ORIGINAL ARTICLE

Serum Bilirubin and Carbohydrate Antigen 19-9 Levels as Predictors of Malignancy in Obstructive Jaundice – A Retrospective Analysis

Devbrata R. Adhikari[1], Hozefa Lokhandwala[1], Bhushan Thombare[1], Ketki Gharpure[1], Rajinder Singh[1], Rajeev M. Joshi[1]*

[1]Department of Surgery, Topiwala National Medical College and BYL Nair Charitable Hospital, Mumbai - 400008 (Maharashtra) India

Abstract:

Background: Obstructive jaundice due to malignant pathology is often associated with high bilirubin levels. This may not always be true as malignant pathologies can still present with low bilirubin levels in the early stages or benign pathologies can present with high levels if there is associated cholangitis. Also, Carbohydrate Antigen (CA19-9) has been an unreliable predictor of malignancy. *Aim and Objectives:* Our study examined the combined accuracy of bilirubin levels and CA19-9, in order to predict malignancy as a cause of obstructive jaundice. *Material and Methods:* Bilirubin levels in a total of 900 patients with obstructive jaundice were analyzed over a period of 5 years in a retrospective study. CA 19-9 levels were also analyzed in those patients suspected to have malignancy on clinical evaluation or imaging (649 patients). The values of bilirubin in isolation and with CA19-9 in combination were used for co relation, along with imaging and histopathology. *Results:* Bilirubin levels in isolation, as a predictor of pathology in patients with obstructive jaundice were highly significant (Area under Curve =0.805; $P < 0.01$). Bilirubin level >7 mg% provided the optimum combined sensitivity and specificity for malignancy (71.9% and 84.9%, respectively). The application of a bilirubin level > 19 mg% achieved specificity of 99.1% for malignancy. The sensitivity and specificity of CA 19-9 in isolation was 70.9% and 78.3% respectively at a cut-off value of 37U/ml. In combination, the sensitivity and the specificity were 87.9% and 91.3% respectively. *Conclusion:* Serum bilirubin and CA 19-9 levels are routinely done as a part of the patients workup for obstructive jaundice. When evaluated in combination the positive predictive value increases significantly to diagnose malignancy especially in cases where it is obscure. It acts as a valuable guide to the surgeon along with other modalities.

Keywords: CA 19-9, Serum Bilirubin, HPB Malignancy

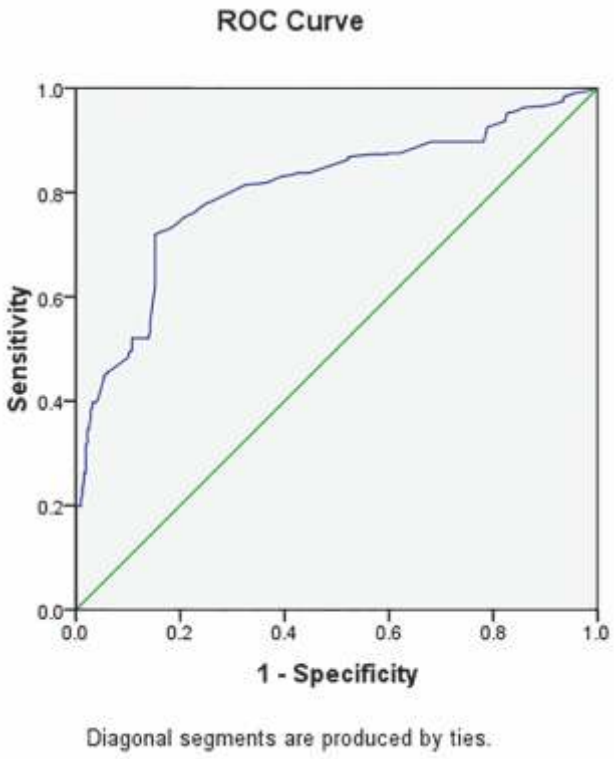
Introduction:

Pancreato-biliary cancers have always required multiple diagnostic modalities. Added the poor prognosis of pancreatic malignancies it becomes imperative to diagnose and treat them quickly [1]. Also diagnosing whether the lesion is benign or malignant can be challenging, even with the advanced imaging and endoscopic techniques at hand. Preoperative histological confirmation of malignancy is difficult given the complex regional anatomy of the hepato-pancreato-biliary system. The values of tumour marker levels are not specific to determine the exact cause of the obstructive jaundice. The accuracy of alkaline phosphatase in differentiating benign from malignant extrahepatic biliary obstruction has been reported to be up to 80% [1]. Carbohydrate Antigen (CA19-9) has been of some value in differentiating between benign and malignant pathology in obstructive jaundice but it has a variable sensitivity and specificity [2]. The radiological modalities for evaluation of these patients include ultrasonography, contrast-enhanced CT scan and Magnetic Resonance Cholangiopancreaticography (MRCP). These

non-invasive diagnostic methods provide information about the site of obstruction, degree of biliary dilatation and the presence of a tumour or distant metastasis. Endoscopic Retrograde Cholangiopancreatography (ERCP) and Percutaneous Transhepatic Cholangiography (PTC) are more accurate imaging tests for bile duct evaluation and allow a tissue diagnosis to be obtained through brush biopsy and cytological examination. However, these are associated with an increased risk of morbidity [3]. EUS and EUS guided FNAC has improved the rate of diagnosis of small lesions to more than 80% [4]. This study examined the sensitivity and specificity of bilirubin and CA 19-9 levels in combination to determine whether they can differentiate between benign and malignant disease.

Material and Methods:

900 patients presenting with obstructive jaundice over a period of 5 years were identified after due permission from the relevant authorities and their data were obtained. Demographic data such as age, sex, history, blood investigations including bilirubin levels were recorded in these 900 patients. Of these, CA 19-9 were analysed in 649 patients suspected of malignancy clinically or radiographically. Selected patients had undergone assessment of jaundice with final diagnosis being made from histopathology of the specimen, intraoperative findings or image-guided biopsy in metastatic patients. Division of patients into benign and malignant groups were done according to their underlying pathology. Data analysis was done with Receiver Operating Characteristic (ROC) and Area under Curve (AUC) values. In a ROC curve, the true positive rate (Sensitivity) is plotted in function of the false positive rate (1-Specificity) for different cut-off points of a parameter. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups. The closer the curve follows the left-hand border the more sensitive it is and the closer it is to the top border the more specific is the value. If the AUC value derived from ROC curve is 1, the predictor is 100% sensitive and specific; if the AUC is 0.5, the predictor is little better than chance alone. The study was approved by the hospital academic committee.



Area under the ROC curve=0.8, Standard error = 0.015, Significance level P < 0.01

Results:

900 patients with obstructive jaundice were identified. Table 1 shows the demographics and bilirubin levels by aetiology. Table 2 shows the final diagnosis in this group. Choledocholithiasis resulted in a majority of patients with obstructive jaundice due to benign disease (65.5%). The second most common cause was CBD stricture (post cholecystectomy / chronic pancreatitis).

Table 1: Demographic Data of Underlying Benign and Malignant Pathology

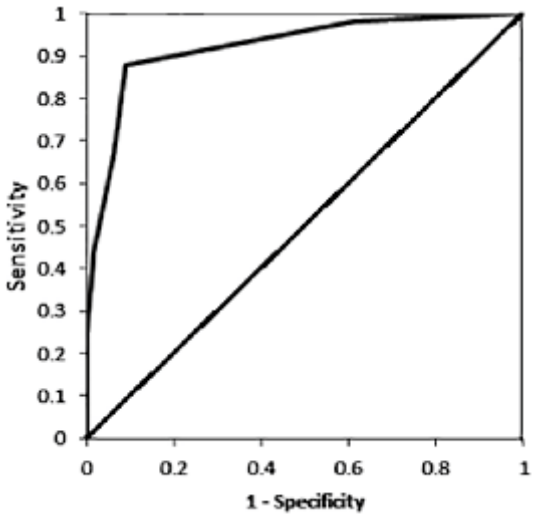
Patients	Total	Benign Pathology	Malignant Pathology
Number	900	316	584
Gender			
Male	508(56.45%)	142(28%)	366(72%)
Female	392(43.55%)	174(44%)	218(56%)

