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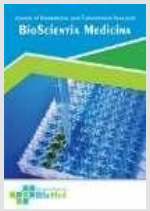

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Correlation of Malignancy in the Hepato-Pancreato-Biliary System with Serum Bilirubin Levels in Extrahepatic Cholestasis Patients

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A B S T R A C T

Background: The incidence of hepato-pancreato-biliary system cancer is increasing worldwide, which has been recognized as a disease that is difficult to diagnose early and has a poor prognosis. No research has yet been conducted in areas with limited resources and health facilities. There is an urgent need for diagnostic methods to recommend further diagnostic modalities in the selection of curative or palliative management. **Methods:** Retrospective data from all cholestatic patients at Dr. M. Djamil General Hospital were collected during the period July 2020-May 2022. The data included demographic characteristics such as age, gender, preoperative, results of bilirubin fraction, and final diagnosis. Data analysis was done by bivariate and multivariate. **Results:** A total of 132 patients were included in this study. 35.6% of them are HPB system malignancies, with Pancreatic Adenocarcinoma being the most common diagnosis (34.4%), more in males (51.06%), and in the age group, 50 years (61.71%) is the most. Only 52.27% of patients underwent preoperative radiological imaging. Bivariate analysis showed a significant relationship between HPB system malignancies with age >50 years (p=0.024) and all bilirubin fractions (p<0.001). Multivariate analysis showed that only the bilirubin fraction was significant for the diagnosis of malignant HPB (p<0.001). **Conclusion:** The bilirubin fraction is a good initial indicator for predicting malignancy in the HPB system in order to increase the effectiveness of the diagnostic modality and reduce the referral duration.

1. Introduction

The incidence of hepato-pancreato-biliary cancer (HPB) is increasing worldwide.[1] The etiology of malignant cholestasis (58.71%) is more common than benign cholestasis (41.29%).[2] The highest incidence of this disease is in the 51-60 year age group. More than half of patients with cholestasis of malignant etiology died within three months of hospital discharge.[3] Differentiating the etiology of benign from malignant cholestasis is a challenge, even with the use of advanced imaging techniques and currently available endoscopic equipment.[4] Statistically, clinical symptoms such as pain,[5,6] anorexia, and weight loss[5,7] make it difficult to differentiate benign from malignant etiology. Malignancies in HPB systems always require multiple diagnostic modalities.[8] The study found that the sensitivity of ultrasound was only 76.6%. [9] A meta-analysis found the MRI (magnetic resonance imaging) modality very sensitive and specific, including for biliary tract stones.[10] Endoscopic ultrasonography (EUS), direct cholangioscopy, and endo cystoscopy

increase the probability of obtaining preoperative tissue. However, the patient underwent resection of the suspicious lesion without histological confirmation of the presence of cancer.[11]

Another study used biochemical parameters as the independent variable and malignancy as the dependent variable, which showed that total bilirubin was the most significant independent factor in malignancy.[12] Several previous studies presented the fact that bilirubin levels had sensitivity and specificity as a predictor of cholestasis but with varying cut-off points.[5,13,14] This study aims to determine the correlation between hepato-pancreato-biliary cancer malignancy and serum bilirubin levels of patients with extrahepatic cholestasis.

2. Methods

This study is an analytical observational study with a cross-sectional approach to determine the correlation between the incidence of malignant HPB system and serum bilirubin levels. The data used are sourced from data in the medical records of patients undergoing examination and treatment at Dr. M. Djamil General Hospital in the 2021-2022 timeframe. A total of 132 research subjects participated in this study who met the inclusion criteria, namely patients with a diagnosis of cholestasis who had multimodality support in the form of laboratory, imaging, and final diagnostics confirmed from histopathological results (study samples with neoplastic etiology) or surgical findings using the ERCP method, direct cholangioscopy, and open surgery. This study has been approved by the medical research ethics committee of Dr. M. Djamil General Hospital, Padang, Indonesia.

Univariate analysis was carried out by analyzing per research variable. In the categorical research variables, which include gender and classification of benign and malignant etiology, an analysis was carried out by looking at the frequency distribution presented in the form of frequency, percentage, and p-value. While continuous data, namely age, and levels of indirect, direct, and total serum bilirubin, are expressed in terms of the average value, standard deviation, median, minimum value, maximum value, and p-value. The diagnostic test was carried out using the Receiver Operating Curve (ROC) procedure with the results of the analysis in the form of Area Under Curve (AUC). Determination of the cut-off point statistically based on the Youden Index, the optimal cut-off point is the value where the sensitivity and specificity curves intersect. The diagnostic ability of serum direct bilirubin levels and total serum bilirubin levels are considered good if the diagnostic parameters are 80%. All analyzes were performed using the MedCalc® Program Version 20110 (MedCalc Statistical Software, Ostend, Belgium). To determine the relationship between indirect, direct, and total bilirubin levels with age, gender, and diagnosis of malignant and benign etiology classification, the Independent Sample T-test was performed. Data analysis was carried out with a 95% confidence level and $\alpha = 0.05$. If the p-value <0.05, it means that there is a significant relationship between the research variables studied. Multivariate analysis using the logistic regression method is carried out on the independent variables that affect the bivariate test. Variable independence can be used as the criteria for diagnosing the malignancy of the HPB system if it has a p-value of <0.05.

