EUROPEAN ACADEMIC RESEARCH
Vol. IV, Issue 12/ March 2017

Impact Factor: 3.4546 (UIF)
DRJI Value: 5.9 (B+)

ISSN 2286-4822
www.euacademic.org

Clinical significance of serum CA 19-9, CA 19-9/CRP ratio and CA19-9/total bilirubin ratio in differentiation between malignant and benign obstructive jaundice

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Abstract:

Background and AIM: *Serum carbohydrate antigen (CA19-9) is increased not only in patients with pancreatic or biliary cancers, but also in benign biliary diseases. The aim of the present study was to investigate the diagnostic value of CA19-9, CA19-9/CRP ratio and CA19-9/total bilirubin ratio in differentiation between benign and malignant obstructive jaundice in Egyptian patients.*

Methods*: The current prospective study included 50 patients with obstructive jaundice who were referred for Endoscopic Retrograde Cholangiopancreatography (ERCP). They were classified into two groups; Group (1): 25 patients with malignant obstructive jaundice, and Group (2) 25 patients with benign obstructive jaundice. All included patients were subjected to: detailed history-taking, full*

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clinical examination and laboratory investigations which included CBC, liver and renal profiles, serum C-reactive protein (CRP) and CA 19-9.

Results: *Before ERCP, CA19-9 levels were significantly higher in malignant than in benign group, but after ERCP, CA19-9 levels became much significantly higher in malignant than in benign group and there was statistically significant decrease in CA19-9 level in the benign group. Serum CA19-9 at cut-off value of 37 U/ml showed sensitivity 80% and specificity 44% in differentiating between malignant and benign obstructive jaundice. When CA19-9 cut-off value was pushed up from 37 to 100 U/ml, the sensitivity decreased to 64% while the specificity increased to 64%. By using CA19-9/total bilirubin ratio (before ERCP) at cut-off value ≤ 15.84, the sensitivity decreased to 68% but specificity increased to 68%. By using the ratio of CA19-9/CRP (before ERCP) at cut-off value ≤ 34.3, the sensitivity and specificity were increased to 84% and 88%, respectively.*

Conclusion: *CA19-9/CRP ratio (before ERCP) at cut-off value ≤ 34.3 has a better sensitivity and specificity to differentiate between the malignant and benign obstructive jaundice than CA19-9 alone and CA19-9/total bilirubin ratio.*

Key words: Serum carbohydrate antigen (CA 19-9), C-reactive protein, bilirubin, malignant, benign, obstructive jaundice.

INTRODUCTION

Obstructive jaundice is the most common condition that is associated with significant elevation in serum carbohydrate antigen (CA 19-9). Elevation of serum CA 19-9 in patients with obstructive jaundice may depend on multiple factors: CA 19-9 production by irritated bile duct cells exposed to the increased biliary pressure [1]; inflammatory proliferation of epithelial cells which produce CA 19-9 [2]; accumulation of CA 19-9 in the lumen due to biliary obstruction and increased permeability between bile and blood with subsequent reflux into the

circulation [3]; decreased clearance of biliary mucins due to cholestasis [4, 5]; and inability to degrade the antigen in the liver due to hepatic dysfunction [6]. Because of these dysfunctions, a strong correlation between serum CA 19-9 concentration and the standard parameters of cholestasis namely alkaline phosphatase, gamma-glutamyl transferase (GGT) and bilirubin has been demonstrated. Therefore, further measurement of CA 19-9 after the jaundice subsides can be helpful in discriminating those patients with persistent elevation of CA 19-9 due to malignancies [7].

CA19-9 is a tumor marker that increases in pancreatic and biliary malignancies and it has been used as a test for their diagnosis. In pancreatic cancer, CA19-9 has been reported to have 70%-80% sensitivity and 80%-90% specificity in tumor diagnosis, whereas in cholangiocarcinoma without history of sclerosing cholangitis, the sensitivity and specificity are 77.9% and 76.3%, respectively [8,9].

CA19-9 is unfortunately increased not only in patients with pancreatic or biliary cancers but also in benign biliary diseases which often present with jaundice and is therefore often misleading, reducing significantly the diagnostic accuracy of this marker [2,5,10]. The relationship between CA19-9 and jaundice has been analyzed and studied to find possible adjustments to increase the sensitivity, specificity and predictive value of the test in differential diagnosis of hepatobiliary diseases associated with jaundice. Therefore, some authors have suggested adjusting CA19-9 value by dividing it by the serum bilirubin value [11,12].