Table 2: Various Diagnosis of the Patients with Obstructive Jaundice

Diagnosis	Patients	Percentage
Benign Pathology		
Choledocholithiasis	207	65.5
CBD Stricture (Post cholecystectomy and Chronic Pancreatitis)	85	26.89
Choledochal Cyst	12	0.04
Hepaticolithiasis	10	0.03
Mirrizi's Syndrome	2	0.01
Total	316	100
Malignant Pathology		
Ampullary Carcinoma	208	35.61
Adenocarcinoma of Pancreas	166	28.42
Cholangiocarcinoma	91	15.58
Klatskin'sTumour	57	0.1
Carcinoma Gall Bladder	42	0.07
Duodenal Carcinoma	20	0.03
Total	584	100

Table 3: Bilirubin Level and Chance of Malignancy in Patients with either Benign or Malignant Causes for Obstructive Jaundice

Bilirubin Levels	Sensitivity %	Specificity %	PPV %	NPV %	LR
3	89.7	21.8	68	53.5	1.14
7	71.9	84.8	89.7	62	4.73
11	51.9	89.2	89.9	50.1	4.82
15	34.6	97.5	96.2	44.6	13.6
19	19.9	99.1	97.5	40.1	20.92



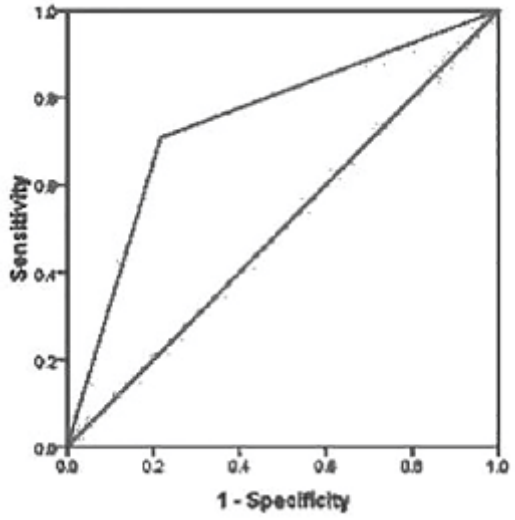
ROC Curve for Sr. Bilirubin, Area under Curve: 0.8, Standard Error: 0.015, Significance Level: P < 0.01 [5]

Table 3 demonstrates the sensitivity and specificity of bilirubin in predicting malignancy in all patients with obstructive jaundice.

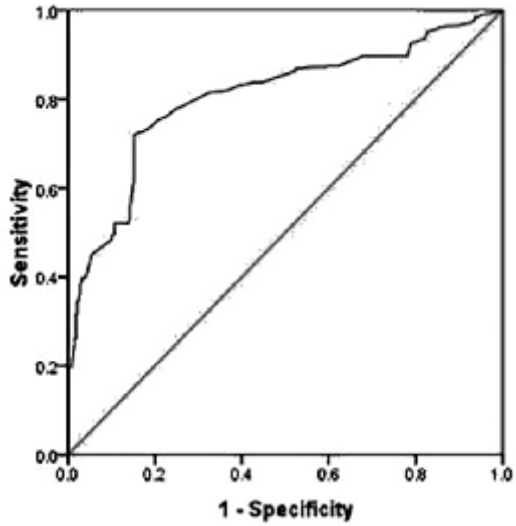
Bilirubin levels of 7 mg% were 71.9% sensitive and 84.8% specific for malignancy (with positive predictive value of 89.7%). Higher cut-offs for bilirubin values resulted in the specificity increasing. Bilirubin levels >19 mg% were 99.1% specific in predicting malignancy (positive predictive value = 97.5%).

Area under the curve values for bilirubin as a predictor of malignancy were significant (Fig. 1) Optimum sensitivity and specificity for malignancy was determined to be at a bilirubin level of >7mg%.

Sensitivity and specificity of CA 19-9 in isolation was 70.9% and 78.3% respectively, at a cut-off unit of 37 U/ml. That means CA 19-9 values were taken above 37 U/ml in all patients as isolated levels of CA 19-9 are poor predictors of cancer[6].



