Original Article

Diagnostic Accuracy of Serum Carbohydrate Antigen 19-9 in Determining Etiology of Obstructive Jaundice

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Abstract

Background: *Serum carbohydrate antigen 19-9 (CA 19-9), a tumour marker for malignancies of the hepatobiliary tract and pancreas, frequently elevated in a number of non-malignant conditions that are associated with jaundice. The CA 19-9 tends to normalize following the restoration of biliary drainage. This study was designed to assess the clinical application of CA19-9 in diagnosing pancreatobiliary malignancies in patients with obstructive jaundice and in discriminating between benign and malignant causes.*

Methods*: Sixty three patients presented with obstructive jaundice on the basis of clinical, biochemical and imaging methods with elevated CA 19-9 were included in this study. Serum CA 19-9 levels were measured on admission and two weeks following endoscopic biliary drainage performed through an ERCP procedure at the department of Gastrointestinal, hepatobiliary and pancreatic disorders (GHPD) of BIRDEM general hospital. Malignant and benign cases were differentiated by ultrasonogram, CT scan, MRCP and morphological findings during ERCP procedure. Diagnostic accuracy of CA19-9 in the detection of malignancy was estimated by the receiver operating characteristic (ROC) curve.*

Results: *Age was 53.76±14.48 years (mean±SD) and sex was 32:31 (M:F). Median value of CA 19-9 in malignant cases was higher (1000 U/ml) than benign cases (93 U/ml) (p=0.001). After biliary drainage serum CA19-9 levels normalized in 15(50%) benign and 1(3%) malignant cases (p=0.001). The AUC of CA 19-9 was 0.825. Sensitivity, specificity, PPV and NPV at cut off value 90 U/ml were 100, 50, 68.8 and 100; at 100 U/ml were 100, 53.3, 70.2 and 100; at 200 U/ml were 90.9, 66.7, 75 and 87, at 500 U/ml were 63.6, 76.7,75 and 65.7 respectively. Diagnostic accuracy of CA 19-9 was observed more at cut off value 200 U/ml.*

Conclusions*: Deranged CA19-9 is frequently observed in benign conditions with jaundice and shown to normalize following improvement of biliary drainage. Caution is necessary in the interpretation of an elevated serum CA 19-9 value as a marker for malignancy, especially in patients with benign cholestasis.*

Keywords: *Carbohydrate antigen 19-9 (Ca 19-9), jaundice, malignant*

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Introduction

CA 19-9 is a tumour associated carbohydrate antigen which was originally isolated from a hybridoma prepared from murine spleen cells immunized with a human colorectal carcinoma cell line. This high-molecular-weight glycoprotein is expressed by several epithelial cancers, as well as in normal pancreatic and biliary ductal epithelial cells and it is also detectable in salivary mucus and meconium.[1] Biliary tract cancer (BTC) is a heterogeneous tumor entity mostly diagnosed at an advanced stage and need palliative treatment with chemotherapy and/or biliary drainage, both of which showing benefits over no therapy or best supportive care.[2-4]

CA 19-9 serum levels have been used for preoperative staging, assessment of resectability and prognosis of pancreato-biliary cancer, as well as diagnosis of tumour recurrence.[5-9] It may also increase in many benign

conditions like cholangitis, choledocholithiasis, papillary stenosis etc., the diagnostic accuracy of such a marker is significantly reduced.[5,6] Thus, CA 19-9 has been used not only as a serum tumour marker for pancreatic and gastrointestinal carcinoma, but also to differentiate benign from malignant diseases of the pancreas.[10-13] Biliary drainage includes ERCP (endoscopic retrograde cholangiopancreatography) sphincterotomy, stone/worm extraction, stent implantation or surgical intervention.

In Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) general hospital, a large number of patients are diagnosed as obstructive jaundice at the department of gastroenterology. These obstructive jaundice patients include both benign and malignant conditions. CA 19-9 is usually elevated in many patients. Most of them undergo ERCP. This study was designed to assess the clinical application of CA19-9 in diagnosing as well as differentiating benign and malignant causes of obstructive jaundice.

Methods

Patients

This study was conducted at the Department of Gastrointestinal, Hepatobiliary and Pancreatic Disorders (GHPD), BIRDEM General hospital Hospital, Dhaka during the period of July 2010 to June 2012. The patients were collected from both inpatient and outpatient department of GHPD of BIRDEM general hospital.

Inclusion criteria

The subjects were of any age with obstructive jaundice and elevated serum levels of CA 19-9 (>37 U/ml).

Exclusion criteria

Subjects were excluded if they had advanced COPD, uncontrolled respiratory distress, gross electrolyte imbalance and recent myocardial infarction, unstable angina, cardiac arrhythmia because they are not fit for ERCP procedure.

