%)	27 (25.7%)	27 (71.1%)	
- Gallbladder cancer	6 (4.1 %)	3 (2.8%)	3 (7.9%)	
- Ampullary carcinoma	7 (4.8%)	7 (6.4%)	0	
- NET	2 (1.4%)	2 (1.8%)	0	
- Metastases	7 (4.8%)	2 (1.8%)	5 (13.2%)	
- High-grade lymphoma	3 (2.0%)	3 (2.8%)	0	
Total bilirubin (mg/dL)	17 (12-22.9)	17.5 (12-23.1)	15.2 (10.2-22.4)	0.686
CA 19-9 (U/mL)	337 (61-1515)	219 (42-1425)	679 (35-1945)	**0.018**
Albumin (mg/dL)	3 (2.5-3.5)	2.8 (2.5-4.5)	3 (2.6-3.5)	0.711
Mortality	64 (43.5%)	46 (42.2%)	18 (47.4%)	**0.003**

CA 19-9: carbohydrate antigen 19-9; NET: neuroendocrine tumor; IQR: interquartile range. Author's own research.

Initial laboratory results showed that patients with pancreatic cancer had median total bilirubin and CA 19-9 levels of 16.5 mg/dL (IQR: 10.9–22.3) and 627 U/mL (IQR: 57–1745), respectively. In comparison, patients with cholangiocarcinoma had higher initial bilirubin levels, with a median of 18.5 mg/dL (IQR: 12.6–23.3), and CA 19-9 levels with a median of 356 U/mL (IQR: 78–1825). In cases of ampullary cancer, the median total bilirubin was 8.95 mg/dL (IQR: 5.3–12.6), and the median CA 19-9 was 27 U/mL (IQR: 2.5–156) (**Table 2**).

Diagnostic Methodologies, Timelines, and Costs Associated with Each Type of Neoplasm

Cholangiocarcinoma showed the highest proportion of unconfirmed histopathological diagnoses (39%), followed by pancreatic cancer (21%). The median time to diagnosis was 47 days (IQR: 14–63) for cholangiocarcinoma, 66 days (IQR: 22–114) for pancreatic cancer, and 123 days (IQR: 34–223) for ampullary cancer. The most frequently used diagnostic techniques were brush cytology for cholangiocarcinoma, interventional radiology for pancreatic cancer, and endoscopy with biopsy for ampullary neoplasms (**Figure 1**).

As shown in **Figure 2**, when we evaluated diagnostic costs, cholangiocarcinoma was the most expensive neoplasm to diagnose, with a mean cost of USD 12,095.20 and a median of 1.69 ERCP procedures performed. Pancreatic cancer followed closely, with a mean cost of USD 11,929.20 (1.72 ERCPs), and ampullary cancer, with USD 11,307.00 (2.0 ERCPs). Cost differences among neoplasms were statistically significant (p <0.005).

Brush Cytology

We evaluated the effectiveness of brush cytology, which revealed a low sensitivity of 20% for pancreatic cancer, with a specificity of 81.7%. In contrast, cholangiocarcinoma showed a slightly higher sensitivity of 25.6% and a specificity of 85.3% (**Table 3**).

Table 2. Classification of malignant biliary neoplasms by type and associated clinical characteristics