ROC Curve for CA 19– 9, AUC: 0.74, Standard Error: 0.03, Significance Level: P < 0.01. Sensitivity and specificity of combined serum bilirubin and CA 19-9 increased to 87.9% and 91.3% respectively.



ROC Curve of Combined Serum Bilirubin and CA 19-9, Area under Curve: 0.92, Standard Error: 0.011, Significance Level: P < 0.001

Table 4: Specificity and Sensitivity Compared with CA 19-9 Alone and in Combination

Modality	Patients	Sensitivity %	Specificity%
Bilirubin(mg/dl)			
>7 mg/dl	468	71.9	84.8
>15mg/dl	210	34.6	97.5
CA 19-9	649	70.9	78.3
Bilirubin + CA 19-9	**649**	**87.9**	**91.3**

Discussion:

The results are suggestive of that, bilirubin levels are an important discriminating parameter in patients with obstructive jaundice. Table 1 shows the demographic data in which females had more incidence of benign disease (44%) whereas males had increased incidence of malignant disease (72%). The highest incidence of benign pathology was CBD stones (65.5%) and ampullary carcinoma was the most common malignant pathology (35.61%) as shown in Table 2. Though sensitivity drops with increasing levels of bilirubin, a markedly raised bilirubin (>7mg %) has an important positive predictive value for the presence of malignancy of 89.7% as shown in Table 3. These findings are in coherence with other papers which have examined bilirubin levels in cancer. Previous studies have found bilirubin to predict malignancy with AUC values of 0.8[3]. Also these values are consistent with the results from the current data. Similar results have been reported by Al-mofleh *et al* [7], Pasanen *et al* [8] and Bain *et al* [9]. Although we do not suggest that bilirubin alone can be used as a sole modality for predicting malignancy in patients with obstructive jaundice, but combination of serum bilirubin with CA 19-9 improves diagnostic yield significantly. The data presented in Table 4 demonstrates the accuracy of bilirubin levels with respect to CA 19.9 in diagnosing the cause of obstructive jaundice and sensitivity and specificity were 87.9% and 91.3% respectively. High serum bilirubin levels may lead to a detailed work up in which the patient may be subjected to tumour markers, CT and MRCP to exclude underlying malignancy [10].

Patients present early in benign diseases as the stone impacted in common bile duct cause pain and septicaemia and leads to earlier presentation of the jaundice and hence bilirubin levels are lower in these patients. Also there is incomplete obstruction of the biliary tree. Biliary epithelial cells secrete mucins carrying CA19-9, therefore the increased values of CA19-9 in serum during obstructive jaundice, reflecting both inflammatory hypersecretion and seepage of biliary mucins into serum [10]. The process reverses during the resolving phase of jaundice and is often associated with a fall in CA19-9 which is greater in benign disease than in malignant [11]. In malignant disease the synthesis of CA19-9 by cancer cells contributes to the total level in a manner independent from any underlying condition [12, 13]. Production and secretion of CA 19-9 from malignant cells are deemed responsible for the

high serum CA 19-9 level in malignancies. The actual reason for the raised CA 19-9 in acute cholangitis is not well understood. Several mechanisms have been postulated as: 1) seepage of CA 19-9 due to biliary tract obstruction from the biliary radicals into blood circulation [14], 2) CA 19-9 production by irritated bile duct cells exposed to increased biliary pressure, 3) increased production of CA 19-9 in the bile ductal epithelium and the mucosa of gall bladder induced by the inflammatory process, 4) the inflammatory cytokines produced in sepsis due to cholangitis probably have some contribution to make. CA 19-9 serum level of <100 U/ml is likely for the tumour to be surgically resectable whereas levels >100 U/ml may suggest metastatic disease [15].

Conclusion:

Serum bilirubin and CA 19-9 levels are routinely done as a part of the patients workup for obstructive jaundice. When evaluated in combination the positive predictive value increases significantly to diagnose malignancy especially in cases where it is obscure. It acts as a valuable guide to the surgeon alongwith other modalities.