Grouping of study subjects

After doing ERCP the study subjects were divided into two groups: group A with benign obstructive jaundice and group B with malignant obstructive jaundice.

Data collection

All data were collected by preformed structured questionnaire from the subject with fulfillment of inclusion and exclusion criteria. Laboratory data including serum carbohydrate antigen 19-9 (CA 19-9), bilirubin, alkaline phosphatase before and two weeks after biliary drainage also recorded.

Laboratory methods

On admission, all patients underwent complete blood count (CBC), serum bilirubin levels, ALT, AST and serum alkaline phosphatase. Instrumental examinations included ultrasonography of whole abdomen, computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). Pathology samples were obtained, when possible, from percutaneous biopsy or fine-needle aspiration cytology, endoscopic biopsy or surgical specimens. All patients underwent ERCP. ERCP was performed by consultant gastroenterologists. Type of biliary drainage was**:** papillotomy, endobiliary stenting, stone extraction or worm extraction and surgery. CA 19-9 serum levels, was measured on admission and two weeks following endoscopic biliary drainage performed through an ERCP procedure. Serum assay for CA19-9 was performed with chemiluminescence EIA method (Kit used: DPC, Immulite, USA).

Ethical clearance

Prior to commencement of this study the protocol was approved by the ethical review committee of Bangladesh Diabetic Samity (BADAS). Informed written consent was taken from each patient before his/her entry into the study and benefits were explained to make their decision to participate in the study. The aims and objectives of the study were explained to the patients in easy, simple and understandable local language. It was assured that all information and records would remain confidential. They were also informed regarding their rights to withdraw themselves at any stage of the study.

Statistical analysis

For the statistical analysis student's t test, non parametric tests-Mann-Whitney U test, Wilcoxon Signed Ranks test performed for continuous variables and Chi square (x^2) test, Fisher's Exact for categorical variables. P value <0.05 was considered as significant. Appropriate statistical analysis of collected data were done using computer statistical package SPSS 16.0 version and appropriate statistical method were used to arrive at conclusion making necessary graphs and tables.

Results

A total of 63 cases of obstructive jaundice with elevated baseline CA 19-9 were included in this study. Of them, male:female were 32:31. The age range was 22-88 years, mean±SD was 53.76±14.48. Smoking history was present in 30.1%, alcohol intake 3.1%, presenting complaints were abdominal pain 73.0%, itching 38.1%, weight loss 7.5% and abdominal lump in 77.7% cases.

Demographic and biochemical parameters of benign and malignant obstructive jaundice patients were shown in table I. Serum bilirubin, alkaline phosphatase and serum CA19.9 were significantly differed among groups at baseline.

Table I. Demographic and biochemical parameters of benign and malignant obstructive jaundice patients at baseline (N=63)

Parameters	Group A benign (N=30)	Group Bmalignant (N=33)	p
Age in years (mean±SD)	52.4±16.6	54.9±12.3	0.503
Sex (male/female)	18/12	14/19	
Serum ALT U/L (mean±SEM)	115.2±20.4	104.6±15.6	0.677
Serum AST U/L (mean±SEM)	105.3±18.4	91.4±10.3	0.505
Serum bilirubin mg/dl (mean±SEM)	7.4±1.1	14.3±1.5	0.001
Serum ALP U/L (mean±SEM)	507.7±53.3	775.7±106.4	0.033
CA 19.9 U/ml (mean±SEM)	309.5±65.6	732.0±58.0	0.000

P value was calculated using 't' test

ERCP showed, carcinoma of pancreas in 14.3%, carcinoma of gall bladder 14.3%, cholangiocarcinoma 11.1%, periampullary carcinoma 12.7%, choledocholithiasis 17.7%, choledocholithiasis with cholangitis 3.25%, papilary stenosis 12.7%, biliary stricture 3.2%, biliary ascariasis 3.2%, chronic calculous pancreatitis 3.2%, chronic pancreatitis involving biliary tree 3.2% and autoimmune pancreatitis 1.6% cases.

Biochemical parameters of benign and malignant cases before and after biliary drainage were shown in Table II. After biliary drainage serum bilirubin and serum ALP were significantly reduced irrespective of etiology. But CA 19.9 only significantly reduced in benign conditions whereas almost no change in malignant cases (p=0.721).

