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Diagnostic yield of biliary brush cytology via ERCP - A 7-year tertiary center experience

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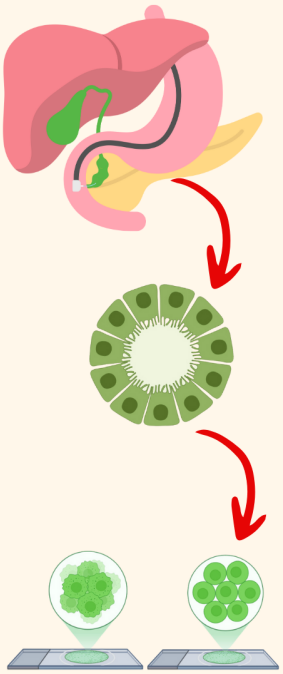
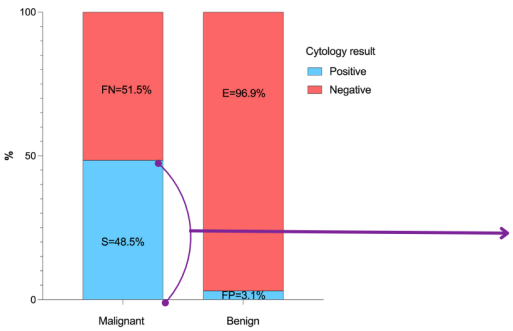
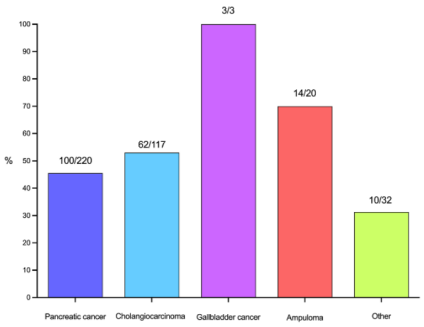
Diagnostic Yield of Biliary Brush Cytology via ERCP: A 7-year Tertiary Center Experience



5309 ERCPs with 518 brush cytology samples from 2016-2022





Factors associated with positive value of the cytology

Older age (OR 1.02, 95% CI 1.01–1.03)

Higher bilirubin (OR 1.05, 95% CI 1.03–1.08)

Biliary brush cytology during ERCP is a safe procedure with low sensitivity but high specificity. Older age and higher bilirubin are associated to positive biliary cytology.

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Diagnostic yield of biliary brush cytology via ERCP - A 7-year tertiary center experience

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Authors' contributions

FJSR contributed to the design of the study. FJSR, BG, PEAM, MOC, ASA, EGJ, ASL contributed to the data collection. FJSR and BG analysed the data. BG drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors have approved the final version of this manuscript.

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Disclosures

FJSR has served as speaker for Viatris Pharmaceuticals and Olympus.

BG has served as a speaker for Abbvie, Janssen, Takeda, Roche, Takeda, Pfizer and Galapagos and has served as an advisor for Roche, Gilead, Abbvie, Galapagos and Takeda.

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ABSTRACT

Background

Biliary brushing cytology during endoscopic retrograde cholangiopancreatography (ERCP) is used to assess the nature of a biliary stricture. Its low sensitivity challenges exclusion of malignancy through this technique. The aim was to evaluate the diagnostic yield of brush cytology in biliary strictures and to identify predictive factors associated with a positive diagnosis of malignancy.

Methods

Observational retrospective study in a tertiary center. All adult patients undergoing a biliary brushing during ERPC from 2016 to 2022 were included. Logistic regression analyses were performed to identify predictive factors for positive brush cytology.

Results

A total of 5309 patients underwent ERCP within the evaluated period. Out of these, biliary brushing was performed in 518 patients including 568 cytology samples, 57.7% (299) were men, median age 74 (64-84) years old. There were 24% (126) benign strictures and 76% (392) malignant of which the most common etiology were pancreatic cancer 42.5% (220/518), followed by cholangiocarcinoma 22.6% (117/518). The sensitivity, specificity, positive predictive value, and negative predictive value were 48%, 98%, 98% and 37%, respectively. Sensitivity was 45% and 52% in pancreatic adenocarcinoma and cholangiocarcinoma, respectively. Older age (OR 1.02, 95% CI: 1.01–1.03, p=0.01) and higher bilirubin (OR 1.05, 95% CI: 1.03–1.08, p<0.001) were independent predictors for brush cytology positivity. There were 9.7% (45/518) post-ERCP complications.

