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Assess the Clinical Significance of Serum CEA and CA 19-9 in Patient with Gastric Cancer

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Abstract **Original Research Article**

Background: Gastric cancer is a leading cancer in Bangladesh as well as a cause for cancer related mortality like that of other Asian countries. Gastric cancer can be a curable disease provided that it is detected at an early stage and treated adequately. Gastric cancer usually does not disseminate prior to involving lymph node, so there is an opportunity to cure the disease before dissemination. Unfortunately, there are many cases where gastric cancer presents as a late case and cause of poor overall survival. Tumor markers are assuming a promising role in various stages of cancer case, which starts from screening to follow up after treatment. Judicial application of Tumor markers in clinical practice need knowledge about the role of tumor markers in any given malignancy. ***Objectives:*** To assess the clinical significance of serum CEA and CA 19-9 in patient with gastric cancer. ***Material & Methods:*** This was a Cross-sectional Observational Study. This study carried out in the Department of Surgery, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh. During the Study period of January, 2017 to December, 2017 (12 months), a total of 54 patients of highly suspected for gastric cancer were enrolled in the study. All patients with history, sign-symptoms and clinical examination suggesting gastric cancer attended in Surgery Department of DMCH for treatment. The patients with gastric cancer were diagnosed by endoscopy and confirmed by biopsy. Purposive sampling (non-randomized) was done according to availability of the patients and strictly considering the inclusion and exclusion criteria. The optimal cut off point for CEA and CA19-9 in gastric cancer patients was determined by using ROC. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Chi-Square test was used to analyze the categorical. ***Results:*** CEA and CA 19-9 marker levels are useful in the preoperative differential diagnosis of Gastric Cancer. The P values <0.05 was considered as statistically significant. Further clinical investigation is necessary to define more reliable markers and to analyze several markers concomitantly with modern imaging techniques. ***Conclusion:*** Tumor markers CEA and CA 19-9 usually widely used for diagnosis of different types of cancer and both tumor markers CEA and CA 19-9 are sensitive marker in comparison to gold standard histopathology. CEA has more area under the curve (AUC) than CA 19-9 and CEA is more sensitive than CA 19-9 after construction at cut off value of ≥2.5 ng/ml for CEA and cut off value of ≥30 U/ml for CA 19-9 as the value with the best combination of sensitivity and specificity for gastric cancer.

Keywords: Gastric Cancer; Tumor marker; Serum CEA; CA 19-9.

1. INTRODUCTION

Cancer represents a big public health issue, its incidence and mortality rate being on the rise. Among all cancers gastric cancer is the fourth most common cancer in the world and the second leading cause of cancer deaths worldwide with more than 7,00,000 deaths annually. In Asia and worldwide, gastric cancer being the second-most common cancer among men and third-most among women [1]. Gastric cancer is a leading cancer in Bangladesh as well as a cause for cancer related mortality like that of other Asian countries [2]. Gastric cancer can be a curable disease

provided that it is detected at an early stage and treated adequately. Gastric cancer usually does not disseminate prior to involving lymph node, so there is an opportunity to cure the disease before dissemination. Unfortunately, there are many cases where gastric cancer presents as a late case and cause of poor overall survival [3]. Tumor markers are assuming a promising role in various stages of cancer case, which starts from screening to follow up after treatment. Judicial application of Tumor markers in clinical practice need knowledge about the role of tumor markers in any given malignancy [4]. Tumor markers such as CEA and CA 19-9 usually widely used for diagnosis of different types of cancer like colorectal cancer & pancreatic cancer. However, when these markers are used individually for gastric cancer diagnosis an inconsistent result usually came out [5, 22]. Therefore, with a hypothesis of combined use of tumor markers may avoid the inconsistence and also increase the sensitivity for the gastric cancer [6]. As an ideal tumor marker is a biochemical indicator which selectively secreted by the cancer cell alone, should theoretically allow a confirm & relatively simple method for diagnosis of cancer. But in reality, tumor markers are neither specific nor sensitive [7]. For the gastric cancer, the most used tumor markers are: CEA and CA 19-9. CEA is a glycoprotein which attached to the surface epithelium of enterocytes and causes cell adhesion [8]. Normal values are of <3 ng/ml for non-smokers & <5 ng/ml for smokers. The half-life of CEA is 3 days on average, so this marker can be repeated in every 7 days. The high pretheraputic of CEA shows correlation with the stage of the gastric cancer [7]. There are some studies which proved the correlation between CEA and the locoregional metastasis is statistically significant [9, 10] for the prediction of gastric cancer. In the case of liver metastasis relapse, CEA level may increase about 3 months prior to the radiological confirmation of the disease [7]. CA 19-9 is a protein which has a role in cell adhesion. Its half-life is 1 to 3 days [11]. It is assayed in peripheral blood. Preoperative CA 19-9 assessed in patients with gastric cancer & showed statistical correlation with lymphnode involvement [12]. In patient with gastric cancer regular assessment of CA 19-9 confirms relapse about 2 months earlier than the radiological confirmation [10]. Patients who have elevated serum CA 19-9 levels are subjected to have significantly higher risk for distant metastasis than those with normal serum CA 19-9 level. Elevated CA 19-9 level also correlate in patients with multiple organ infiltration, advanced lymph node metastasis, peritoneal metastasis, liver metastasis, or other distant metastasis [13]. For the CA 19-9 sensitivity ranging between 68 and 92% [14]. A promising technique to overcome the insensitivity of a single tumor marker is the simultaneous assay of several markers, given that cancer cells are biochemically heterogeneous and may synthesize a broad spectrum of tumor markers. Performing a series of assays can prevent missing a potential cell marker.

