

## ORIGINAL ARTICLE

# Admission Serum Bilirubin Fractions and Magnetic Resonance Cholangiopancreatography for Differentiating Choledocholithiasis from Pancreatobiliary Malignancy in Extrahepatic Obstructive Jaundice: A Retrospective Diagnostic Accuracy Study

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## ABSTRACT

**Background:** Distinguishing benign from malignant extrahepatic obstructive jaundice before surgery determines whether patients proceed to stone clearance or to oncological staging and resection.

**Objective:** To evaluate the diagnostic accuracy of admission serum bilirubin fractions and preoperative magnetic resonance cholangiopancreatography (MRCP) for differentiating choledocholithiasis from pancreatobiliary malignancy.

**Methods:** This single-center retrospective study, reported according to STARD 2015, included 50 consecutive patients (71 screened) treated at Dr. Mohammad Hoesin Central General Hospital, Palembang, Indonesia, in 2024–2025. Admission bilirubin fractions and 1.5-T MRCP were compared with operative or biopsy histopathology using receiver operating characteristic analysis, Wilson 95% confidence intervals (CIs), likelihood ratios, and exploratory Firth logistic regression.

**Results:** Histopathology showed choledocholithiasis in 39 patients (78.0%) and pancreatobiliary carcinoma in 11 (22.0%). Direct bilirubin (median 13.7 vs 8.7 mg/dL;  $p = 0.003$ ), total bilirubin ( $20.17 \pm 6.78$  vs  $13.02 \pm 7.64$  mg/dL;  $p = 0.007$ ), and common bile duct diameter ( $26.00 \pm 8.60$  vs  $18.49 \pm 9.06$  mm;  $p = 0.018$ ) were greater in malignancy. Direct bilirubin  $\geq 9.65$  mg/dL (AUC 0.797) and total bilirubin  $\geq 14.3$  mg/dL (AUC 0.773) each had a sensitivity of 90.9% (95% CI 62.3–98.4%), with specificities of 56.4% and 61.5% and negative predictive values of 95.7% and 96.0%. For MRCP, sensitivity was 63.6% and specificity 94.9%; accuracy reached 88.0%, LR+ was 12.4, and the adjusted odds ratio was 21.65 (95% CI 3.12–150.24).

**Conclusion:** Admission bilirubin flagged most cancers but also many stone patients, whereas MRCP rarely mislabeled stones but missed some tumors. A sequential pathway using both needs external validation.

## 1. Introduction

Extrahepatic obstructive jaundice is a common problem in hepatopancreatobiliary surgery. It results from mechanical obstruction to the flow of conjugated bile along the extrahepatic biliary tree, from the hepatic hilum to the ampulla of Vater.<sup>1,2</sup> Its causes fall into two groups: benign conditions, principally choledocholithiasis and benign inflammatory strictures, and pancreatobiliary malignancies, including extrahepatic cholangiocarcinoma, pancreatic-head ductal adenocarcinoma, periampullary carcinoma, and gallbladder carcinoma infiltrating the bile duct.<sup>1–3</sup> Patients in both groups present with scleral icterus, dark urine, pale stools, and conjugated hyperbilirubinemia, yet perioperative morbidity and long-term survival depend mainly on the underlying cause rather than on the biochemical severity of cholestasis.<sup>1,4</sup> Analyses from the Global Burden of Disease Study and from referral centers in Asia and Africa show that pancreatic cancer mortality continues to rise, that biliary tract cancer mortality is highest in high-income Asia Pacific and rising in South Asia, and that pancreatobiliary

malignancies often reach surgical centers late, after silent retroperitoneal or periductal progression.<sup>2,5,6</sup>

Mechanical obstruction of biliary outflow alters hepatic, renal, hemostatic, and immunological function, so operating on a jaundiced patient carries increased risk.<sup>4</sup> Normal biliary ductal pressure is about 7 to 14 cm H<sub>2</sub>O; when intraductal pressure exceeds about 25 cm H<sub>2</sub>O, cholangiovenous and cholangiolymphatic reflux occur, and sustained distension disrupts the canalicular tight junctions (zonula occludens-1 and claudin-1), allowing conjugated bilirubin and bile acids to regurgitate into the hepatic sinusoids and the systemic circulation.<sup>4,7–9</sup> At the molecular level, cholestasis reduces canalicular excretion through multidrug resistance-associated protein 2 (MRP2/ABCC2) and the bile salt export pump (BSEP/ABCB11) and upregulates the basolateral efflux transporters MRP3/ABCC3 and MRP4/ABCC4, which divert bilirubin glucuronides into the blood.<sup>10,11</sup> At the same time, the absence of bile salts in the duodenum prevents micellar absorption of vitamin K and hence the hepatic gamma-carboxylation of coagulation factors II, VII, IX, and X, while intestinal mucosal atrophy and tight-junction breakdown

promote portal endotoxemia, Kupffer-cell activation, systemic release of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-6 (IL-6), renal vasoconstriction, and postoperative sepsis.<sup>4</sup>

In malignant obstruction, diagnostic delay or misattribution to stone disease can allow an early, resectable tumor to progress to locally advanced or metastatic disease that is suitable only for palliative decompression.<sup>12-14</sup> Conversely, misclassifying choledocholithiasis or inflammatory papillitis as a malignant stricture exposes patients to unnecessary pancreatoduodenectomy or major hepatectomy, operations with appreciable mortality and long-term exocrine and endocrine morbidity.<sup>15-20</sup> Accurate, rapid, and inexpensive preoperative differentiation therefore decides whether patients proceed to single-stage laparoscopic common bile duct exploration (LCBDE) or endoscopic retrograde cholangiopancreatography (ERCP) stone extraction, or to multidisciplinary oncological staging and curative-intent resection.<sup>21,22</sup> Serum bilirubin fractionation is a widely available, inexpensive first-line test whose values reflect the duration and completeness of ductal occlusion.<sup>12,15</sup> Choledocholithiasis typically causes intermittent, partial "ball-valve" impaction within a compliant duct, which allows periodic decompression and produces moderate, fluctuating hyperbilirubinemia. Pancreatic-head adenocarcinoma and distal cholangiocarcinoma, by contrast, cause progressive circumferential infiltration that leads to complete ductal occlusion and steadily rising direct and total bilirubin.<sup>12,23-26</sup>

MRCP complements this biochemical assessment by mapping the anatomy and is the standard noninvasive test for evaluating the extrahepatic biliary tree and pancreatic duct.<sup>16,21</sup> It uses heavily T2-weighted sequences in which static or slow-moving fluid in the ducts gives a high signal against suppressed background tissue. MRCP therefore shows the level, length, filling defects, and stricture morphology of an obstruction without ionizing radiation, iodinated contrast, or the procedural risks of diagnostic ERCP and percutaneous transhepatic cholangiography (PTC), such as post-ERCP pancreatitis, cholangitis, hemorrhage, and duodenal perforation.<sup>3,21</sup> Endoscopic ultrasound (EUS) studies further suggest that combining biochemical triggers with MRCP morphology and quantitative duct measurements can streamline referral, avoid redundant endoscopic procedures, and improve preoperative planning.<sup>27,28</sup> However, the sensitivity of MRCP alone falls in small, non-mass-forming periductal-infiltrating cholangiocarcinomas and in short periampullary strictures that mimic stone-related or inflammatory disease, so it needs direct comparison with an independent histopathological reference standard.<sup>16,26,28,29</sup>

The literature on machine-learning classifiers, pre-procedural imaging pathways, and quantitative biliary biomarkers in obstructive jaundice is growing,<sup>30-34</sup> but studies that compare admission bilirubin fractions with preoperative MRCP against tissue diagnosis remain few in Indonesian referral practice; a bilirubin-based study from West Sumatra is a notable exception.<sup>12</sup> At Dr. Mohammad Hoesin Central General Hospital in Palembang, the principal surgical referral center for South Sumatra and neighboring provinces and the main teaching hospital of the Faculty of Medicine, Universitas Sriwijaya, patients often present after long pre-referral intervals, and access to magnetic resonance imaging and therapeutic endoscopy must be rationed across a high-volume surgical case mix. Locally derived receiver operating characteristic (ROC)-based bilirubin cutoffs, and their performance alongside 1.5-tesla (1.5-T) MRCP and common bile duct (CBD) diameter, are therefore needed before a stepwise triage pathway can be

proposed.<sup>34-37</sup> Following the Standards for Reporting of Diagnostic Accuracy Studies (STARD 2015),<sup>35</sup> this study aimed to: (1) compare admission total, direct, and indirect serum bilirubin and MRCP-measured CBD diameter between histopathologically confirmed choledocholithiasis and pancreatobiliary malignancy; (2) determine the ROC area under the curve (AUC), Youden-optimal cutoffs, sensitivity, specificity, positive and negative predictive values (PPV, NPV), likelihood ratios (LR+, LR-), and diagnostic odds ratios (DOR) of the bilirubin fractions and preoperative MRCP against operative or biopsy histopathology; (3) evaluate the agreement between bilirubin thresholds and MRCP and identify independent predictors with Firth penalized logistic regression; and (4) propose, for future validation, a stepwise diagnostic pathway for referral centers.

## 2. Methods

### 2.1 Study design, reporting standards, and clinical setting

This single-center, observational diagnostic accuracy study used retrospectively collected cohort data and is reported according to STARD 2015.<sup>35</sup> It was conducted by the Department of Surgery (Division of Digestive Surgery) together with the Departments of Radiology, Anatomical Pathology, and Pharmacology at Dr. Mohammad Hoesin Central General Hospital, Palembang, South Sumatra, Indonesia, the main surgical referral hospital for South Sumatra and the primary teaching hospital of the Faculty of Medicine, Universitas Sriwijaya. Two prespecified index tests, admission serum bilirubin fractions (total, direct, and indirect) and the preoperative 1.5-T MRCP impression supplemented by CBD diameter measurement, were evaluated separately and in multivariable combination against a reference standard of histopathological diagnosis from surgical resection or tissue biopsy specimens. Clinical, biochemical, radiological, and operative records were retrieved for consecutive adult admissions treated between January 1, 2024, and December 31, 2025, and statistical analysis was completed between November 2025 and April 2026.

