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Advantages of Total Bilirubin for Predicting Malignant Obstructive Jaundice, A Combination of the Pandemic Era and Limited Resources Settings

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Abstract

BACKGROUND: Hepatopancreatobiliary (HPB) cancer incidence and mortality are increasing worldwide. An initial diagnostic predictor is needed for recommending further diagnostic modalities, referral, and curative or palliative decisions. There were no studies conducted in area with limited accessibility setting of the COVID-19 pandemic, coupled with limited human resources and facilities.

AIM: We aimed to investigate the advantages of total bilirubin for predicting malignant obstructive jaundice, a combination of the pandemic era and limited resources settings.

METHODS: Data from all cholestasis jaundice patients at M. Djamil Hospital in Pandemic COVID-19 period from July 2020 to May 2022 were retrospectively collected. The data included demographics, bilirubin fraction results, and final diagnosis. Bivariate analysis for obtain demographic risk factor, and Receiver Operating Characteristics (ROC) analysis for getting bilirubin value.

RESULTS: Of a total 132 patients included, 35.6% were malignant obstructive jaundice, and Pancreatic adeno ca was the most malignant etiology (34.4%). Bivariate analysis showed a significant correlation between age and malignant etiology (p = 0,024). Direct and total Bilirubin reach the same level of Area Under Curve (AUC). Total bilirubin at the cutoff point level of 10.7 mg/dl had the most optimal results on all elements of ROC output, AUC 0.88, sensitivity 76.6%, specificity 90.1%, +LR 8.14, and -LR 0.26.

CONCLUSION: The bilirubin fraction is a good initial indicator for differentiating benign and malignant etiology (AUC 0.8–0.9) in pandemic era and resource-limited areas to improve diagnostic effectiveness and reduce referral duration.

Introduction

Incidence and mortality from hepatopancreatobiliary (HPB) cancer is increasing worldwide [1]. There were no studies conducted in the area with limited accessibility setting of the COVID-19 pandemic [2], [3], [4], [5], coupled with low human resources and facilities [6], in the treatment of malignant obstructive jaundice which known to have early diagnostic difficulties and poor prognosis [7], [8], [9]. Diagnostic challenge come along with sporadically presenting and lack of marker [9]. Early diagnostics play a key role in managing the complete anatomy of hepatobiliary pancreatic disease, tumor marker, USG, MSCT, MRCP, ERCP, and laparoscopic coming as diagnostic techniques and modalities with various capabilities and availability. For late-detected diseases disorders, pre-operative drainage is more helpful in improving operative treatment outcomes and prolonging survival [10], [11], [12]. The previous research publications on total bilirubin from different times and sample backgrounds, show the ability and variation of threshold value as a predictors of malignant obstructive jaundice [13], [14], [15]. Within the existing limitations, against time, to prevent further consequences of obstructive malignant jaundice, an initial diagnostic predictor is needed for recommending further diagnostic modalities, referral, and curative or palliative decisions [13].

Materials and Methods

This study was conducted retrospectively on the medical records of 132 patients who came to the M. Djamil General Hospital with chief complaints of obstructive jaundice during the COVID-19 pandemic period (July 2020−May 2022). Patient data obtained from the results of the MSCT, MRCP, ERCP, and

surgery reports. Malignancy data are evidenced by the results of the Pathology Anatomy. This research was conducted after reached ethical approval No. LB.02.02/5.7/152/2022. The anonymity of identity, results of clinical examinations, investigations, diagnosis, and results of patient therapy are well protected.

Demographic characteristics were recorded such as age, sex, imaging modalities, bilirubin fraction levels at the beginning of admission, and a definitive diagnosis. Patients were divided into two groups based on the classification of definitive diagnosis, benign etiology, and malignant etiology. Patients who have a concurrent benign and malignant etiology classification, medical jaundice, post percutaneous biliary drainage (PBD)/biliodigestive bypass, and acute complications after HPB surgery were excluded from the study.

