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Assessment of the utility of the serum CA 19-9 in between benign and malignant pancreatic disease a study of 50 cases.

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Abstract:
Background: *Pancreatic cancer is considered to be one of the leading causes of cancer deaths in advanced countries and it is on the rise in developing countries like India and Bangladesh. A large number of patients with pancreatic cancer receive only palliative therapy due to advanced stage at presentation. Pancreatic cancer is the fifth leading cause of cancer related death in the US with an annual incidence rate of 9 cases per 100,000 people. Approximately 28,000 to 30,000 cases of pancreatic cancer (ductal adenocarcinoma being the most common form) are diagnosed per year. Men are at a slightly greater risk compared to women.* ***Objectives:*** *To assess the utility of the serum CA 19-9 in between benign and malignant pancreatic disease.* ***Material & Methods:*** *A Cross Sectional Observational Study was conducted over a period of one year July 2016 to June 2017 in Department of Surgery, Dhaka Medical College Hospital, Dhaka. A Total of 50 patients were included in this study. All patients with history, sign-symptoms and clinical examination suggesting pancreatic disease attended in Dhaka Medical College Hospital for treatment. Data were collected from these patients by preformed questionnaire and finally data were analyzed Analysis was done by SPSS 22.0 for windows software.* ***Results:*** *The CA 19-9 marker levels are useful in the preoperative differential diagnosis of malignant and benign pancreatic disease. The major limitations of the methods are false-negative and false-positive results affecting the diagnostic reliability of the tests. Further clinical investigation is necessary to define more reliable markers and to analyze several markers concomitantly with modern imaging techniques.* ***Conclusion:*** *Having increased levels of the CA 19-9 markers in patients with pancreatic pathology usually indicates a malignant nature of the lesion.*

Key Wards: *Pancreatic Cancer; CA 19-9, Benign and Malignante,*

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I. Introduction

A large number of patients with pancreatic cancer receive only palliative therapy because of advanced stage at presentation. Pancreatic cancer is the fifth leading cause of cancer related death in the US with an annual incidence rate of 9 cases per 100,000 people. Approximately 28,000 to 30,000 cases of pancreatic cancer (ductal adenocarcinoma being the most common form) are diagnosed per year. Men are at a slightly greater risk compared to women [12]. It is 11th most common cancer in the UK (2014), accounting for 3% of all new cases. In males, it is the 12th most common cancer, and is the ninth in females. The incidence of pancreatic cancer in India is low (0.5-2.4 per 100,000 men and 0.2-1.8 per 100,000 women). The incidence of pancreatic cancer is higher within the urban male populations of western and northern parts of India but time trends show that this figure is increasing for both carcinoma of the pancreas and also periampullary tumors [4]. The annual pancreatic cancer load of India in 2001 was approximately 14,230 patients: the estimated current figure is approximately 17,000 and is probably going to extend within the near future. The death rate of pancreatic cancer in India is 2.6%. The prevalence of it is 0.68% in Bangladesh [32]. The annual mortality rate per 100,000 people regarding pancreatic cancer in Bangladesh has increased by 12.7% since 1990, an average of 0.6% per year. The chances of survival for untreated patients are very poor. Considering the average of all stages of the disease, 1-year survival rate is 19% and the 5-year survival rate is 4%. At the time of diagnosis approximately 80% of all pancreatic cancers are metastatic, leaving complete resection as the choice of treatment for only 20% of patients. The 5-year survival of operated patients approaches 40% when performed at specialized medical hospitals [11].