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Conclusions

Biliary brushing cytology during ERCP is a safe procedure with low sensitivity but high specificity. Older age and higher bilirubin are associated to positive biliary cytology.

Keywords: Cholangiocarcinoma. Pancreatic cancer. Biliary brush cytology. ERCP.

1. INTRODUCTION

Hepato-biliary tract malignancies, such as cholangiocarcinoma and pancreatic cancer have experienced a notable increase in incidence over recent decades. These tumours are associated with high lethality, making early diagnosis crucial.[1–3]

These malignancies often present with biliary strictures, and endoscopic retrograde cholangiopancreatography (ERCP) is commonly performed as the initial step to facilitate bile drainage.[4] The conventional approach for diagnosing biliary strictures involves brush cytology, allowing tissue sample collection for pathological examination during the ERCP procedure. This technique has historically been favoured due to its low complication rate, ease of use and widespread availability.[5,6] However, in the recent years, alternative methods such as forceps biopsy during cholangioscopy or endoscopic ultrasonography-guided fine needle aspiration/biopsy have emerged.[7] While these newer techniques may improve specimen adequacy, they require specialized training and devices and lead to an overall increased cost of the procedure.[8]

One of the major limitations of brushing cytology is the low sensitivity. According to the American Gastroenterological Association's 2023 guidelines, a meta-analysis of 1,556 patients showed a composite sensitivity of only 41.6% for brush cytology, with subsequent studies reporting sensitivities clustering around 50-60%.[9] This low sensitivity is primarily due to the desmoplastic nature of cholangiocarcinoma and its tendency for subepithelial spread, which makes obtaining adequate cytological samples challenging.[10] Various factors influencing the sensitivity of brush cytology have found that increased age, higher serum bilirubin levels, and the presence of a mass on cross-sectional imaging are patient-related factors that increase the sensitivity of

brush cytology.[11,12]

Despite these limitations, brush cytology remains a cost-effective option, particularly in lower-income countries where the incidence of biliary malignancies is higher. Its affordability and convenience, especially in regions with limited resources, ensure its continued use.

The aim of this study was to evaluate the diagnostic yield of brush cytology in biliary strictures, identify predictive factors associated with a positive malignancy diagnosis, and assess the safety of the procedure.

2. METHODS

2.1 Study design

This was a retrospective, observational, cohort study performed at Reina Sofía University Hospital in Córdoba, a tertiary referral centre in Andalucia, Spain. The hospital provides coverage as a basic hospital to 457,424 inhabitants, as a provincial referral hospital to 777,966 inhabitants, and as a regional referral centre to 1,122,902 inhabitants.[13] Regarding advanced therapeutic endoscopy, such as ERCP, our hospital serves as a provincial referral centre since it is the only public hospital in Cordoba where these techniques are performed. Additionally, it holds a regional role in certain cases, being the referral centre for liver transplants for Cadiz and occasionally performing advanced endoscopic procedures for Jaen both nearby provinces.

2.2 Participants

All adult patients (>18 years old) who underwent a biliary brushing during ERPC from 2016 to 2022 were included. All the patients had signed informed consent for the procedure to be performed.

2.3 Data collection

Baseline demographic data and follow-up data were collected via review of electronic medical records. Data regarding type of malignancy diagnosis, location of the stricture, biochemical parameters at the time of ERCP, and adverse events were collected. All

biliary brush cytology were analysed by the pathology department at Reina Sofía University Hospital.

2.4 Primary and secondary outcomes

Primary outcome was the metrics of diagnostic accuracy for biliary brush cytology. Secondary outcomes included the identification of predictive factors associated with a positive result of the cytology; to characterize the differences between malignant and benign strictures at admission and to describe the complication rate of the procedure.

