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Original research article

Correlation of preoperative serum CEA, CA19-9 and CA72-4 with staging, pathological grade and lymph node status in carcinoma stomach: An observational study

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Abstract

Introduction: Gastric cancer is one of the most common cancers worldwide. Early gastric cancer is typically small and asymptomatic, and the high mortality from gastric cancer is mainly due to late presentation. Surgical resection of the primary tumor and regional lymph nodes (RLNs) along with adjuvant treatment is the only curative approach. However, overall prognosis remains poor, with 5-year survival rates of only 20%. Many studies have identified high preoperative levels of CEA as a poor prognostic factor for patients with potentially resect able GC. Other published works have suggested that a combination of CEA, CA 19.9 and the relatively new marker CA 72.4 provides additional prognostic information on these patients, with preoperative positivity for one of them considered as evidence of a high recurrence risk even in the early stages.

Materials and Methods: This is a prospective observational study which included all the patients who underwent treatment for Gastric carcinoma, in the Department of Surgical Gastroenterology at Nizam's Institute of Medical Sciences, Hyderabad, over a period of 2 years from 1st March 2017 to 30th April 2019. Correlation of the tumour marker values were done with staging, tumor differentiation and lymph node involvement in Gastric cancer subjects. Appropriate analysis were carried out by use of Student‘s t-test, Fishers Exact Test and Chi Square test for categorical data.

Results: Out of all the parameters (pre-operative CEA, CA19-9 and CA72-4,) elevated CA19-9 was the most sensitive marker associated with advanced stage and none of above tumour markers correlate with grade of tumour. CA72 -4 is least sensitive marker associated with advanced stage of tumour.

Conclusion: Preoperative increased Serum levels of CA 19 -9 is associated with advanced TNM stage of Carcinoma Stomach as compared to CEA and CA 72-4 No significant association could be demonstrated between these tumor markers with grade or histology of malignancy.

Increased Serum CA 19-9 is perhaps an independent predictor of advanced stage and poor prognostic factor in patients with Gastric carcinoma. Hence, the patients with increased Serum CA 19-9 is associated with advanced stage and may require neoadjuvant therapy unless there is no contraindication for neoadjuvant therapy. However, long term follow-up studies and survival analysis and further randomized control studies are needed to substantiate this observational study.

Keywords: Gastric carcinoma, CEA, Ca 19-9, prognosis.

Introduction

Gastric cancer is one of the most common cancers worldwide. Gastric cancer used to be the leading cause of cancer deaths in the world until the 1980s when it was overtaken by lung cancer [1]. Gastric cancer is the second most common cause of death from cancer worldwide, and in many Asian countries, such as China, Japan and Korea. The worldwide incidence of gastric cancer has declined rapidly over the

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recent few decades. Early gastric cancer is typically small and asymptomatic, and the high mortality from gastric cancer is mainly due to late presentation. Epidemiological data from Asia have shown that individuals who test positive for H pylori have at least a two-times increased risk of developing gastric cancer compared with those who test negative. Evidence suggests that smoking increases the risk of gastric cancer, especially intestinal cancer of the distal stomach [2]. The incidence of gastric cancer varies with different geographic regions. Rates are highest in Eastern Asia, Eastern Europe, and South America, while the lowest rates are in North America and parts of Africa. Over 70 percent of gastric cancers occur in developing countries. Gastric cancer is more common in men than in women, in both developed and developing countries [3].

Surgical resection of the primary tumor and regional lymph nodes (RLNs) along with adjuvant therapy is the only curative approach. However, overall prognosis remains poor, with 5-year survival rates of only 20%. There are two major prognostic factors: depth of stomach wall tumoral invasion and involvement of RLN. Tumor markers, which are often measured for early detection of several cancers and on follow-up after radical surgery, have not been shown to be specific for GC [4].

However, the carcinoembryonic antigen CEA and the carbohydrate antigen CA 19.9 are commonly used as serum markers for this neoplasm. Many studies have identified high preoperative levels of CEA as a poor prognostic factor for patients with potentially resect able GC [5]. Other published works have suggested that a combination of CEA, CA 19.9, and the relatively new marker CA 72.4 provides additional prognostic information on these patients, with preoperative positivity for one of them considered as evidence of a high recurrence risk even in the early stages [6].