As the pancreas is the retroperitoneal organ, the diagnosis of pancreatic carcinoma has got some difficulties and always the patient presented as a late case. However, variety of continually evolving imaging modalities are available to assist diagnose pancreatic carcinoma in patients in whom the disease is usually recommended clinically. These include the following: Computed tomography (CT), Transcutaneous ultrasonography (TUS), Endoscopic ultrasonography (EUS), Magnetic resonance imaging (MRI), Endoscopic retrograde cholangiopancreatography (ERCP), Positron emission tomography (PET) which has a good role for diagnosis and staging of pancreatic carcinoma. Despite the use of advanced imaging methods and image-guided biopsy procedures in differentiating the pancreatic carcinoma from benign pancreatic diseases, diagnostic limitations still exist. Besides, these procedures have drawbacks since they can be performed only in experienced centers, are invasive and expensive. The people of our country are poor and there are still lack of awareness. In addition, there is no medical insurance facility available in Bangladesh. Different serum tumor markers are being investigated as simple and inexpensive methods in the diagnosis of pancreatic carcinoma. The CA 19-9 is reported to have sensitivity ranging between 68 and 92% [25]; [20]; [26], [24]. It is also stated that the value of these two tumor markers decrease in differentiating the benign and malignant pancreatic diseases [15]; [22] & [16]. There are very few studies investigating the importance of serum CA 125 level in the diagnosis of pancreatic carcinoma [6]; [28]; [8]. In our study, the value of the serum tumor markers CA 19-9 alone or in combination, in benign and malignant pancreatic diseases was assessed. A total of 50 patients of pancreatic disease were admitted between July 2016 to June 2017, was enrolled in the study. The association of CA 19-9 was assessed by determining P values for trends. The multivariate linear regression analysis was used to adjust for clinico-pathological confounding factors to analyze the main outcome measures.

II. Materials and Methods

A Cross Sectional Observational Study was conducted over a period of one year July 2016 to June 2017 in Department of Surgery, Dhaka Medical College Hospital, Dhaka. A Total of 50 patients were included in this study. All patients with history, sign-symptoms and clinical examination suggesting pancreatic disease attended in Dhaka Medical College Hospital for treatment. Data were collected from these patients by preformed questionnaire and finally data were analyzed Analysis was done by SPSS 22.0 for windows software.

III. Results

The study was carried out during the period of July 2016 to June 2017. Total 50 patients with history, sign-symptoms and clinical examination suggesting pancreatic disease (both benign and malignant) attended in Dhaka Medical College Hospital for treatment were included for the study.

Table no 1: Age distribution of the patients (n=50)

Age (years)	Number of patients	Percentage (%)
30-45	15	30.0
46-60	17	34.0
≥ 61	18	36.0
Total	50	100.0
Mean±SD	53.4±13.1	
Range	(30 – 77) years	

Table no 1 shows the age distribution of the study patients, age range between 30-77 years. Mean±SD age of the patients was 53.4±13.1 years. 36.0% patients were aged above 61 years and 34.0% patients age was within 46-60 years.

Table no 2: Distribution of the patients by sex (n=50)

Sex	Number of patients	Percentage (%)
Male	30	60.0
Female	20	40.0
Total	50	100.0

Table no 2 shows the distribution of by sex. Maximum patients were male 60.0% and rest 40.0% patient were female. Male: Female ratio was 1.5:1.

Table no 3: Distribution of the study patients by type of pancreatic disease (n=50)

Type of disease	Benign Pancreatic Disease (n=22) No. (%)	Malignant Pancreatic Disease (n=28) No. (%)	P value
Benign	22(100.0%)	0(0.0%)	0.001[s]

Acute pancreatic disease	6(27.3%)	0(0.0%)	
Chronic pancreatitis	10(45.5%)	0(0.0%)	
Pancreatic pseudocyt	6(27.3%)	0(0.0%)	
Malignant	0(0.0%)	28(100.0%)	

s= significant, P value reached from Fisher's exact test

Table no 3 showed 27.3% patients had acute pancreatic disease, 45.5% patients had chronic pancreatitis, 27.3% patients had pancreatic pseudocyst in benign group.

Table no 4: Comparison between histopathological finding and CA 19-9 evaluation for pancreatic disease (n=50)

CA 19-9	n	Benign Pancreatic Disease No. (%) (n=22)	Malignant Pancreatic Disease No. (%) (n=28)	P value
Positive	31	3(13.6%)	28(100.0%)	<0.001[S]
Negative	19	19(86.4%)	0(0.0%)	

Data were expressed as frequency and percentage.
Fisher's exact test was performed to see the association between benign and malignant pancreatic disease. In CA19-9, in malignant group 100% patients found that the test is significantly high but only 3 patients (13.6%) the test was positive.