2.5 Definitions

Stricture location was considered as extrahepatic strictures, located outside the liver, perihiliar, the ones located at the hepatic hilium and intrahepatic strictures, the ones located inside the liver.[14,15] Early adverse events due to ERCP were considered when occurring within the first 48 hours after ERCP and delayed adverse events were those that occurred after 48 hours.

2.6 Sample collection

For bile duct cytology sampling, we used the RX Cytology Brush Wireguided Cytology Brush (Boston Scientific, Marlborough, MA, USA). This is a double-lumen wireguided catheter designed for cell collection and the detection of malignant neoplasms in the biliary duct. The device features a reinforced metal tube in the handle for reliable actuation, a distal radiopaque marker for fluoroscopic visualization and positioning, and an open channel that allows for quick exchange of the guidewire. The brush lumen can also be used to inject contrast dye through the proximal luer. The catheter has an outer diameter of 8 Fr, a working length of 200 cm, and is compatible with a 0.035-inch guidewire.

In our center, endoscopic ultrasound (EUS)-guided sampling is performed for pancreatic lesions generally on the same day or within the same week as biliary drainage but prior to it. However, at the time of ERCP, pathology results from EUS are not yet available. Given the safety profile of brush cytology and the potential for

inadequate sampling via EUS, biliary brushing is still routinely performed during ERCP, even in cases of suspected pancreatic neoplasms. This dual approach aims to maximize the chances of obtaining diagnostic tissue without delaying biliary decompression.

In cases where cytology sample was insufficient or negative, but there was a high clinical suspicion of malignancy, the final diagnosis was determined through additional sampling. This was achieved either by endoscopic ultrasound-guided sampling, cholangioscopy with direct forceps biopsy, or, ultimately, through histopathological analysis of the surgical specimen in patients who underwent surgery.

2.7. Statistical analysis

SPSS Version 25 [IBM Inc., Armonk, NY] and Prism Version 9.5 [Graphpad Software, San Diego, CA, USA] were used for statistical analyses and generation of graphs. Descriptive statistics are presented as medians with interquartile range [IQR] for continuous variables, and frequencies with percentages for categorical variables. For comparison of non-parametric continuous variables, the Mann–Whitney U test was used. For comparison of categorical variables, the chi-squared test was used. Univariate and multivariate logistic regression analyses were performed to identify predictive factors for positive brush cytology result and to identify predictive factors of malignant nature of the stricture. A p-value <0.05 was considered significant.

2.7 Ethics

The study was carried out in accordance to the European General Data Protection Regulation (GDPR) 2016/679 and the Spanish Data Protection Organic Law 3/2018. The protocol was approved by the Research Ethic Committee of Cordoba (code: CITOBILISV1. Internal code: 6116). The study complies with the ethical guidelines of the 1975 Declaration of Helsinki.[16]

3. RESULTS

Study population

A total of 5309 patients underwent ERCP within the evaluated period. Out of these, biliary brushing was performed in 10.7% (570/5309) ERCPs from 518 patients having a biliary stricture, leaving 518 cytology samples for analysis. There were 57.7% (299/518) men and median age of the cohort was 75 years old (64-84), Table 1.

The etiology of the stricture was malignant in 75.7% (392/518) of the cases and benign in 24.3% (126/518). The most common malignant etiology was pancreatic adenocarcinoma 42.5% (220/518), followed by cholangiocarcinoma 22.6% (117/518). Regarding benign etiology, the most frequent cause was undetermined stricture 15.1 (78/518) followed by chronic pancreatitis stricture 4.1% (21/518) and postsurgical 3.1% (16/518). These strictures were mostly located in the extrahepatic segment of the bile duct 90.2% (467/518) with only 8.1% (42/518) and 1.7% (9/518) located hepatic hilium and intrahepatic respectively.

Biochemical blood test results showed a significant difference between patients with a malignant or benign stricture in total bilirubin at the time of admission (11.7mg/dL vs 11.7 mg/dL, $p<0.0001$), aspartate aminotransferase (AST/GOT) (150 U/L vs 51 U/L, $p<0.0001$), alanine aminotransferase (ALT/GPT) (204 U/L vs 60 U/L, $p<0.0001$), alkaline phosphatase (ALP/AF) (487 U/L vs 242 U/L, $p<0.0001$), and gamma-glutamyl transferase (GGT) (847 U/L vs 284 U/L, $p<0.0001$) and Cancer Antigen 19-9 (CA 19-9) (124.8 U/mL vs 41, $p=0.008$) and Carcinoembryonic Antigen (CEA) (2.5 ng/mL vs 1.3, $p=0.001$) Figure 1.