2. OBJECTIVES

General objective

- To assess the clinical significance of serum CEA, CA 19-9 in patient with gastric cancer.

Specific objectives

- To describe the clinical characteristics of gastric cancer.
- To describe the metastatic features and stage of the disease.
- To evaluate the clinical significance of multiple tumor markers with the clinicopathological character.
- To assess the utility of multiple tumor marker as predictor of locoregional and distant metastasis.
- To evaluate the sensitivity and specificity of CEA and CA19-9 in various population of gastric cancer.
- To construct new cut off point of CEA and CA 19-9 for the best combination of sensitivity and specificity in gastric cancer patients of Bangladesh.

3. REVIEW OF LITERATURE

Haraguchi studied to investigated the depth of tumor invasion and tumor size in resected specimens from patients with gastric cancer and assessed the clinical utility of primary tumor score (PTS) calculated by tumor depth and size as a prognostic marker [15]. They classified 247 patients with gastric cancer into three groups based on cut-off values for deeper tumor invasion (pT2–T4) and larger tumor size (≥ 45 mm) as a PTS of 2 (both abnormalities), 1 (one abnormality), or 0 (neither abnormality). PTS correlated significantly with lymph node metastasis, lymphovascular invasion, and stage ($P < 0.0001$ each). Survival differences among groups based on PTS were significant ($P < 0.0001$). Multivariate analysis identified PTS alone as an independent prognostic factor ($P = 0.0363$). PTS derived from primary tumor information alone is a potentially useful marker for predicting tumor progression and prognosis in postoperative patients with gastric cancer. [7] Studied progress made in the last few years made available a large amount of information that needs to be integrated and ordered by oncologists. Tumor markers are one of the pieces that physicians need to fit into the bigger puzzle. This article will detail the most frequent etiologies for the surges in the carcinoembryonic antigen (CEA), cancer-related antigen 72-4 (CA 72-4), cancer-related antigen 19-9 (CA 19-9) serum levels and their indications. Although tumor markers are an invaluable asset to medical practice, their role in screening, diagnosis and oncologic treatment remains poorly standardized. Ongoing or future clinical trials will shed light on pending problems. [16] Study CA 72-4 is evaluated and compared with CEA and CA 19-9 in various populations of patients with gastric cancer and benign disease; for 52 patients with gastric adenocarcinoma and 57 patients without neoplastic disease CEA, CA 19-