Variable	Pancreatic Cancer (n = 68)	Cholangiocarcinoma (n = 54)	Gallbladder Cancer (n = 6)	Ampullary Neoplasm (n = 7)	Metastase (n = 7)	Lymphoma (n = 3)	Benign Strictures (n = 22)
Age (years)	60.5 (55-76)	81 (61-81)	63.5 (55-71)	79 (72-82)	59 (52.5-63.5)	58 (57-77)	46 (38-61)
Total bilirubin (mg/dL)	16.5 (10.9-22.3)	18.5 (12.6-23.3)	17.5 (13.6-37.1)	8.95 (5.3-12.6)	15 (12.2-24)	20.5 (7.1-23.7)	3.4 (2.1-5.5)
Alkaline phosphatase	502 (310-739)	518 (339-938)	480 (384-655)	685 (253-685)	388 (298-461)	496 (125-630)	310 (242-381)
CA 19-9 (U/mL)	627 (57-1745)	356 (78-1825)	31.6 (2.1-222)	27 (2.5-156)	297 (233-2220)	194 (173-215)	17 (1.5-31.6)
Albumin (mg/dL)	3.1 (2.6-3.6)	2.7 (2.3-3.1)	3.1 (2.4-3.5)	3.5 (3.4-3.7)	3.5 (3.2-4.1)	2.7 (2.3-3.1)	3.6 (3.3-4.6)
AST (U/L)	151 (110-252)	168 (93-200)	117 (87-175)	114 (26-306)	148 (137-161)	225 (37-279)	89 (110-156)
ALT (U/L)	167 (101-285)	120 (71-190)	95 (83-174)	143 (11-422)	19 (14-33)	110 (60-156)	24 (34-45)
Histopathological confirmation (%)	79%	61%	100%	100%	100%	100%	N/A
Time to diagnosis (days)	66 (22-114)	47 (14-63)	17 (13-96)	123 (34-233)	19 (14-33)	195 (80-586)	N/A
Stricture length (cm)	2.1 (1.7-3)	2 (1.5-3)	3 (1-3.5)	1 (1-1.8)	3 (1.4-3)	3 (1.2-4.1)	1.3 (1-1.8)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CA 19-9: carbohydrate antigen 19-9; N/A: not applicable. Author's own research.

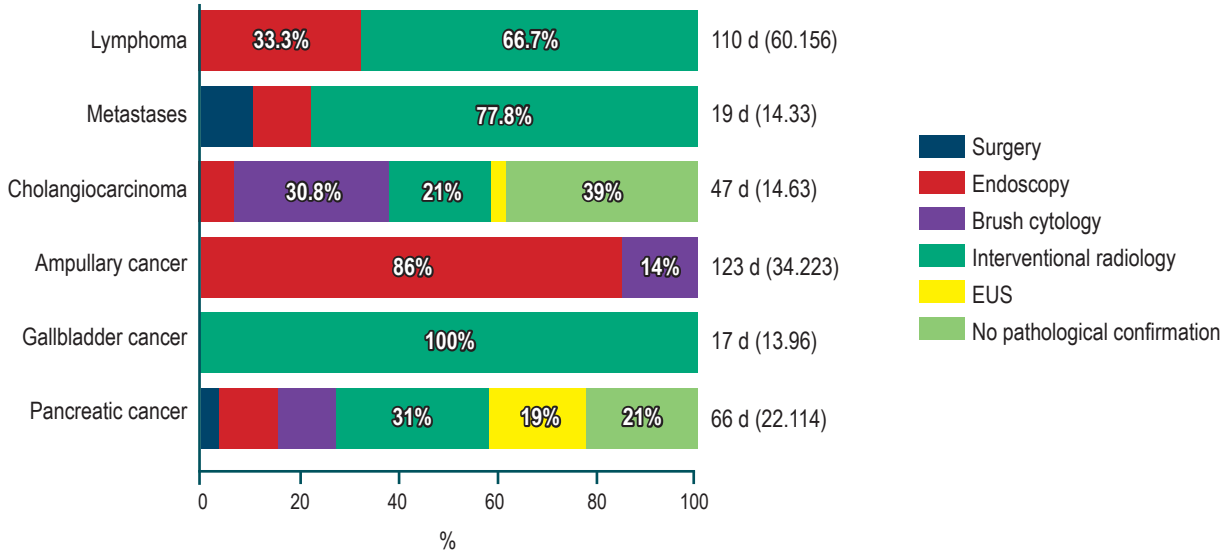


Figure 1. Assessment of diagnostic timelines and modalities according to the type of biliary tract neoplasm. d: days. Author's file.