Table II. Biochemical parameters before and after biliary drainage

Parameters	Before	After	P
Serum bilirubin mg/dl (mean±SEM)			
Benign (n=30)	7.4±1.1	2.5±0.4	0.000
Malignant (n=33)	14.3±1.5	5.3±0.6	0.000
Serum ALP (U/L) (mean±SEM)			
Benign (n=30)	507.7±53.3	183.9±17.8	0.000
Malignant (n=33)	775.8±106.4	383.5±55.4	0.000
CA 19.9 (U/ml) (mean±SEM)			
Benign (n=30)	309.6±65.6	101.2±26.3	0.000
Malignant (n=33)	732.0±58.0	713.6±75.9	0.721

P value was calculated using 't' test

Table III shows, diagnostic accuracy at different cut off values at 90, 100, 200 and 500 U/ml arbitrarily. But accuracy was more when cut off value of CA 19-9 was 200 U/ml.

Table III. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy at different cut off values of CA 19-9

Validity test	COV 90	COV100	COV200	COV500
Sensitivity	100.0	100.0	90.9	63.6
Specificity	50.0	53.3	66.7	76.7
PPV	68.8	70.2	75.0	75.0
NPV	100.0	100.0	87.0	65.7
Accuracy	76.2	77.8	79.4	69.8

COV= Cut off value, PPV = Positive Predictive Value, NPV = Negative Predictive Value

In figure-1 receiver operating curve (ROC) of CA 19.9 shown. Area under the curve value was 0.825.

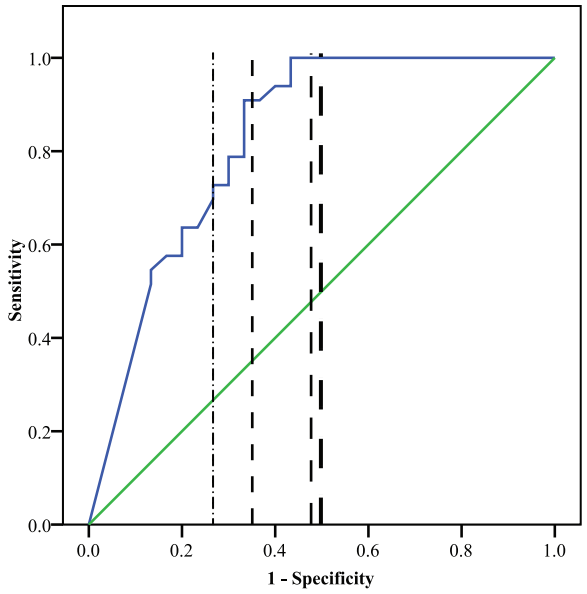

Figure 1. *ROC curve of CA 19-9.*

Discussion

The aim of this study was to assess the role of CA19-9 in discriminating benign and malignant causes of obstructive jaundice. We observed that patients with benign diseases, sequential sampling shows improvements of CA19-9 following relief of biliary obstruction. Marelli D. and colleagues[14] recently demonstrated that CA19-9 levels fall to normal when patients with benign pancreaticobiliary diseases are stented, but remain elevated in cases when a malignancy is present.

In this study the mean serum bilirubin of benign obstructive jaundice was 7.4 mg/dl, median 4.7 mg/dl, range 2.1-22.4 mg/dl before biliary drainage and mean 2.5 mg/dl, median 1.7 mg/dl, range 0.4-9.1 mg/dl after biliary drainage. The mean ALP was 507.8 U/L before and 184.0 U/L after drainage in this group. Ong SL et al[15] found mean serum bilirubin 15.5mg/dl, range 1.2-26.0 mg/dl before biliary drainage and 8.2 mg/dl and range 1.2-14.5 mg/dl after biliary drainage in benign obstructive jaundice. The mean ALP in their study was 640 U/L before and 330 U/L after drainage.