9 and CA 72-4 were evaluated before treatment. Sensitivity of the tumor markers CA 72-4, CA 19-9 and CEA at the recommended cut-off level in all 52 patients were 58%, 50% and 35% respectively. When all three markers were used, the sensitivity increased to 75%. Concerning the prognostic value of these markers, for non metastatic patients, multivariate analyses indicated that none of the markers were significant, when adjusted for gender and age (which were indicators of poor prognosis); patients with abnormal values of CA72-4 tended to have shorter survival than patients with normal values ($p < 0.07$). The determination and application of optimal cut-off values based on ROC curve and logistic regression analysis could improve the diagnosis of gastric cancer based on common tumor markers. [17] Explore the diagnostic value of joint detection of thymidine kinase 1 (TK1), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9) and carbohydrate antigen 72-4 (CA 72-4) in the diagnosis of GC and CRC, and to evaluated the relationship between TK1 expression and clinical pathological characteristics in the patients. Serum TK1, CA 19-9, CA 72-4 and CEA levels were measured in 169 patients with GC, 344 patients with CRC and 75 healthy controls using electro-chemiluminescence. The TK1 concentration was significantly higher in patients with cancer than in healthy controls and patients with clinical stage III+IV had higher TK1 levels than clinical stage I+II ($P<0.05$). The levels of TK1 is significantly associated with tumor stage, lymph node metastasis, distant metastasis, tumor differentiation and age ($P<0.05$). When the tumor markers (TK1, CA 19-9 and CA 72-4) were detected respectively, the area under receiver operating characteristics curve (AUC) of TK1 for three cancers was the highest (0.823-0.895). Overall, 389 patients with GC either located in the gastric cardia (132), the pyloric antrum (112) or the body of the stomach (145) were included in the study. Serum levels of CEA and CA 19-9 were detected with the ECLIA method. First, the serum level of CEA in GC patients with a cardia-located cancer was significantly higher than in patients with pyloric antrum-located cancer ($p=0.050$). Secondly, serum CA 19-9 levels in females with cardia-located GC were significantly higher than those in males with the same type of tumor ($p=0.037$ and $p=0.033$, respectively). Additionally, multiple linear regression analysis showed that preoperative levels of CEA was correlated to TNM stages, CA 19-9 levels are correlated to both gender and distant metastasis. During follow-up there were 115 deaths. Median survival time for GC patients with negative preoperative CEA was 18.07 months, and was 10.97 months for patients with preoperative CEA positive levels ($p=0.0005$). Similarly, the median survival time for GC patients with negative preoperative. The preoperative levels of CEA, CA 19-9 were closely related to TNM grade, gender, distant metastasis and ascites. These makers seem to play important roles in predicting recurrence and metastasis, and in evaluating prognosis. [18] Study the prognostic value of preoperative serum levels of carcinoembryonic antigen (CEA) and CA 19-9 tumor markers was investigated in patients with gastric cancer. [28] To compare and analyze the present and newer oncogenic markers which help in diagnosis of different types of cancers. Tumor markers are substances that are produced by cancer or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. Eighty-two patients who underwent surgical resection of gastric cancer were entered in the study. CA 19-9 was more frequently positive in patients with advanced tumors ($p = 0.01$) and with serosal ($p=0.04$), lymph node ($p= 0.008$) and peritoneal involvement ($p=0.02$). CEA was more frequently positive in patients with liver metastasis ($p=0.03$). Low 3-year cumulative survival was significantly associated with elevated serum levels of CA 19-9 ($p=0.001$) and CEA ($p<0.001$).

4. MATERIALS & METHODS

Study design

Cross-sectional observational Study.

Place of study

Department of Surgery, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh.

Study period

January, 2017 to December, 2017 (12 months).

Study population

A total of 54 patients of highly suspected for gastric cancer were enrolled in the study. All patients with history, sign-symptoms and clinical examination suggesting gastric cancer attended in Surgery Department of DMCH for treatment. The patients with gastric cancer were diagnosed by endoscopy and confirmed by biopsy.

Sampling technique

Purposive sampling (non-randomized) was done according to availability of the patients and strictly considering the inclusion and exclusion criteria. All patients with history, sign-symptoms and clinical examination highly suggestive of gastric cancer.

Study procedure

This study was conducted to describe the clinical characteristics of gastric cancer patients and to assess the utility of CEA and CA 19-9 in diagnosis and staging of gastric cancer. A total of 54 patients of highly suspected for gastric cancer were enrolled in the study, between January, 2017 and December, 2017. The baseline serum CEA and CA19-9 concentrations were measured by enzyme immunoassay in a single laboratory at Bangabandhu Sheikh Mujib Medical University, Dhaka. The CEA and CA19-9 mass (in micrograms), representing the total amount of CEA and CA19-9 protein within the circulation was calculated as serum CEA and CA19-9 concentration X estimated plasma volume. The estimated plasma volume (in liters)

was calculated by 5% of the total body weight. The association of histopathological type with CEA & CA-19-9 concentration, total circulating CEA & CA-19-9 level and plasma volume was assessed by determining P-values for trends. The cut-off value that can differentiate between cancer and benign condition is undoubtedly different. The normal reference values as follows: CEA < 5 ng/ml, CA 19-9 < 35 U/ml.

Data Collection Procedure

Data were collected with a pre-tested structured questionnaire containing history, clinical examination, laboratory investigations findings.