Procedure characteristics

Out of the total ERCPs with brush cytology in 6.6% (34/518) precut sphincterotomy was needed; standard sphincterotomy was done in 87.5 % (453/518) and stricture dilation with 10Fr cathether in 56.6% (293/518). In 89.2% (462/518) of the patients biliary prothesis was placed to secure biliary drainage and in 17% (88/518) pancreatic prothesis was placed to prevent from post-ERCP pancreatitis.

Diagnostic Accuracy Metrics

There were 5.4% (28/518) samples with insufficient tissue for analysis and these were excluded. The sensitivity, specificity, positive predictive value, and negative predictive value of the brush cytology were 48.5% (191/ (191+203)), 96.9% (93/ (93+3)), 98% (191/194) and 37% (93/296), respectively, Figure 2. Sensibility reached 45.5% in pancreatic cancer, 53% in cholangiocarcinoma, 100% in gallbladder cancer, 70% in intraductal ampuloma and 31.3% in other malignant strictures, Figure 3.

Factors associated with malignant nature of the stricture

Taking into consideration the clinical characteristics and laboratory results at admission, we found that both higher bilirubin levels (OR 1.12; 95% CI 1.03-1.22, p=0.006) and higher ALT levels (OR 1.01; 95% CI 1.003-1.019, p=0.011) were the only two factors associated, in both univariate and multivariate analyses, with the malignant nature of the stricture, Table 2. Other factors, such as age, stricture location, and AST, lost significance in the multivariate model.

Predictive factors for cytology positivity

Regarding the factors associated with test positivity in patients with a malignancy-related stricture, we found that older age (OR 1.02; 95% CI 1.01-1.03, p=0.01) and higher bilirubin levels (OR 1.05; 95% CI 1.03-1.08, p<0.001) were the only variables that increased the diagnostic yield of cytology, Table 3.

Safety

There were 9.7% (45/518) complications of which there were 17 (3.3%) early acute post-ERCP cholangitis, 10 (1.9%) pancreatitis, 9 (1.7%) post-procedural bleeding, 2 (0.4%) liver abscesses, 2 (0.4%) perforations and 3 (0.6%) bacteriemia. One patient died as a complication of a post-ERCP pancreatitis. These complications were not associated with any of the specific procedure characteristics (precut, sphincterotomy, dilation, biliary or pancreatic prothesis need).

4. DISCUSSION

Our study provides valuable insights into the real diagnostic performance of the brush cytology of the biliary strictures. We evaluated all the patients who underwent biliary drainage for strictures between 2016 and 2022, encompassing a cohort of 518 patients. Additionally, we analyzed the clinical and laboratory factors associated with cytology positivity and the malignant nature of the lesions.

The overall sensitivity of biliary cytology in our study was 48.5%, with a specificity of 96.9%, a positive predictive value of 98%, and a negative predictive value of 37%. These results align with prior studies reporting the high specificity of this technique, making a positive cytology result highly reliable.[5] However, its limited sensitivity introduces a substantial risk of false negatives. Previous studies have reported a sensitivity range of 40–60% for biliary cytology,[17,18] particularly in cholangiocarcinoma, where the desmoplastic tumor architecture and subepithelial infiltration hinder the retrieval of representative malignant cells.[19] In our study, sensitivity was notably lower in pancreatic adenocarcinoma (45.5%) and cholangiocarcinoma (53%), reinforcing the need for complementary diagnostic strategies when these are available. The reduced sensitivity in pancreatic malignancies is expected, as cytology is performed in the main bile duct, meaning that extrinsic compressions without direct ductal invasion may not yield malignant tissue through brushing cytology. Furthermore, 5.4% of the cytology samples in our study were deemed inadequate for analysis, further limiting the overall sensitivity of the technique when cellularity is insufficient. The biliary brushing technique itself is straightforward, making it unlikely that endoscopist experience is a major contributing factor. However, previous studies have suggested that increasing the number of brush passes can enhance diagnostic yield.[7] Obtaining enough tissue sample is one of the limitations of the cytology for which newer techniques such cholangioscopy-guided biopsy sampling has proven to increase the sensitivity in randomized controlled trials.[20]