References

1. Dumitra S1, Jamal MH, Aboukhalil J, Doi SA, Chaudhury P, Hassanain M, Metrakos PP, Barkun JS. Pancreatic cancer and predictors of survival: comparing the CA 19-9/bilirubin ratio with the McGill Brisbane Symptom Score. *HPB (Oxford)* 2013; 15: 1002-09.
2. Morris-Stiff G, Teli M, Jardine N, Puntis MC. CA19-9 antigen levels can distinguish between benign and malignant pancreaticobiliary disease. *Hepatobiliary Pancreat Dis Int* 2009; 8(6): 620-26.
3. Saluja SS, Sharma R, Pal S, Sahni S, Chattopadhay TK. Differentiation between benign and malignant hilar obstructions using laboratory and radiological investigations: a prospective study. *HPB (Oxford)* 2007; 9 (5):373-82.
4. Schneider AR, Nerlich A, Topalidis T, Schepp W. Specialized clinical cytology may improve the results of EUS (endoscopic ultrasound)-guided fine-needle aspiration(FNA) from pancreatic tumors. *Endosc Int Open* 2015; 3(2): E134-37.
5. Garcea G, Ngu W, Neal CP, Dennison AR, Berry DP. Bilirubin levels predict malignancy in patients with obstructive jaundice. *HPB (Oxford)* 2011; 13(6): 426-30.
6. Hai Jie Hu, Hui Mao, Yoong-Qiong Tan, Anuj Shrestha, Wen-Jie Ma, Qin Yang *et al*. Clinical value of preoperative CA 19-9 and Ca 125 levels in predicting the resectability of hilar cholangiocarcinoma. *Springerplus* 2016; 5:551.
7. Al-Mofleh IA, Aljebreen AM, Al-Amri SM, Al-Rashed RS, Al-Faleh FZ, Al-Freihi HM, *et al*. Biochemical and radiological predictors of malignant biliary strictures. *World J Gastroenterol* 2004; 10 (10):1504-07.
8. Pasanen P, Pikkarainen P, Alhava E, Partanen K, Penttila I. Value of serum alkaline phosphatase, aminotransferases, gamma-glutamyltransferase, leucineaminopeptidase, and bilirubin in the distinction between benign and malignant diseases causing jaundice and cholestasis: results from a prospective study. *Scand J Clin Lab Invest* 1993; 3 (1):35-9.
9. Bain VG, Abraham N, Jhangri GS, Alexander TW, Henning RC, Hoskinson ME, *et al*. Prospective study of biliary strictures to determine the predictors of malignancy. *Can J Gastroenterol* 2000; 14 (5):397-402.
10. Andersson M, Kostic S, Johansson M, Lundell L, Asztély M, Hellström M. MRI combined with MR cholangiopancreatography versus helical CT in the evaluation of patients with suspected periampullary tumours: a prospective comparative study. *Acta Radiol* 2005; 46 (1):16-27.
11. La Greca G1, Sofia M, Lombardo R, Latteri S, Ricotta A, Puleo S, Russello D. Adjusting CA19-9 values to predict malignancy in obstructive jaundice: Influence of bilirubin and C-reactive protein. *World J Gastroenterol* 2012; 18(31): 4150–55.

12. Marrelli D, Caruso S, Pedrazzani C, Neri A, Fernandes E, Marini M, Pinto E, Roviello F. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. *Am J Surg* 2009; 198 (3): 333-39.
13. Mann DV, Edwards R, Ho S, Lau WY, Glazer G. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. *Eur J Surg Oncol* 2000; 26 (5):474-79.
14. Kim HJ1, Kim MH, Myung SJ, Lim BC, Park ET, Yoo KS, Seo DW, Lee SK, Min YI. A new strategy for the application of CA 19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. *Am J Gastroenterol* 1999; 94 (7):1941-46.
15. Ballehaninna UK, Chamberlain RS. Serum CA 19-9 as a Biomarker for Pancreatic Cancer - A Comprehensive Review. *Indian J Surg Oncol* 2011; 2(2):88-100.

[*] ***Author for Correspondence:*** *Dr. Devbrata R Adhikari, 504 B, Gold Coin, Tardeo Road, Mumbai 400034 India*
Email: docdev84@yahoo.com Cell: 09870106727