Data analysis

Descriptive statistics for continuous variables such as laboratory parameters were calculated and reported as the mean (±SD). The quantitative observations were indicated by frequencies and percentages. Sensitivity specificity PPV, NPV and accuracy of CEA and CA19-9 for gastric cancer patients were calculated by validity test. The optimal cut off point for CEA and CA19-9 in gastric cancer patients was determined by using ROC. Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Chi-Square test was used to analyze the categorical. P values <0.05 was considered as statistically significant.

Ethical consideration

In this study, keeping compliance with Helsinki Declaration for Medical Research Involving Human Subjects 1964, the nature and purpose of the study will be informed in detail to all participants. Voluntary participations will be encouraged. There will be no physical, psychological and social risk to the subjects. Informed and understood written consent will be taken from every patient before enrollment. Privacy, anonymity and confidentiality of data information identifying any patient will be maintained strictly. Each patient will enjoy every right to participate of refuse or even withdrawn from the study at any point of time. Before starting this study ethical clearance will be taken from Ethical Review Committee (ERC) of DMCH. Data taken from the participants will be coded and regarded as confidential and kept locked under investigator for purposeful use only. No intervention, no further investigation, experimental new drug will be administered and no placebo will be used here.

5. RESULTS

This is a cross-sectional observational study conducted among the clinically suspected gastric cancer patients with a view to establish tumor marker CEA and CA 19-9 as the most reliable diagnostic tool as well as predictor of locoregional and distant metastasis. A total 54 patients with clinical diagnosis of gastric cancer were purposively selected and subjected to endoscopic biopsy for histological diagnosis.

Table-1: Distribution of study participants by demographic variable (n=54)

Demographic variable	Frequency	Percentage
Age (years)		
≤40	2	3.7
41-50	8	14.8
51-60	21	38.9
61-70	17	31.5
>70	6	11.1
Mean±SD	59.5	±9.7
Range (min-max)	38	-78
Sex		
Male	35	64.8
Female	19	35.2
BMI (kg/m^2)		
Low (<18.5)	35	64.8
Normal (18.5-24.9)	19	35.2
Mean±SD	17.5	±2.4
Range (min-max)	12.9	-24.1

Table 1 shows that majority (38.9%) participants were belonged to age 51-60 years. Mean age was found 59.5± SD 9.7 years with range from 38 to 78 years. Almost two third (64.8%) patients were male and rest 19 (35.2%) were female. Mean BMI was found 17.5±2.4 kg/m^2 with range from 12.9 to 24.1 kg/m^2.

Table-2: Distribution of study participants according to clinical characteristics (n=54)

Clinical characteristics	Frequency	Percentage
Anaemia		
Mild	25	46.3
Moderate	19	35.2
Severe	10	18.5
Jaundice		
Present	32	59.3
Absent	22	40.7

Almost half (46.3%) patients had mild anaemia followed by 19(35.2%) with moderate anaemia and 10(18.5%) with severe anaemia. Majority 32(59.3%) of patients had jaundice.

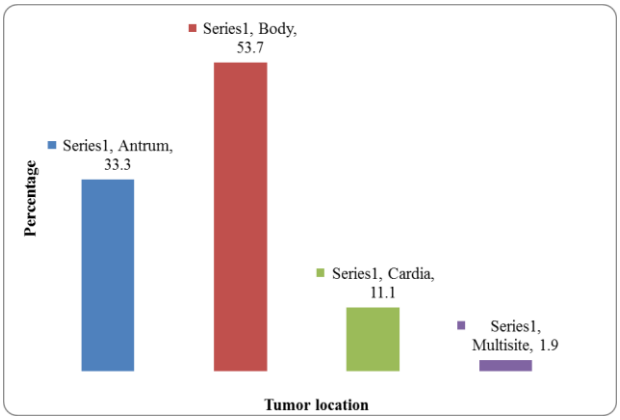

Fig-1: Bar diagram shows tumor location of the study participants (n=54)

Figure 1 shows that most of the cancer were located at body 29(53.7%) followed by antrum 18(33.3%), cardia 6(11.1%) and multisite 1(1.9%).

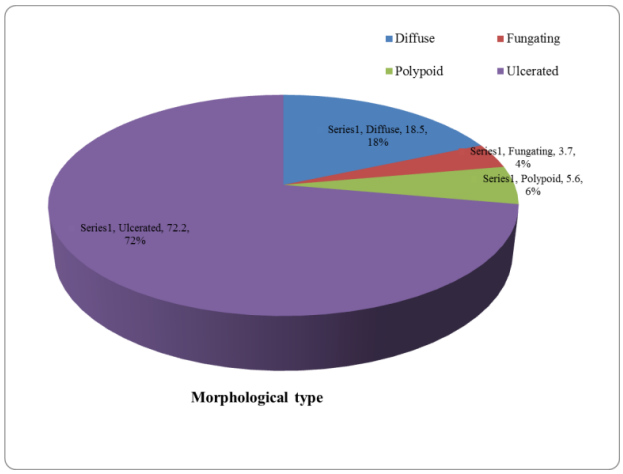

Fig-2: Pie chart shows morphological type of study participants (n=54)

Figure 2 shows the morphological type is seen at endoscopy. Almost three fourth (72.7%) patients were found with ulcerated type followed by 10(18.5%) in diffuse type, 3(5.6%) in polypoid type and rest 2(3.73%) in fungating type.