All data processing using the MedCalc® application Version 20110, diagnostic test using Receiver operating characteristic (ROC) output; AUC, AUC comparison, Cutoff point, sensitivity, specificity, positive Likelihood ratio (+LR), and Negative likelihood ratio (-LR). AUC value > 0.90 is considered very excellent, while AUC 0.80–0.90 is considered excellent. AUC value of 0.7–0.8 is considered acceptable, AUC 0.50–0.70 is considered poor, and AUC < 0.50 indicates no discrimination. Test results with p-value < 0.05 were accepted as statistically significant correlation.

Results

Analyses were carried out on data from 132 patients who met the study criteria. Based on the gender of the patient, 71 (53.8%) were male and 61 (42.6%) females. Demographic age data obtained mean of the patients was 49.97 ± 12.62 years with a range of 21−86 years. The percentage of the benign obstructive jaundice group (63.4%) was higher than malignant etiology (36.6%). Radiological utilization (MSCT, MRCP, and ERCP) was only performed in 52.27% of patients. Demographic data and population characteristics are presented in the Table 1.

Table 1: The demographic and characteristics of study

Variables	n (%)	Median	Range	Mean ± SD
Sex				
Male	71 (53.78)			
Female	61 (46.28)			
Age (years)		49	21–86	49.97 ± 12.62
<50	68 (51.5)			
≥50	64 (48.5)			
Etiology				
Benign	85 (64.39)			
Malignant	47 (35.6)			
Bilirubin (mg/dl)				
Indirect		1.7	0.2–11.9	2.66 ± 2.73
Direct		6.37	0.7–25.9	7.25 ± 5.16
Total		7.72	1.1–32.4	9.95 ± 7.5
Preoperative radiology				
Yes	69 (52.27)			
No	63 (47.72)			
Modality radiology				
CT scan	47 (68.12)			
MRCP	15 (21.74)			
ERCP	7 (10.14)			

SD: Standard deviation.

Percentage of definitive diagnosis in benign etiology was dominated by choledocholithiasis n = 71 (82.55%), while in malignant etiology classification, a definitive diagnosis was found with Pancreas Adeno Carcinoma n = 16 (34.04%) as the most. Complete data on the distribution of diagnoses are presented in the Table 2.

From the results of the diagnostic test for each fraction of bilirubin, the ROC interpretation was found to be in a good range (0.80−0.90). Total bilirubin AUC (0.882) is the highest compared to Direct Bilirubin (0.878) and Indirect Bilirubin (0.852) as shown in the Figure 1.

The cutoff point which is translated as the optimal value of sensitivity and specificity (Youden Index) on the ROC curve, indirect bilirubin is obtained at levels of 2.6 (interval 2.3−3.1) mg/dl, direct bilirubin 7.8 (interval 7.2−9.5) mg/dl and total bilirubin were found at 10.7 (9.9−13.1) mg/dl (Tables 3 and 4).

