Original Article

Prognostic Relevance of Significantly Raised CA 19-9 with Choledocholithiasis to Malignant Pathologies of HBS: An Early Experience in Dept. of Hepatobiliary Surgery at ShSMCH, Dhaka

Ahmed A[1], Shahriar S[2], Shimu F[3], Alam SMSU[4], Sarker RD[5]

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Abstract

***Background**: Conventionally it is assumed that raised level of CA 19-9* (Carbohydrate antigen 19-9) *is related to malignancies of liver, pancreas and biliary tract. Through our early experience in Shaheed Suhrawardy Medical College Hospital we found that raised level of CA 19-9 is not associated only with malignancies but also with other benign disorders of HBS. The aim of this study was to explore the relationship of raised CA 19-9 with hepatobiliary disorders other than malignancies.*

***Result:** We encountered a total of* 57 cases *at our department of Hepatobiliary Surgery where patients presented with classical features of obstructive jaundice with pain, anorexia and vomiting. Routine investigations of USG and MRCP revealed stone disease in the CBD. Fifty-seven patients with obstructive jaundice were studied retrospectively. Serum CA19-9 levels and some additional biochemical parameters were evaluated before and after treatment. CA 19-9 levels were significantly elevated in most patients, along with levels of total bilirubin, alkaline phosphatase (ALP), and gamma glutamyl transpeptidase (GGT), and 10 patients with benign disorders had extraordinarily high levels of these markers (> 1000 U/mL). The mean CA 19-9 level in the malignant group was greater than that in the benign group (826.83 ± 557.34 vs. 401.92 ± 483.92 U/mL, P = 0.005), and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CA19-9 were 100%, 7.69%, 33.33% and 47.47%, respectively. CA19-9 levels in the whole cohort were correlated with ALP (r = 0.77, P < 0.001), GGT (r = 0.83, P < 0.001), bilirubin (r = 0.69, P < 0.001), and CRP (r = 0.37, P = 0.004). The reduction in serum level of CA19-9 after treatment in the malignant group was remarkably less than that observed in the benign group (97.26 ± 123.24 U/mL vs. 352.71 ± 397.29 U/mL, P < 0.001). CA 19-9 levels may not be sufficient to distinguish between malignant and benign obstructive jaundice diseases. So raised CA 19-9 can obviously denote any hepatobiliary disease other than malignancy that will start to decline 1 to 28 days later after extraction of stone.*

***Conclusion:** In conclusion, it is obvious that raised level of CA 19-9 is associated not only with malignancies but also with other benign disorders of HBS to a larger scale.*

Key Words:
Carbohydrate Antigen 19-9, Tumor marker, CBD, Choledocholithiasis, MRCP.

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1. Dr. Akhter Ahmed, Associate Professor, Department of Surgery, Shaheed Suhrawardy Medical College
2. Dr. Shaon Shahriar, Assistant Professor, Department of Surgery, Shaheed Suhrawardy Medical College
3. Dr. Farhana Shimu, Associate Professor, Department of Radiology & Imaging, Dhaka Central International Medical College & Hospital.
4. Dr. S.M. Syeed-Ul-Alam, Associate Surgeon, Department of Surgery, Shaheed Suhrawardy Medical College Hospital
5. Dr. Rajib Dey Sarker, Registrar, Department of Surgery, Shaheed Suhrawardy Medical College Hospital

Correspondence: Dr. Akhter Ahmed, Associate Professor, Department of Surgery, Shaheed Suhrawardy Medical College, Phone:01612848278, E-mail: akhterssmc22ahmed@gmail.com

Introduction

Our OPD compiles of both malignant and benign pathologies of the biliary tree. The benigns, including inflammatory stricture secondary to choledocholithiasis, Mirizzi syndrome, extrahepatic localized form of primary sclerosing cholangitis (PSC), idiopathic benign focal stricture, and benign tumors, are possible differential diagnoses of bile duct carcinoma[1]. But we found the stone diseases mostly in our country. Current imaging modalities can reliably distinguish many of these entities.[2] However,

cases in which obstructive jaundice and dilated ducts present together can lead to a misdiagnosis because of the high degree of similarity between benign and malignant biliary diseases in terms of clinical manifestations and imaging findings using ultrasound (US), magnetic resonance cholangiopancreatography (MRCP) and computerized tomography (CT). It is therefore desirable to have a serological test that can rapidly differentiate between benign and malignant conditions of this system in order to allow the prioritization of patients with malignancy and to avoid possible surgical complications in benign cases where surgery is unnecessary. However, to the best of our knowledge, no such test is currently available.