Table-3: Distribution of the study participants according to tumor size (n=54)

Size of tumor (cm)	Frequency	Percentage
<2	17	31.5
>2	37	68.5

Table 3 shows tumor size among the study population, it was observed that 37(68.5%) patients had tumors size >2 cm and 17(31.5% had tumors size <2 cm).

Table-4: Distribution of study participants according to metastatic features (n=54)

Metastatic features	Frequency	Percentage
Ascites		
Present	32	59.3
Absent	22	40.7
Lymphnode metastasis		
Positive	34	63.0
Negative	20	37.0
Vascular metastasis		
Involved	23	42.6
Not involved	31	57.4
Hepatic metastasis		
Present	26	48.1
Absent	28	51.9

Table 4 shows metastatic features of the study participants based on CT scan findings. It is observed that majority of patients 32(59.3%) patients had ascites, while 34(63.0%) was found with lymphnode metastasis, 23(42.6%) patients were found with vascular involvement and 26(48.1%) were found with hepatic metastasis.

Table-5: Distribution of study participants according to histopathological type (n=54)

Histopathological report	Frequency	Percentage
Positive	51	94.4
Negative	3	5.6

Table 5 shows histopathological type after endoscopic biopsy among the study participants. There were 51(94.4%) patients are found positive for gastric cancer and 3(5.6%) had negative histopathological type and they were advised for follow up.

Table-6: Distribution of study participants according to TNM staging (n=54)

TNM stage	Frequency	Percentage
Stage I	3	5.6
Stage II	19	35.2
Stage III	23	42.6
Stage IV	9	16.7

Table 6 shows TNM staging of study population. It is shown that majority of cases present with advanced stage. Only 3(5.6%) cases were in stage I followed by 19(35.2%) in stage II, 23(42.6%) in stage III & 9(16.7%) found in stage IV.

Table-7: Distribution of study participants according to CEA (n=54)

CEA (ng/ml)	Frequency	Percentage
<5 (Normal)	22	40.7
≥5 (Elevated)	32	59.3
Mean±SD	30.4	±26.2
Range (min-max)	1.12	-72.8

Table 7 shows the pre-operative CEA level among the study participants. There were 32(59.3%) of patients are found with elevated CEA ≥5 ng/ml while 22(40.7%) patients had normal CEA <5 ng/ml. The mean CEA was 30.4 ± SD 26.2 ng/ml with range from 1.12 to 72.8 ng/ml.

Table-8: Distribution of study participants according to CA 19-9 (n=54)

CA 19-9 (U/ml)	Frequency	Percentage
<35 (Normal)	25	46.3
≥35 (Elevated)	29	53.7
Mean±SD	41.9	±19.9
Range (min-max)	12.1	-73.8

Table 8 shows the pre-operative CA 19-9 level among the study participants. There were 29(53.7%) of patients are found CA 19-9 ≥35 U/ml while 25(46.3%) patients had normal CA 19-9 <35 U/ml. The mean CA 19-9 is found 41.9±19.9 U/ml with range from 12.1 to 73.8 U/ml.

Table-9: Comparison between histopatholocal finding and CEA evaluation for gastric cancer (n=54)

CEA	Histopatholocal finding		
	Positive	Negative	Total
≥5 ng/ml	32 (True positive)	0 (False positive)	32
<5 ng/ml	19 (False negative)	3 (True negative)	22
Total	51	3	54

Table 9 shows that CEA evaluation for gastric cancer is noted true positive among 32 cases, false negative in 19 cases and true negative in 3 cases of histopatholocal finding.

Table-10: Comparison between histopatholocal finding and CA 19-9 evaluation for gastric cancer (n=54)

CA 19-9	Histopatholocal finding		
	Positive	Negative	Total
≥35 U/ml	29 (True positive)	0 (False positive)	29
<35 U/ml	22 (False negative)	3 (True negative)	25
Total	51	3	54

Table 10 shows that CA 19-9 evaluation for gastric cancer is noted true positive among 29 cases, false negative in 22 cases and true negative in 3 cases of histopatholocal finding.