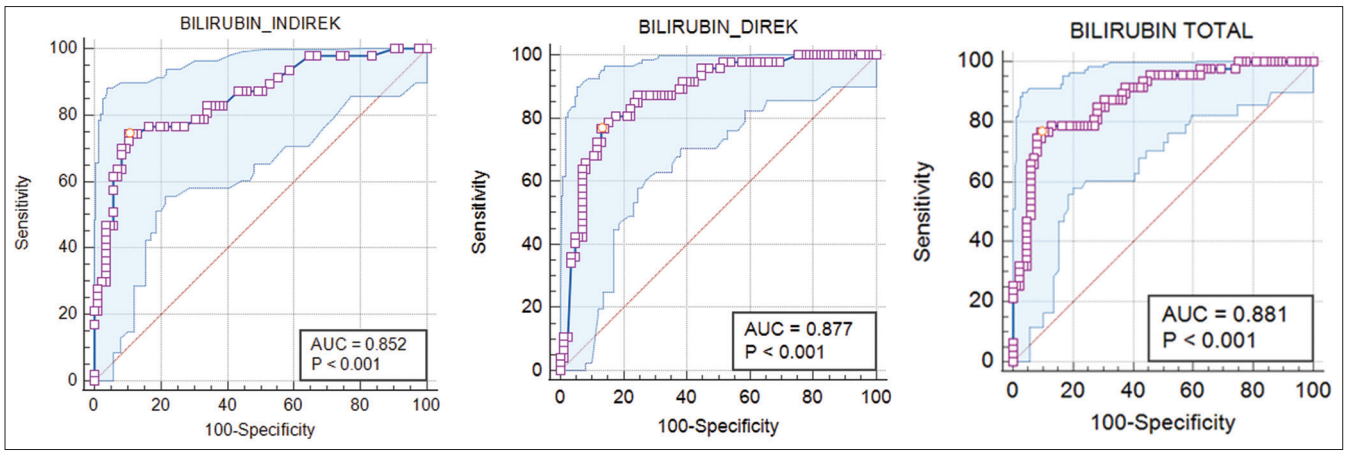

Figure 1. ROC Bilirubin Fraction

Table 2: Definitive diagnosis of samples

Diagnosis	n (%)
Benign etiology	
Choledocholithiasis	70 (82.35)
Divertikel duodenum	4 (4.71)
Mirizzi syndrome	4 (4.71)
Chronic pancreatitis	3 (3.53)
Granulomatose biliary inflamation	2 (2.35)
Caroli syndrome	1 (1.18)
Pancreatolithiasis	1 (1.18)
Malignant etiology	
Pancreatic adeno carcinoma	16 (34.04)
Metastasis carcinoma	9 (19.15)
Hepatocellular carcinoma	8 (17.02)
Ampullary carcinoma	5 (10.64)
Cholangio carcinoma	5 (10.64)
Neuroendocrine pancreatic carcinoma	2 (4.26)
Gallbladder carcinoma	1 (2.13)
Malignant lymfoma	1 (2.13)

Total bilirubin at the cutoff point level of 10.7 mg/dl had the most optimal results on all elements of ROC output, sensitivity 76.6%, specificity 90.1%, +LR 8.14, and -LR 0.26. The ROC comparison results did not show any significant difference between each bilirubin fraction (Figure 2) (Table 5).

Discussion

Research on demographic characteristics found age variables had an influence on cholestasis etiology, according to research by Mofleh *et al*., Bain *et al*., and Saluja *et al*. [16], [17], [18], but research by Garcea *et al*. with larger samples (1026 samples), found no influence of age on malignant etiology [13]. The differences in the results of the study may be due to sporadic data (incidence) obtained not from screening protocols as can already be carried out in countries with moderately advanced sociodemographic index, so it does not describe the overall rate (prevalence) of HPB cancer [9]. An increase in life expectancy in developed countries, will also increase the likelihood of cancer discovery at an advanced age [19].