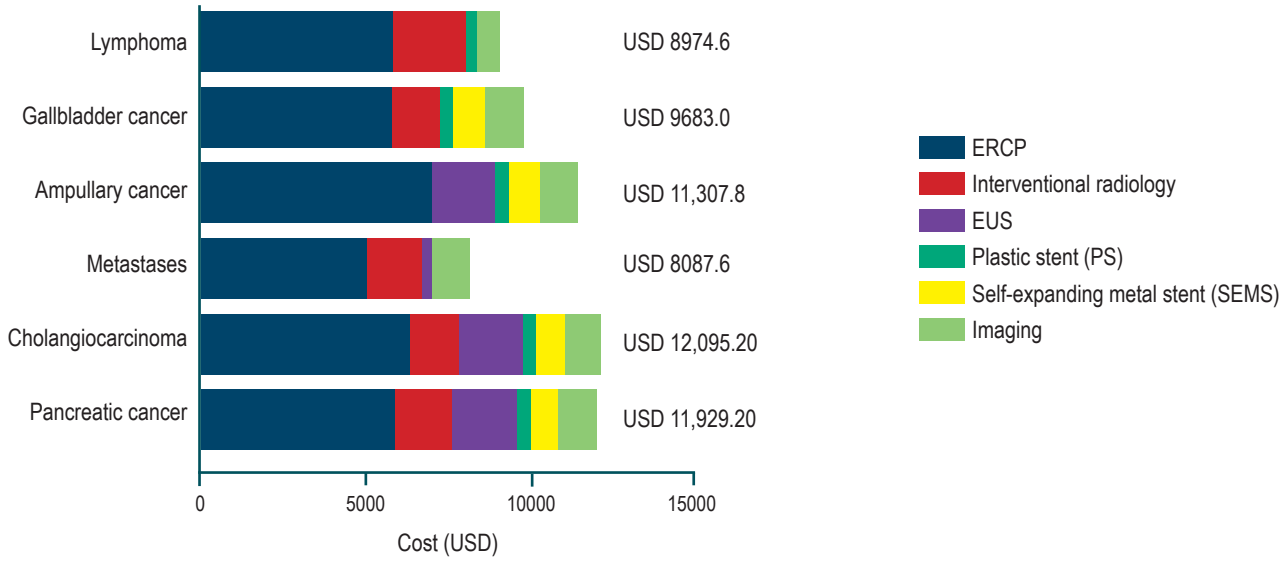


Figure 2. Assessment of diagnostic costs in US dollars for different types of malignant biliary neoplasms. ERCP: endoscopic retrograde cholangiopancreatography; SEMS: self-expanding metal stent; PS: plastic stent; USD: United States dollars; EUS: endoscopic ultrasound. Author's file.

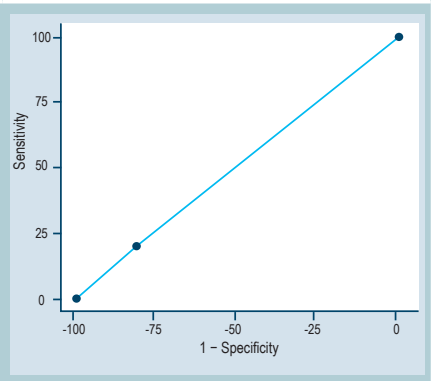
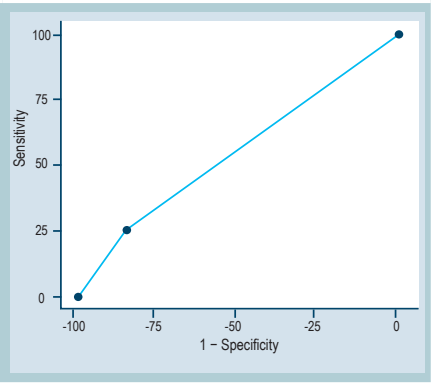
Predictors of Malignant Biliary Strictures

ROC analysis identified predictive variables for malignant biliary strictures, including total bilirubin, CA 19-9 levels, stricture length, and age, all of which showed robust area under the curve (AUC) values. In particular, a total bilirubin cutoff value >8.9 mg/dL yielded a positive predictive value (PPV) of 98%, and a stricture length greater than 1.5 cm also indicated a high PPV of 99%. **Figure 3** provides detailed information on these results, and **Table 4** presents the associated risk increase according to each predictive factor.