Table no 5: Assessment of tumor marker in the diagnosis of pancreatic disease (n=50)

Diagnostic validity test with 95% CI				
Tumor marker	Sensitivity (%)	Specificity (%)	PPV	NPV
CA 19-9	90.32%	100.0%	100.0%	86.36%
	(74.2% to 97.8%)	(82.2% to 100.0%)		

As seen in Table no 5, the markers were assessed individually. CA 19-9 had sensitivity of 90.32% and specificity was 100.0%.

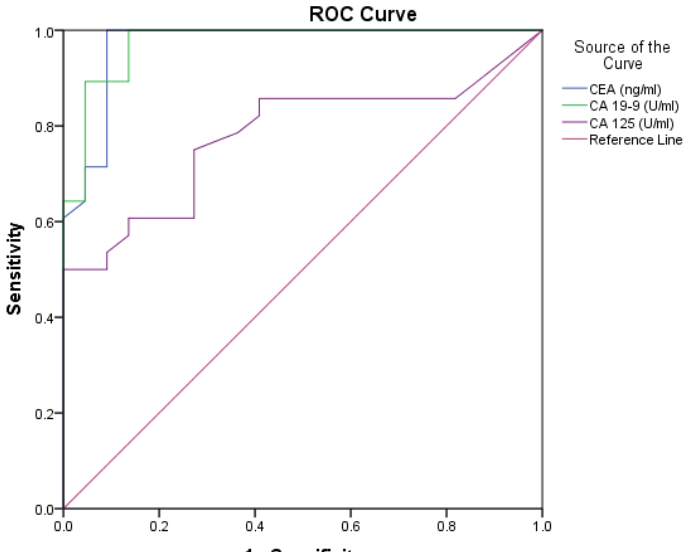

Figure 1: Receiver-operator characteristic curves of CA 19-9.

Receiver-operator characteristic (ROC) curve of CA 19-9 for prediction of pancreatic disease

Receiver-operator characteristic (ROC) were constructed using CA 19-9 of the patients with pancreatic disease, which gave a CA 19-9 cut off value of (≥38.0 U/ml) as the value with a best combination of sensitivity and specificity for pancreatic disease. At this cut-off value the sensitivity and specificity of CA 19-9 in diagnosing pancreatic disease were found to be 96.4% and 86.4%, respectively.

Table no 6: Receiver-operator characteristic (ROC) curve of CA 19-9 for prediction of pancreatic disease

	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Lower bound
CA 19-9 (U/ml)	≥38.0	96.4	86.4		0.936	0.936