### 2.2 Eligibility criteria, case ascertainment, and sampling

Cases were identified by searching the institutional medical record registry, the surgical logbooks of the Division of Digestive Surgery, the hepatobiliary magnetic resonance imaging (MRI)/MRCP archive of the Picture Archiving and Communication System (PACS), and the Department of Anatomical Pathology database. The search used clinical diagnosis keywords (obstructive jaundice, extrahepatic biliary obstruction, choledocholithiasis, biliary stricture, cholangiocarcinoma, gallbladder carcinoma, periampullary carcinoma, and pancreatic-head tumor) and the corresponding International Classification of Diseases, Tenth Revision (ICD-10) codes (K80.3–K80.5, K83.1, C22.1, C23, C24.0–C24.9, and C25.0). All eligible adult admissions were sampled consecutively to preserve the clinical spectrum of surgical referrals. Inclusion required all of the following: (1) age >18 years at the index admission; (2) clinical and biochemical presentation of extrahepatic obstructive jaundice; (3) quantitative admission serum bilirubin fractions (total, direct, and indirect) measured before biliary instrumentation or surgical decompression; (4) preoperative 1.5-T MRCP with a formal hepatobiliary radiology report and CBD diameter measurement; and (5) definitive etiological verification by operative or biopsy histopathology classifying the obstruction as benign (choledocholithiasis) or malignant (pancreatobiliary carcinoma). Exclusion criteria were: (1) extrahepatic obstruction from non-calculous, non-

neoplastic causes such as postoperative benign stricture, hepatobiliary parasitic infestation, or trauma; (2) chronic parenchymal liver disease or decompensated cirrhosis that could confound hepatic bilirubin metabolism; and (3) incomplete clinical records or absence of confirmatory tissue histopathology.

### 2.3 Sample size

The minimum sample size was calculated a priori with the single-proportion diagnostic accuracy formula  $n = Z_{\alpha}^2 \times P \times Q / d^2$ , using  $Z_{\alpha} = 1.96$  for a two-sided 95% confidence level ( $\alpha = 0.05$ ), an expected proportion correctly predicted by serum bilirubin of  $P = 0.971$  based on prior work,<sup>12</sup>  $Q = 1 - P = 0.029$ , and an absolute precision of  $d = 0.05$ . This gave  $n = (3.8416 \times 0.971 \times 0.029) / 0.0025 = 43.27$ , that is, a minimum of 44 patients. All 50 consecutive eligible patients who met the inclusion criteria during the study period were analyzed.

### 2.4 Index test 1: admission serum bilirubin fractions

Venous blood was collected from all patients on admission, before any endoscopic, percutaneous, or operative biliary decompression. Serum total and direct (conjugated) bilirubin were measured in milligrams per deciliter (mg/dL; 1 mg/dL = 17.104  $\mu$ mol/L) in the central clinical pathology laboratory with an automated colorimetric diazo-coupling/enzymatic vanadate oxidation spectrophotometric assay under daily quality-control calibration. Direct bilirubin measures the water-soluble glucuronide-conjugated fraction (bilirubin diglucuronide and monoglucuronide) together with albumin-bound delta bilirubin, whereas total bilirubin measures all serum bilirubin after an accelerator brings the unconjugated fraction into the reaction.<sup>38,39</sup> Indirect (unconjugated) bilirubin was calculated as total minus direct bilirubin. The laboratory staff who performed the assays were blinded to the MRCP findings and histopathological diagnoses.

### 2.5 Index test 2: preoperative 1.5-T MRCP protocol, morphological criteria, and blinding

Preoperative MRCP was performed on 1.5-T superconducting MRI systems with phased-array body coils after a 4- to 6-hour fast. The protocol comprised breath-hold axial and coronal T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequences, fat-suppressed T2-weighted turbo spin-echo sequences, and heavily T2-weighted two-dimensional (2D) thick-slab and three-dimensional (3D) isotropic fast spin-echo sequences reconstructed with maximum intensity projection (MIP) and multiplanar reformation (MPR). All MRCP studies were interpreted by staff radiologists experienced in hepatobiliary imaging without knowledge of the final histopathology. Each examination was classified into a prespecified dichotomous impression: (1) malignant, defined by a soft-tissue mass, a long or irregular stricture with asymmetric margins, abrupt ductal tapering, or a malignant pattern of proximal ductal dilation; or (2) benign, defined by discrete intraluminal T2-hypointense calculous filling defects or a short, regular, smooth stricture.<sup>16,28,36</sup> The maximal internal transverse diameter of the CBD proximal to the obstruction was recorded in millimeters, and a macroscopic CBD stricture was recorded as present or absent. The index tests preceded the reference standard in every case, and no MRCP impression was indeterminate.

### 2.6 Reference standard: operative and biopsy histopathology

The reference standard, applied to all 50 included patients (100.0% verification), was the histopathological diagnosis of specimens obtained at operative resection or exploration or by tissue biopsy. Specimens were fixed in 10% neutral buffered

formalin, embedded in paraffin, sectioned at 4  $\mu$ m, stained with hematoxylin and eosin (H&E), and interpreted by senior anatomical pathologists without reference to the serum bilirubin values or the MRCP impression. Histopathology classified the cause of obstruction as either benign, that is, choledocholithiasis with benign biliary mucosa free of neoplasia ( $n = 39$ ; 78.0%), or malignant, that is, invasive adenocarcinoma of the extrahepatic bile duct (cholangiocarcinoma), pancreatic head, periampullary region, or gallbladder invading the extrahepatic biliary tree ( $n = 11$ ; 22.0%).

### 2.7 Clinical covariates and statistical analysis

Age (years), sex, duration of jaundice before admission (days), and documented comorbidities (diabetes mellitus, hypertension, and previous jaundice) were recorded to describe the groups and to assess baseline balance. Analyses were performed with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA), and a two-sided  $p < 0.05$  indicated statistical significance. The normality of continuous variables was assessed with the Shapiro–Wilk test (W statistics are given in Tables 1 and 2). Normally distributed variables (total bilirubin and CBD diameter) were summarized as mean  $\pm$  standard deviation (SD) with 95% confidence intervals (CIs) and compared with the independent-samples Student's  $t$ -test, reporting the mean difference ( $\Delta$ ) and Cohen's  $d$ . Non-normally distributed variables (age, jaundice duration, direct bilirubin, and indirect bilirubin) were summarized as median (minimum–maximum) and interquartile range (IQR), with the mean  $\pm$  SD for reference, and compared with the Mann–Whitney  $U$  test, reporting  $U$ ,  $Z$ , and the rank-biserial correlation ( $r_{rb}$ ). Categorical variables were compared with Fisher's exact test, with odds ratios (OR) and phi ( $\phi$ ) coefficients.

ROC analysis estimated the AUC (95% CI) of each bilirubin fraction and of CBD diameter, and optimal cutoffs were identified with Youden's index ( $J = \text{sensitivity} + \text{specificity} - 1$ ). From 2 $\times$ 2 tables against histopathology, we calculated sensitivity, specificity, PPV, NPV, overall accuracy, LR+, LR–, and DOR, with Wilson score 95% CIs for all proportions. Agreement between the bilirubin thresholds and the MRCP impression was also evaluated, recognizing that MRCP is not the reference standard. Because malignant events were few, a multivariable Firth penalized maximum-likelihood logistic regression model was fitted to estimate adjusted odds ratios (aOR) for direct bilirubin, MRCP impression, and CBD diameter. The cutoffs and the model were derived and evaluated in the same patients and are therefore exploratory.<sup>40,41</sup>

### 2.8 Ethical approval

The study was approved by the CMHC Research Center Ethics Committee, Indonesia (Protocol No.2026/0417), and all personal identifiers were removed before analysis. Consent and compliance with the Declaration of Helsinki are described in the Declarations.

## 3. Results

### 3.1 Participant flow, baseline profile, and common bile duct diameter

Between January 2024 and December 2025, 71 consecutive adult patients with extrahepatic obstructive jaundice who had both an admission serum bilirubin measurement and preoperative 1.5-T MRCP were screened for eligibility. Twenty-one patients (29.6%) were excluded: 8 because of non-calculous, non-malignant causes of obstruction (benign postoperative stricture, parasitic infestation, or trauma), 6 because of chronic parenchymal liver disease or cirrhosis, and 7 because of incomplete records without histopathological

confirmation. All 50 remaining eligible patients (100.0%) completed both index tests and underwent histopathological verification; 39 (78.0%) had a benign cause (choledocholithiasis) and 11 (22.0%) a malignant

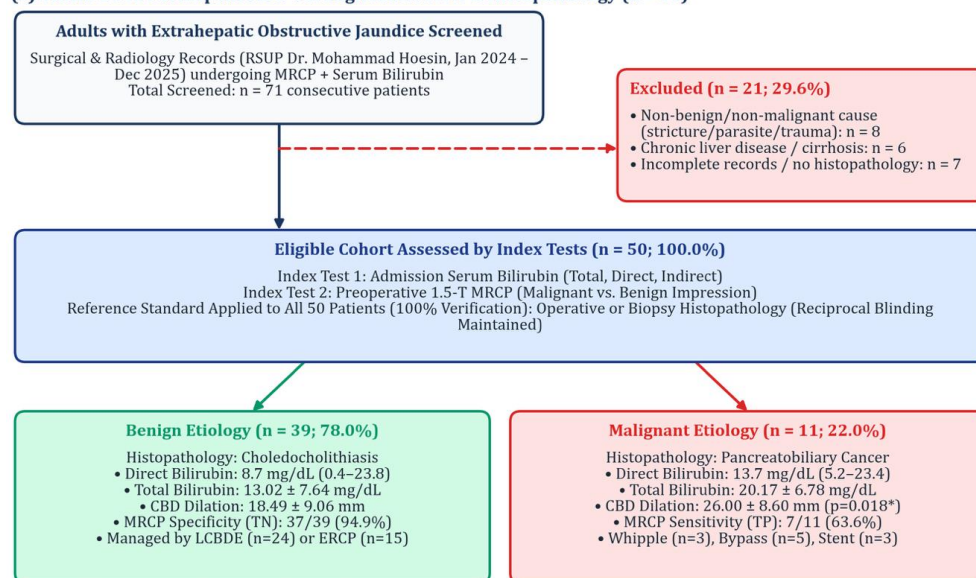
pancreatobiliary cause. Figure 1 shows the flow of participants through screening, eligibility assessment, index testing, and reference-standard classification, and Table 1 gives the baseline sociodemographic, clinical, and morphometric characteristics.