Carbohydrate antigen 19-9 (CA 19-9), first isolated by Koprowski in 1979[3], was initially considered to be a tumor marker associated with colon cancer, but was later found to be a useful tumor marker for pancreatobiliary malignancies.[4,5] Steinberg[6]reported that a CA 19-9 value > 1,000 U/mL usually indicated digestive tract cancer and had a specificity > 99% for pancreatic cancer.

This finding suggests that CA 19-9 is a suitable marker for distinguishing malignant pancreatobiliary disease from jaundice or a dilated bile duct. However, CA 19-9 is also upregulated in other malignant tumors, including gastric, ovarian, hepatocellular, and colorectal carcinoma, as well as many benign conditions of the biliary tree, suggesting that CA 19-9 may not be suitable for distinguishing between benign or malignant disease.[7,8,9,10]

In this study, we found that the specificity, positive predictive value (PPV), and negative predictive value (NPV) for CA 19-9 in distinguishing benign and malignant disease were relatively low, despite evels being higher in the malignant group. Our findings suggest that the serum level of CA 19-9 cannot be regarded as a gold standard for diagnosis, but rather as a helpful adjunct when attempting to identify biliary malignancy.

Materials and Methods

Study subjects

Between November 2018 and October 2019, 57 consecutive patients admitted to our department at Shaheed Shuhrawardy Medical College Hospital, Dhaka, Bangladesh, with a diagnosis of *obstructive* jaundice from Hepatobiliary OPD, were studied retrospectively. The preliminary diagnosis was based on findings of a liver function test, ultrasonography and MRCP. All the detailed clinicopathological and follow-up outcome data were collected from hospital notes, physician records, or the patients themselves. This study was prepared and analyzed in the Department. All subjects provided written informed consent.

Methods

Levels of CA 19-9, ALP, GGT, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, and C reaction protein (CRP) were determined at the time of admission for all patients. The patients included in our study underwent ultrasonography (US), helical CT, and MRCP before treatment. Serum levels of CA 19-9, ALP, GGT, AST, ALT, CRP, and bilirubin were measured again 14 days after treatment. The upper normal limit of CA 19-9 serum concentration was 37 U/mL.

Results

Demographic characteristics of subjects

Fifty-seven patients with obstructive jaundice were studied. The age of these patients ranged from 32 to 82 years (mean ± standard deviation, 59.56 ± 13.22 years). The majority of patients (35) were female. The etiology of malignant disease was cholangiocarcinoma in 10 cases, papillary carcinoma in 2 cases, and pancreatic head carcinoma in 6 cases, whilst common bile duct (CBD) stone and inflammatory stricture were the most frequent pathology in the benign group, being present in 39 cases.

Pre-treatment levels of CA 19-9 and other biochemical markers

The demographic characteristics and laboratory biochemical parameters of these patients are listed in

Table I

Demographic characteristics and clinical laboratory parameters in the patients studied

Variables		Values
Total number of patients (n)		57
Age (years)		59.56 ± 13.22
Gender	Female	35
	Male	22
Etiology	Malignant	18
	Benign	39
CA19-9 (mean ± SD, U/ml)		536.11 ± 541.22
ALP (mean ± SD, U/L)		420.37 ± 358.17
GGT (mean ± SD, U/L)		416.77 ± 344.82
ALT (mean ± SD, U/L)		109.65 ± 64.99
AST (mean ± SD, U/L)		99.23 ± 57.07
T-bil (mean ± SD, µmol/L)		119.19 ± 53.48
CRP (mean ± SD, mg/L)		41.09 ± 14.69
CA19-9 (mean ± SD, U/ml)		536.11 ± 541.22
ALP (mean ± SD, U/L)		420.37 ± 358.17