3. Results

The percentage of cholestasis in benign etiology (64.39%) was higher than that of malignant etiology (35.6%). Based on gender, there are more male samples than females, with a ratio of 71(53,78%):61(46,28%). Furthermore, the sex comparison in each etiology of cholestasis also shows the same thing. Analysis of age data obtained the mean age (±SD) 49.97±12.62. In benign etiology, the median age was 47 years with an age range of 21-86 years, while in malignant etiology, the median age was greater, namely 54 years with an age range of 30-83 years. Analysis of independent variables from laboratory examination results means serum ± SD, indirect bilirubin levels 1.49±1.36 mg/dL, direct

bilirubin 4.81±3.65 mg/dL, and total bilirubin 6.31±4.72 mg/dL obtained in the classification of benign etiology. Meanwhile, in the classification of malignant etiology, the mean ± SD level of indirect bilirubin was 4.79 ± 3.27 mg/dL, direct bilirubin was 11.56 ± 4.70 mg/dL, and total bilirubin was 16.35 ± 7.32 mg/dL. The results of the analysis showed that the levels of indirect, direct, and total bilirubin were greater in cholestasis of malignant etiology than in benign etiology.

Table 1. Sample characteristics

Characteristics	**n**	**%**
Total sample	132	
Gender		
Male	71	53.78
Female	61	46.28
Age		
<50 years	68	51.5
≥50 years	64	48.5
Etiology		
Benign	85	64,39
Malignant	47	35.6
Preoperative Radiological Examination		
Performed	69	52.27
Not performed	63	47.72
Radiological modality		
CT scan	47	68.12
MRCP	15	21.74
ERCP	7	10.14

Utilization of preoperative radiological modalities was only performed on 52.27% of samples. The radiological modalities that are widely used are CT scan (68.12%), MRCP (21.74%) and the lowest is ERCP (10.14%).

Table 2. Characteristics of variable age and bilirubin fraction

Characteristics	**Median**	**Range of values**	**Mean±SD**
Age (Years)	49	21-86	49.97±12.62
Indirect Bilirubin (mg/dL)	1.7	0.2-11.9	2.66 ±2.73
Direct Bilirubin (mg/dL)	6.37	0.7-25.9	7.25±5.16
Total Bilirubin (mg/dL)	7.72	1.1-32.4	9.95±7,5

The percentage of definitive diagnoses in benign etiology was dominated by choledocholithiasis in 71 patients (82.55%), while in the classification of malignant etiology, a definitive diagnosis (anatomical pathology) of Adeno Carcinoma Pancreas was found in 16 patients (34.04%) as the most. The full data of the distribution of diagnoses are presented in Table 3.

Table 3. List of definitive diagnoses

Diagnosis	n	%
Benign Etiology		
Choledocholithiasis	70	82.35%
Diverticula Duodenum	4	4.71%
Mirizzi syndrome	4	4.71%
Chronic pancreatitis	3	3.53%
Granulomatous inflammation	2	2.35%
Caroli syndrome	1	1.18%
Pancreatolithiasis	1	1.18%
Malignant Etiology		
Adeno Ca Pancreatic	16	34.04%
Metastatic Ca	9	19.15%
Hepatocellular Ca	8	17.02%
Ampullary Ca	5	10.64%
Cholangio Ca	5	10.64%
Neuroendocrine Ca Pancreatic	2	4.26%
Gallbladder Ca	1	2.13%
Malignant lymphoma	1	2.13%

Diagnostic test results using the ROC method on each fraction of bilirubin, the results of the interpretation of AUC are in the good range (0.80-0.90).

Table 4. ROC of bilirubin fraction

Parameters	Indirect Bilirubin	Direct Bilirubin	Total Bilirubin
AUC	0.852	0.877	0.881
Cut-off point (mg/dl)	2.6	7.8	10.7
p-value (<0.05)	<.0001	<.0001	<. 0001

The cut-off point, which is translated as the optimal value of sensitivity and specificity (Youden Index) on the ROC curve, indirect bilirubin is found at 2.6 mg/dl, direct bilirubin is 7.8 mg/dl, and total bilirubin is found at 10.7 mg /dl. Next cut-off point The bilirubin fraction was used as the basis for grouping in correlation analysis.