**Table 1.** Baseline demographic, clinical, and morphometric characteristics by histopathological etiology (n = 50).

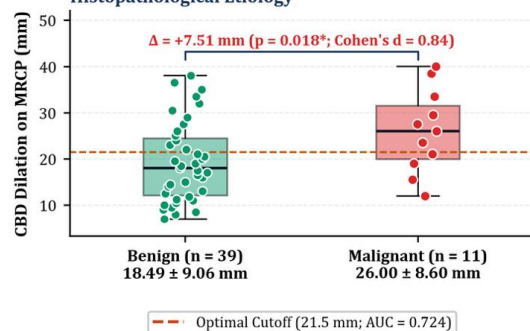
| Characteristic                                                     | Benign etiology<br>(choledocholithiasis)<br>n = 39 (78.0%) | Malignant etiology<br>(pancreatobiliary<br>cancer)<br>n = 11 (22.0%) | Effect size and 95% CI                               | Shapiro-Wilk W (p);<br>p value                |
|--------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------------------------------------|------------------------------------------------------|-----------------------------------------------|
| Age, years — median (min–max)<br>[IQR; mean ± SD]                  | 54 (4–75)<br>[44.0–62.0; 52.41 ± 14.85]                    | 56 (30–70)<br>[47.5–63.5; 54.18 ± 11.92]                             | U = 212.5; Z = -0.047<br>$r_{tb} = 0.009$            | W = 0.918 (p = 0.008);<br>0.963 <sup>a</sup>  |
| Jaundice duration, days — median (min–max)<br>[IQR; mean ± SD]     | 14 (2–365)<br>[7.0–30.0; 31.64 ± 59.42]                    | 14 (3–90)<br>[10.0–30.0; 23.82 ± 24.95]                              | U = 204.5; Z = -0.238<br>$r_{tb} = 0.047$            | W = 0.452 (p < 0.001);<br>0.812 <sup>a</sup>  |
| CBD diameter on MRCP, mm — mean ± SD<br>[95% CI; median (min–max)] | 18.49 ± 9.06<br>[15.55–21.43; 18.0 (7.0–38.0)]             | 26.00 ± 8.60<br>[20.22–31.78; 26.0 (12.0–40.0)]                      | $\Delta = +7.51$ mm [1.36–13.66]<br>Cohen's d = 0.84 | W = 0.961 (p = 0.194);<br>0.018 <sup>b*</sup> |
| Male sex — n (%) (total 23; 46.0%)                                 | 17 (43.6)                                                  | 6 (54.5)                                                             | OR = 1.55 (0.41–5.96)<br>$\phi = 0.091$              | 0.733 <sup>c</sup>                            |
| Female sex — n (%) (total 27; 54.0%)                               | 22 (56.4)                                                  | 5 (45.5)                                                             | OR = 0.64 (0.17–2.47)<br>$\phi = -0.091$             | 0.733 <sup>c</sup>                            |
| Diabetes mellitus — n (%) (total 1; 2.0%)                          | 1 (2.6)                                                    | 0 (0.0)                                                              | $\phi = -0.076$                                      | 1.000 <sup>c</sup>                            |
| CBD stricture on MRCP — n (%) (total 5; 10.0%)                     | 3 (7.7)                                                    | 2 (18.2)                                                             | OR = 2.67 (0.39–18.32)<br>$\phi = 0.145$             | 0.301 <sup>c</sup>                            |

<sup>a</sup>Mann–Whitney U test; <sup>b</sup>independent-samples Student's t-test; <sup>c</sup>Fisher's exact test. \*p < 0.05 (two-sided). No patient in either group had documented hypertension or previous jaundice (0/39 and 0/11). Abbreviations: CBD, common bile duct; CI, confidence interval; IQR, interquartile range; MRCP, magnetic resonance cholangiopancreatography; OR, odds ratio;  $r_{tb}$ , rank-biserial correlation; SD, standard deviation; W, Shapiro–Wilk statistic.

**(a) STARD 2015 Participant Flow Through Index Tests & Histopathology (n = 50)**



**(b) Common Bile Duct Dilatation by Histopathological Etiology**



**(c) Baseline Categorical Characteristics (Age: 54 vs 56 yr, p=0.963)**

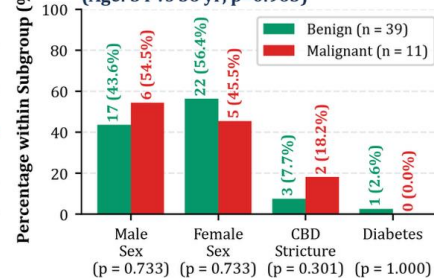


**Figure 1.** Participant flow and baseline characteristics. (a) STARD 2015 flow of participants through screening (n = 71), exclusions (n = 21), index testing, and histopathological classification (n = 50: 39 benign [78.0%], 11 malignant [22.0%]). (b) Distribution of common bile duct (CBD) diameter on MRCP by etiology (26.00 ± 8.60 vs. 18.49 ± 9.06 mm; p = 0.018; Cohen's d = 0.84; ROC AUC 0.724; optimal cut off 21.5 mm). (c) Baseline categorical characteristics by etiology. ERCP, endoscopic retrograde cholangiopancreatography; LCBDE, laparoscopic common bile duct exploration; MRCP, magnetic resonance cholangiopancreatography; TN, true negative; TP, true positive.

Median age was similar in the benign and malignant groups (54 years [range 4–75; IQR 44.0–62.0; mean  $52.41 \pm 14.85$ ] vs. 56 years [range 30–70; IQR 47.5–63.5; mean  $54.18 \pm 11.92$ ]; Mann-Whitney  $U = 212.5$ ,  $Z = -0.047$ ,  $r_{rb} = 0.009$ ,  $p = 0.963$ ), as was the duration of jaundice before admission (median 14 days in both groups; range 2–365 days [IQR 7.0–30.0] in benign vs. 3–90 days [IQR 10.0–30.0] in malignant disease;  $U = 204.5$ ,  $Z = -0.238$ ,  $r_{rb} = 0.047$ ,  $p = 0.812$ ). The sex distribution was balanced (male 17/39 [43.6%] and female 22/39 [56.4%] in benign vs. male 6/11 [54.5%] and female 5/11 [45.5%] in malignant disease; overall 23 males [46.0%] and 27 females [54.0%]; OR = 1.55, 95% CI 0.41–5.96;  $\phi = 0.091$ ; Fisher's exact  $p = 0.733$ ). Diabetes mellitus was present in 1 benign patient (2.6%) and no malignant patient (0.0%;  $p = 1.000$ ), and no patient in either group had documented hypertension or previous jaundice. Among the variables in Table 1, only CBD diameter on MRCP differed significantly; it was greater in the malignant group ( $26.00 \pm 8.60$  mm [95% CI 20.22–31.78; median 26.0, range 12.0–40.0] vs.  $18.49 \pm 9.06$  mm [95% CI 15.55–21.43; median 18.0, range 7.0–38.0]; mean difference  $\Delta = +7.51$  mm, 95% CI 1.36–13.66 mm;  $t = 2.456$ ,  $df = 48$ ,  $p = 0.018$ ; Cohen's  $d = 0.84$ ). Its ROC AUC was 0.724 (95% CI 0.562–0.886), with an optimal cutoff of  $\geq 21.5$  mm (sensitivity 72.7% [8/11] and specificity 66.7% [26/39]; counts in Section 3.6). A CBD stricture was recorded more often in malignancy (2/11 [18.2%] vs. 3/39

[7.7%]; overall 5/50 [10.0%]), but the difference was not significant (OR = 2.67, 95% CI 0.39–18.32;  $\phi = 0.145$ ; Fisher's exact  $p = 0.301$ ).

### 3.2 Admission serum bilirubin fractions by histopathological etiology

Table 2 and Figure 2 give the bilirubin fractions by etiology. Direct (conjugated) bilirubin on admission was clearly higher in malignancy: median 13.7 mg/dL (range 5.2–23.4; IQR 12.15–15.65; mean  $13.92 \pm 4.68$  mg/dL, 95% CI 10.78–17.06) against 8.7 mg/dL in benign disease (range 0.4–23.8; IQR 5.30–9.90; mean  $8.32 \pm 4.96$  mg/dL, 95% CI 6.71–9.93) (Mann-Whitney  $U = 87.0$ ,  $Z = -2.978$ ,  $r_{rb} = 0.594$ ,  $p = 0.003$ ). Total bilirubin showed the same pattern. In the malignant group it averaged  $20.17 \pm 6.78$  mg/dL (95% CI 15.62–24.72; median 22.6, range 7.2–31.6, IQR 15.75–27.35); in the benign group,  $13.02 \pm 7.64$  mg/dL (95% CI 10.54–15.50; median 13.5, range 0.9–26.3, IQR 7.55–19.15) ( $t = 2.804$ ,  $df = 48$ ;  $\Delta = +7.15$  mg/dL, 95% CI 2.02–12.28; Cohen's  $d = 0.96$ ;  $p = 0.007$ ). Indirect bilirubin behaved differently. Its median of 5.6 mg/dL in malignancy (range 2.0–9.6; IQR 4.55–8.20; mean  $6.25 \pm 2.48$ ) did not differ significantly from 3.6 mg/dL in benign disease (range 0.5–10.2; IQR 2.20–5.25; mean  $4.69 \pm 3.12$ ) ( $U = 141.5$ ,  $Z = -1.712$ ,  $r_{rb} = 0.340$ ,  $p = 0.087$ ). Most of the discrimination in post-hepatic obstruction therefore appears to lie in the conjugated fraction.

**Table 2.** Admission serum bilirubin fractions by histopathological etiology (n = 50).

| Serum bilirubin fraction                                          | Benign etiology<br>n = 39 (78.0%)               | Malignant etiology<br>n = 11 (22.0%)            | Test statistic and effect size                                        | Shapiro-Wilk W (p);<br>p value                      |
|-------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------|-----------------------------------------------------|
| Direct bilirubin, mg/dL — median (min-max) [IQR; mean $\pm$ SD]   | 8.7 (0.4–23.8) [5.30–9.90; 8.32 $\pm$ 4.96]     | 13.7 (5.2–23.4) [12.15–15.65; 13.92 $\pm$ 4.68] | $U = 87.0$ ; $Z = -2.978$<br>$r_{rb} = 0.594$                         | $W = 0.912$ ( $p = 0.005$ );<br>0.003 <sup>a*</sup> |
| Indirect bilirubin, mg/dL — median (min-max) [IQR; mean $\pm$ SD] | 3.6 (0.5–10.2) [2.20–5.25; 4.69 $\pm$ 3.12]     | 5.6 (2.0–9.6) [4.55–8.20; 6.25 $\pm$ 2.48]      | $U = 141.5$ ; $Z = -1.712$<br>$r_{rb} = 0.340$                        | $W = 0.924$ ( $p = 0.012$ );<br>0.087 <sup>a</sup>  |
| Total bilirubin, mg/dL — mean $\pm$ SD [95% CI; median (min-max)] | $13.02 \pm 7.64$ [10.54–15.50; 13.5 (0.9–26.3)] | $20.17 \pm 6.78$ [15.62–24.72; 22.6 (7.2–31.6)] | $t = 2.804$ ; $\Delta = +7.15$ mg/dL [2.02–12.28]; Cohen's $d = 0.96$ | $W = 0.956$ ( $p = 0.134$ );<br>0.007 <sup>b*</sup> |

<sup>a</sup>Mann-Whitney  $U$  test (non-normally distributed fractions); <sup>b</sup>independent-samples  $t$ -test (normally distributed total bilirubin). \* $p < 0.05$ . SI units: 1 mg/dL bilirubin = 17.104  $\mu$ mol/L (direct bilirubin median 234.3 vs. 148.8  $\mu$ mol/L; total bilirubin mean 345.0 vs. 222.7  $\mu$ mol/L). Abbreviations as in Table 1.