DISCUSSION

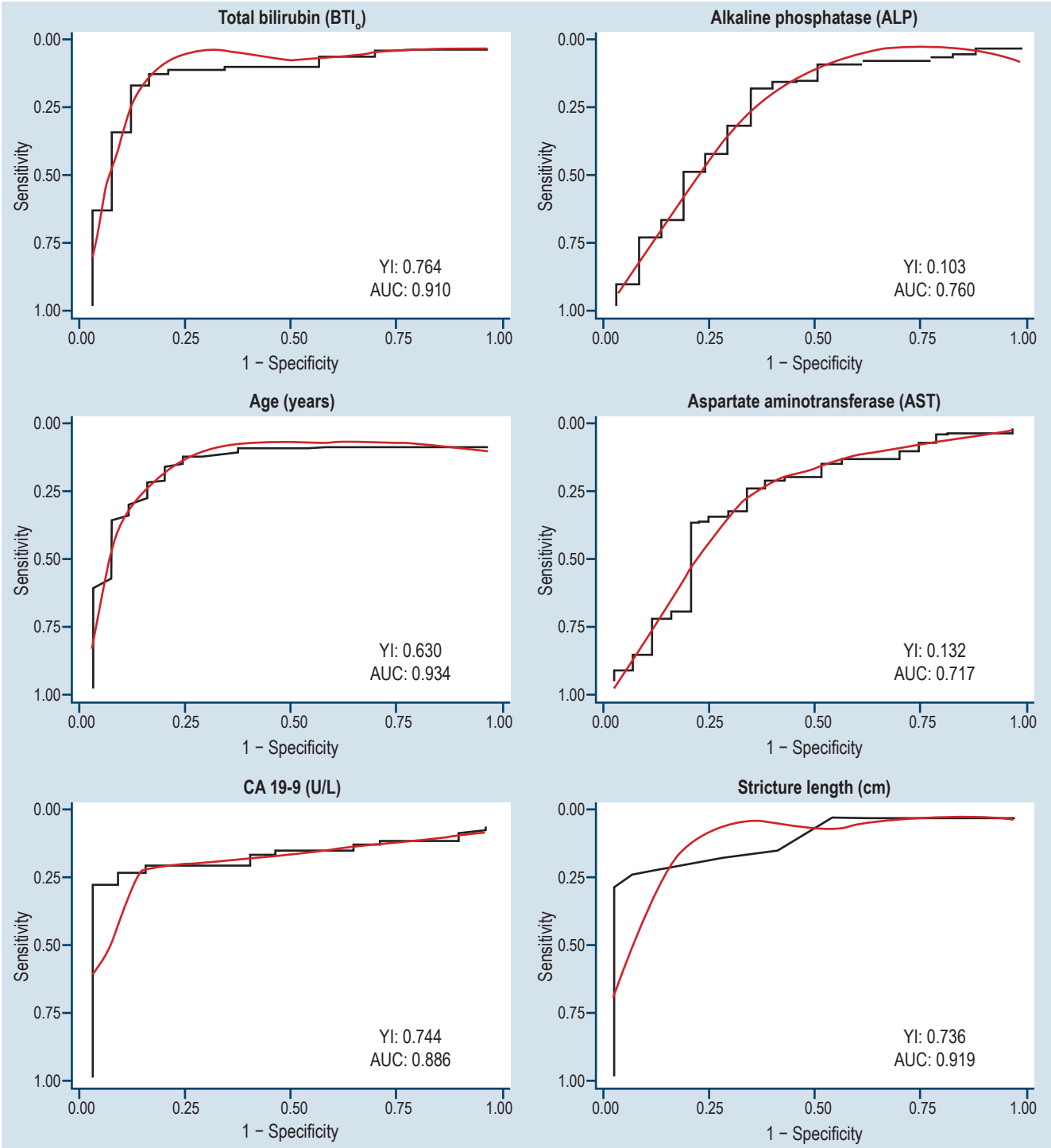
Malignant biliary strictures represent one of the most challenging diagnoses in clinical practice because of the

Table 3. ROC Curves of Cytological Brush STUDIES in Malignant Biliary Strictures

Pancreatic Cancer								
Scale: Cytology Dx								
Cutoff Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden Index	AUC	Metric Score	ROC Curve: Cytology Dx
1	100%	0%	36.04%	NaN%	0.0000	0.508	1.00	
2	20%	81.69%	38.1%	64.44%	0.0169	0.508	1.02	
Cholangiocarcinoma								
Scale: Cytology Dx								
Cutoff Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden Index	AUC	Metric Score	ROC Curve: Cytology Dx
1	100%	0%	38.74%	NaN%	0.000	0.554	1.00	
2	25.58%	85.29%	52.38%	64.44%	0.109	0.554	1.11	