In our study in benign disease the mean, median and range of CA19-9 was 309.6 U/ml, 93 U/ml and 37.8-1000.0 U/ml respectively before drainage. In malignant disease the mean, median and range of CA19-9 were 732.0 U/ml, 1000 U/ml and 115-1000 U/ml respectively before drainage. After drainage in benign disease the values were 101.2 U/ml, 36.6 U/ml and 12-649 U/ml. In malignancy, these were 713.6 U/ml, 743 U/ml and 19-2000 U/ml respectively. CA19-9 levels were significantly higher in malignancies (median 399.0, range 0.6–10,000 U/mL) compared to benign diseases (median 64.6 and range 0.6-10,000 U/mL). Median and range of CA19-9 after biliary drainage were 163.2 and 0.6 to 10,000 in malignant vs. 17.7 and 0.6 to 982.8 in benign was shown by Marrelli D, et al.[14] Study by Gareth Morris-Stiff and colleagues showed that the CA19-9 levels were significantly greater for malignant than for benign disease with medians of 500 U/ml and 20 U/ml, respectively.[16] Two weeks after biliary drainage, serum CA19-9 levels became normal (i.e. below the reference value) in 15(50%) benign and only 1(3%) malignant obstructive jaundice (p=0.001). In 20(66.7%) of benign jaundice CA19-9 reduced more than 50% but this fall was only in 5(15.2%) of malignant jaundice (p=0.001). This rate of normalization and or significant fall of CA19-9 were another differentiating point between benign and malignant obstruction. By Marrelli D et al[14] a different trend of CA19-9 decrease was observed between the 2 groups. In patients with benign diseases, jaundice relief was associated with a decrease of serum CA19-9 in all cases except one. In the malignant group, CA19-9 following biliary drainage was found to be elevated in 16 patients (42%), remained steady in 3 and decreased in 19 (50%). There was a simultaneous 44% reduction in median CA19-9 level and median bilirubin following intervention. In a subgroup of jaundiced patients (16 benign and 15 malignant cases), follow-up CA19-9 levels were determined 2 weeks after biliary drainage by Mann DV et al.[17] The median CA19-9 level was lower in benign cases (102 U/ml) than those with pancreatobiliary tumours (910 U/ml; P<0.01), although the overlap was substantial. In benign jaundiced cases, a positive correlation was observed between bilirubin and CA19-9 elevation (R=0.41, p<0.01). Relief of jaundice was associated with a fall in CA19-9 level in all benign cases and in nine of the 15 with malignancy. Ahmet K et al reported a case where patient had an impacted stone in the common bile duct and cholangitis, with a CA19-9 level of more than 1,500 U/ml, which raised the question of a malignant condition. An exceedingly elevated level of CA19-9 was detected just after surgery and this

finding prompted to perform further evaluation to exclude malignancy. CA19-9 level repeated on the 15th postoperative day was 282 U/ml and was 43 U/ml one month after the surgery.[18] Diagnostic accuracy of CA19-9 in the detection of malignancy was estimated by the ROC curve. The AUC of CA19-9 was 0.825. In the study of Gareth Morris-Stiff et al[16] the AUC for CA19-9 on the ROC analysis was 0.871 (95% CI: 0.820-0.922). The study by Marrelli D et al revealed the AUC 0.724 95% [CI] 0 .634 –0.815).[14] Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) in different cut off values of CA19-9 were measured. At cut off value 90 U/ml these were 100, 50, 68.8 and 100; at 100 U/ml were 100, 53.3, 70.2 and 100; at 200 U/ml were 90.9, 66.7, 75 and 87, at 500 U/ml were 63.6, 76.7, 75 and 65.7 respectively. Diagnostic accuracy of CA19-9 value at 200 was observed more. At the cut off value of 50, Gareth Morris-Stiff et al showed the sensitivity, specificity, PPV and NPV for CA19-9 differentiating malignant versus benign disease were 84.9, 69.7, 67.7 and 86.1, respectively. When standard radiology was also included in the decision process, the results improved with a sensitivity of 97.2, a specificity of 88.7, a PPV of 86.6 and a NPV of 97.7.[16] Study by Duffy M et al showed sensitivity, specificity, PPV and NPV of the marker for distinguishing between malignant and benign pancreatic or biliary diseases as 96, 52, 79 and 89. Increasing the cut-off point to 100 U/ml sensitivity was 98 and specificity 68. At a cut-off point of 1000 U/ml, specificity was 99.8 but sensitivity was only 41.[19] By Marrelli D et al with a cut-off level of 90 U/ml, sensitivity and specificity were 75 and 61, respectively. Sensitivity and specificity using the 300 U/mL cut-off level were 53 and 80, respectively.[14] Laurent-Puig P et al found the sensitivity, specificity, PPV and NPV as 96, 52, 79 and 89.[20]

Difference of validity tests shown by different studies were due to taking the cut off value at different level into the consideration. In our study as only those obstructive jaundice patients having elevated CA 19-9 (>37 U/ml) were included, so the test values differ from literature. Some studies assessed the role of serum level of CA 19-9 in patients with obstructive jaundice for differentiating the benign from malignant.

Conclusion

In obstructive jaundice when diagnostic uncertainty persists after clinical examination and laboratory investigations, CA19-9 assay obtained before and after resolution of cholestasis may be useful in determining the diagnostic and therapeutic courses. Using the cut off value 200U/ml, diagnostic accuracy of CA 19-9 to differentiate malignant from benign obstructive jaundice was observed more in this study. Further large scale multicenter study should be done to make a consensus about the role of this tumor marker in diagnosing and differentiating the obstructive jaundice.

Conflict of interest: None

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