Table-11: Sensitivity, specificity, accuracy, positive and negative predictive values of the CEA and CA 19-9 evaluation for prediction of gastric cancer.

Validity test	CEA	CA 19-9
Sensitivity	62.7	56.9
Specificity	100.0	100.0
Accuracy	64.8	59.3
Positive predictive value	100.0	100.0
Negative predictive value	13.6	12.0

Table 11 shows that sensitivity of CEA vs histopathological findings was 62.7%, specificity 100.0%, accuracy 64.8%, positive and negative predictive values were 100.0% and 13.6% respectively.

Sensitivity of CA 19-9 vs histopathological findings was 56.9%, specificity 100.0%, accuracy 59.3%, positive and negative predictive values were 100.0% and 12.0% respectively.

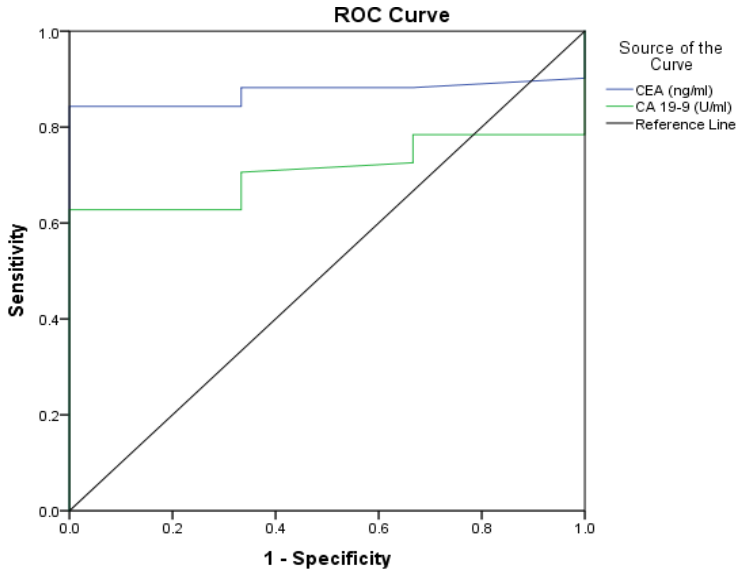

Fig-3: Receiver-operator characteristic curves of CA 19-9 and CEA.

Receiver-operator characteristic (ROC) curve of CA 19-9 and CEA for prediction of gastric cancer. The area under the receiver-operator characteristic (ROC) curves for the gastric cancer predictors is depicted in table XVI. Based on the receiver-operator characteristic (ROC) curves CEA has the best area under curve. Receiver-operator characteristic (ROC) were constructed using CA 19-9 and CEA of the patients with gastric cancer, which gave a CEA cut off value of (≥2.5 ng/ml) as the value with a best combination of sensitivity and specificity for gastric cancer. At this cut-off value the sensitivity and specificity of CA 19-9 in diagnosing gastric cancer were found to be 64.7% and 66.7%, respectively. At this cut-off value the sensitivity and specificity of CEA in diagnosing gastric cancer were found to be 84.3% and 66.7%, respectively.

Table-12: Receiver-operator characteristic (ROC) curve of CA 19-9 and CEA for prediction of gastric cancer

Tumor Markers	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
CEA (ng/ml)	≥2.5	84.3	66.7	0.873	0.781	0.964
CA 19-9 (U/ml)	≥30.0	64.7	66.7	0.709	0.571	0.847

6. DISCUSSION

This is a cross-sectional observational study conducted among the clinically suspected gastric cancer patients with a view to establish tumor marker CEA and CA 19-9 as the most reliable diagnostic tool for gastric cancer. A total 54 patients with clinical diagnosis of gastric cancer were purposively selected and subjected to endoscopic biopsy for histological diagnosis.