On the other hand, these tumors are more prevalent in lower-income countries, where the sustainability of the healthcare system is a major concern, making cost considerations crucial. The analysis of factors associated with a higher likelihood of

positive cytology identified two key variables. Advanced age was significantly correlated with increased cytology positivity (OR 1.02, 95% CI: 1.01–1.03, p=0.01), likely reflecting a higher prevalence of biliary malignancies in elderly patients. Additionally, elevated total bilirubin levels (OR 1.05, 95% CI: 1.03–1.08, p<0.001) correlated with an increased diagnostic yield of cytology. These higher bilirubin levels likely indicate more complete strictures, which in turn increase the likelihood of retrieving tumor cells during brushing.

Regarding the malignant nature of strictures, both univariate and multivariate analyses identified higher total bilirubin (OR 1.12, 95% CI: 1.03–1.22, p=0.006) and ALT elevation (OR 1.01, 95% CI: 1.003–1.019, p=0.011) as the only laboratory parameters significantly associated with malignancy. ALT elevation reflects hepatic injury secondary to chronic biliary obstruction, distinguishing it from acute biliary obstruction typically seen in choledocholithiasis. As previously reported, tumor markers did not differentiate malignant from benign strictures of uncertain origin. This finding is consistent with reports indicating that tumor markers frequently rise non-specifically in the setting of biliary obstruction, potentially explaining their lack of discriminatory power.[21,22]

No significant differences were found when analyzing the location of strictures. This finding should be interpreted with caution as this very likely reflects selection bias, as intrahepatic strictures, most commonly malignant, often require drainage via alternative techniques such as percutaneous transhepatic cholangiography rather than ERCP.

It is important to note that in our cohort, the relatively high proportion of brush cytology samples in pancreatic tumors reflects our institutional protocol, where brush cytology is still obtained during biliary drainage due to the delay in pathology reports from EUS-guided sampling (which is performed before the ERCP) and the risk of possible inadequate tissue acquisition via EUS, this dual approach aims to maximize the chances of obtaining diagnostic tissue.

Finally, the early complications observed in our cohort are similar to those observed when brush cytology is not performed which generally range in between 7-11%. [23]

Several limitations of our study should be acknowledged. First, its retrospective design inherently carries potential biases including the lack of standardization of the number of brushing passes. Second, the absence of a comparator limits our ability to assess the performance of alternative diagnostic techniques. Additionally, the inclusion of tumors of different origins may have introduced heterogeneity, potentially influencing the lack of stronger associations when analyzing predictors of cytology positivity or malignancy. Nevertheless, our study represents the second-largest published cohort evaluating the utility and accuracy of biliary brush cytology. Furthermore, it incorporates several routinely assessed biochemical parameters in the context of biliary obstruction, providing a more comprehensive understanding of their diagnostic implications.

Overall, our study underscores the strengths and limitations of biliary cytology. While its high specificity ensures a reliable diagnosis in positive cases, its suboptimal sensitivity highlights the need for adjunctive diagnostic approaches such as fluorescence in situ hybridization (FISH), direct tissue sample, or next-generation sequencing to improve the detection of biliary malignancies. Further studies incorporating these techniques may refine the diagnostic algorithm for patients with biliary strictures of uncertain etiology. Despite its limitations, our findings highlight the utility of biliary cytology as a tool for confirming biliary malignancy at a very low cost and with no increased risk of complications compared to standard ERCP.