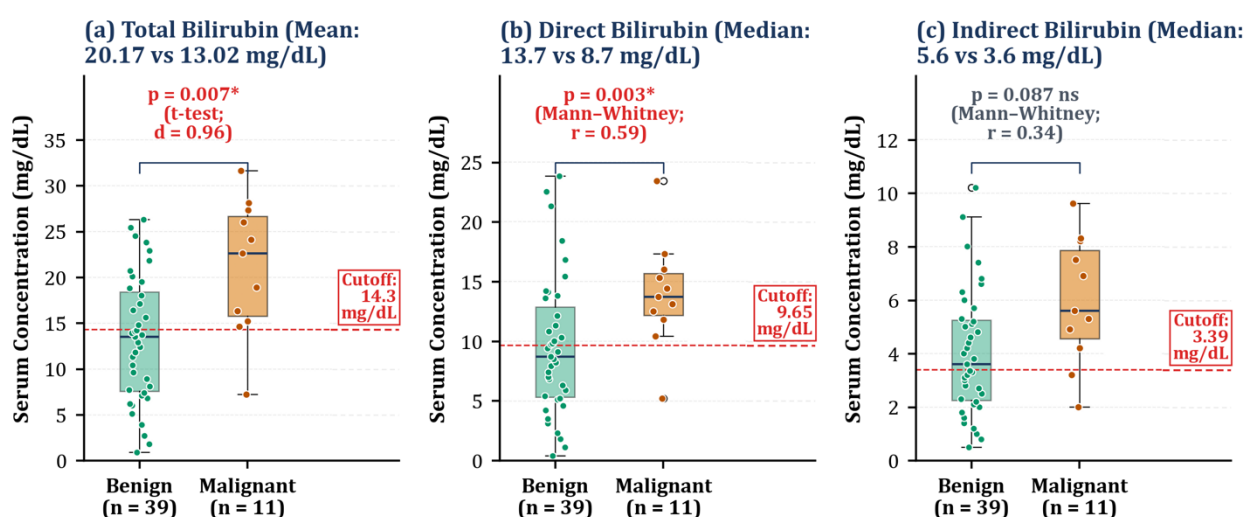


**Figure 2.** Box plots with individual patient values of admission (a) total bilirubin (Youden cutoff 14.3 mg/dL), (b) direct bilirubin (cutoff 9.65 mg/dL), and (c) indirect bilirubin (cutoff 3.39 mg/dL) by histopathological etiology (n = 50). Boxes show the median and interquartile range; dashed lines mark the cutoffs. \* $p < 0.05$ ; ns, not significant.

### 3.3 ROC discrimination and diagnostic accuracy of the bilirubin fractions

Figure 3 shows the ROC curves of the bilirubin fractions and the multivariable model, and Table 3 gives the Youden-optimal cutoffs, 2×2 counts, and accuracy measures with Wilson 95% CIs. Direct bilirubin discriminated best among the fractions (AUC 0.797, 95% CI 0.658–0.936;  $p = 0.003$ ), followed by total

bilirubin (AUC 0.773, 95% CI 0.626–0.920;  $p = 0.006$ ) and indirect bilirubin (AUC 0.670, 95% CI 0.492–0.848;  $p = 0.087$ ). At its Youden-optimal cutoff of  $\geq 9.65$  mg/dL ( $J = 0.473$ ), direct bilirubin gave 10 true positives (TP), 17 false positives (FP), 1 false negative (FN), and 22 true negatives (TN): sensitivity 90.9% (95% CI 62.3–98.4%), specificity 56.4% (41.0–70.7%), PPV 37.0% (21.5–55.8%), NPV 95.7% (79.0–99.2%), and

accuracy 64.0% (50.1–75.9%), with LR+ = 2.09 (95% CI 1.39–3.12), LR– = 0.16 (0.02–1.07), and DOR = 12.94 ( $p = 0.007$ ).

Total bilirubin behaved much like direct bilirubin. At  $\geq 14.3$  mg/dL ( $J = 0.524$ ) it detected the same 10 of 11 cancers, so sensitivity was again 90.9% (95% CI 62.3–98.4%). It mislabeled fewer stone patients, though: 15 rather than 17 (TN = 24). That raised specificity to 61.5% (45.9–75.1%), PPV to 40.0% (23.4–59.3%), NPV to 96.0% (80.5–99.3%), and accuracy to 68.0%

(54.2–79.2%), with LR+ 2.36 (1.52–3.67), LR– 0.15 (0.02–0.97), and DOR 16.00 ( $p = 0.003$ ). Indirect bilirubin lagged behind. A cutoff of  $\geq 3.39$  mg/dL ( $J = 0.305$ ; 9 TP, 20 FP, 2 FN, 19 TN) produced a sensitivity of 81.8% (52.3–94.9%) and a specificity of only 48.7% (33.9–63.8%); its PPV was 31.0% (17.3–49.2%), NPV 90.5% (71.1–97.3%), and accuracy 56.0% (42.3–68.8%), with LR+ 1.60 (1.05–2.41), LR– 0.37 (0.10–1.36), and DOR 4.28 ( $p = 0.091$ ).

**Table 3.** Diagnostic performance of serum bilirubin fractions against the histopathological reference standard ( $n = 50$ ).

| Fraction (2×2 counts)                         | AUC (95% CI)         | Cutoff, mg/dL ( $J$ ) | Sensitivity % (95% CI) | Specificity % (95% CI) | PPV % (95% CI)   | NPV % (95% CI)   | Accuracy % (95% CI) | LR+ (95% CI)<br>LR– (95% CI)<br>DOR ( $p$ )            |
|-----------------------------------------------|----------------------|-----------------------|------------------------|------------------------|------------------|------------------|---------------------|--------------------------------------------------------|
| Direct bilirubin (TP 10, FP 17, FN 1, TN 22)  | 0.797* (0.658–0.936) | $\geq 9.65$ (0.473)   | 90.9 (62.3–98.4)       | 56.4 (41.0–70.7)       | 37.0 (21.5–55.8) | 95.7 (79.0–99.2) | 64.0 (50.1–75.9)    | 2.09 (1.39–3.12)<br>0.16 (0.02–1.07)<br>12.94 (0.007*) |
| Total bilirubin (TP 10, FP 15, FN 1, TN 24)   | 0.773* (0.626–0.920) | $\geq 14.3$ (0.524)   | 90.9 (62.3–98.4)       | 61.5 (45.9–75.1)       | 40.0 (23.4–59.3) | 96.0 (80.5–99.3) | 68.0 (54.2–79.2)    | 2.36 (1.52–3.67)<br>0.15 (0.02–0.97)<br>16.00 (0.003*) |
| Indirect bilirubin (TP 9, FP 20, FN 2, TN 19) | 0.670 (0.492–0.848)  | $\geq 3.39$ (0.305)   | 81.8 (52.3–94.9)       | 48.7 (33.9–63.8)       | 31.0 (17.3–49.2) | 90.5 (71.1–97.3) | 56.0 (42.3–68.8)    | 1.60 (1.05–2.41)<br>0.37 (0.10–1.36)<br>4.28 (0.091)   |

Cutoffs were derived by maximizing Youden's index ( $J = \text{sensitivity} + \text{specificity} - 1$ ). Reference standard: operative or biopsy histopathology (malignant  $n = 11$ , benign  $n = 39$ ). 95% CIs for proportions were computed with the Wilson score method; CIs for likelihood ratios were computed from the 2×2 counts (log method). \* $p < 0.05$ . Abbreviations: AUC, area under the receiver operating characteristic curve; DOR, diagnostic odds ratio; FN, false negative; FP, false positive; LR+, positive likelihood ratio; LR–, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

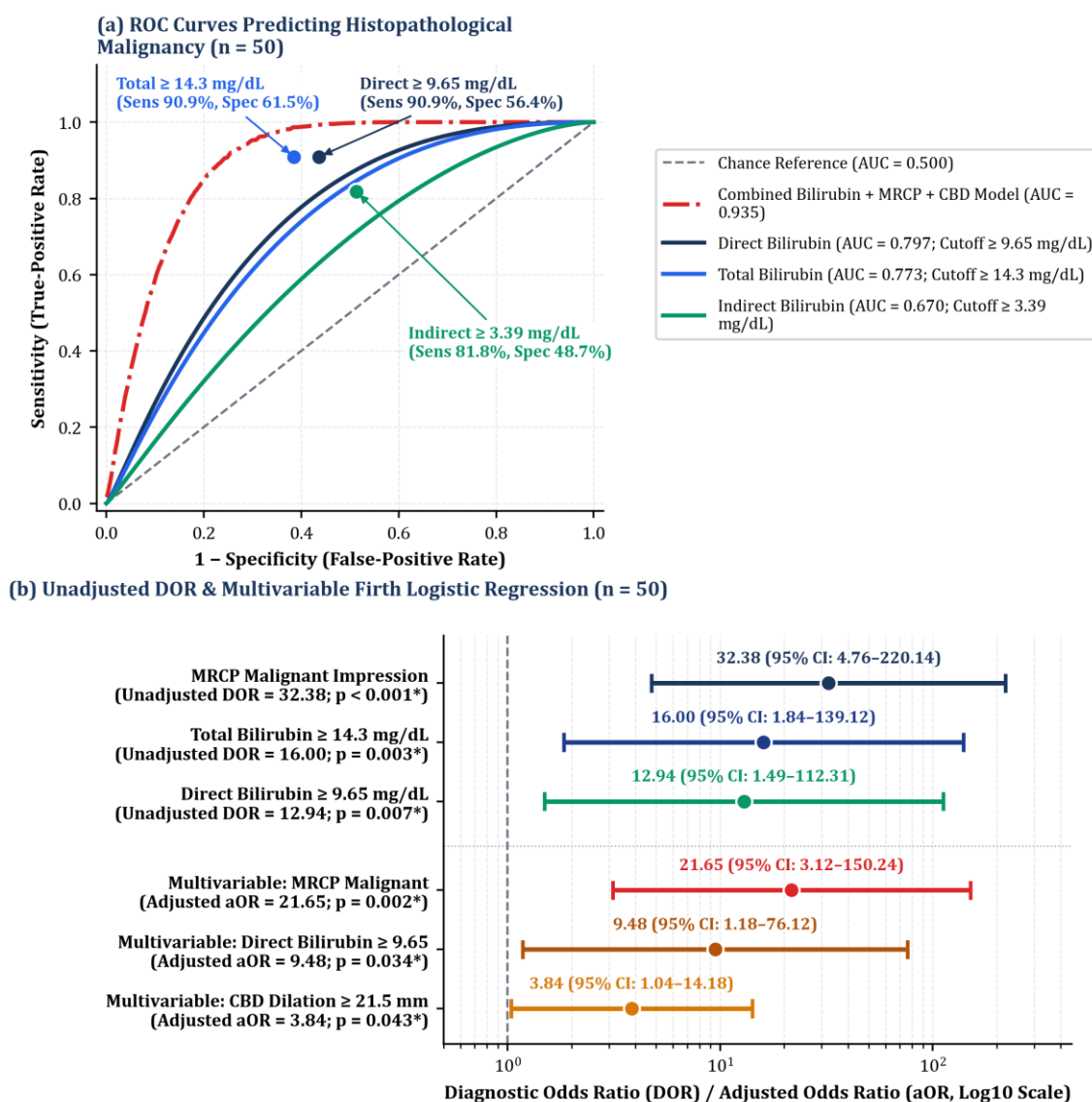


**Figure 3.** (a) Receiver operating characteristic (ROC) curves for direct bilirubin (AUC 0.797; 95% CI 0.658–0.936), total bilirubin (AUC 0.773; 0.626–0.920), indirect bilirubin (AUC 0.670; 0.492–0.848), and the multivariable combined model (apparent AUC 0.935; 0.854–1.000) for histopathological malignancy; circles mark the Youden-optimal operating points. (b) Forest plot of unadjusted diagnostic odds ratios (DOR) and multivariable Firth adjusted odds ratios (aOR) with 95% confidence intervals. AUC, area under the curve; CBD, common bile duct; MRCP, magnetic resonance cholangiopancreatography.