AUC: area under the curve; Dx: diagnosis; NaN%: not a number; NPV: negative predictive value; PPV: positive predictive value. Author's own research.

inherent difficulty in obtaining adequate histopathological samples to establish a definitive diagnosis. Although imaging techniques such as magnetic resonance imaging (MRI) and endoscopic procedures such as ERCP and EUS are essential tools in the initial evaluation of biliary strictures, determining the exact etiology remains difficult when there are no obvious findings, such as tumor masses or stones. This study provides relevant evidence in this area by highlighting the difficulties gastroenterologists face in confirming a diagnosis of malignant biliary stricture (MBS) in routine clinical practice, particularly in resource-limited settings. Our results show that ampullary cancer was the etiology associated with the longest mean time to diagnosis. Among the most frequent causes of MBS, cholangiocarcinoma achieved histological confirmation in 61% of cases, whereas pancreatic cancer reached a diagnostic rate of 79%. Patients without a definitive diagnosis required a greater number of procedures, which translated into a significant increase in diagnostic costs. We also identified the following variables as predictors of malignancy in biliary strictures: age at diagnosis ≥47 years, total bilirubin ≥8.9 mg/dL, CA 19-9 ≥35 U/mL, and stricture length ≥1.5 cm.



Variables	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
BTI_0 (mg/dL)	8.9	85	90	98	52	0.910
ALP (IU/L)	110	99	11	88	67	0.760
*ALT (IU/L)	40	97	9	82	50	0.556
AST (IU/L)	37	98	14	83	75	0.717
CA 19-9 (U/mL)	35	81	93	98	40	0.886
Stricture length (cm)	1.5	78	95	99	40	0.919
Age (years)	47	99	63	94	93	0.934

Figure 3. Receiver operating characteristic (ROC) analysis results for predicting malignant biliary strictures. *Analysis not shown in the graph. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AUC: area under the curve; BTI_0: baseline total bilirubin; NPV: negative predictive value; PPV: positive predictive value; YI: Youden index. Author's file.

Table 4. Odds Ratios for Variables Associated with Malignant Biliary Strictures

Variable	Odds Ratio	95% CI	*p*-Value*
Cholelithiasis	0.34	0.045-0.932	**0.0001**
CA 19-9 (>34 U/mL)	4.23	1.145-9.92	**0.003**
BTI_0 (>8.9 mg/dL)	3.41	1.322-7.942	**0.021**
AST	1.43	0.034-8.521	0.472
ALT	1.52	0.041-9.328	0.645
Age (>47 years)	4.11	1.56-7.83	**0.0001**
Stricture length (>15 mm)	5.65	2.31-8.94	**0.0031**

*Statistically significant p values are shown in bold. ALT: alanine aminotransferase; AST: aspartate aminotransferase; BTI_0: baseline total bilirubin; CA 19-9: carbohydrate antigen 19-9; CI: confidence interval. Author's own research.

Our findings highlight cholangiocarcinoma and pancreatic cancer as the leading causes of MBS. The median time to histological confirmation of pancreatic cancer was 66 days, and interventional radiology was the most frequently used diagnostic method (31%), whereas EUS was used in only 19% of cases. Despite the presence of a pancreatic mass, histological confirmation was not obtained in 21% of patients. The economic impact was substantial: the average cost of diagnosing pancreatic cancer at our hospital was approximately USD 12,000, excluding additional expenses such as hospitalization, professional fees, or associated complications. Limited availability of supplies for performing EUS-guided fine-needle aspiration (EUS-FNA) required us to rely on interventional radiology as the primary method for obtaining histopathological samples. Previous studies have demonstrated the high efficacy of EUS-FNA in diagnosing pancreatic masses ≥2 cm, with success rates exceeding 90%[10,20,21]. In contrast, ERCP currently plays a limited role and is primarily reserved for biliary drainage[1,22,23]. Both the American Society for Gastrointestinal Endoscopy (ASGE) and the European Society of Gastrointestinal Endoscopy (ESGE) recommend EUS-FNA as the first-line diagnostic approach in distal strictures with a pancreatic mass, and the use of combined methods when such a mass is absent[24,25].