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Table 1. Baseline characteristics and blood parameters upon admission

N=518	**Total**	**Malignant stricture**	**Benign stricture**	**p**
Men, n (%)	299 (57.7)	76 (56.9)	233 (60.3)	0.498
Age, median (IQR)	75 (64-84)	75 (65-83.8)	73.5 (61-84)	0.06
Malignant stricture, n (%)	392 (75.7)	392 (75.7)	-	-
Benign stricture, n (%)	126 (24.3)	-	126 (24.3)	-
Stricture location - Extrahepatic - Hepatic Hilium - Intrahepatic	 467 (90.2) 42 (8.1) 9 (1.7)	 355 (90.6) 34 (8.7) 3 (0.8)	 112 (88.9) 8 (6.3) 6 (4.8)	0.009

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Billirrubin, mg/dL, median (IQR)	9.7 (3.5-15.5)	11.7 (7-17.5)	1.8 (0.6-4.5)	<0.0001
GOT, U/L, median (IQR)	133 (72-217)	150 (97-243)	51 (26-124)	<0.0001
GPT, U/L, median (IQR)	169 (81-312)	204 (114-346)	69 (22-151)	<0.0001
AF, U/L, median (IQR)	430 (254-735)	487 (302-802)	242 (109-449)	<0.0001
GGT, U/L, median (IQR)	683(310-1244)	847 (470-1335)	284 (102-620)	<0.0001
CRP, g/L, median (IQR)	18.7 (7-51.1)	19 (7.6-46.3)	16.7 (4-76.7)	0.897
CA 19.9, U/mL, median (IQR)	112 (26-726)	124.8 (28-798)	41 (12.6-124)	0.008
CEA, ng/mL, median (IQR)	2.4 (1.1-5.2)	2.5 (1.4-5.5)	1.3 (0.5-2.6)	0.001
Leukocytes, Ux10^9, median (IQR)	7400 (5797-9810)	7320 (5780-9870)	7700 (6020-9790)	0.542

ALT/GPT: Alanine aminotransferase; AST/GOT: aspartate aminotransferase; CA 19.9: Cancer Antigen 19.9; CEA: Carcinoembryonic Antigen; ALP/FA: alkaline phosphatase; GGT: gamma-glutamyl transferase; IQR: Interquartile range; OR: Odds ratio; p: p-valor; CRP: C-reactive protein

Table 2. Factors associated to malignant nature of the stricture

	Univariate			**Multivariate**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	1.02	1.003-1.033	0.017	1.05	0.99-1.10	0.058
Male	1.15	0.765-1.734	0.498			
Stricture location (Ref intrahepatic)	8.50 6.34	1.741-41.49 1.560-26.76	0.008 0.010	3.47 1.48	0.15-80.39 0.09-23.22	0.43 0.78

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Hiliar Extrahepatic						
Billirrubin	1.25	1.19-1.31	<0.0001	**1.12**	**1.03-1.22**	**0.006**
GOT	1.01	1.01-1.02	<0.0001	0.99	0.99-1.01	0.628
GPT	1.01	1.006-1.01	<0.0001	**1.01**	**1.003-1.019**	**0.011**
AF	1.002	1.002-1.003	<0.0001	1.00	0.99-1.002	0.954
GGT	1.001	1.001-1.002	<0.0001	1.00	0.99-1.002	0.452
CA 19.9	1.00	1.00-1.00	0.317			
CEA	1.22	1.002-1.476	0.047	1.21	0.97-1.49	0.085
CRP	0.99	0.99-1.01	0.499			
Leukocytes	1.00	1.00-1.00	0.146			

ALT/GPT: Alanine aminotransferase; AST/GOT: aspartate aminotransferase; CA 19.9: Cancer Antigen 19.9; CEA: Carcinoembryonic Antigen; ALP/FA: alkaline phosphatase; GGT: gamma-glutamyl transferase; IQR: Interquartile range; OR: Odds ratio; p: p-valor; CRP: C-reactive protein

Table 3. Factors associated with positive value of the cytology

	Univariate			**Multivariate**		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age	1.02	1.01-1.04	0.006	1.02	1.01-1.03	**0.01**
Male	1.32	0.92-1.32	0.129			
Stricture location (Ref intrahepatic)						
Hiliar	2.15	0.40-11.7	0.374			
Extrahepatic	2.06	0.42-10.0	0.118			
Billirrubin	1.05	1.03-1.09	<0.001	1.05	1.03-1.08	**<0.001**