### 3.4 Diagnostic accuracy of preoperative 1.5-T MRCP

Table 4 gives the 2×2 classification of MRCP against histopathology. MRCP correctly classified 7 of 11 malignant cases (TP = 7) and 37 of 39 benign cases (TN = 37), with 4 false negatives and 2 false positives; overall, 9 MRCP impressions (18.0%) were malignant and 41 (82.0%) benign. MRCP had a sensitivity of 63.6% (95% CI 35.4–84.8%), a specificity of 94.9%

(83.1–98.6%), a PPV of 77.8% (45.3–93.7%), an NPV of 90.2% (77.5–96.1%), and an accuracy of 88.0% (76.2–94.4%), with Youden's J = 0.585 and Fisher's exact  $p < 0.001$ . The likelihood ratios, which do not depend on prevalence, were LR+ = 12.41 (95% CI 2.97–51.84) and LR– = 0.38 (0.18–0.84), and the DOR was 32.38 (4.76–220.14). MRCP was therefore specific and confirmatory but only moderately sensitive.

**Table 4.** Preoperative MRCP impression versus the histopathological reference standard: 2×2 classification and diagnostic performance (n = 50).

| Preoperative 1.5-T MRCP impression                                            | Histopathology: malignant (n = 11) | Histopathology: benign (n = 39) | Row total n (%) | Diagnostic accuracy (Wilson 95% CI) and likelihood ratios                                  |
|-------------------------------------------------------------------------------|------------------------------------|---------------------------------|-----------------|--------------------------------------------------------------------------------------------|
| Malignant impression (mass, long/irregular stricture, abrupt ductal tapering) | 7 (TP)<br>(63.6% of malignant)     | 2 (FP)<br>(5.1% of benign)      | 9 (18.0)        | Sensitivity 63.6% (35.4–84.8%)<br>Specificity 94.9% (83.1–98.6%)<br>PPV 77.8% (45.3–93.7%) |
| Benign impression (intraluminal stone defect, short/regular stricture)        | 4 (FN)<br>(36.4% of malignant)     | 37 (TN)<br>(94.9% of benign)    | 41 (82.0)       | NPV 90.2% (77.5–96.1%)<br>Accuracy 88.0% (76.2–94.4%)<br>Youden's J 0.585                  |
| Column total — n (%)                                                          | 11 (22.0)                          | 39 (78.0)                       | 50 (100.0)      | LR+ 12.41 (2.97–51.84)<br>LR– 0.38 (0.18–0.84)<br>DOR 32.38 (4.76–220.14); $p < 0.001^*$   |

\*Fisher's exact test. Abbreviations: DOR, diagnostic odds ratio; FN, false negative; FP, false positive; LR+, positive likelihood ratio; LR–, negative likelihood ratio; MRCP, magnetic resonance cholangiopancreatography; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

### 3.5 Agreement of bilirubin thresholds with MRCP and overall comparison

Table 5 compares the bilirubin thresholds with the radiologist's MRCP impression, which is an imperfect comparator rather than the reference standard (9 MRCP-malignant and 41 MRCP-benign cases). Both thresholds were exceeded by 8 of the 9 MRCP-malignant cases, a positive percent agreement of 88.9% (95% CI 56.5–98.0%). They differed in the MRCP-benign group: total bilirubin <14.3 mg/dL occurred in 24 of 41 cases (58.5%; 43.4–72.2%) and direct bilirubin <9.65 mg/dL in 22 of 41

(53.7%; 38.7–67.9%). Among patients above each threshold, 8 of 25 (32.0%; 17.2–51.6%) and 8 of 27 (29.6%; 15.9–48.5%) had a malignant MRCP impression; among those below, 24 of 25 (96.0%; 80.5–99.3%) and 22 of 23 (95.7%; 79.0–99.2%) had a benign one. Overall agreement was 64.0% (32/50; 50.1–75.9%) for total bilirubin and 60.0% (30/50; 46.2–72.4%) for direct bilirubin. Figure 4 compares the two index tests against histopathology and with each other: the bilirubin thresholds were sensitive with a high NPV, whereas MRCP was specific with a high LR+.

**Table 5.** Agreement of serum bilirubin thresholds with the preoperative MRCP impression (n = 50).

| Agreement parameter (MRCP impression as comparator)                  | Total bilirubin ≥14.3 mg/dL (n = 25 positive) | Direct bilirubin ≥9.65 mg/dL (n = 27 positive) | Underlying 2×2 counts (9 MRCP-malignant, 41 MRCP-benign)              |
|----------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------|
| Sensitivity vs. MRCP (positive percent agreement), % (Wilson 95% CI) | 88.9 (56.5–98.0)                              | 88.9 (56.5–98.0)                               | 8/9 MRCP-malignant cases exceeded both thresholds                     |
| Specificity vs. MRCP (negative percent agreement), % (Wilson 95% CI) | 58.5 (43.4–72.2)                              | 53.7 (38.7–67.9)                               | Total <14.3: 24/41 MRCP-benign<br>Direct <9.65: 22/41 MRCP-benign     |
| PPV vs. MRCP, % (Wilson 95% CI)                                      | 32.0 (17.2–51.6)                              | 29.6 (15.9–48.5)                               | Total ≥14.3: 8/25 MRCP-malignant<br>Direct ≥9.65: 8/27 MRCP-malignant |
| NPV vs. MRCP, % (Wilson 95% CI)                                      | 96.0 (80.5–99.3)                              | 95.7 (79.0–99.2)                               | Total <14.3: 24/25 MRCP-benign<br>Direct <9.65: 22/23 MRCP-benign     |
| Overall agreement, % (Wilson 95% CI)                                 | 64.0 (50.1–75.9)                              | 60.0 (46.2–72.4)                               | Total: (8 + 24)/50 = 32/50<br>Direct: (8 + 22)/50 = 30/50             |

The preoperative MRCP impression (9 malignant, 41 benign) is used here only as a non-reference comparator to evaluate agreement; the values describe biochemical–radiological agreement, not diagnostic accuracy against histopathology. Abbreviations as in Tables 3 and 4.

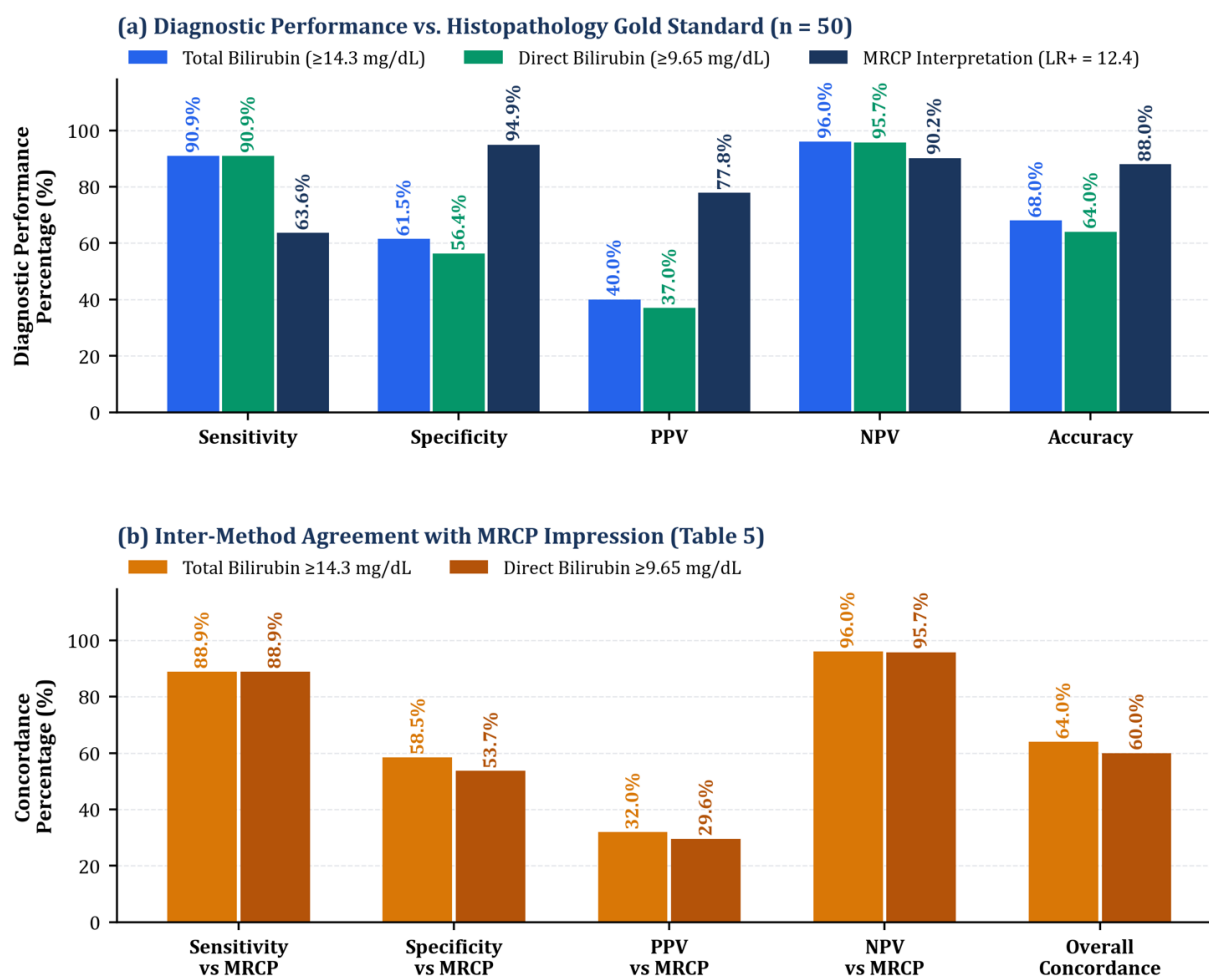


**Figure 4.** (a) Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of total bilirubin ( $\geq 14.3$  mg/dL), direct bilirubin ( $\geq 9.65$  mg/dL), and preoperative MRCP against histopathology (n = 50). (b) Agreement of the bilirubin thresholds with the MRCP impression, which is not the reference standard (Table 5). LR+, positive likelihood ratio; MRCP, magnetic resonance cholangiopancreatography.