A new tumour-associated glycoprotein antigen, TAG-72, has been identified. This oncofoetal antigen, a high-molecular-weight mucin glycoprotein, is detectable in the sera of patients with a variety of gastrointestinal adenocarcinomas, the preliminary findings of some recent studies suggest that CA 72-4 is a reliable tumour marker in gastric cancer. It is observed in advanced stages higher tumour marker positivity rates, achieving statistical significance with CA 72.4, but less tendency with CEA and CA 19.9 positivity [7].

Carbohydrate antigen 19-9 (CA 19-9) has recently been developed of digestive tract malignancies. The CA 19-9 antibody has been obtained by immunizing mice with human colorectal cell line. The tumour marker CA 19-9 is a sensitive marker for pancreatic and hepatobiliary malignancies. The highest frequency of elevated serum CA 19-9 level is found in patients with pancreatic cancer. Occasionally reported in other primary neoplasms, it is most often associated with the gastrointestinal tract. It is also associated with advanced Carcinoma Stomach [8].

The presence of specific carcinoembryonic antigen (CEA) in the human digestive system was first reported by Gold and Freedman. It is now widely accepted as a tumour marker. The determination of CEA levels in patients with colorectal carcinoma is useful to assess cancer progression and recurrence and to evaluate the effect of cancer chemotherapy.

However, there are few reports on CEA in gastric cancer patients. The plasma CEA levels of gastric cancer patients preoperatively and periodically after the operation to examine whether CEA represents a tumour marker in gastric cancer and whether the CEA level is of predictive value in determining the cancer stage and the recurrence of gastric cancer [9].

Tumor markers, which are often measured for early detection of several cancers and on follow-up after radical surgery, have not been shown to be specific for GC.

However, the carcinoembryonic antigen CEA and the carbohydrate antigen CA 19.9 are commonly used as serum markers for gastric neoplasm. Many studies have identified high preoperative levels of CEA as a poor prognostic factor for patients with potentially resectable GC [10].

Materials and Methods

Study site

This is a prospective observational study which included all the patients who underwent treatment for Gastric carcinoma, in the department of Surgical Gastroenterology at Nizam's Institute of Medical Sciences, Hyderabad, over a period of 2 years from 1st March 2017 to 30th April 2019.

Data was derived from the patient's records maintained by the medical records department at our institute.

Study population

Biopsy proven cases of Gastric Carcinoma treated at Nizam's Institute of Medical Sciences, Hyderabad during the study period. After clearance from Institutional Ethical Committee and Review Board, records of patients with biopsy proven Gastric Carcinoma treated between March 2017 and April 2019 at our institute were reviewed.

Inclusion criteria

- All the patients more than 18 years of age undergoing treatment for biopsy proven Gastric Carcinoma.

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Exclusion criteria

- Gastric cancer patients who are unfit for surgery.

Description of procedure followed in study (Methodology)

1. All biopsy proven cases of Gastric carcinoma had preoperative estimation of Carbohydrate antigen19-9, CEA and Cancer Antigen72-4.
2. Co-relation of all these values were done with staging, tumor differentiation and lymph node involvement in Gastric cancer subjects.
3. Preoperative staging work up were done as per standard protocol with history and clinical examination, Esophagogastroduodenoscopy, CECT abdomen and Chest.
4. Patients were offered treatment as per staging workup and as per standard guidelines in form of curative/palliative surgery/chemotherapy.
5. Adjuvant therapy were given to patients as per standard guidelines.

Method of CA19-9, CEA and CA72-4

1. Serum CA19-9, CEA and were estimated in biochemistry laboratory using agglutination reaction and reviewed from the patient records.
2. CEA levels >5ng/ml was taken as positive (colorectal cancer. Cancer 58: 603-610, 1986) [59].
3. CA19-9 of >37u/ml was taken as significant.
4. CA 72-4 >6 u/ml was taken as significant (J. Clin. Lab. Anal., J: 360-369, 1989) [58].

CA 72-4, CEA, and CA 19-9 Radioimmunoassay

Serum TAG-72 antigen levels were determined by a double-determinant immunoradiometric assay kit, CA 72-4. Briefly, 100 n of specimen in the presence of 100 n\ of phosphate buffer were incubated at 37Â °C for 4 h with beads coated with MAb CC49. The beads were washed 3 times with distilled water and incubated with "'I-B72.3 for 18 to 20 h at 4'C. After 3 washes with distilled water, bound radioactivity was measured in a gamma counter. TAG-72 levels, expressed as units/ml, were determined by converting cpm to concentration values using a concurrently obtained standard curve. The cut off limit for this assay is set at 6 units/ml [58].