Inflammation contributes to elevating the CA19-9 value and it can be assessed by monitoring the acute-phase proteins: one of these is the C-reactive protein (CRP) which rises in response to infection, injury and neoplasm. CRP can influence multiple stages of inflammation [13,14]. It can activate the complement system and can bind to phagocytic cells. Also it can

initiate elimination of pathogens with both humoral and cellular effector systems of inflammation [14]. CRP plays a role in host defense and in clearance of necrotic and apoptotic cells [15].

Markedly elevated levels of CRP are strongly associated with infection, most often bacterial, were found in approximately 80% of patients with values in excess of 10 mg/dL (100 mg/L) and in 88-94% of patients with values over 50 mg/dL [16]. Levels of CRP may also be elevated in patients with viral infections, although often not to the degree seen in patients with bacterial infection [17].

The aim of the present study was to investigate the diagnostic value of CA19-9, CA19-9/CRP ratio and CA19-9/total bilirubin ratio in differentiation between benign and malignant obstructive jaundice in Egyptian patients.

PATIENTS AND METHODS

The current prospective study was conducted at Ain Shams University Hospital, Internal Medicine, Hepatology and Gastroenterology Department and Tropical Medicine Department during the period from January 2015 to October 2016. The study included 50 Egyptian patients with obstructive jaundice who were referred to Endoscopy Unit for Endoscopic Retrograde Cholangiopancreatography (ERCP). They were classified into two groups; 25 patients with malignant obstructive jaundice in group (1) and 25 patients with benign obstructive jaundice in group (2)

Patients with other causes of jaundice, those with normal-sized CBD or intrahepatic biliary radicles, those who were not fit for ERCP and those with disseminated malignancy were excluded.

Informed written consent was obtained from each patient prior to inclusion. The study protocol was approved by

the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

All included patients were subjected to:

1- **Detailed history-taking and full clinical examination.**
2- **Laboratory investigations:**

Venous blood (10 ml) was withdrawn aseptically into a sterile disposable syringe from each patient, where 2 ml was placed in EDTA vacutainer for performing complete blood count (CBC), 2 ml was collected on citrate for PT and INR determination, and 6 ml was collected in 2 plain vacutainers to be clotted and centrifuged for biochemical markers including AST, ALT, bilirubin, albumin, creatinine, BUN, CRP and CA19-9.

- CBC was done using Coulter counter (T660) (Beckman. Coulter, California, USA).
- Liver profile (Serum AST, ALT, total and direct bilirubin, serum albumin, serum alkaline phosphatase, gamma-glutamyl transferase), and renal profile (serum creatinine and BUN) were measured on Synchron CX9 auto-analyzer (Beckman Instruments Inc.; Scientific Instruments Division, Fullerton, CA 92634-3100, USA) applying enzymatic colorimetric method.
- Prothrombin time (PT) and INR were measured by Diagnostica Stago (Asnieres, France).
- Serum C-reactive protein (CRP) was assessed at the time of admission by particle-enhanced immunoturbidimetric method using latex particles coated with monoclonal anti-CRP antibodies and turbidimetry reading of the precipitate with Cobas 6000 analyzer (Roche Diagnostics, Ltd. CH-6343 Rotkreuz Switzerland). The limit of quantification for CRP assay was 0.5 mg/L.

- Serum CA 19-9 was done before then after release of the obstruction of the CBD by 7-10 days; it was assessed by chemiluminescent immunometric technique on Cobas e411 immunoanalyzer (Roche Diagnostics, USA). With measuring range (0.60 - 1000 U/mL) and standard cut-off value 37 U/mL as determined by the manufacturer.
- CA 19-9/CRP ratio and CA19-9/total bilirubin ratio before ERCP were calculated

3- Imaging

- Abdominal ultrasonography with special emphasis on: The liver echogenicity, presence of any focal lesions (the number, site, size, echogenicity), portal vein diameter and patency, ascites, diameter of CBD and presence of intrahepatic and extrahepatic bilary radicles dilatation, presence of calcular cholecystitis &size of gall bladder, and presence of any pancreatic masses.
- Abdominal computed tomography (CT): was done for patients suspected to have malignant obstructive jaundice.

4- Endoscopic Retrograde Cholangio-pancreatography (ERCP): It was done for all included patients and biopsies were taken from lesions that were suspected to be malignant.