In this present study it was observed that majority (38.9%) participants were belonged to age 51-60 years. Mean age was found 59.5± SD 9.7 years with range from 38 to 78 years. Almost two third 35(64.8%) patients were male and rest 19 (35.2%) were female. [19] Found male were twice than the female that is dissimilar with our study may be due to geographical variance. Mean BMI was found 17.5±2.4 kg/m^2 with range from 12.9 to 24.1 kg/m^2. Similar observation was found [20] study they showed the patients contained 741 (73.7) male and 264 (26.3%) female with the median age of 61.5 years. There observation was approximately similar to our study. In this study it was observed that most of the cancer were located at body 29(53.7%) followed by antrum 18(33.3%), cardia 6(11.1%) and multisite 1(1.9%). [15] Study observed that 104 cases were found in differentiated histological type and 143 in undifferentiated histological type out of 247 study subjects. In this study it was observed that 3(5.6%) cases are in stage I followed by 19(35.2%) in stage II, 23(42.6%) in stage III & 9(16.7%) found in stage IV. In different observation was found [15] they observed that 139 (56.27%) cases were found in stage I, 44(17.81%) cases in stage II and 64(25.9%) cases in stage III. In this present study it was observed that 32(59.3%) of patients are found with elevated CEA ≥5 ng/ml while 22(40.7%) patients have normal CEA <5 ng/ml. The mean CEA was 30.4 ± SD 26.2 ng/ml with range from 1.12 to 72.8 ng/ml. [15] Study showed that 49 cases was found CEA <5 ng/ml, 196 was CEA ≥5 ng/ml and 2 was not done. [7] In the case of liver metastasis relapse, the CEA level may increase approximately 3 months prior to the radiological confirmation of the disease. In this current study it was observed that 29(53.7%) of patients are found CA 19-9 ≥35 U/ml while 25(46.3%) patients have normal CA 19-9 <35 U/ml. The mean CA 19-9 is found 41.9±19.9 U/ml with range from 12.1 to 73.8 U/ml. [15] study revealed 31 cases was found CA 19-9 <37 U/ml, 221 was CA19-9 ≥37 U/ml and 5 was not done. Kim et al. (2009) study observed that the median baseline and peak CA 19-9 levels were 276 U/ml (range, 41-13300 U/ml) and 370 U/ml (range, 73-20000 U/ml), respectively. [6] Study observed that the mean CA 19-9 was found 22.8±39.1 U/ml. In the monitoring of patients with gastric cancer, the regular assessment of CA 19-9 serum levels confirms relapse approximately 2 months earlier than the radiological method [10]. In this study it was observed that more than one third (36.4%) patients are belonged to age 61-70 years with normal CEA and 14(43.8%) present among the age range 51-60 with elevated CEA group. More than half (54.5%) patients are male with normal CEA and 23(71.9%) with elevated CEA group. There are 4(18.2%) patients with node positive has normal CEA and 30(93.8%) who are node positive also has elevated CEA. Only one (4.5%) patients with vascular metastasis have normal CEA and 22(68.8%) patients with vascular metastasis have elevated CEA. Four (18.2%) cases with hepatic metastasis have normal CEA and 22(68.8%) patients have hepatic metastasis with elevated CEA. Which are statistically significant ($p<0.05$) between the groups. [20] Observed that 81 cases were found tumor stage 3 in CEA positive and 546 in CEA negative. The difference was statistically significant ($p<0.05$) between the groups. [21] Study observation showed that the mean CEA was found 25.06±8.45 ng/ml in ascites and 8.55±20.23 ng/ml in without ascites group. The difference was statistically significant ($p<0.05$) between the groups. [18] CEA positivity was associated with liver and peritoneal invasion, but did not have an association with either histological type or tumor stage. In this present study it is observed that almost one third (32.0%) patients are belonged to age 61-70 years in normal CA 19-9 and 9(31.0%) in elevated CA 19-9 group. Majority (56.0%)

