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ORIGINAL ARTICLE

Serum CEA and CA 19-9 Level in Gastric Adenocarcinoma and Their Correlations with Histopathological Grading and Staging

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ABSTRACT

Background & objective: Tumour markers are used clinically as an adjunct to diagnosis, staging and monitoring the prognosis of the diseases. Increased level of serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9) in patients with gastric adenocarcinoma may alert the physicians about the advancement of the disease including metastasis. So, knowledge of association of serum tumour marker levels with different grades and stages of gastric adenocarcinoma may help in choosing better management option which may result in better outcome. The present study was, undertaken to find the association of CEA and CA19-9 with grades and stages of gastric adenocarcinoma.

Methods: This cross-sectional analytical study was conducted in the Department of Pathology, Rajshahi Medical College over a period of two years from July 2017 to June 2019. All patients histologically confirmed of having gastric adenocarcinoma were the study population. A total of 66 patients of gastric adenocarcinoma were consecutively included in the study. In order to find the association, CEA and CA19-9 were divided into two categories at a cut-off value 10 ng/ml and 150 U/ml respectively. Accordingly, any values of CEA > 10 ng/ml and any values of CA19-9 > 150 U/ml were considered as positive for carcinoma. These cut-off values were used arbitrarily based on the findings of the previous studies. Likewise, tumour grades and stages were divided into high-grade (moderate and poorly differentiated) and low-grade (well-differentiated) and Stage I&II and stage III&IV. Then the CEA and CA19-9 values were compared between histological grades and stages.

Result: The serum levels of two markers (CEA and CA19-9) were almost identically distributed between high- and low-grade tumours (p=0.871 and p=0.811 respectively). Analysis of the diagnostic accuracies demonstrated that CEA at a cut-off value of 10 ng/ml had moderate sensitivity (70.6%) and low specificity (31.2%) with overall diagnostic accuracy being 51.5%, while the CA19-9 at a cut-off value of 150 U/ml had poor sensitivity (52.9%) and poor specificity (50%) with overall diagnostic accuracy being poor (51.5%). But when the two diagnostic markers were combined together, the sensitivity sharply rose to 94%, but at the extreme compromise of specificity (3.1%). The kappa analyses revealed that the two diagnostic markers had fair agreement (22.7% agreement) in the differentiation of high-grade tumours from the low-grade ones (k-value=0.227, p=0.048).

Conclusion: The study concluded that the serum levels of CEA and CA19-9 are almost similar between the high- and low-grade tumours indicating that neither of the two markers is a sensitive marker in differentiating the high-grade tumours from the low-grade ones. The sensitivity of CEA is modest, but its specificity is poor, while the CA19-9 has poor sensitivity and poor specificity with overall diagnostic accuracy being poor. When the diagnostic modalities were combined together, the sensitivity improves but at the great compromise of specificity.

Key words: Gastric adenocarcinoma, CEA, CA19-9, high-grade, low-grade, early stage and advanced stage gastric adenocarcinoma etc.

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INTRODUCTION:

Gastric cancer (GC) remains the fourth most commonly diagnosed cancer and third leading cause of cancer deaths worldwide.[1] Although the incidence rate is decreasing in certain regions, almost 951,600 new patients were diagnosed with GC in 2012.[1] Gastric carcinoma is two times more likely to occur in male than that in female. In Bangladesh GC is the fourth most common cancer.[2] Among all types of gastric carcinoma, adenocarcinoma is the most common (more than 90%). Other less common gastric carcinomas are gastric lymphoma, gastric carcinoid and gastrointenstinal stromal tumor.[3]

Gastric cancer is often diagnosed at an advanced stage and the survival rate is low.[4] The tumor-node-metastasis (TNM) classification is the most important prognostic factor in gastric cancer, but it is still difficult to obtain complete prognostic information.[5] Therefore, it is important to identify tumour markers that are simple, feasible, and less costly, for the assessment of clinicopathologic characteristics, diagnosis and prediction of prognosis. As the survival rate of patients with GC remains relatively poor and surgery & chemotherapy result in an unsatisfactory prognosis, serum tumor markers might be useful for diagnosis, for predicting survival rates & for monitoring recurrence following surgery.[1,6] (Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are commonly used markers for gastric adenocarcinoma. Elevation of CEA and CA19-9 level correlates well with the degree of tumour differentiation as well as extension of tumour mass.[7] A recent study showed that combined estimation of serum CEA & CA19-9 has further increased the sensitivity in the diagnosis of gastric adenocarcinoma as well its histological differentiation.[8]

Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 are the most frequently used clinical markers in the diagnosis, treatment and prognosis of GC.[9,10] However, the specificity and sensitivity of serum tumor markers considered in isolation are not satisfactory in GC, particularly in its early-stage diagnosis.[11] Therefore, some researchers have previously used combinations of markers, since they can improve the sensitivity for diagnosis of GC.[12,13] Studies have demonstrated that the sensitivities of CA72-4, CEA, cancer antigen 125 (CA125) and CA19-9 for GC were 33.0, 25.5, 31.1 and 38.7%, respectively. However, the sensitivity of the four markers in combination increased to 66.0%. Similarly, the individual sensitivities of CEA and CA19-9 were 30 and 42%, respectively, although this increased to 58% when CEA and CA19-9 were combined together.[8,14] The above results may be explained simply by different markers being positive in different patients. The present study is, therefore, intended to correlate serum CEA and CA19-9 levels with histological type, grade and stage of gastric adenocarcinoma in order to determine the association of these two markers with histological grading and staging of gastric of adenocarcinoma as well as to differentiate high-grade from low-grade and advanced stage from early-stage tumours.

METHODS:

This cross-sectional analytical study was conducted in the Department of Pathology, Rajshahi Medical College & Hospital, Rajshahi, Bangladesh between July 2017 to June 2019. All patients who are clinically suspected and were later on histopathologically diagnosed as gastric adenocarcinoma were eligible for the study. A total 66 patients were consecutively included in the study. In order to find the association, CEA and CA19-9 were arbitrarily divided into two categories at a cut-off value 10 ng/ml[14] and 150 U/ml respectively based on the findings of the previous studies. Accordingly, any values of CEA > 10 ng/ml and any values of CA19-9 > 150 U/ml were considered as positive for carcinoma. Likewise, tumour grades and stages were divided into high-grade (moderate and poorly differentiated) and low-grade (well-differentiated) and Stage I & II (early stage) and stage III & IV (advanced stage). Then the CEA and CA19-9 values were compared between histological grades and stages.

Data were processed and analyzed using computer software SPSS (Statistical Package for Social

Sciences) verson 25.0. The test statistics used to analyze the data were descriptive statistics and Chi-square (χ^2) or Fisher's Exact Probability Test. The diagnostic accuracies (sensitivity, specificity) of the CEA and CA19-9 were evaluated by the comparing the findings of the two diagnostic modalities with those of histopathology. The agreement between the two diagnostic modalities was tested using kappa- statistics (k-statistics), whereby a kappa value of 0–0.2 was considered as poor agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 good agreement and 0.91–1.0 as excellent agreement. The level of significance was set at 5% and $p < 0.05$ was considered significant.

RESULTS:

Out of 66 study subjects, 18(27.3%) were 31-40 years, 16(24.2%) 41-50 years, 10(15.1%) 51-60 years and 18(27.3%) > 60 years old. A few were 30 or<30 years old. The median age of the study subjects was 50 years (range: 21-115 years). Majority (79%) of the study subjects was male with male to female ratio being roughly 4:1. Abdominal pain and weight loss were invariably complained by the patients. Over 80% of the patients had significant anaemia and 72.7% had dehydration (Table I). Over 60% of the tumours was 5 or < 5 cm in size and majority (93.9%) was located at antrum. The mean size of the tumour was 5.36 cm with smallest and the biggest tumours being 3 and 6 cm respectively (Table II). Nearly half (48.5%) of the tumours were well-differentiated, 39.4% moderately differentiated & the rest 12.1% poorly differentiated. Signs of vascular embolism was evident in half (48.5%) of the cases. Nearly three quarters (72.7%) of the patients had T3 wall invasion (muscle depth) and 21.3% T2 invasion. In terms of nodal status 54.5% were N0, 36.4% N1 and 9.1% N2. A few (6.1%) had distant metastasis. TNM staging revealed that 21.2% were at Stage I, 30.2% at Stage II and 48.5% at Stage III (Table III).

Data show that high grade gastric adenocarcinoma is less likely to occur in elderly subjects (age>60 years) (p=0.070). However, sex was not found to be associated with histological grade of gastric adenocarcinoma (p=0.635). Neither CA19-9 nor CEA was observed to be associated with grade of the tumour (p=0.811 and p=0.871 respectively) (Table IV). Neither of the demographic characteristics (age or sex) nor tumour markers (CA 19-9 or CEA) were found to be associated with staging of the tumour (p=0.131, p=0.465, p=0.811 & p=0.871 respectively) (Table V).