5- Histopathological or cytological examinations were performed for biopsies

Statistical analysis:

The collected data were coded, tabulated, and statistically analysed using IBM SPSS statistics, V. 22.0 (Statistical Package for Social Sciences, software version 22.0), IBM Corp., Chicago, USA, 2013. Categorical variables were expressed as percentages which were analysed by Chi- square test,

independent t-test and Fisher's Exact test. Continuous variables were presented as mean ± standard deviation (SD) and range (minimum and maximum) which were analysed by Mann-Whitney U test. Comparison between variables in different times was analysed by ANOVA test. A P value < 0.05 was considered statistically significant.

RESULTS

The present study included 50 patients with obstructive jaundice who underwent ERCP at Ain Shams University Hospital. They were assigned into two groups. Twenty five patients in group (1) with malignant obstructive jaundice, 13 males and 12 females, with a mean age of 56.72 ± 10.6 years. The etiologies of malignant obstruction were variable: (cancer pancreas 48%, cholangiocarcinoma 12%, periampullary carcinoma 16%, gall bladder carcinoma 4%, and malignant CBD stricture 20%). In group (2), 25 patients with benign obstructive jaundice; 14 males and 11 females, with a mean age of 49.28 ± 14.78 years. The etiologies of benign obstruction were variable: (CBD stones 64%, biliary pancreatitis 12%, chronic papillitis 4%, and CBD stricture 20%). There was statistically significant difference between both groups regarding age (P-value=0.046).

Table (1): Comparison between the two groups regarding laboratory findings:

	Group				T-test	P- value
	Malignant		Benign			
	Mean	±SD	Mean	±SD		
Hb (gm/dl)	11.03	1.85	12.10	1.84	2.063	0.045*
TLC	7.28	3.11	7.10	3.43	0.199	0.843
Plts	263.16	99.43	266.08	97.40	0.105	0.917
AST (U/l)	178.56	67.85	212.28	67.37	1.763	0.084
ALT (U/l)	207.12	79.00	277.24	68.41	3.355	0.002*
T.Bil (mg/dl)	11.16	3.10	5.53	1.73	7.939	<0.001*
D.Bil (mg/dl)	8.09	2.56	3.70	1.19	7.763	<0.001*
Alb (g/dl)	3.54	0.53	3.85	0.38	2.344	0.023*
Alk.P (U/l)	471.28	210.35	305.96	69.79	3.730	<0.001*
GGT (U/l)	1328.24	809.95	849.64	139.78	1.318	0.194
Creat (mg/dl)	0.95	0.27	1.03	0.26	1.094	0.280
CRP (mg/l)	6.22	8.76	11.86	11.06	2.024	0.048*
CA19-9 (U/ml)	1155.06	879.79	402.41	261.99	2.525	0.015*

Hb: haemoglobin, TLC: total leucocytic count, Plts: platelets, AST: aspartate aminotransferase, ALT: alanine aminotransferase, T.Bil: Total Bilirubin, D.Bil: Direct Bilirubin, Alb: albumin, Alk.P: alkaline phosphatase, GGT: gamma-glutamyl transferase, Creat: Creatinine, CRP: C-reactive protein.
*Significant.

There was a significant difference between the two groups as regard Hb, ALT, albumin and CRP as they were higher in the benign group. However, serum total, direct bilirubin and alkaline phosphatase levels were much higher in malignant group with a highly significant difference **(Table 1)**.

Within group (2), the highest median level for total bilirubin was detected in patients with cholangiocarcinoma which was statistically significant. In addition, the highest median levels for CRP and CA19-9 were detected in patients with cholangiocarcinoma but with no statistical significance **(Table 2)**.

Table (2): Comparison between serum total bilirubin, CRP and CA19-9 median levels in different subgroups of the malignant group at time of admission:

Malignant groups		Range	Median	Mean Rank	X^2	P-value
Total Bilirubin (mg/dl)	CBD malignant stricture	8.2 - 17.2	9.94	12.40	8.615	0.035*
	Cancer pancreas	9.36 - 12.6	11.29	12.38		
	Cholangio carcinoma	12.6 - 17.4	16.30	21.83		
	Ampullary cancer	5.88 - 12.5	6.49	6.00		
CRP (mg/l)	CBD malignant stricture	0.6 - 1.5	1.26	7.50	3.996	0.262
	Cancer pancreas	0.8 - 48.5	1.96	12.71		
	Cholangio carcinoma	1.2 - 5.99	5.96	16.17		
	Ampullary cancer	1.2 - 4.95	4.50	15.38		
CA19-9 (U/ml) Before ERCP	CBD malignant stricture	30 - 510.54	313.00	11.40	1.968	0.579
	Cancer pancreas	29 - 3729	461.00	13.50		
	Cholangio carcinoma	2.08 - 2800	2600.00	15.33		
	Ampullary cancer	20 - 321.55	196.00	8.75		