Cholangiocarcinoma was diagnosed predominantly in hilar strictures (71%) and was also the second most frequent cause among distal strictures. Our study demonstrates the diagnostic challenges associated with this entity, as nearly 40% of patients did not achieve histological confirmation despite undergoing multiple diagnostic procedures. The mean time to diagnosis was 47 days, underscoring the need for more effective and timely diagnostic strategies. ERCP with endoscopic brush cytology was performed in 31% of cases and showed a sensitivity of 25.6% and a specificity of 85.3%, values lower than those reported in the literature (sensitivity: 35%–41%; specificity >79%) [11–14]. Many patients required multiple ERCP procedures to achieve a cytological diagnosis, with an estimated average cost of USD 12,095 per case. ESGE guidelines recommend brush cytology and fluoroscopy-guided biopsies for hilar malignant biliary strictures, while reserving EUS for accessible extraluminal lesions[25]. In contrast, the ASGE indicates that cholangioscopy-guided biopsy during ERCP increases diagnostic sensitivity in proximal or non-distal strictures, particularly after an initial nondiagnostic ERCP and in experienced centers. In distal strictures without a visible mass, ERCP combined with cholangioscopy is suggested after prior unsuccessful attempts, although this recommendation is conditional and based on low-quality evidence[24,25].

Standard techniques (brush cytology and biopsy) continue to show low sensitivity (34% and 50%, respectively), whereas cholangioscopy achieves diagnostic accuracies of 80%–85%[3,11,13,14]. Given that 51% of cholangiocarcinomas in our cohort were intrahepatic or perihilar, early use of cholangioscopy—even during the first ERCP—could optimize diagnostic sensitivity and reduce long-term costs.

In this study, we identified significant predictive factors that allow malignant biliary strictures to be distinguished from benign ones. Among these, stricture length emerged as the strongest predictor of malignancy, with an odds ratio of 5.65. These findings are consistent with previous studies indicating that a stricture length greater than 14.5 mm constitutes a robust indicator of malignancy[4,7,26]. Elevated CA 19-9 levels are also widely recognized as biomarkers of pancreatobiliary neoplasms, and our findings confirm that a cutoff value greater than 35 U/mL is closely associated with an increased risk of malignancy. In addition, prior studies have shown that baseline bilirubin levels between 6.0 and 8.4 mg/dL significantly increase the likelihood of a malignant etiology[7,16,27]. Based on these results, we propose that patients presenting with multiple risk factors—such as increased stricture length, elevated CA 19-9 levels, and elevated serum bilirubin—undergo comprehensive diagnostic evaluation before a stricture is classified as benign, in order to optimize early detection of malignancy and reduce diagnostic delay.

Our main limitations were related to the lack of resources for obtaining histopathological diagnoses. In most cases, we opted to perform ERCP with brush cytology and biopsy as the initial diagnostic strategy because access to advanced endoscopic methods, such as cholangioscopy

and EUS, was limited. This situation reflects the challenges of working in a real-world, resource-constrained environment. In addition, our patient selection was restricted to those requiring ERCP, as these were the only patients who could be managed in our department.

This study highlights the diagnostic challenges associated with malignant biliary strictures, particularly the difficulty of obtaining adequate histopathological samples to confirm malignancy. Conventional methods used during ERCP, such as brush cytology and endoscopic biopsy, demonstrated low diagnostic accuracy, leading to the need for additional procedures and increases in diagnostic costs and timelines. Based on our findings, we recommend early integration of advanced techniques, such as EUS and cholangioscopy, into the initial diagnostic algorithm. Implementing this proactive, stepwise approach could increase diagnostic sensitivity, reduce the number of invasive procedures, and optimize the use of hospital resources. Ultimately, systematic application of these strategies has the potential to accelerate definitive diagnosis, improve clinical outcomes, and possibly enhance the prognosis of patients with suspected malignant biliary strictures.

Ethical Statement

This study was approved by the hospital's Bioethics Committee.

Conflict of Interest

The authors declare no potential conflicts of interest.

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Use of Artificial Intelligence

No artificial intelligence was used in the preparation of this work.

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