

# Diagnostic Accuracy of Clinical Features, Laboratory Features, and Ultrasound Imaging Compared to Intraoperative Findings in Patients with Obstructive Jaundice

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## ABSTRACT

**Introduction:** Jaundice due to biliary obstruction can be caused by a diverse group of diseases, including both benign and malignant etiologies. This study aimed to evaluate the accuracy of clinical features, laboratory features, and ultrasound imaging in diagnosing the etiology of obstructive jaundice with intraoperative findings as the gold standard.

**Methods:** This was an observational cross-sectional analytic study conducted on 49 subjects by obtaining patients' data from medical records in the Medical Record Center Dr. Soetomo General Academic Hospital, Surabaya. Collected data were statistically analyzed using a diagnostic test.

**Results:** In this study, sensitivity (Sn), specificity (Sp), and accuracy of each feature in differentiating masses and stones as the etiology of obstructive jaundice were obtained. Progressive jaundice had Sn 88.2%, Sp 37%, and accuracy 56.8%. Complaints of fever had Sn 73.9%, Sp 90.9%, and accuracy 79.4%. Courvoisier's law had Sn 61.5%, Sp 61.5%, and accuracy 61.5%. Serum CA 19-9 had Sn 75%, Sp 58.3%, and accuracy 67.9%. Ultrasound imaging had Sn 81.8%, Sp 100%, and accuracy 93.3%.

**Conclusion:** Ultrasound imaging had the highest accuracy in diagnosing the etiology of obstructive jaundice, followed by complaints of fever, serum CA 19-9, Courvoisier's law, and progressive jaundice, respectively.

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## Introduction

Jaundice is a state of yellowish staining of the skin, sclera, and mucous membranes caused by the accumulation of bilirubin. This bile pigment is clinically manifested when serum bilirubin levels exceed 2 mg/dL. Several conditions can cause jaundice, including extrahepatic biliary obstruction, intrahepatic diseases, or high bilirubin production due to increased red blood cell hemolysis. Obstructive jaundice refers to the extrahepatic biliary obstruction which occurs due to a blocked bile duct caused by stones or tumor in the lumen of the bile duct or extraluminal masses which compress over it and block the channel of drainage where the bile duct meets the duodenum.<sup>1</sup> In Croatia, obstructive jaundice increased significantly in the elderly population and was more common in women, with gallstones being the most common cause. Pancreatic adenocarcinoma is now the most common etiology of malignant extrahepatic bile duct obstruction.<sup>2</sup>

Clinical signs and symptoms in patients with obstructive jaundice include icteric skin and/or sclera, dark urine, pale stools, and general itching. Complaints of fever, biliary colic, and intermittent jaundice can be diagnosed with choledocholithiasis. A palpable right upper quadrant mass, weight loss, anorexia, and painless progressive jaundice suggest malignant obstruction.<sup>3</sup> Palpable enlarged gallbladder (Courvoisier's law) indicates malignant etiology.<sup>4</sup>

Based on previous studies, a tumor marker known as CA 19-9 has a sensitivity of approximately 70-80% and a specificity of approximately 80-90% in diagnosing pancreatic adenocarcinoma. Unfortunately, elevated CA 19-9 is also found in other benign hepatobiliary diseases, which leads to reduced accuracy.<sup>5</sup> Ultrasound imaging is routinely used to evaluate obstructive jaundice because it represents an affordable price and non-invasive radiological examination. However, ultrasound is less able to accurately diagnose the various causes and sites of an extrahepatic biliary obstruction than other imaging modalities. On the other hand, magnetic resonance cholangiopancreatography (MRCP) has the highest sensitivity and specificity in diagnosing the true etiology of extrahepatic biliary obstruction.<sup>6</sup>

Malignant underlying diseases have a worse prognosis than CBD stones. Therefore, knowing the cause of obstructive jaundice before surgery is essential.<sup>7</sup> This study aimed to assess the accuracy of clinical features, laboratory tests, and ultrasound imaging in diagnosing the underlying cause of post-hepatic jaundice with intraoperative results as the gold standard because MRCP is not always available in healthcare settings.