In each group of benign etiology and malignant etiology, the same results were obtained, where male samples were more than female samples. The analysis did not find a correlation between sex variables and the etiology of cholestasis p=0,216 (significant<0.05). The results of the analysis of the research variables are presented in Table 5. Using the median age of 50 years, the samples were divided into 2 groups. Based on the independent sample t-test analysis, it was found that the correlation between age and the etiology of cholestasis was Sig.(2-tailed) 0.024 (*p<0.05*), the results of the same test for all variables of the bilirubin level fraction were p<0.05, indicating that there is a correlation between bilirubin levels and the etiology of cholestasis.

Table 5. Bivariate Analysis with etiology of extrahepatic cholestasis

Characteristics	Malignant Etiology	Benign Etiology	p-value (<0.05)
Gender			0.216
Male	24(51.06%)	47(55.29%)	
Female	23(48.94%)	38(44.71%)	
Age			0.024
<50 years	18(38.29%)	49(57.64%)	
≥50 years	29(61.71%)	35(42.35%)	
Indirect Bilirubin			<0.001
<Cut off point 2.6 mg/dL	12(25.43%)	75(88.24%)	
≥Cut off point 2,6 mg/dL	35(74.47%)	8(11.76%)	
Direct Bilirubin			<0.001
< Cut off point 7.8 mg/dL	11(23,40%)	73(85.88%)	
≥Cut off point 7,8 mg/dL	36(76,60%)	12(14.12%)	
Total Bilirubin			< 0.001
<Cut off point 10.7 mg/dL	11(23.40%)	76(89.41%)	
≥Cut off point 10,7 mg/dL	36(76,60%)	9(10.59%)	

After performing coding on the independent variables that had a correlation with malignant cholestasis, then grouped the samples based on the cut-off point. Multivariate analysis was performed to obtain a p-value <0.05 on the indirect bilirubin, direct bilirubin, and total bilirubin variables. Age variable obtained p-value>0.05 on multivariate assays with each bilirubin fraction.

Table 6. Multivariate analysis

Independent variable	p-value (<0.05)
Age-Indirect Bilirubin	
Age (>50 years)	0.053
Indirect bilirubin	<0.001
Age-Direct Bilirubin	
Age (>50 years)	0.053
Direct bilirubin	<0.001
Age-Total Bilirubin	
Age (>50 years)	0.072
Total bilirubin	<0.001

Result Analysis logistic regression showed that the age variable had no effect on the diagnostic screening of patients when multivariate analysis was performed with each indirect bilirubin/direct bilirubin/total bilirubin. Only the bilirubin fraction has an effect as a criterion for diagnosing HPB system malignancies.

4. Discussion

Gender variables did not have a significant influence on the etiology of cholestasis. Pancreatic cancer and gallbladder cancer are associated with a lifestyle that is at risk of causing obesity, as is commonly found in western countries, especially in the female sex, while liver cancer is mostly associated with hepatitis B and hepatitis C virus infections which are mostly found in the male sex. Thus, epidemiologically, there is heterogeneity of exposure to risk in the sexes of the HPB cancer group.[15-18] The results of this study found that the highest percentage of diagnoses in benign etiology was choledocholithiasis, 82.35%, and malignant etiology was pancreatic adenoca, 34.04%. This is in line with the research results, which found that 89.2% choledocholithiasis and 36.6% pancreatic

adenocarcinoma were the most common diseases in each etiology. Another study in 36 cholestatic patients showed that head cancer was the most common etiology of malignancy. The results differ from other studies, which stated that cholangiocarcinoma (43%) was the most common in malignant etiology and choledocholithiasis (22%) in benign etiology. Carcinoma is found in periampullary (32%) and gallbladder malignancy (32%) as the most common etiology of extrahepatic cholestasis. The variation of the highest incidence of HPB cancer is influenced by various etiologies and risk factors according to variations in geography, lifestyle, type of infection, autoimmune diseases, chemicals/carcinogens, metabolic diseases, and benign HPB diseases.[19-23]

The mean and median values of the bilirubin fraction in each etiology were significantly different. This was due to differences in the pathophysiology of obstruction and the patient's chief complaint. Obstruction in malignant etiology is progressive, whereas, in choledocholithiasis, it is influenced by disimpaction and regression of inflammation. As a consequence, bilirubin levels of benign etiology at admission were lower than those of malignant etiology. Another thing can be caused by an increase in biliary tract dilatation which allows disimpaction (ball-valve effect) to prevent an increase in bilirubin levels. Whereas in other chronic inflammation, influenced by the effect of increasing and recurrence of the inflammatory process that occurs, in contrast to malignant etiology, obstruction occurs, which is progressive. This study does not suggest the use of bilirubin levels independently in predicting the etiology of cholestasis. Bilirubin levels are useful for 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 extrahepatic cholestasis. Bilirubin levels can be used as an adjunct to other modalities or as a consideration in selecting advanced diagnostic modalities and initial therapy for patients with malignant cholestasis.[24,25]

5. Conclusion

The bilirubin fraction is a good initial indicator to predict malignancy in the HPB system to increase the effectiveness of diagnostic modalities and reduce the referral duration.

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