The sensitivity of CEA in correctly differentiating high grade tumours from the low-grade ones was 70.6%, while the specificity of the test in correctly ruling out those who did not have high grade tumours was 31.2%. The positive and negative predictive values (PPVs) of the test were 52.2% and 50.0% respectively. The percentages of false positive and false negative yielded by the test were 47.8% and 50.0% respectively. The overall diagnostic accuracy of the CEA was (51.5%). The sensitivity of CA19-9 in correctly differentiating between high- and low-grade tumours was 52.9%, while the specificity of the test in correctly excluding those who did not have malignancy was 50.0%. The positive and negative predictive values (PPVs) of the test were 52.9% and 50.0% respectively. The percentage of false positive and false negative yielded by the test were 47.1% and 50.0% respectively. The overall diagnostic accuracy of the test was 51.5%. The combined sensitivity of CEA and CA-19-9 was 94.1%, while the combined specificity of the two markers in correctly excluding those who did not have adenocarcinoma was 3.1%. The positive and negative predictive values (PPVs) of the test were 50.8% and 33.3% respectively. The percentage of false positive and false negative yielded by the test were 49.2% and 66.7% respectively. The overall diagnostic accuracy of the combined CEA & CA19-9 was 50.0%.

The test of agreement between the CEA and CA19-9 using kappa-statistics shows that the two diagnostic modalities had fair agreement in the differentiation of high grade tumours from the low grade ones (k-value = 0.227, p = 0.048). In 22.7% cases the two diagnostic modalities were in agreement (Table VI).

Table I. Distribution of study subjects by demographic and clinical features (n = 66)

Demographic & clinical features	Frequency	Percentage
Age* (years)		
≤ 30	4	6.1
31 – 40	18	27.3
41 – 50	16	24.2
51 – 60	10	15.1
> 60	18	27.3
Sex		
Male	52	79
Female	14	21
Clinical presentation		
Abdominal Pain	66	100
Weight loss	66	100
Anaemia	54	81.8
Dehydration	48	72.7

***Median ± SEM** = (50.0 ± 3.2) years; **Range** = 21 – 115 years.

Table II. Morphological characteristics of tumour (n = 66)

Morphological variables	Frequency	Percentage
Size of tumour* (cm)		
≤ 5	40	60.6
> 5	26	39.4
Location		
Cardia	00	0.0
Body	4	6.1
Antrum	62	93.9

***Median ± SEM** = (5.36 ± 1.67) cm; **Range** = 3 – 9 cm.

Table III. Histological characteristics of tumour (n = 66)

Morphological variables	Frequency	Percentage
Differentiation		
Well-differentiated	32	48.5
Moderately differentiated	26	39.4
Poorly differentiated	08	12.1
Vascular embolism	32	48.5
Wall invasion		
T1	02	3.0
T2	14	21.3
T3	48	72.7
T4a	02	3.0
Nodal status		
N0	36	54.5
N1	24	36.4
N2	6	9.1
Distant metastasis		
M0	62	93.9
M1	4	6.1
TNM Staging of tumour		
Stage I	14	20
Stage II	21.2	30.3
Stage III	32	48.5

Table IV: Association of tumour grade with demographic characteristics and tumour markers

Characteristics	Tumour grade		p-value
	High (n = 34)	Low (n = 32)	
Age* (years)			
> 60	6(17.6)	12(37.5)	0.070
≤ 60	28(82.4)	20(62.5)	
Sex*			
Male	26(76.5)	26(81.3)	0.635
Female	8(23.5)	6(18.7)	
CA19-9* (U/ml)			
> 150	18(52.9)	16(50.0)	0.811
≤ 150	16(47.1)	16(50.0)	
CEA* (ng/ml)			
> 10	24(70.6)	22(68.8)	0.871
≤ 10	10(29.4)	10(31.2)	

*Data were analyzed using **Chi-square (χ^2) Test** and were presented as **n(%).** Figures in the parentheses denote corresponding percentage

Table V: Association of tumour grade with demographic characteristics and tumour markers

Characteristics*	Tumour grade		p-value
	Stage I/II (n = 34)	Stage III/IV (n = 32)	
Age (years)			
> 60	6(18.8)	12(35.3)	0.131
≤ 60	26(81.2)	22(64.7)	
Sex			
Male	24(75.0)	28(82.4)	0.465
Female	8(25.0)	6(17.6)	
CA19-9 (U/ml)			
> 150	16(50.0)	18(52.9)	0.811
≤ 150	16(50.0)	16(47.1)	
CEA (ng/ml)			
> 10	22(68.8)	24(70.0)	0.871
≤ 10	10(31.2)	10(29.4)	

*Data were analyzed using **Chi-square (χ^2) Test** and were presented as **n (%).** Figures in the parentheses denote corresponding percentage

Table VI. Agreement between abdominal CEA and CA19-9

Characters studied or modalities of diagnosis	Measures of agreement	
	Kappa statistics	P-value
CEA ng/ml CA19-9 (U/ml)	0.227	< 0.048