## Methods

This was an analytical, cross-sectional, observational study using patient data from the medical records in the

Medical Record Center Dr. Soetomo General Academic Hospital, Surabaya, including information on progressive jaundice, fever, Courvoisier's law, serum CA 19-9, ultrasound findings related to etiology of biliary obstruction, and intraoperative findings.

The population studied were all medical records of patients with obstructive jaundice who were admitted to the Surgical Inpatient Unit and underwent surgery from January 2014 until June 2018, and did not have any history of biliary tract surgery before being hospitalized in that period. Samples were taken by total sampling. The inclusion criteria in this study were all medical records included in the population. Incomplete medical records were excluded from this study.

SPSS software version 16 and Ms. Excel Spreadsheets (2010) were used for data entry, calculations, and analysis. Descriptive statistics and diagnostic tests were used in the evaluations. This study had obtained ethical approval by Ethical Committee for Health Research Dr. Soetomo General Academic Hospital, Surabaya.

## Results

This study used medical records of patients with CBD stones, tumor/neoplasms of the bile ducts (cholangiocarcinoma), tumor/neoplasms of ampulla Vater, and tumor/neoplasms of the head of the pancreas as preoperative diagnosis who were admitted to the Surgical Inpatient Unit Dr. Soetomo General Academic Hospital, Surabaya, and underwent surgery from January 2014 until June 2018, and did not have any history of biliary tract surgery before being hospitalized in that period. This study found 98 medical records with 49 sample data that could be evaluated.

Table 1. Characteristics of the subjects

Age (years old)	Sex	Intraoperative findings			
		Masses		Stones	
		N	%	N	%
20 - 29	Male	0	0	1	3.1
	Female	0	0	2	6.3
30 - 39	Male	1	5.9	3	9.4
	Female	0	0	2	6.3
40 - 49	Male	2	11.8	10	31.1
	Female	1	5.9	6	18.7
50 - 59	Male	5	29.2	2	6.3
	Female	2	11.8	2	6.3
60 - 69	Male	2	11.8	2	6.3
	Female	3	17.7	1	3.1
≥ 70	Male	1	5.9	1	3.1
	Female	0	0	0	0
<b>Total</b>		17	100	32	100

Source: Research data, processed

Table 2. Clinical features and intraoperative findings

Clinical features	Intraoperative findings		Total
	Masses	Stones	
<b>Progressive jaundice (N = 44)</b>			
Present	15	17	32
Absent	2	10	12
Total	17	27	44
Clinical features	Intraoperative findings		Total
	Masses	Stones	
<b>Complaints of fever (N = 34)</b>			
Present	17	1	18
Absent	6	10	116
Total	23	11	34
Clinical features	Intraoperative findings		Total
	Masses	Stones	
<b>Courvoisier's law (N = 26)</b>			
Present	8	5	13
Absent	5	8	13
Total	13	13	26

Source: Research data, processed

Table 3. Laboratory features and intraoperative findings

Laboratory features	Intraoperative findings		Total
	Masses	Stones	
<b>Serum CA 19-9 (U/ml)</b>			
≥ 37	12	5	17
< 37	4	7	11
Total	16	12	28

Source: Research data, processed

Table 5. Diagnostic value of clinical features, laboratory tests, and ultrasound imaging in distinguishing masses and stones as the etiology of obstructive jaundice

Parameters	Number of samples (N)	Diagnostic value (%)				Accuracy
		Sensitivity (Sn)	Specificity (Sp)	Positive predictive value	Negative predictive value	
<b>Clinical features</b>						
Progressive jaundice	44	88.2	37	46.9	83.3	56.8
Complaints of fever	34	73.9	90.9	94.4	62.5	79.4
Courvoisier's law	26	61.5	61.5	61.5	61.5	61.5
<b>Laboratory features</b>						
Serum CA 19-9	28	75	58.3	70.6	63.6	67.9
<b>Ultrasound imaging</b>	30	81.8	100	100	90.5	93.3