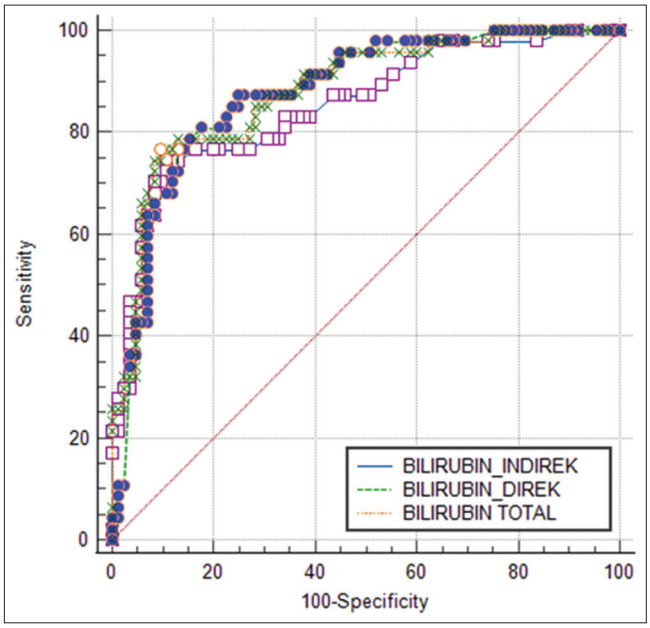

Figure 2. Comparison ROC

The gender variable does not have a significant influence on the etiology of cholestasis, these results corresponded to the research of Garcea *et al*., Mofleh *et al*., Saluja *et al*., and Bain *et al*. [13], [16], [17], [18]. Pancreas cancer and gallbladder cancer are associated with a lifestyle that is at risk of obesity, as is found in western countries, especially in the female sex, while liver cancer is widely associated with hepatitis B and hepatitis C virus infections which are mostly found in the male sex [19]. So that epidemiologically, there is a heterogenecity of exposure to certain risk factors in the sex of the HPB cancer group.

Table 3 : Bivariate analysis between independent variables and etiology

Variables	p (p < 0.05)
Sex	0.216
Age	0.024
Indirect bilirubin (mg/dL)	< 0.001
Direct bilirubin (mg/dL)	< 0.001
Total bilirubin (mg/dL)	< 0.001

The results of this study found that the highest percentage of diagnosis in benigna etiology was choledocholithiasis 82.35% and maligna etiology was Adeno Ca Pancreas 34.04%. This is in line with the results of the research of Garcea *et al*., which found that choledocholithiasis 89.2% and adeno Ca. pancreas 36.6% as the most diseases in each of the etiologies. [13] Gupta *et al*. (2017) in 36 cholestasis patients showing pancreatic cancer is the most frequent etiology for malignancy [20]. Different results from the study of Mofleh *et al*. in Saudi Arabia (2004), Cholangiocarcinoma (43%) was the most in the etiology of maligna and choledocholithiasis (22%) in the etiology of benigna [16]. Shukla *et al*. (2018) obtained periampula carcinoma (32%) and gallbladder malignancy (32%) as the most extrahepatal cholestasis etiologies [21]. The highest incidence variation in HPB cancer is influenced by various etiologies and risk factors according to variations in geography, lifestyle, type of infection, autoimmune diseases, chemical/carcinogenic substances, metabolic diseases, and HPB benign disease [9].

Table 4: Summary of receiver operating characteristics parameter

Parameter	Indirect bilirubin	Direct bilirubin	Total bilirubin
AUC	0.852	0.877	0.881
Cutoff point (mg/dl)	2.6	7.8	10.7
Sensitivity (%)	74.47	76.6	76.6
Specificity (%)	89.41	87.06	90.59
Positive LR	7.03	5.92	8.14
Negative LR	0.29	0.27	0.26
p (<0.05)	< 0.0001	< 0.0001	< 0.0001

AUC: Area under curve, LR: Likelihood ratio.

The mean and median values of the levels of the bilirubin fraction from each etiology differ significantly, the bilirubin level of benign etiology at

admission was lower than the malignant etiology, this is due to differences in the pathophysiology, obstruction in malignant etiology is increase progressively, while in choledocholithiasis it is influenced by disimpaction and regression mechanisms [13]. Another thing can be caused by dilatation of the bile ducts which allows the ball valve effect and further prevents the increase in bilirubin levels. Meanwhile, other chronic inflammation, it is influenced by the effect of the inflammatory process that increases and repeats.

Table 5: Bilirubin receiver operating characteristics comparison

Parameter comparison	p
Bilirubin Indirek~Bilirubin Direk	0.3123
Bilirubin Indirek~Bilirubin Total	0.1269
Bilirubin Direk~Bilirubin Total	0.5784

Bilirubin levels are a good etiological discriminator in extrahepatal cholestasis patients. Level direct bilirubin fraction and total bilirubin are at the same AUC level (good interpretation), although they have a slight difference where the total bilirubin level AUC is higher than the direct bilirubin level. The AUC value of >0.8 has the understanding that, the use of bilirubin levels for etiological discriminators in 100 patients, the right conclusion will be obtained in >80 patients [22].