While in group (2), the highest median level for total bilirubin was detected in patients with CBD stone, and the highest median levels for both CRP and CA19-9 were detected in patients with biliary pancreatitis but there was no statistical significance **(Table 3)**.

Table (3): Comparison between serum total bilirubin, CRP and CA19-9 median levels in different subgroups of the benign group at time of admission:

Benign groups		Range	Median	Mean Rank	X^2	P-value
Total Bilirubin (mg/dl)	CBD stone	3.2 - 7.1	5.63	13.06	1.872	0.392
	CBD benign stricture	3.17 - 10.6	5.26	13.80		
	Biliary pancreatitis	3.18 - 6.22	3.85	7.33		
CRP (mg/l)	CBD stone	0.83 - 50	3.47	12.25	4.327	0.115
	CBD benign stricture	1.12 - 5	2.31	9.00		
	Biliary pancreatitis	9.63 - 50.84	10.33	19.67		
CA19-9 (U/ml) Before ERCP	CBD stone	2 - 1233.1	42.00	12.31	0.107	0.948
	CBD benign stricture	22.6 - 664.6	55.00	13.40		
	Biliary pancreatitis	22.24 - 77.8	61.00	12.00		

Table (4): Comparison of serum total bilirubin and CA19-9 levels before and after ERCP between the two groups and in each group:

Total Bilirubin (mg/dl)		Before ERCP	After ERCP	Paired t-test	
		Mean ± SD	Mean ± SD	t	P-value
Malignant Group		11.16 ± 3.10	3.07 ± 1.57	15.164	<0.001*
Benign Group		5.53 ± 1.73	0.84 ± 0.10	12.434	<0.001*
T-test	t	7.939	7.067		
	P-value	<0.001**	<0.001**		
CA19-9 (U/ml)					
Malignant Group		1155.06 ± 879.79	936.36 ± 866.82	0.225	0.824
Benign Group		402.41 ± 261.99	11.97 ± 9.20	3.149	0.004*
T-test	t	2.525	5.334		
	P-value	0.015*	<0.001**		

***** Significant.

** Highly significant.

Before and after ERCP, total bilirubin levels were higher in malignant group with a highly significant difference. When we compared between total bilirubin levels before and after ERCP in each group, there was a highly significant decrease in bilirubin levels in both groups **(Table 4)**.

Before ERCP, CA19-9 levels were higher in malignant group than in benign group with a statistically significant difference, but after ERCP, CA19-9 levels became much higher in malignant group than in benign group with a highly significant difference and there was statistically significant decrease in CA19-9 level in the benign group **(Table 4)**.

Table (5): Correlation between total bilirubin, CRP, CA19-9 before ERCP, CA19-9 /total bilirubin (before ERCP), CA19-9 before ERCP/CRP and all laboratory investigations done for patients in the current study:

	Total Bilirubin (mg/dl)		CRP (mg/l)		CA19-9 (U/ml) Before ERCP		CA19-9 (U/ml) /total bilirubin (before ERCP)		CA19-9 (U/ml)/CRP (before ERCP)	
	r	P-value	r	P-value	r	P-value	r	P-value	r	P-value
CRP (mg/l)	0.016	0.912					0.557	<0.001*	-0.518	<0.001*
CA19-9 (U/ml) Before ERCP	0.535	<0.001*	0.459	<0.001*			0.943	<0.001*	-0.303	0.032*
AST (U/l)	-0.167	0.246	-0.007	0.962	-0.143	0.322	0.001	0.992	-0.090	0.535
ALT (U/l)	-0.349	0.013*	-0.021	0.884	-0.284	0.046*	-0.110	0.448	-0.106	0.463
Albumin (g/dl)	-0.389	0.005*	-0.052	0.717	-0.178	0.217	-0.077	0.595	-0.178	0.216
Alk.p (U/l)	0.415	0.003*	0.093	0.520	0.117	0.420	0.099	0.492	0.378	0.007*
G.G.T (U/l)	0.336	0.017*	-0.078	0.589	0.293	0.039*	0.166	0.249	0.017	0.905
INR	0.290	0.041*	-0.090	0.533	0.000	0.999	-0.043	0.765	0.276	0.052
PT (sec.)	0.205	0.153	-0.018	0.902	0.043	0.768	0.008	0.955	0.300	0.034*
Hb (g/dl)	-0.151	0.296	-0.062	0.667	-0.077	0.597	-0.103	0.477	-0.038	0.793
TLC	0.175	0.225	0.212	0.139	0.333	0.018*	0.359	0.010*	-0.163	0.259
Plts.	-0.067	0.642	0.203	0.158	0.084	0.564	0.117	0.420	-0.245	0.087
Creat. (mg/dl)	-0.210	0.143	0.264	0.064	-0.130	0.370	-0.093	0.522	-0.192	0.183

CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Alk.P: alkaline phosphatase, GGT: gamma-glutamyl transferase, INR: international normalized ratio, PT: prothrombin time, Hb: haemoglobin, TLC: total leucocytic count, Plts: platelets, Creat: Creatinine.
*Significant.

Total bilirubin had a significant positive correlation with the alkaline phosphatase, GGT and INR and a highly significant positive correlation with CA19-9 before ERCP. Regarding CA19-9 before ERCP, there was a highly significant positive correlation between it and CRP and a significant positive correlation with GGT and TLC. Regarding CA19-9 /total bilirubin ratio (before ERCP), it showed a highly significant positive correlation with CA19-9 before ERCP and CRP and a significant positive correlation with TLC. Finally, CA19-9/CRP

ratio (before ERCP) had a significant positive correlation with the alkaline phosphatase and PT **(Table 5)**.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CA19-9 at cut-off values 37 U/ml were 80%, 44%, 59% & 69% respectively. When CA19-9 cut-off value was pushed up from 37 (U/ml) to 100 (U/ml) the sensitivity decreased (64%) while the specificity increased (64%) **(Table 6)**.

Table (6): Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for different CA19-9 cut-off values:

	Sensitivity	Specificity	PPV	NPV
CA19-9 cut-off 37 (U/ml)	80%	44%	59%	69%
CA19-9 cut-off 100 (U/ml)	64%	64%	64%	64%

With CA19-9/total bilirubin before ERCP at cut-off value ≤ 15.84, the sensitivity decreased to 68% but specificity increased to 68% with PPV 68% **(Table 7, Figure 1)**.

Table (7): Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for CA19-9/total bilirubin ratio before ERCP:

	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
CA19-9/ T-bilirubin ratio	≤ 15.84	68%	68%	68%	68%	61.0

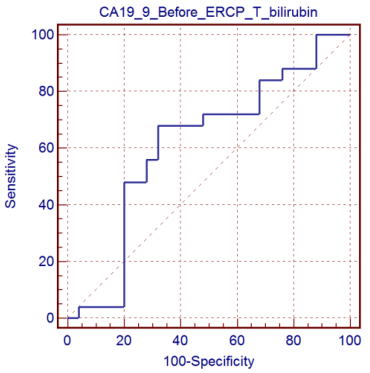

Fig. (1): ROC curve detecting decrease in the sensitivity and increase in the specificity at Cut-off value ≤ 15.84 when dividing CA19-9 value by serum total bilirubin level before ERCP.

At Cut-off value ≤ 34.3 for CA19-9/CRP ratio, the sensitivity and specificity were increased to 84% and 88%, respectively with PPV 87.5% **(Table 8, Figure 2)**.

Table (8): Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for CA19-9 before ERCP after dividing it by CRP:

	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
CA19-9 before ERCP/CRP	≤ 34.3	84%	88%	87.5 %	84.6 %	89.0

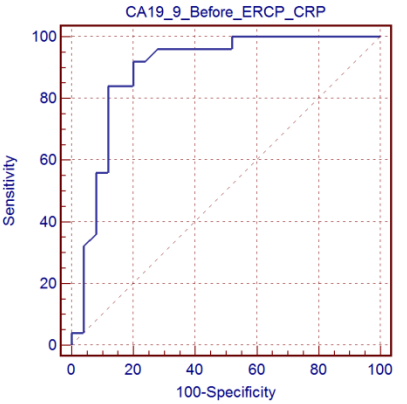

Fig. (2): ROC curve detecting increasing in the sensitivity and specificity at cut-off value ≤ 34.3 when CA19-9 was divided by CRP.