patients are male in normal CA 19-9 and 21(72.4%) in elevated CA 19-9 group. Almost two third (64.0%) patients have low BMI with normal CA 19-9 and 19(65.5%) with elevated CA 19-9 group. The difference is not statistically significant (p>0.05) between the groups. [20] Study observed that 94 cases were belonged to age ≥60 years in CA 19-9 positive and 521 in CA 19-9 negative. 109 cases were male in CA 19-9 positive and 632 in CA 19-9 negative. The difference were not statistically significant (p>0.05) between the groups. [7] Study identified a predictive role of the pre-therapeutic values of CEA and CA 19-9, which were correlated with the TNM stage, lymph node invasion and the T category. [19] Study observed that there were no significant sex differences between patients with elevated and those with normal serum levels for either CEA or CA19-9. According to a previous report (in Japanese) of the results of treatment for stomach carcinoma in Japan, the sex ratio of patients was 66.4% men and 33.6% women, or about 2: 1. [19] Study, the proportion of men was a little higher. It is likely that CEA and CA19-9 levels are increased in patients with multiple organ infiltration, advanced lymph node metastasis, or liver metastasis, or when other distant metastasis occurs. In this study it was observed that 10(40.0%) patients with jaundice have found in normal CA 19-9 and 22(75.9%) cases seen in elevated CA 19-9. Patients with ascites are 10(40.0%) who has normal CA 19-9 while 22(75.9%) patients with ascites are in elevated CA 19-9. There are 9(36.0%) patients with node positive has normal CA 19-9 and 25(86.2%) who are node positive also has elevated CA 19-9. Three (12.0%) patients with vascular metastasis has normal CA 19-9 and 20(69.0%) patients with vascular metastasis has elevated CA 19-9. Seven (28.0%) cases with hepatic metastasis have normal CA 19-9 and 19(65.5%) patients have hepatic metastasis with elevated CA 19-9. Majority (56.0%) of the patients have found in stage III with normal CA 19-9 and 13(44.8%) patients of stage II have elevated CA 19-9. Which are statistically significant (p<0.05) between the groups. [20] Study observed that 113 cases was found tumor stage 3 in CA 19-9 positive and 514 in CA 19-9 negative. Whereas in our study we found CA19-9 is more useful in prediction of stage of gastric cancer. In this study it was observed that receiver-operator characteristic (ROC) were constructed using CA 19-9 and CEA of the patients with gastric cancer, which gave a CEA cut off value of (≥2.5 ng/ml) as the value with a best combination of sensitivity and specificity for gastric cancer. At this cut-off value the sensitivity and specificity of CA 19-9 in diagnosing gastric cancer were found to be 64.7% and 66.7%, respectively. At this cut-off value the sensitivity and specificity of CEA in diagnosing gastric cancer were found to be 84.3% and 66.7%, respectively. CEA level is a predictor of distant metastasis [24, 25]. CEA and CA 19-9 act as intercellular adhesion molecules, and cells expressing these glycoproteins may have a greater invasive potential [26]. CEA may be involved in tumor cell adhesion to liver parenchyma, which might explain the correlation between the levels of CEA and liver involvement. Moreover, a correlation between CEA and proliferating cell nuclear antigen has been described, suggesting that cells expressing this antigen will exhibit an increased proliferating activity [27]. In study of [6] revealed Aare under curve was 0.767 with the sensitivity and specificity of CEA in diagnosing gastric cancer were found to be 58.4% and 83.4%, respectively. Aare under curve was 0.566 with the sensitivity and specificity of CA 19-9 in diagnosing gastric cancer was found to be 30.2% and 92.8%, respectively. [17] The sensitivity and specificity of CEA in diagnosing gastric cancer were found to be 39.6% and 97.3%, respectively. The sensitivity and specificity of CA 19-9 in diagnosing gastric cancer were found to be 53.8% and 88.0%, respectively. [23] Study observed that the median baseline and peak CA 19-9 levels were 276 U/ml (range, 41-13300 U/ml) and 370 U/ml (range, 73-20000 U/ml), respectively. [20] They found sensitivity, specificity, PPV and NPV for CEA 13.75%, 94.59%, 74.75% and 48.50% respectively and for CA19-9 sensitivity, specificity, PPV and NPV for CEA 20%, 92.87%, 76.60% and 49.58% respectively which was different from our study may be due to sample size.

Limitations of the study

Since this a hospital based study, the incidence does not reflect the actual incident of the community. The present study was conducted at a very short period of time and small sample size.

7. CONCLUSION AND RECOMMENDATION

In conclusion, both tumor markers CEA and CA 19-9 are sensitive marker in comparison to gold standard histopathology. Among these two CEA is more sensitive. For the tumor markers progression and as prediction of locoregional and distant metastasis further strengthen by ROC curve. The ROC curve gave CEA has more area under the curve (AUC) than CA 19-9 and CEA is more sensitive than CA 19-9 after construction of ROC curve. After ROC curve at cut off value of ≥2.5 ng/ml for CEA and cut off value of ≥30 U/ml for CA 19-9 as the value with the best combination of sensitivity and specificity for gastric cancer. At this cut-off value the sensitivity and specificity of CA 19-9 in diagnosing gastric cancer were found to be 64.7% and 66.7%, respectively and for CEA were found to be 84.3% and 66.7%, respectively. Further studies can be undertaken by including large number of patients in a tertiary hospital for long duration. Further studies are required to determine whether these screening cut-off points exhibit similar sensitivity and specificity for predicting gastric cancer. Since early detection of gastric cancer and to assess the utility of multiple tumor marker as predictor of locoregional and distant metastasis is the goal of CEA and CA19-9 measurement, sensitivity and specificity testing are required prior to adopting new screening cut-off points. Further studies are required to determine

the optimal cut of values of tumor markers CEA & CA19-9 to improve the TNM staging based on these markers.

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