### 3.6 Definitive surgical management and multivariable logistic regression

Table 6 summarizes definitive management by etiology, and Table 7 gives the multivariable Firth penalized logistic regression. The 11 malignancies comprised 5 extrahepatic cholangiocarcinomas (45.5%), 3 pancreatic-head adenocarcinomas (27.3%), 2 periampullary carcinomas (18.2%), and 1 gallbladder carcinoma invading the bile duct (9.1%). Three of these patients (27.3% of the malignant group;

6.0% of the cohort) had resectable tumors and underwent curative pancreatoduodenectomy (Whipple procedure), 5 (45.5%; 10.0%) underwent palliative surgical biliary bypass by hepaticojejunostomy, and 3 (27.3%; 6.0%) received palliative endoscopic or percutaneous biliary stenting. Of the 39 patients with choledocholithiasis, 24 (61.5% of the benign group; 48.0% of the cohort) underwent single-stage LCBDE with cholecystectomy, and 15 (38.5%; 30.0%) underwent ERCP stone clearance with or without cholecystectomy.

**Table 6.** Definitive surgical management by histopathological etiology (n = 50).

| Definitive management pathway                              | Benign (n = 39) | Malignant (n = 11) | Total cohort (n = 50) | Comment                                                                      |
|------------------------------------------------------------|-----------------|--------------------|-----------------------|------------------------------------------------------------------------------|
| Malignant: pancreatoduodenectomy (curative Whipple)        | 0 (0.0%)        | 3 (27.3%)          | 3 (6.0%)              | Resectable (1 distal cholangiocarcinoma, 1 pancreatic head, 1 periampullary) |
| Malignant: biliary bypass/hepaticojejunostomy (palliative) | 0 (0.0%)        | 5 (45.5%)          | 5 (10.0%)             | Unresectable, locally advanced (open surgical bilioenteric bypass)           |
| Malignant: endoscopic/percutaneous stenting (palliative)   | 0 (0.0%)        | 3 (27.3%)          | 3 (6.0%)              | Metastatic or unfit (ERCP/PTBD stenting with biopsy histopathology)          |
| Benign: LCBDE + cholecystectomy (single-stage surgery)     | 24 (61.5%)      | 0 (0.0%)           | 24 (48.0%)            | Laparoscopic duct exploration                                                |
| Benign: ERCP stone clearance ± cholecystectomy             | 15 (38.5%)      | 0 (0.0%)           | 15 (30.0%)            | Endoscopic sphincterotomy and stone extraction                               |

Percentages in the benign and malignant columns refer to each etiology group. Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; LCBDE, laparoscopic common bile duct exploration; PTBD, percutaneous transhepatic biliary drainage.

In the multivariable Firth model (omnibus  $\chi^2 = 26.84$ , df = 3,  $p < 0.001$ ; Nagelkerke  $R^2 = 0.642$ ), a malignant MRCP impression (aOR = 21.65, 95% CI 3.12–150.24,  $p = 0.002$ ), admission direct bilirubin  $\geq 9.65$  mg/dL (aOR = 9.48, 95% CI 1.18–76.12,  $p =$

0.034), and CBD diameter  $\geq 21.5$  mm (aOR = 3.84, 95% CI 1.04–14.18,  $p = 0.043$ ) were each independently associated with histopathological malignancy. The combined model had an apparent (in-sample) ROC AUC of 0.935 (95% CI 0.854–1.000).

**Table 7.** Multivariable Firth penalized-likelihood logistic regression for histopathologically confirmed malignancy (n = 50).

| Predictor                                    | Benign<br>(n = 39) | Malignant<br>(n = 11) | Total<br>(n = 50) | aOR (95% CI)        | p value |
|----------------------------------------------|--------------------|-----------------------|-------------------|---------------------|---------|
| Preoperative MRCP malignant impression       | 2/39 (5.1%)        | 7/11 (63.6%)          | 9/50 (18.0%)      | 21.65 (3.12–150.24) | 0.002*  |
| Admission direct bilirubin $\geq 9.65$ mg/dL | 17/39 (43.6%)      | 10/11 (90.9%)         | 27/50 (54.0%)     | 9.48 (1.18–76.12)   | 0.034*  |
| CBD diameter $\geq 21.5$ mm on MRCP          | 13/39 (33.3%)      | 8/11 (72.7%)          | 21/50 (42.0%)     | 3.84 (1.04–14.18)   | 0.043*  |

Omnibus likelihood-ratio  $\chi^2 = 26.84$ ,  $df = 3$ ,  $p < 0.001$ ; Nagelkerke  $R^2 = 0.642$ ; apparent (in-sample) ROC AUC of the combined model 0.935 (95% CI 0.854–1.000). The cutoffs were derived in the same data, and the model has 11 events for three predictors; the estimates are exploratory. \* $p < 0.05$ . Abbreviations: aOR, adjusted odds ratio; CBD, common bile duct; MRCP, magnetic resonance cholangiopancreatography.

## 4. Discussion

### 4.1 Principal findings

In this retrospective, histopathology-referenced study of 50 consecutive patients with extrahepatic obstructive jaundice, admission direct and total bilirubin were significantly higher in malignant obstruction, and the CBD on MRCP was wider. Direct bilirubin discriminated best among the fractions (AUC 0.797 at  $\geq 9.65$  mg/dL), followed closely by total bilirubin (AUC 0.773 at  $\geq 14.3$  mg/dL). Both fractions were sensitive (90.9%), with high NPVs (95.7% and 96.0%) and low point estimates of LR– (0.16 and 0.15), but only moderately specific (56.4% and 61.5%) at their Youden-optimal cutoffs. Preoperative 1.5-T MRCP showed the opposite profile: it was specific (94.9%), accurate (88.0%), and confirmatory (LR+ 12.4; DOR 32.38), but only moderately sensitive (63.6%). Combined with CBD diameter ( $26.00 \pm 8.60$  vs.  $18.49 \pm 9.06$  mm;  $p = 0.018$ ; Cohen's  $d = 0.84$ ; cutoff  $\geq 21.5$  mm) in multivariable Firth logistic regression, direct bilirubin  $\geq 9.65$  mg/dL (aOR = 9.48), a malignant MRCP impression (aOR = 21.65), and CBD diameter  $\geq 21.5$  mm (aOR = 3.84) gave an apparent (in-sample) AUC of 0.935, which suggests that the biochemical and radiological tests are complementary rather than interchangeable.

### 4.2 Comparison with published bilirubin thresholds

Our ROC results agree with the published literature on serum bilirubin in obstructive jaundice, although they lie at its higher-sensitivity and lower-specificity end.<sup>12,15,22,42</sup> In a comparable Indonesian referral setting at Dr. M. Djamil Hospital, West Sumatra, Suchitra et al. analyzed 132 patients with cholestatic jaundice (35.6% malignant) and reported a total-bilirubin AUC of 0.88 at a cutoff of 10.7 mg/dL (sensitivity 76.6%, specificity 90.1%, LR+ 8.14, LR– 0.26).<sup>12</sup> In a European cohort of 74 patients with biliary obstruction undergoing ERCP, Krupa et al. showed that serum bilirubin separated benign choledocholithiasis ( $>11 \mu\text{mol/L}$  [0.64 mg/dL]) from malignant pancreatic or biliary tumors ( $>59 \mu\text{mol/L}$  [3.45 mg/dL]), while shifts in the ratio of conjugated to unconjugated bile salts reflected neoplastic biliary stasis.<sup>42</sup> Peng et al. (339 patients; training AUC 0.920, validation AUC 0.848)<sup>15</sup> and Boyd et al. (265 patients; CA 19-9/[bilirubin – 1] ratio model AUC 0.91)<sup>22</sup> showed that combining total or direct bilirubin with carcinoembryonic antigen (CEA), the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), or carbohydrate antigen 19-9 (CA 19-9) improves benign-versus-malignant separation; Azam et al., in contrast, found that the CA 19-9/total bilirubin ratio performed no better than chance, whereas the CA 19-9/CRP ratio did.<sup>43</sup> Recent machine-learning work by Wen et al. (MOLT model AUROC 0.862) included admission bilirubin fractions among its predictors, although CA 19-9, CEA, and age contributed more,<sup>30</sup> and Rattanapitoon et al. discussed how such models could be integrated into clinical practice.<sup>31</sup>

### 4.3 Case-mix spectrum and cutoff calibration

The higher Youden cutoffs in our cohort (14.3 mg/dL for total and 9.65 mg/dL for direct bilirubin) and their moderate

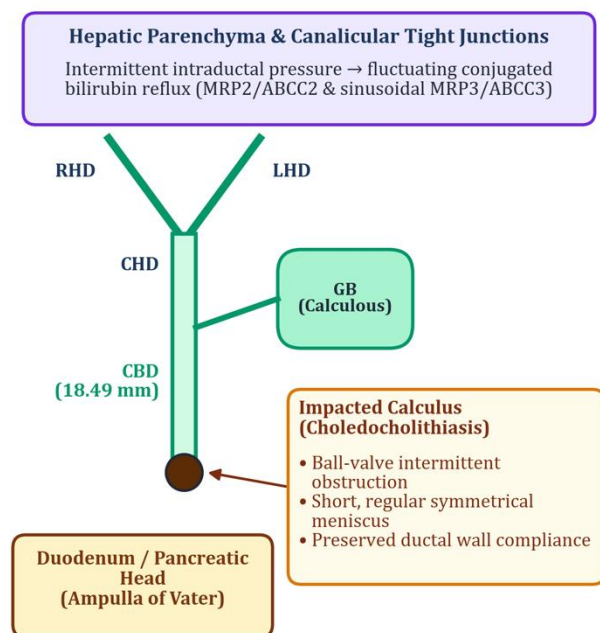
specificity (56.4%–61.5%), compared with oncology-enriched series, may reflect two features of the case mix.<sup>1,2,12</sup> First, the cohort was predominantly benign (78.0% choledocholithiasis vs. 22.0% malignancy); by Bayes' theorem, this lowers the PPV (37.0%–40.0%) of any moderately specific threshold and raises its NPV (95.7%–96.0%). Second, as the main referral center for South Sumatra, Dr. Mohammad Hoesin Central General Hospital receives a filtered spectrum of complex, chronic, or impacted CBD stones, with a mean CBD diameter of  $18.49 \pm 9.06$  mm and a mean total bilirubin of  $13.02 \pm 7.64$  mg/dL in the benign group, whereas small uncomplicated stones often pass spontaneously or are treated at secondary hospitals.<sup>33,44</sup> This referral pattern may explain why 15 of 39 benign patients had a total bilirubin  $\geq 14.3$  mg/dL. It also means that serum bilirubin is better used as a sensitive trigger for further imaging than as a stand-alone test; with only 11 malignant cases, the upper 95% limits of LR– (0.97–1.07) do not support its use to rule out malignancy on its own.<sup>45</sup>