The normal range of CA 19-9, ALP, GGT, ALT, AST, total bilirubin, and CRP levels used in our hospital were 0 to 37 U/mL, 39 to 117 U/L, 11 to 49 U/L, 11 to 40 U/L, 15 to 40 U/L, 25 to 125 ìmol/L, and 0 to 10 mg/L, respectively. Almost every patient in our study had an elevated serum CA19-9 level, and 10 patients with benign disease had an extremely high concentration (> 1000 U/mL).

The serum level of total bilirubin (TBil), ALP, and GGT was high in all patients, and the serum level of ALT and AST was predominantly high in benign cases. The mean serum CA 19-9 level in the entire study cohort was 536.11 ± 541.22 U/mL. The average serum CA 19-9 concentration was significantly higher in patients with malignant disease (826.83 ± 557.34 U/mL) than in patients with benign disease (401.92 ± 483.92 U/mL) (P = 0.005).

However, when 37 U/mL was used as a cut-off value, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for CA 19-9 were 100%, 7.69%, 33.33%, and 47.47%, respectively. Furthermore, significant differences in ALP, GGT, and TBil levels were identified between the malignant and benign groups (687.94 ± 267.30 U/mL vs. 296.87 ± 327.90 U/mL, P < 0.001; 675.94 ± 223.93 U/mL vs. 297.15 ± 326.01 U/mL, P < 0.001; and 172.17 ± 48.02 U/mL vs. 94.74 ± 35.21, P < 0.001, respectively) (Table 2).

In addition, for the whole cohort, there was a significant correlation between the serum CA 19-9 level and levels of TBil (r = 0.69, P < 0.001), ALP (r = 0.77, P < 0.001), GGT (r = 0.83, P < 0.001), and CRP (r = 0.37, P = 0.004). However, while there was a significant association of CA 19-9with ALP, GGT, and TBil in the benign group, there was no significant association between CA 19-9 and these markers in the malignant group.

Table-II

Comparison of clinical parameter between variable groups.

Parameters	Values in variety groups		P Value
	Benign (n = 39)	Malignant (n = 18)	
CA19-9 (U/ml)	401.92 ± 483.92	826.83 ± 557.38	0.005
ALP (U/L)	296.87 ± 327.90	687.94 ± 267.30	0.0001
GGT (U/L)	297.15 ± 326.01	675.94 ± 223.93	0.0001
ALT (U/L)	110.67 ± 62.26	89.78 ± 27.71	0.018
AST (U/L)	104.18 ± 53.24	81.61 ± 17.41	0.086
Bilirubin (µmol/L)	94.74 ± 35.21	172.17 ± 48.02	0.0001
CRP (mg/L)	48.38 ± 16.56	36.11 ± 7.71	0.082

Table-III

Values	Total		P Value	Benign		P Value	Malignant		P Value
(Means ± SD)	Before	After		Before	After		Before	After	
CA19-9	536.11 ± 541.22	162.61 ± 246.64	0.0001	401.92 ± 483.92	50.51 ± 32.91	0.0001	826.83 ± 557.38	628.22 ± 387.81	0.0001
ALP	420.37 ± 358.17	92.00 ± 77.10	0.0001	296.87 ± 327.90	67.15 ± 56.38	0.0001	687.94 ± 267.30	145.83 ± 89.39	0.0001
GGT	416.77 ± 344.82	98.18 ± 84.59	0.0001	297.15 ± 326.00	69.74 ± 56.14	0.0001	675.94 ± 223.93	159.78 ± 103.20	0.0001
ALT	109.65 ± 64.99	43.28 ± 15.40	0.0001	110.67 ± 62.26	37.33 ± 9.67	0.0001	89.78 ± 27.71	56.17 ± 17.75	0.0001
AST	99.23 ± 57.07	42.74 ± 14.94	0.0001	104.18 ± 53.24	37.15 ± 10.11	0.0001	81.61 ± 17.41	54.83 ± 16.73	0.0001
T-bil	119.19 ± 53.48	42.53 ± 15.82	0.0001	94.74 ± 35.21	35.64 ± 8.96	0.0001	172.17 ± 48.02	57.44 ± 17.35	0.0001
CRP	41.09 ± 14.69	24.51 ± 4.57	0.0001	43.39 ± 16.57	23.10 ± 3.17	0.0001	36.11 ± 7.71	27.56 ± 5.65	0.0001