IV. Discussion

This is cross sectional study carried out in the Department of Surgery, Dhaka Medical College Hospital, Dhaka during the period July 2016 to June 2017 included 50 patients with history, sign-symptoms and clinical examination suggesting pancreatic disease. The aim of the study is to assess the relation between the level of serum CA 19-9 in benign and malignant pancreatic disease. In this study the age range was between 30-77 years. Mean±SD age of the patients was 53.4±13.1 years. Maximum patients were male 60.0% and 40.0% patient was female. Male: Female ratio was 1.5:1. [1] reported in a study with the aim of 2 neoplastic markers, cancer antigen (CA) 19-9 in the differential diagnosis of pancreatic tumors, ages ranged between 26 and 78 years. In our study, the sensitivity of CEA in pancreatic carcinoma and benign pancreatic diseases (acute pancreatitis, chronic pancreatitis and pancreatic pseudocyst) was the highest (93.3%) among the three tumor markers we used in our study, which had a specificity of 100% regarding the recommended cut-off level. In this study, CA 19-9 had the sensitivity (90.32%) for the pancreatic carcinoma, with a specificity of 100%. Sensitivity was reported to range between (74.2% to 97.8%) and specificity between (82.2% to 100.0%). [3] reported CA 19-9 had the highest sensitivity (81.3%) for the pancreatic carcinoma, with a specificity of 75.9%. Many studies demonstrate sensitivity was range between 68 and 92% [6]; [28] and specificity between 78 and 94.7% [25] [26]. On the other hand, in our study only 9.1% patients were positive in benign cases, regarding CA19-9. [3] showed CA 19-9 positivity in benign pancreatic diseases with jaundice was as high as 64.7% for the recommended cut-off levels and 41.2% for the high cut-off levels. Also in some other studies, high positivity rates of CA 19-9 in benign obstructive jaundice were found, which returned to normal or so after the relief of the jaundice; on the other hand, CA 19-9 levels usually remained high in malignant obstructive jaundice after the palliative biliary by-pass [6]; [20]; [22] and [16]. CA 19-9 antigen is synthesized both by the epithelial cells of the normal biliary tract and by the tumor cells and excreted within the bile [16]. It is suggested that the CA 19-9 antigen, which is high in concentration in the bile of the patients with benign and malignant obstructive jaundice, refluxes into the bloodstream due to the increase in the permeability between bile and blood, secondary to the bile stasis; moreover, it is stated that there can be an inability to degrade the antigen in the liver due to a hepatic dysfunction [20]. Therefore, remeasurement of CA 19-9 after the jaundice subsides can be useful in differential diagnosis of some CA 19-9-positive patients with obstructive jaundice, and if the concentration is still high, then the malignancy potential is high. [9] suggested that cutoff levels of 120 IE/liter for CA 19-9 and differentiating between malignant and benign diseases of the pancreas, the gallbladder, and the bile duct. No false-positive findings were then seen in benign disease. So, the sensitivity of CA 19- 9 by 10.6%, reduced its specificity by 15.6%. On the other hand, sensitivity reduced to unacceptable values for the combinations which increased the specificity. For this reason, the diagnostic value of CA 19-9 alone in pancreatic carcinoma. [28] suggested that CA 19-9 combination provided 97% sensitivity and 96% specificity in differential diagnosis between pancreatic carcinoma and chronic pancreatitis, thus it had a higher predictive value than using each marker alone. [2] and [6] stated CA 19-9 combination is not useful in the diagnosis of pancreatic carcinoma. [3] reported, the ratio of unresectable tumors was significantly higher in the marker-positive patients when compared with marker-negative patients, referring the recommended cut-off levels for each marker. Regarding the high cut-off levels, the ratio of unresectable tumors was significantly higher only in CA 19-9-positive patients. Depending on these findings, it should be taken into account that the probability of unresectability is higher in marker-positive patients. [22] CA 19-9 is useful in predicting resectability, while found that CA 19-9 levels were significantly lower in patients with resectable tumors than in those with unresectable tumors. In present study, regarding CA19-9 100% cases were carcinoma positive and 13.6% positive in benign cases and 85.7% patients were carcinoma positive. Currently available cancerous markers seem to be of too little sensitivity to be used in the detection of early pancreatic carcinoma. In most cases, the marker level is in the normal range or its increase is of low value for the diagnosis. In small tumors with a diameter not exceeding 2 cm, both sensitivity and specificity of the CA 19-9 test have been reported to be lower than 50% [1] & [19]. In this present study shows that receiver-operator characteristic (ROC) were constructed using CA 19-9 of the patients with pancreatic disease, which gave a CA 19-9 cut off value of (≥38.0 U/ml) as the value with a best combination of sensitivity and specificity for pancreatic disease. At this cut-off value the sensitivity and specificity of CA 19-9 in diagnosing pancreatic disease were found to be 96.4% and 86.4%, respectively.

V. Conclusion

In summary, the CA 19-9 marker levels are useful in the preoperative differential diagnosis of malignant and benign pancreatic disease. The major limitations of the methods are false-negative and false-positive results affecting the diagnostic reliability of the tests. Further clinical investigation is necessary to define more reliable markers and to analyze several markers concomitantly with modern imaging techniques.

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