### 4.4 Pathophysiological basis of the biochemical and ductal differences

The parallel rise of conjugated bilirubin (median 13.7 vs. 8.7 mg/dL;  $p = 0.003$ ) and CBD diameter ( $26.00 \pm 8.60$  vs.  $18.49 \pm 9.06$  mm;  $p = 0.018$ ) in malignancy may be explained by anatomical, biophysical, and molecular mechanisms, which this study did not measure; Figure 5 summarizes them schematically.<sup>4,23,42</sup> Malignant extrahepatic obstruction from pancreatic-head ductal adenocarcinoma, distal cholangiocarcinoma, or periampullary carcinoma is driven by infiltrating glands within an abundant desmoplastic stroma, which typically forms a sclerosing, circumferential lesion that narrows the ductal lumen.<sup>25,26,29</sup> Because resistance to bile flow rises steeply as the lumen narrows, continuous neoplastic narrowing keeps intraductal pressure above the reflux range (about 25 cm H<sub>2</sub>O).<sup>4,7</sup> In an extrahepatic biliary tree not previously stiffened by chronic stone-related fibrosis (the anatomical basis of Courvoisier's law), sustained intraductal hypertension produces progressive dilation; in our malignant group the mean CBD diameter was  $26.00 \pm 8.60$  mm. This agrees with the 3D quantitative MRCP+ volumetry of Eurboonyanun et al., who found a threefold larger total biliary tree volume in malignant than in benign strictures (53.10 vs. 16.70 mL;  $p = 0.001$ ).<sup>34</sup> Within the liver, sustained back-pressure disrupts canalicular tight junctions, allows cholangiovenous reflux, reduces canalicular MRP2/ABCC2 excretion, and upregulates basolateral MRP3/ABCC3 efflux of conjugated bilirubin.<sup>4,8,10,11</sup> Because hepatic conjugation is preserved in post-hepatic obstruction, the regurgitated pigment is predominantly direct (conjugated) bilirubin,<sup>46</sup> whereas choledocholithiasis produces intermittent ball-valve impaction that allows periodic decompression and results in lower bilirubin levels and milder ductal dilation.<sup>23</sup>

**(a) Benign Obstruction — Choledocholithiasis (n = 39; 78.0%)**

CBD Dilation:  $18.49 \pm 9.06$  mm | Direct Bilirubin: 8.7 mg/dL | Total: 13.02 mg/dL

**(b) Malignant Obstruction — Pancreatobiliary Cancer (n = 11; 22.0%)**

CBD Dilation:  $26.00 \pm 8.60$  mm (p=0.018\*) | Direct: 13.7 mg/dL (p=0.003\*) | Total: 20.17 mg/dL (p=0.007\*)

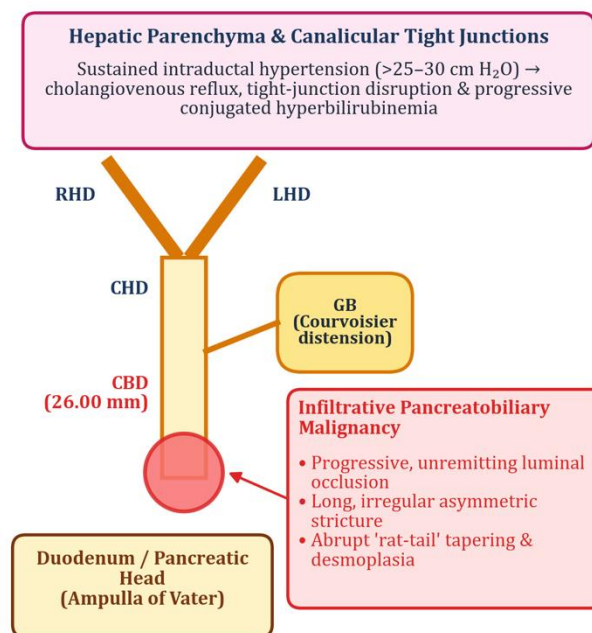


**Figure 5.** Schematic of the proposed anatomical and pathophysiological contrast between (a) choledocholithiasis (n = 39; 78.0%), with intermittent ball-valve impaction, milder common bile duct dilation, and lower direct bilirubin, and (b) malignant pancreatobiliary obstruction (n = 11; 22.0%), with infiltrative tumor growth, sustained intraductal hypertension, cholangiovenous reflux, greater duct dilation, and higher direct and total bilirubin. Values are the group summaries of this study; the mechanisms shown were not measured. CBD, common bile duct; CHD, common hepatic duct; GB, gallbladder; LHD, left hepatic duct; MRP, multidrug resistance-associated protein; RHD, right hepatic duct.

#### 4.5 MRCP performance and sources of false-negative readings

The specificity (94.9%; 95% CI 83.1–98.6%) and accuracy (88.0%; 95% CI 76.2–94.4%) of preoperative 1.5-T MRCP in our study are close to published benchmarks, including the 96.3% specificity and 96.1% accuracy reported by Begum et al. in 103 histopathologically verified patients,<sup>16</sup> the 91.9% specificity and 92.3% accuracy (AUC 0.95) reported by Al-Dulaimi et al. for CBD stones in 691 patients,<sup>47</sup> and comparative MRCP-versus-ERCP series by Siddique et al.<sup>3</sup> and Kumar et al.<sup>21</sup> In emergency department patients, Mutlu Eren et al. reported low sensitivities of initial ultrasonography (20.83%) and computed tomography (57.55%) for choledocholithiasis, which illustrates the limits of first-line imaging.<sup>48</sup> Our MRCP sensitivity for malignancy (63.6%; 7/11), however, was lower than the 95.9% and 95.7% reported by Begum et al.<sup>16</sup> and Shabanikia et al.<sup>28</sup> This shortfall reflects the behavior of extrahepatic cholangiocarcinoma and periampullary tumors. Periductal-infiltrating cholangiocarcinomas often spread longitudinally along the subepithelial bile duct wall and perineural spaces without forming a discrete mass, producing short strictures whose appearance on unenhanced T2-weighted images can overlap with that of stone-related or inflammatory strictures.<sup>26,29,36,49–51</sup> Small ampullary or pancreatic-head tumors can also be obscured by sphincter of Oddi contraction or duodenal fluid, and routine non-contrast MRCP lacks the dynamic contrast-enhanced multiphase computed tomography (CT)/MRI and diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping that improve the detection of subtle wall thickening, for which Shabanikia et al. reported a malignancy cutoff of >2.75 mm.<sup>28,36,51,52</sup> Distinguishing pancreatic-head cancer from distal cholangiocarcinoma is also difficult before resection.<sup>53</sup>

#### 4.6 Complementary role of endoscopic ultrasound, quantitative imaging, and artificial intelligence

Because routine 1.5-T MRCP had a false-negative rate of 36.4% (4/11) in our series, a benign-appearing MRCP cannot exclude malignancy when direct bilirubin ( $\geq 9.65$  mg/dL), total bilirubin ( $\geq 14.3$  mg/dL), and CBD diameter ( $\geq 21.5$  mm) are markedly elevated. The 2025 European Society of Gastrointestinal Endoscopy (ESGE) guideline by Facciorusso et al.<sup>37</sup> recommends EUS-guided tissue acquisition (EUS-TA) for distal strictures in jaundiced patients, and the Korean practice guidelines by Kim et al.<sup>51</sup> state that EUS may be considered when cross-sectional imaging shows unexplained CBD dilation or an indeterminate stricture without a visible mass.<sup>37,51,54</sup> Mahajan et al. showed that EUS achieved 95.65% sensitivity, 94.23% specificity, and 95.04% accuracy in patients with a dilated CBD and non-diagnostic CT/MRI and identified a baseline bilirubin  $\geq 10$  mg/dL and a CBD diameter  $\geq 16$  mm as high-specificity triggers for a positive EUS diagnosis,<sup>27</sup> and Gadour et al. confirmed in a 2025 meta-analysis that EUS-guided fine-needle aspiration (EUS-FNA) outperforms conventional sampling methods.<sup>54</sup> Further adjuncts may reduce false-negative diagnoses and avoid unnecessary ERCP: deep-learning convolutional neural networks (DenseNet121 reached 97% accuracy for detecting CBD dilation on MRCP in the study by Er Ulubaba et al.);<sup>55</sup> risk prediction for post-ERCP cholangitis<sup>32</sup> and antiviral prophylaxis against hepatitis B reactivation after percutaneous drainage;<sup>56</sup> EUS staging of extrahepatic cholangiocarcinoma (Orzan et al.);<sup>57</sup> and prediction of spontaneous CBD stone clearance (Correia et al.).<sup>44</sup>