The results of a diagnostic test by Ghosh *et al*. in India in 2019, a prospective study of 76 cases, obtained the average age of cholestasis patients 53 years, AUC Bilirubin total 0.84, sensitivity 75% and specificity 76% at cutoff total bilirubin levels of 11.4 mg/dl [23], compared to the study, this study resulted in cutoff point lower at total bilirubin levels of 10.7 mg/dl, with average age (49.9 years), higher AUC (0.88), sensitivity (76.6%), and specificity (90.59%). Although the study has a different design, the AUC is in the same range (0.8–0.9). The similarities between these studies may be motivated by sociodemographic similarities, limited access, and health programs.

In 2011, Garcea *et al*. (AUC: 0.8; $p < 0.001$) received a lower cutoff point, where the bilirubin level >100 μmol/l (>5.85 mg/dl) had sensitivity (71.9%) and specificity (86.9%). [13] The Garcea *et al*., study had a larger sample, conducted on 1026 samples. But to obtain +LR which is almost the same as this study (+LR = 8.14), it was obtained at bilirubin levels >150 μmol/l (8.77 mg/dl). The cutoff point was higher in this study, probably due to sporadic disease discoveries. This happens because there are no obvious clinical symptoms in the form of pain, (16.24) anorexia and weight loss [16], [18], [24] it is related to the natural nature of HPB tumors that are indole so that they are slow to show symptoms coupled with the low accuracy of diagnostic markers [9].

Another possibility is due to the decrease in health access by patients during the Span of the Covid-19 pandemic in Indonesia, where only 52.27% of samples underwent preoperative radiology diagnostic examinations. This is supported by the findings of Moynihan *et al*. that overall there was a reduction in the use of health-care facilities by 37%, even in diseases that had a milder complaint rate, a greater decrease was obtained (45%) [2], [3], [4], [5]. Furthermore, social phenomena in this area that result in delays in treatment to the nearest hospital due to the belief/ culture of patients and families seeking/trying traditional or alternative medicine first as stated in the results of the study by Widayanti *et al*. [25].

Lower cutoff points were also obtained in several studies with an AUC of 0.8, including by Mofleh *et al*. set total bilirubin levels of 84 μmol/l (4.74 mg/dl), sensitivity 98.6%, specificity 59.3%, and +LR 2.42 [26]. In this study, the use of cutoff point 4.6 mg/dl, gave a sensitivity of 95.74%, specificity of 48.24%, +LR 1.85. Researchers understand that the use of bilirubin fractions for diagnostic purposes requires higher sensitivity values, but has the risk of increasing false positive results.

Bain *et al*. (2000) set a cutoff point of 4.38 mg/dl. [11]. But in contrast to this study, the results of the prospective study of Bain *et al*., obtained by not including the diagnosis of choledocholithiasis as a sample of the etiology of cholestasis benigna. In this study, choledocholithiasis was the highest percentage of diseases of the overall cholestasis etiology and the highest bilirubin levels of other benigna etiology diseases.

Another study by Liu *et al*. (2018) showed the results of ROC analysis of total bilirubin levels with low AUC (AUC = 0.590) when compared to AUC ratio ca 19-9/total bilirubin level (AUC = 0.889, ratio = 0.88) [27]. Boyd *et al*. found the same thing, that the ratio of Ca 19–9 and Bilirubin showed better diagnostic strength than diagnostic strength if tested separately, although separate test values showed proportional ability as initial diagnostics and improved patient management [28].

This study does not suggest the independent use of bilirubin levels in predicting cholestasis etiology, bilirubin levels are useful as a comparison with other commonly used modalities such as laboratory results (Gamma GT and ALP), tumor markers, and advanced radiological examinations. Multimodality management is required in patients with extrahepatal cholestasis [13]. Bilirubin levels can be used in addition to other modalities or as a consideration for the selection of advanced diagnostic modalities or initial therapy of malignant cholestasis patient.

Conclusion

The bilirubin fraction is a good initial indicator for differentiating benign and malignant etiology (AUC 0.8-0.9) in pandemic era and resource-limited areas in

order to improve diagnostic effectiveness and reduce referral duration.

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