DISCUSSION

The diagnostic role of CA19-9 as a test for the detection of pancreato-biliary malignancy remains poorly defined, because the utility of CA19-9 has several confounding limitations. False positive elevations in CA19-9 exist in benign conditions such as primary sclerosing cholangitis, primary biliary cirrhosis, obstructive jaundice and pancreatitis [10]. Even CA19-9 is elevated in diseases that were not related to the hepatobiliary tract such as interstitial pulmonary disease [18], collagen vascular disorders and heavy tea consumption [19]. All that suggests that CA19-9 may be expressed as a marker of a

systemic inflammatory response. Furthermore, CA19-9 has also been shown to be up-regulated in other malignant tumours including gastric, colorectal and ovarian carcinoma [20]. However, the most common cause of false positive CA19-9 is obstructive jaundice [21].

Physiologically, biliary epithelial cells secrete mucins carrying the epitope of CA19-9, hence the high level of CA19-9 in serum during the obstructive jaundice, reflecting both inflammatory hypersecretion and leakage of biliary mucins into serum. This process can be reversed by resolution of the jaundice, which is often associated with a fall in CA19-9 greater in benign disease than in malignant [10]. Because in malignant disease the synthesis of CA19-9 by proliferating cells contributes to the total level in a manner independent from any associated condition [5].

In order to demonstrate the clinical interpretation and diagnostic value of an elevated serum CA19-9 level with coexistent obstructive jaundice, the present study analyses a possible relationship between CA19-9, bilirubin and inflammation, expressed as CRP value, aiming to find a ratio or a better corrective factor to increase predictively of CA19-9 and reduce the number of misleading false positive results.

The present study included 50 Egyptian patients with obstructive jaundice who underwent ERCP at Ain Shams University Hospital. They were assigned into two groups. Group (1) included 25 patients with malignant obstructive jaundice (cancer pancreas 48%, cholangiocarcinoma 12%, periampullary carcinoma 16%, gall bladder carcinoma 4%, and malignant CBD stricture 20%), and Group (2) included 25 patients with benign obstructive jaundice (CBD stones 64%, biliary pancreatitis 12%, chronic papillitis 4%, and CBD stricture 20%).

In the current study, regarding the total and direct serum bilirubin levels at time of admission, there was a highly

significant difference between the two groups with much higher levels in malignant group. Similar findings were reached by Kasapidis *et al.* [22] and La Greca *et al.* [23].

In the current study, the serum bilirubin levels before and after release of obstruction were significantly higher in malignant group and when we compared between serum bilirubin level before and after release of obstruction in each group, there was a highly significant decrease in bilirubin level.

When we compared the baseline CA19-9 level between both groups, there was a statistically significant difference; it was higher in malignant group than benign. This agrees with Budzynska *et al.* [24] and Lin *et al.* [25].

In the current study, before release of obstruction, CA19-9 levels were higher in malignant group than benign with a significant difference; but after release of obstruction, the CA19-9 levels became much higher in malignant group than benign with a highly significant difference and there was statistically significant decrease in CA19-9 level in benign group. This is consistent with Kondo *et al.* [26]. The serum level of CA19-9 in many patients with pancreaticobiliary cancer did not decrease back to the normal range, which is partly attributable to the uncontrolled growth of aberrant epithelial cells and their continuous secretion of this antigen. In contrast, most cases of benign disease showed a full clinical and biochemical recovery. Thus, elevated CA19-9 level should be interpreted cautiously in patients with obstructive jaundice, unless these high levels persist after the obstruction has been removed. A repeat assay for CA19-9, performed 2 or 3 weeks after resolution of jaundice, may help in differentiating between malignant and benign strictures. Also observations in the current study agree with the study performed by Lin *et al.* [25], as they found that the serum level of CA19-9 in the malignant group reduced by a markedly lesser extent than that in the benign group ($P < 0.001$). Almost every patient with malignant

disease still had a high level of CA19-9 after treatment, except for those who underwent surgery.

Additionally, the current study agrees with Marrelli *et al.* [10] who studied 128 patients with obstructive jaundice including 87 patients with pancreatico-biliary malignancies and 42 patients with benign diseases. CA 19-9 serum levels were elevated in 61% of benign causes and 86% of malignant causes, which resulted in a reduction in accuracy to 61%. Following biliary drainage, CA 19-9 serum levels decreased in nearly all benign cases (98%) but in only 50% of patients with malignant biliary obstruction.