**Discussion**

In this study, the mean age of the subjects was 48.8 years old and ranged from 24 to 77 years old. Other studies found the mean age to be 51 years old.<sup>8</sup> In a study by Gupta *et al.* (2018), the youngest was 25 years old, and the oldest was 72.<sup>9</sup> The subjects who had masses as the cause of obstructive jaundice were 17 (34.7%) patients, and 32 (65.3%) had stones as the cause of obstructive jaundice. Previous studies also found CBD stones to be the most frequent cause of obstructive jaundice.<sup>10,11</sup> Five male subjects in the age group 50-59 years old had masses as the cause of obstructive jaundice. The higher incidence of pancreatic malignancy in males may be associated with alcohol abuse and smoking, which are more common in males.<sup>12</sup> Ten male patients in the age group 50-59 years

Table 4. Ultrasound imaging and intraoperative findings

Ultrasound imaging	Intraoperative findings		Total
	Masses	Stones	
Masses	9	0	9
Stones	2	19	21
Total	11	19	30

Source: Research data, processed

Table 1 shows that the average age of the subjects was 48.8 years old and ranged from 24 to 77 years old. 17 (34.7%) patients had masses as the underlying etiology of obstructive jaundice, and 32 (65.3%) patients had stones as the cause of obstructive jaundice. In 49 subjects, five male subjects in the age group 50-59 years old had masses. On the other hand, stones were predominant in male subjects who were included in the age group 40-49 years old, as many as ten patients.

The results of ultrasound imaging that only showed dilatation of the intrahepatic and extrahepatic bile ducts were found in one subject that had masses, and there was one case which had stones. Three other indeterminate cases only showed dilatation of the bile ducts on ultrasound imaging which turned out to be stones during surgery.

old had masses as the cause of obstructive jaundice. Shehu, *et al.* (2015) found that the etiology of obstructive jaundice, whether benign or malignant, is dominated by males.<sup>13</sup>

There was false positive in 17 (38.6%) subjects with progressive jaundice and had stones as the cause of obstructive jaundice, which led the examination to become nonspecific in distinguishing masses and stones as the etiology of obstructive jaundice. The false negative was found in 2 (4.6%) subjects without progressive jaundice and had masses as the cause of obstructive jaundice. This is probably due to variations in periampullary malignancies that are not followed by gradual disruption of bile flow to cause total biliary obstruction and lead to progressive jaundice.

Complaints of fever in this study was defined as the state of body temperature  $\geq 38^{\circ}\text{C}$  during episodes of jaundice, which indicated a bacterial infection in extrahepatic bile ducts or acute cholangitis. The disorder is mainly caused by obstruction of the bile duct, either partial or total, with CBD stones as the most common underlying disease.<sup>14</sup> Cholangitis is a serious complication in malignant biliary obstruction, and carcinoma of ampulla Vater frequently causes cholangitis. Complaints of fever in patients with obstructive jaundice may predict a benign etiology, such as CBD stones.<sup>13</sup> False positive was obtained in one subject (2.9%) with complaints of fever and had masses as the cause of obstructive jaundice, supported by a study in Japan that stated cholangitis rarely occurs in malignant obstructive jaundice.<sup>15</sup>