DISCUSSION:

In this study we analyzed the diagnostic accuracy of the two common clinical serum tumor markers CEA and CA19-9 for differentiating high-grade gastric adenocarcinoma from the low-grade and advanced stage from early-stage tumours. We compared the serum levels of these two markers between histologically diagnosed high & low-grade tumours, and found that the serum level of CEA and the serum level CA19-9 were almost similar between the high- and low-grade tumours indicating that CEA and CA19-9 are not sensitive markers in differentiating the high-grade tumours from the low-grade ones. The analysis of diagnostic accuracy demonstrated that CEA at a cut-off value of 10 ng/ml had moderate sensitivity (70.6%) and low specificity (31.2%) with overall diagnostic accuracy being 51.5%, while the CA 19-9 at a cut-off value of 150 U/ml had poor sensitivity (52.9%) and poor specificity (50%) with overall diagnostic accuracy being poor (51.5%). But when the two diagnostic markers were combined together, the sensitivity sharply rose to 94.1%, but at the hard compromise with specificity (3.1%).

He and associates[15] took the upper limits of normal values of four markers (AFP, CEA, CA125 and CA19-9) as cut-off value to determine the status of the clinical specimens. They found that the specificity of four markers in the diagnosis of gastric cancer was more than 95%, when used individually, but the sensitivity was very low, ranging from 4.7% to 20.8%, and area under the curve (AUC) was no more than 0.6 or 60%.[16] Thus, a single marker for clinical gastric cancer diagnosis is very limited.[17] When the four markers were combined, the sensitivity of the diagnosis of gastric cancer reached 40.3%, but was still not ideal. Yang et al[12] demonstrated that the sensitivities of CA72-4, CEA, cancer antigen 125 (CA125) and CA19-9 for GC diagnosis were 33.0, 25.5, 31.1 and 38.7%, respectively. However, the sensitivity of the four markers in combination increased to 66.0%. Similarly, the individual sensitivities of CEA and CA19-9 were 30 and 42%, respectively, although this increased to 58% when CEA and CA19-9 were combined.[8] Ychou et al[14] reported a similar result, with a sensitivity of 75% when CA72-4, CEA and CA19-9 were combined. In a recent study, Yu and colleagues[18] demonstrated the sensitivity of three biomarkers, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and CA72-4 in combination to be greater than that of any of the biomarkers considered in isolation in cases of gastric cancer (GC) diagnosis.

Thus, the findings of the present study and those of other investigators presented above may be explained simply by different markers being positive in different patients which is further strengthened by the fair agreement (only 22.7% agreement) between the two markers, CEA and CA 19-9 resulting from the kappa analysis in the present study. However, the fundamental cause of underlying this phenomenon remains to be fully elucidated.

Carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and CA72-4 are the most frequently used clinical markers for the diagnosis of gastric carcinoma, for predicting survival rates and for monitoring recurrence following surgery.[1,6] It has been demonstrated that they are useful in the diagnosis, treatment and prognosis of GC.[9,10,19,20] However, the specificity and sensitivity of serum tumor markers considered in isolation are not satisfactory in the diagnosis of GC in its early stage.[11] Therefore, some researchers have previously used combinations of markers, since they can improve the sensitivity for diagnosis of GC.[13,15,21] To improve the sensitivity of gastric cancer diagnosis, He et al[15] performed logistic regression analysis and used ROC curve to determine the optimum cut-off values. With the use of optimum cut-off values, for CEA the sensitivity was increased from 17.4% to 58.4%, while the specificity was decreased from 99.1% to 83.4%. Earlier studies performed in Chinese population also gave consistent results.[22,23] The present study also demonstrated that while combination of the markers CEA and CA 19-9 improved the sensitivity to great extent (94.1%), the specificity is reduced to an inappreciably low level (3.1%). Although some previous studies

reported that the age, gender, stage and sites of gastric cancer would affect serum marker levels[24,25] in the present study, neither age nor gender was found to be associated with histological grade or staging of the gastric adenocarcinoma.

CONCLUSION:

From the findings of the study, it appears that the serum levels of CEA and CA19-9 are almost identical between the high- and low-grade tumours indicating that the two markers are not sensitive markers in differentiating the high-grade tumours from the low-grade ones. The diagnostic accuracy of CEA at cut-off value of 10 ng/ml offers moderate sensitivity but low specificity with overall diagnostic accuracy being poor, while the CA-19-9 at a cut-off value of 150 U/ml possesses poor sensitivity and poor specificity with overall diagnostic accuracy being poor. But when the diagnostic modalities are combined together, the sensitivity steeply increases but at the gross compromise of specificity.

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