CEA serum levels were determined using a CEA RIA MAb kit. Several different cut off limits, ranging from 2.5 to 10.0 ng/ml, have been used for the analysis of CEA serum levels. In the present study, we used a cut off limit of 5.0ng/ml for better specificity [59].

CA 19-9 serum levels were determined as previously described using the suggested cut off limit of 37 units/ml [60].

The cut-off values of above markers was determined using receiver operating characteristic (ROC) curve analyses. The recommended cut-off value was based on the most prominent point on the ROC curve for “sensitivity” and “1-specificity”, respectively. The ideal cut-off values was defined using the Youden index (maximum (sensitivity, specificity-1).

The area under the ROC (AUROC) curve also was calculated.

Pathologic analysis

The specimen was processed after formalin fixation.

The pathologic parameters analysed include.

1. Differentiation of tumor (well/moderately/poorly differentiated).
2. TNM stage of the tumor.

Follow up

Patients were followed up post-surgery/palliative therapy every 3 to 6 months as per standard protocol. However, since the study period was only 2 years, recurrence and survival were not studied as the follow up period would not be adequate to reach statistical significance.

Statistical analysis

The data of the present study were entered into the computer and after its proper validation; check for error, coding & decoding it was compiled and analyzed with the help of SPSS 20 software for windows. Appropriate analysis were carried out by use of Student‘s t-test, Fishers Exact Test and Chi Square test for categorical data.

All numerical variable were summarized as mean ± standard deviation and median ± IQR (Interquartile range) based on normality. All categorical variable was summarized as percentages. P value <0.05 were considered significant. Parameters were recorded and arranged on Microsoft Excel spreadsheet (Microsoft, Seattle, WA) version 2010. All graphs and tables were made using Excel spreadsheet.

Sample size calculation

Based on the previous studies [52] which investigated correlation of CA 19-9, CEA and CA72-4 with staging of gastric carcinoma, expected prevalence is taken as 0.29.

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The formula (Daniel, 1999) to calculate the sample size is given by:

$$n = \frac{Z^2 P\,(1 - P)}{d^2}$$

where
n = Sample size
Z = Z statistic for a level of confidence.
Z statistic (Z): For the level of confidence of 95%, which is conventional.
Z value is 1.96.
P = Expected prevalence or proportion.
d = Precision.
Based on the above formula the expected sample size is calculated to be 63 Sample size
Sample Size is 63 but in 2 years we got around 51.
Bibliography was written in Vancouver system.

Results

A total of 51 patients, who underwent surgery for Gastric carcinoma are included in our study with a median age of 54 years and age ranging from 22 to 80. The number of males and females were 35 and 16 respectively with a male to female ratio of 2.18:1. None of our patients had received neoadjuvant therapy.

Presenting Symptoms

41 patients had undergone elective surgery whereas 10 patients had emergency surgeries. Most of the patients (> 90%) among the emergency group had presented with gastric outlet obstruction. Elective group has varied presentations, most common being weight loss, accounting for > 37% and others in a decreasing frequency were abdominal pain, dysphagia, and early satiety (Table 1, Fig 1a, Fig 1b).

Table 1

Type	Number (%)
Elective	41(80)
Weight loss	15(37)
Abdominal pain	14((34)
Dysphagia	4(10)
Early Satiety	8(19)
Emergency	10(20)
Obstruction	9(90.)
Bleeding	1(10)