Fig..-1: *MRCP Images of Choledocholithiasis*

Image Courtesy: Dr. Akhter Ahmed

Nineteen (19) of these 57 patients had extraordinarily high levels of CA19-9 (> 1000 U/mL) before treatment, 10 of whom were found to have benign disease such as Choledocholithiasis with inflammatory stricture, including 5 patients originally thought to have a malignant disorder and who underwent resection on this basis.

Discussion

Choledocholithiasis, are prevalent in our country of Bangladesh because of the eating habits and dietary components. In certain circumstances, some bile duct stricture disorders may be mistaken as malignant disease because of similar clinical, biochemical, and imaging findings. It has recently been suggested that some markers, particularly serum CA 19-9, enhance the diagnostic potential of advanced imaging modalities such as CT, MRCP, and endoscopic ultrasonography (EUS), thus aiding diagnosis in these complex cases[2,11].

In contrast, Jalanko H showed that CA19-9 levels are moderately elevated in 15-36% of patients with benign pancreatic, liver, and biliary tract diseases.[12] Some other researchers have also demonstrated that CA19-9 levels are elevated in benign biliary disorders such as choledocholithiasis and Mirizzi's syndrome.[13,14,15,16]

They suggested that CA19-9 is not a suitable marker for distinguishing between malignant and benign conditions. Therefore, in the present study, we measured the serum level of CA 19-9 along with that of some other biochemical markers in a cohort of patients with biliary obstructive disorders in order to investigate the diagnostic potential of these markers for identifying malignant disease.

In our study, all 57 patients presented with jaundice and dilatation of the bile duct. Ultimately 39 patients had benign conditions, mostly calculus in the bile duct, which is a common disease in our region.

In clinical practice, some patients with a benign stricture can have an extremely high level of serum CA19-9. Cholangitis may result in high serum levels of CA 19-9.[22] Kim also considered that CA 19-9 was a more useful diagnostic marker for patients without cholangitis or cholestasis.[23] The presence of cholangitis and a long history of benign stricture might contribute to the decrease in specificity of CA 19-9 among patients with obstructive jaundice

CA 19-9 is a serum glycoprotein and can be secreted by epithelial cells in the pancreas, biliary tract, and other digestive ducts; therefore, it is not surprising that CA 19-9 level is elevated in gastrointestinal carcinomas. However, it is less clear why CA 19-9 level is elevated in some benign diseases, especially biliary obstructive disorders. Von Ritter found that mucins secreted from normal human gallbladder epithelial cells (HGBECs) carried the CA 19-9 epitope and that during inflammatory biliary disease,[24] leakage of biliary mucins into serum may lead to the non-specific elevation of CA19-9 in serum. Another possible source might be irritated bile duct cells exposed to increased biliary pressure and the increased proliferation of epithelial cells due to inflammation.[23,25] Therefore, as every subject in our study presented with typical obstructive jaundice, malignant or benign, almost all of these patients had elevated serum levels of CA19-9. This

might explain the different results regarding the diagnostic potential of CA19-9, whereby it could distinguish between benign and malignant biliary disease in studies with cohorts in which almost 50% of the patients did not have jaundice.

In conclusion, although only a few patients were included in this study, the results suggest that CA 19-9 levels alone cannot differentiate between malignant and benign obstructive jaundice upon initial presentation.

Conflict of Interest : None

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