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GOT	1.00	1.00-1.00	0.062	1.00	0.99-1.00	0.500
GPT	1.00	0.99-1.00	0.424			
AF	1.00	1.00-1.00	0.246			
GGT	1.00	1.00-1.00	0.227			
CA 19.9	0.99	0.99-1.00	0.145			
CEA	1.00	1.00-1.00	0.917			
CRP	1.00	0.99-1.00	0.963			
Leukocytes	1.00	1.00-1.00	0.390			

ALT/GPT: Alanine aminotransferase; AST/GOT: aspartate aminotransferase; CA 19.9: Cancer Antigen 19.9; CEA: Carcinoembryonic Antigen; ALP/FA: alkaline phosphatase; GGT: gamma-glutamyl transferase; IQR: Interquartile range; OR: Odds ratio; p: p-valor; CRP: C-reactive protein

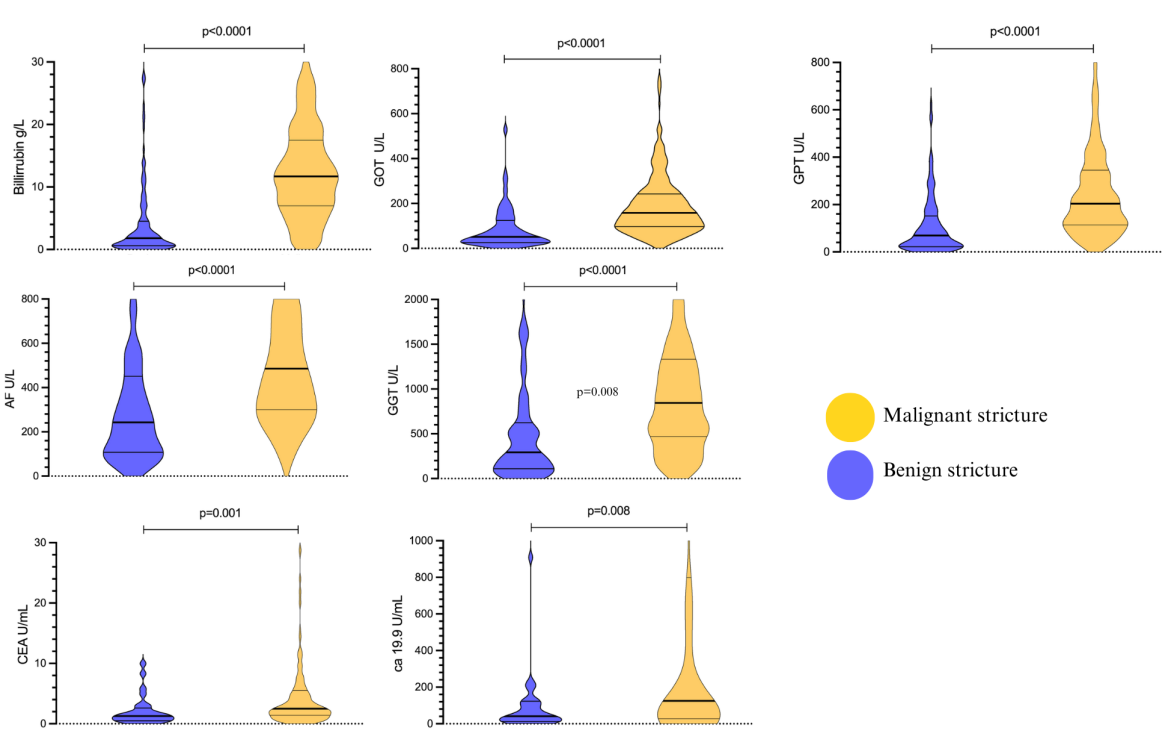

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Figure 1. Baseline biochemical parameters. Violin plots show median (solid line), IQR (dotted line), maximum and minimum. Outliers were removed for graph representation but accounted for statistical comparison. Mann–Whitney U test was used to compare medians.