In the current study, when we considered the cut-off value of CA19-9 at 37 U/ml, the sensitivity, specificity and positive predictive value (PPV) were 80%, 44%, and 59%, respectively, but when we increased the cut-off value of CA19-9 to 100 U/mL, the sensitivity decreased to 64% but specificity increased to 64% with a PPV of 64%. This is consistent with La Greca *et al.* [23], when they were considering the CA19-9 cut-off level of 32 U/mL, 42 of 51 patients (82.3%) in the malignant group and 28 of 51 (54.9%) in the benign group were positive for CA19-9 (P = 0.002). The area under the curve or probability that a patient diagnosed with malignant jaundice has a major value of CA19-9 compared to a patient diagnosed with benign jaundice was 0.71, sensitivity specificity and PPV were 82.3%, 45% and 59.1% respectively. But increasing the cut-off level of CA19-9 to 100 U/mL, the difference between the two groups increased: 35.3% in benign jaundice and 68.6% in malignant jaundice (P = 0.0007), sensitivity specificity and PPV were 68.6%, 64.7% and 60%, respectively. They also found that changing the cut-off level alters the sensitivity and specificity, but by pushing up the cut off level in spite of an increase of specificity, they have obtained a reduction in the sensitivity of the test.

Inflammation may have a role and an effect on CA19-9 clinical value. C-reactive protein (CRP), synthesized in hepatocytes, is one of the acute-phase proteins which are components of the innate immune responses that increase after infections, trauma, burns, tissue infarction, inflammatory process and tumors. In general, increased CRP levels in malignant disease could also be caused by an inflammatory response to tumor invasion [27].

Padillo *et al.* [28] analysed CRP in 24 patients with jaundice and found that CRP levels were significantly higher in patients with cancer, differently from the current study_which showed the CRP serum levels were higher in benign than in malignant obstructive jaundice and higher in patients with CBD stones than in those with pancreatic cancer. However, our study is in agreement with La Greca *et al.* [23] who found that CRP serum levels are higher in benign than in malignant obstructive jaundice and higher in patients with CBD stones than those with pancreatic cancer.

In the current study, although the overall increase of the CA19-9 in benign jaundice was inferior compared to that observed in malignancies, there was an overlap of values between cancer and non-cancer causes. This results in a low accuracy of CA19-9 to diagnose pancreatic-biliary malignancies in patients with jaundice. This is different from what has been shown in other studies that CA19-9 is useful in the differentiation of pancreatobiliary disease and when using an optimized cut-off and combining with routine radiology [20]. Even when considering a cut-off level of 100 U/mL, the specificity is still 64% as a result of this diagnostic overlap. The American Society of Clinical Oncology does not currently advocate using of CA19-9 for screening, evaluation of respectability or disease follow-up [29].

For this reason, some authors suggested pushing up the cut-off level to 300 U/mL in presence of cholangitis and

cholestasis to increase CA19-9 specificity, but this was associated with a significant decrease of sensitivity [2].

Ong *et al.* [21] have shown that the association of elevated levels of CA19-9 with the diagnosis of cancer is significantly obscured in the face of obstructive jaundice, and because the bilirubin level correlates with CA19-9, they suggest that this value should be adjusted for hyperbilirubinemia and this agrees with the current study.

Hence, based on the knowledge that in benign jaundice high levels of CA19-9 are an expression of obstruction and inflammation and CRP levels are higher in this group of patients, the most appropriate adjusting factor could be the CRP and not the bilirubin level, so by adjusting this value with the CRP, it is possible to increase the reliability of the test. In the current study, by using the bilirubin as an adjusting factor, the specificity reaches 68%, and the sensitivity falls down to 68% as a tool to differentiate between benign and malignant obstructive jaundice. By using the CRP value as an adjusting factor, which better reflects the inflammatory status, we obtained 84% sensitivity, 88% specificity and 87.5% PPV as a tool to differentiate between benign and malignant obstructive jaundice. So, the level of CA19-9/CRP ratio has a better sensitivity and specificity than the level of CA19-9/bilirubin in predicting malignant etiology.

CONCLUSION

CA19-9/CRP ratio at cut off value ≤ 34.3 has a better sensitivity and specificity to differentiate between the malignant and benign obstructive jaundice than CA19-9 alone and CA19-9/total bilirubin ratio.

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