#### 4.7 Proposed stepwise pathway and surgical implications for referral centers

The data suggest a pragmatic stepwise diagnostic and surgical pathway (Figure 6) for rationing imaging and endoscopic

capacity at referral hospitals; it is offered as a hypothesis for external validation.<sup>1,2,12,37</sup> In stage 1, admission bilirubin fractionation provides an immediate, widely available biochemical trigger: patients with direct bilirubin  $\geq 9.65$  mg/dL (sensitivity 90.9%, NPV 95.7%, LR<sup>-</sup> = 0.16, aOR = 9.48) or total bilirubin  $\geq 14.3$  mg/dL (sensitivity 90.9%, NPV 96.0%, LR<sup>-</sup> = 0.15) would be prioritized for expedited 1.5-T MRCP. Patients below both thresholds had about a 4.0% post-test risk of malignancy in this sample and could follow standard-schedule imaging and stone clearance, but this was not tested prospectively and 1 of the 11 cancers fell below both thresholds.<sup>33,44,45</sup> In stage 2, 1.5-T MRCP supplies a specific anatomical map (specificity 94.9%, accuracy 88.0%, LR<sup>+</sup> 12.4, aOR = 21.65) together with CBD diameter (cutoff  $\geq 21.5$  mm, aOR = 3.84). It separates choledocholithiasis, which in our cohort was managed definitively by single-stage LCBDE with cholecystectomy (24/39; 61.5%) or ERCP stone clearance (15/39; 38.5%), consistent with the prospective comparative study by Hajong et al.,<sup>58</sup> from pancreatobiliary malignancy, which requires multidisciplinary oncological staging according to the British Society of Gastroenterology guidelines (Rushbrook et al.)<sup>26</sup> and the 2026 international consensus

statement on cholangiocarcinoma (Banales et al.).<sup>59</sup> Combining contrast-enhanced MRI/MRCP with multiphase contrast-enhanced CT helps when the two are discrepant or indeterminate (Yoo et al.),<sup>60</sup> and molecular and histological profiling helps distinguish distal cholangiocarcinoma from pancreatic-head ductal adenocarcinoma (Gkoutakos et al.).<sup>25</sup> In our malignant subgroup (n = 11), late presentation limited curative pancreatoduodenectomy to 3 patients (27.3%), whereas 5 (45.5%) required open bilioenteric bypass and 3 (27.3%) palliative stenting, a pattern of late presentation also described at referral centers in Malawi<sup>2</sup> and Rwanda (Ingabire et al.).<sup>61</sup> For resectable tumors scheduled for pancreatoduodenectomy or major hepatectomy, recent studies support selective preoperative biliary drainage (PBD), mainly in patients with severe hyperbilirubinemia (above about 171–256  $\mu\text{mol/L}$ ) or prolonged waiting times (Guo et al.,<sup>62</sup> Elnour et al.,<sup>63</sup> and Li et al., threshold  $\geq 171$   $\mu\text{mol/L}$ ),<sup>64</sup> and in perihilar cholangiocarcinoma (Chen et al.<sup>50</sup> and Luyten et al.<sup>65</sup>). Our diagnostic threshold of 14.3 mg/dL (244.6  $\mu\text{mol/L}$ ) addresses a different question, the detection of malignancy, but falls within this range of drainage thresholds.

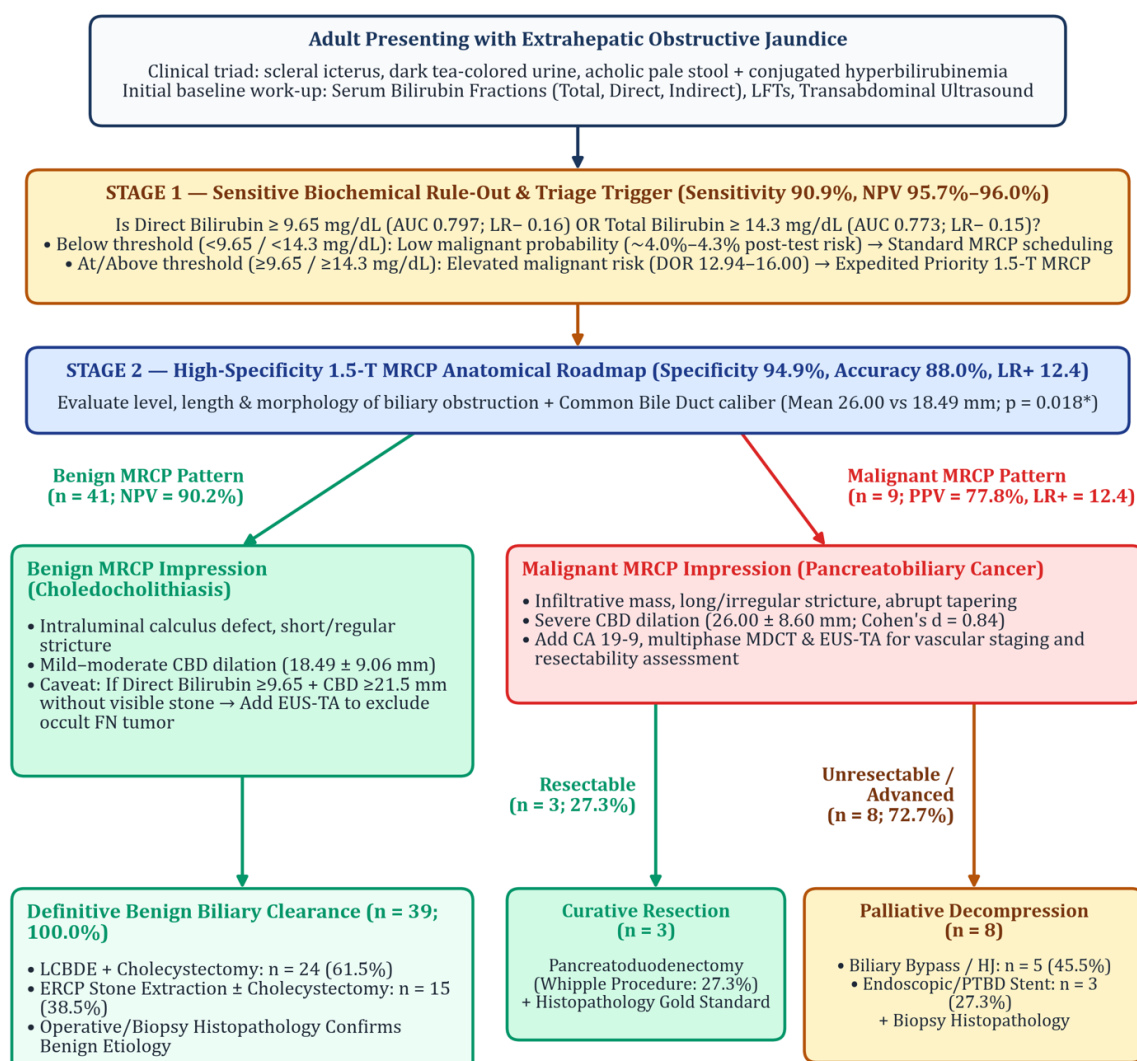


**Figure 6.** Proposed stepwise diagnostic and surgical pathway for adults with extrahepatic obstructive jaundice at referral centers, offered for external validation: admission bilirubin thresholds (stage 1, sensitive priority trigger: direct  $\geq 9.65$  mg/dL or total  $\geq 14.3$  mg/dL), preoperative 1.5-T MRCP with CBD diameter (stage 2, specific confirmation), selective EUS-guided tissue acquisition and CA 19-9 staging, and histopathology-referenced definitive management. Counts in the management boxes are histopathological groups. CA 19-9, carbohydrate antigen 19-9; CBD, common bile duct; DOR, diagnostic odds ratio; EUS-TA, endoscopic ultrasound-guided tissue acquisition; FN, false negative; HJ, hepaticojejunostomy; LCBDE, laparoscopic common bile duct exploration; LFTs, liver function tests; MDCT, multidetector computed tomography; PTBD, percutaneous transhepatic biliary drainage.

#### 4.8 Strengths, limitations, and future directions

The strengths of this study include verification of all 50 included patients against a histopathological reference standard, blinding of the index tests to histopathology through their sequence (all index tests preceded tissue diagnosis), reporting according to STARD 2015 with Wilson 95% CIs and likelihood ratios, and multivariable Firth logistic regression combining biochemical and morphometric predictors.<sup>35</sup> The study also has limitations. The total sample ( $n = 50$ ) and the malignant subgroup ( $n = 11$ ) are small, which widens the confidence intervals around sensitivity and the likelihood ratios, and the design is single-center and retrospective. Excluding patients without tissue confirmation ( $n = 7$ ) may introduce partial-verification bias, which can inflate sensitivity and attenuate specificity.<sup>35</sup> The benign group consisted only of choledocholithiasis because benign strictures and other non-calculous causes were excluded ( $n = 8$ ); this narrower spectrum is likely to make the index tests look more accurate than they would be in unselected jaundiced patients.<sup>40</sup> The Youden cutoffs were derived in the same dataset and were then entered, dichotomized, into a three-predictor model fitted to 11 events, so the cutoffs, the aORs, and the apparent AUC of 0.935 are optimistic and require external validation.<sup>40,41</sup> Where choledocholithiasis was confirmed by stone extraction rather than tissue, the reference standard is effectively composite.<sup>66</sup> Finally, ductal wall thickness was not graded quantitatively, and DWI-MRI and serum CA 19-9 were not available for all patients. Prospective multicenter Indonesian studies with larger malignant cohorts, CA 19-9-based markers,<sup>22,43</sup> quantitative 3D MRCP+ volumetry,<sup>34</sup> multiphase multidetector CT/MRI,<sup>60</sup> and selective EUS-guided tissue acquisition<sup>37,54,67</sup> are needed to validate and calibrate this stepwise approach externally.

## 5. Conclusion

In adults with extrahepatic obstructive jaundice at a single Indonesian referral center, admission direct bilirubin (median 13.7 vs. 8.7 mg/dL; AUC 0.797 at  $\geq 9.65$  mg/dL) and total bilirubin (mean  $20.17 \pm 6.78$  vs.  $13.02 \pm 7.64$  mg/dL; AUC 0.773 at  $\geq 14.3$  mg/dL) were sensitive (90.9%) but nonspecific markers of pancreatobiliary malignancy, with high NPVs (95.7%–96.0%) in this sample, whereas preoperative 1.5-T MRCP was specific (94.9%), accurate (88.0%), and confirmatory (LR+ 12.4; DOR 32.38) but less sensitive (63.6%). CBD diameter on MRCP added independent information ( $26.00 \pm 8.60$  vs.  $18.49 \pm 9.06$  mm; cutoff  $\geq 21.5$  mm), and a model combining direct bilirubin  $\geq 9.65$  mg/dL (aOR = 9.48), a malignant MRCP impression (aOR = 21.65), and CBD diameter  $\geq 21.5$  mm (aOR = 3.84) reached an apparent AUC of 0.935. A sequential pathway in which admission bilirubin prioritizes MRCP, EUS-guided tissue acquisition resolves discordant cases, and histopathology guides surgical triage may speed the preoperative separation of benign from malignant obstruction, but it requires prospective external validation before clinical use.

## 6. Declarations

### Ethics Approval and Consent to Participate

This study received ethical approval from the CMHC Research Center Ethics Committee, Indonesia (Protocol No. 2026/0417). Written informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki.

### Consent for Publication

Not applicable; no individually identifiable patient data or images are presented.

### Availability of Data and Materials

The de-identified analytical dataset supporting the conclusions of this study is available from the corresponding author upon reasonable academic request.

### Artificial Intelligence Use Statement

None.

### Author Contribution Statement

M.F.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. M.H.K.: Supervision, Validation (operative management classification and clinical interpretation), Writing – review & editing. T.: Supervision, Methodology (diagnostic accuracy design), Validation (biostatistics), Writing – review & editing. All authors read and approved the final manuscript.

### Funding Statement

None.

### Conflict of Interest / Competing Interests

The authors declare that they have no financial or non-financial competing interests.

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