Courvoisier's law refers to a palpable gallbladder in patients with obstructive jaundice generally caused by malignancies. Intermittent biliary obstruction caused by CBD stones results in fibrosis of the gallbladder that occurs chronically. Therefore, the gallbladder cannot be enlarged and palpable.<sup>16</sup> In Pakistan, there was a case of a 65-year-old woman with a bulging abdominal mass in the right upper quadrant. Surgery was performed based on suspicion of malignancy by the presence of Courvoisier's law. The surgeon discovered a stone within CBD that caused biliary tract dilatation without masses on the periampullary region and head of the pancreas during the operation. After CBD exploration, a relatively large stone was found attached to the ostium, which connected CBD to the duodenum and made complete obstruction. Thus, Courvoisier's law tends to be a subjective sign, prone to human error and misinterpretation. The enlarged gallbladder may not be palpable during examination but is clearly found during the operation.<sup>4</sup>

CA 19-9 is physiologically produced by epithelial cells lining the bile ducts. Its serum level is increased in the presence of hepatobiliary malignancy. Bile duct obstruction caused by CBD stones will disrupt the function of the bile duct epithelial cells due to the inflammatory process. As compensation, the proliferation of epithelial cells will increase secretion and release CA 19-9 into circulation.<sup>17</sup> This explains the elevated serum levels of CA 19-9, also seen in benign obstructive jaundice, rendering CA 19-9 unable to distinguish between masses and stones as the cause of obstructive jaundice.<sup>18</sup> On the other hand, one study concluded that serum CA 19-9 is useful to distinguish between masses and stones as the etiology of post-hepatic jaundice, as well as increased diagnostic value, either using appropriate cut-off value or combining serum CA 19-9 examination with imaging modalities which is routinely performed on patients with obstructive jaundice. Serum CA 19-9 does not have a high specificity because this tumor marker is also produced by malignant tumors outside hepatopancreatobiliary systems, and its level increases even in benign diseases.<sup>19</sup> Khalifa, *et al.* (2016) found a cutoff value of 40.5 U/mL for predicting malignancy as a cause of obstructive jaundice.<sup>20</sup> An exact cutoff value for CA 19-9 cannot be determined in this study due to the small number of samples. Therefore, further studies in larger populations are needed to determine an appropriate cut-off

value for CA 19-9 to obtain higher accuracy in differentiating masses and stones as the underlying etiology of obstructive jaundice.

Ultrasound imaging is the first line of radiological examination in patients clinically suspected of having obstructive jaundice because it has an important role in detecting and evaluating the biliary tract obstruction, including the location and cause of obstruction.<sup>10</sup> However, ultrasound has several weaknesses as it is operator-dependent and less able to visualize the biliary tract obstruction in obesity.<sup>21</sup> One study in Iraq reported ultrasound imaging which showed CBD stones, but endoscopic retrograde cholangiopancreatography (ERCP) examination found a tumor in the distal part of CBD. This finding may be due to the limitation of ultrasound in assessing the structures around distal CBD and the pancreas, which are often blurred due to increased intestinal gas. In addition, the bile cannot be seen on ultrasound, causing CBD stones to be difficult to distinguish from the periductal structure. In such conditions, the visualization of CBD stones can be missed, or intraluminal structures seen on ultrasound are interpreted as tumor. If ultrasound does not exhibit dilated bile duct, the stones may be small to cause biliary dilatation in the proximal part.<sup>22</sup> Furthermore, patients with CBD stones usually have pain that is quite bothering their daily activities, which leads the patient to seek help from a physician before obvious bile duct dilatation can be detected by ultrasound imaging.<sup>20</sup>

### Strength and Limitations

This study is expected to be used as a reference for further research to determine the diagnostic value of the combination of clinical parameters, laboratory parameters, and ultrasound imaging compared with the intraoperative findings. We recommend other study to include larger sample size in order to get better representative of the population and will hence provide more accurate results.

### Conclusion

Ultrasound imaging can be considered as the most accurate examination to find out the etiology of obstructive jaundice when there are limited facilities in medical centers.

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### Conflict of Interest

The authors declared there is no conflict of interest.

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### Ethical Clearance

This study had received ethical clearance from Ethical Committee for Health Research Dr. Soetomo General

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