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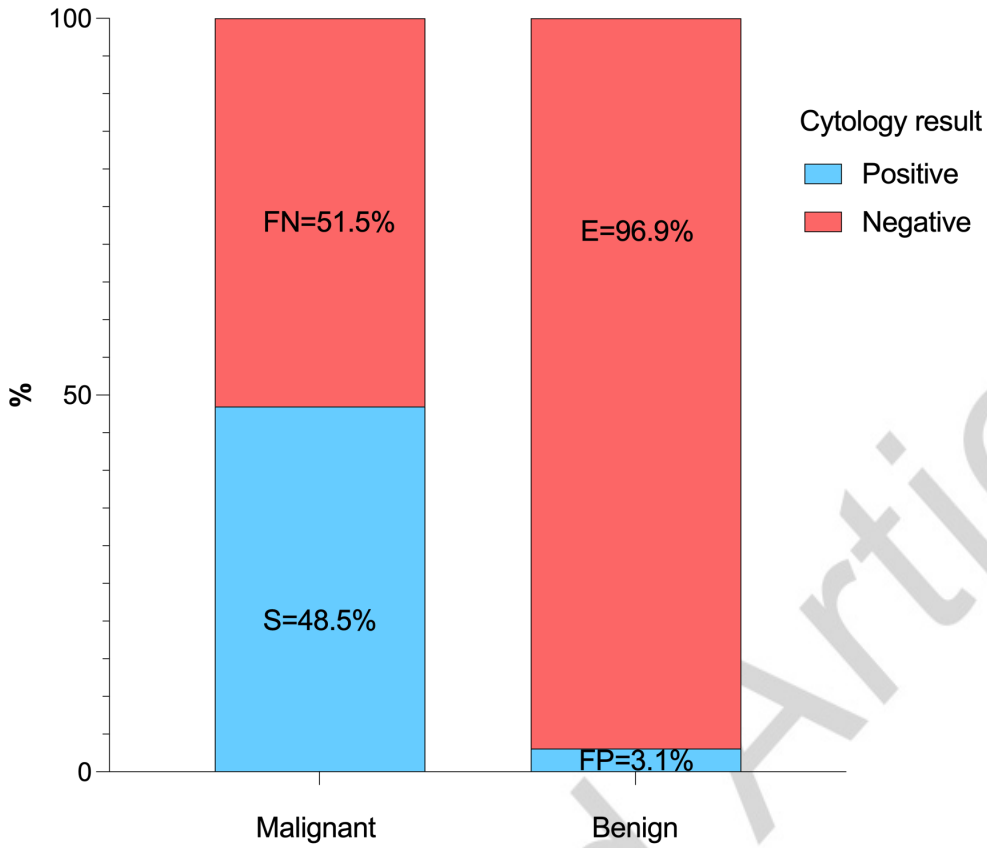

Figure 2. E: Especificity; FN: false negative; FP: false positive; S: Sensibility.

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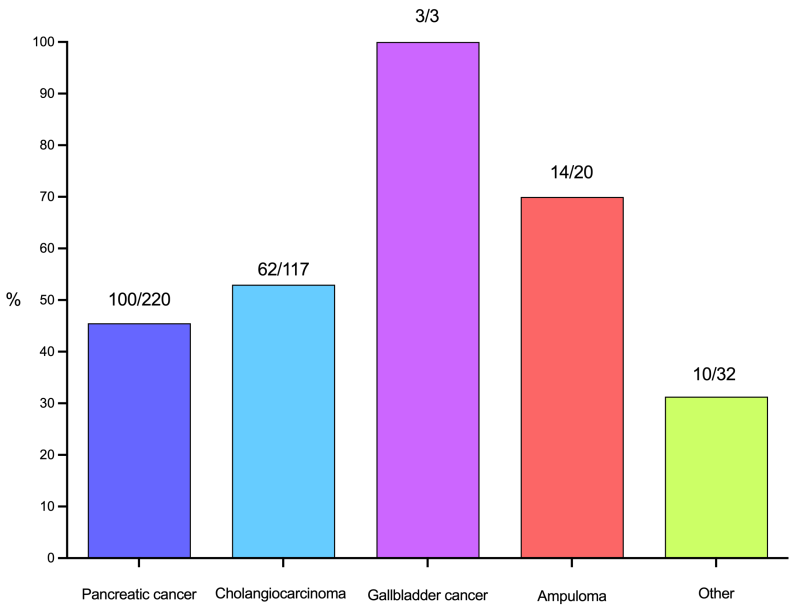

Figure 3. Biliary brush cytology positivity depending on the tumour.

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