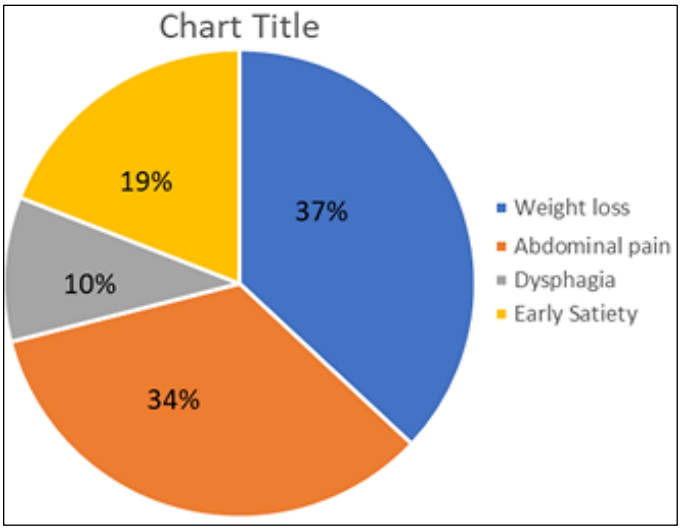

Fig 1a: Elective cases-presenting symptoms

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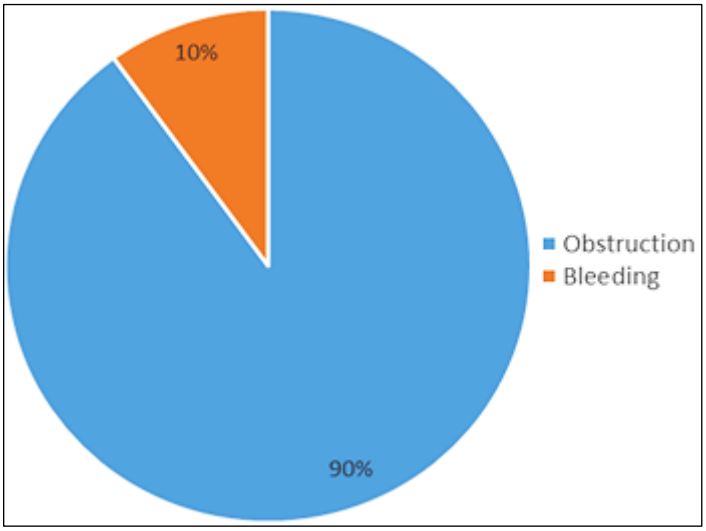

Fig 1b: Emergency Cases-Presenting symptoms

Location of tumour

Most of Patients have growth in distal part of stomach (antrum and distal body) that is 45 and rest of patients had growth in proximal body of stomach including GEJ that is 6.
Table 2, 2a

Table 2: Location of tumour (Stomach)

Antrum	37(72)
Distal body	8(16)
GEJ	2(4)
Proximal body	4(8)

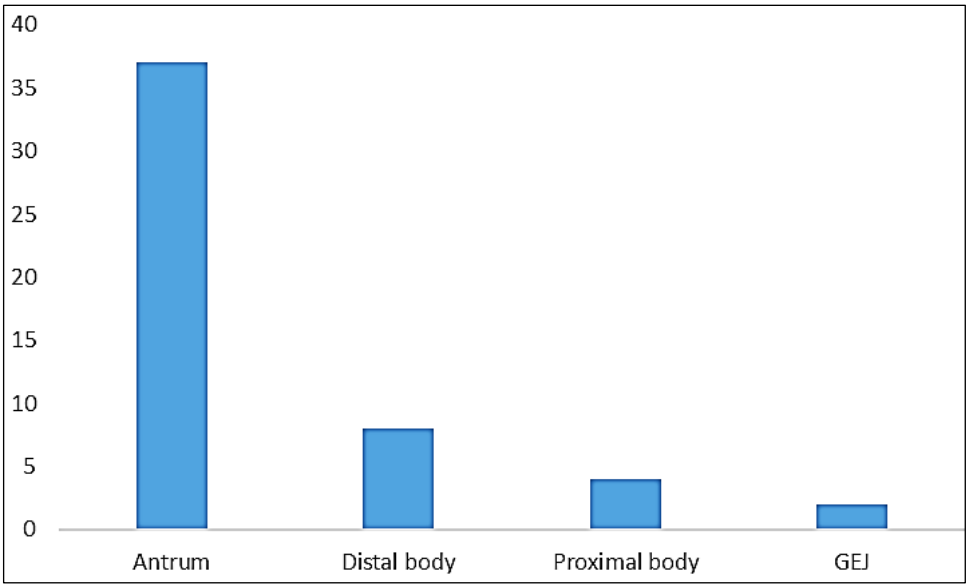

Fig 2

Surgical treatment

Elective patients underwent surgery on basis of location of growth. Out of 41 Electives patients 35 had growth in distal stomach and 6 had growth in proximal part of stomach. Emergency Patients under went surgery according to presentation of patient as follows 3 patients underwent palliative Gastrojejunostomy, 5 underwent feeding jejunostomy, 1 underwent palliative gastrectomy for bleeding and 1 underwent staging laparoscopy and Biopsy. Table 3, 3a, 3b

Table 3: Surgery

Elective (41)		**Emergency (10)**
D2 Distal Gastrectomy	35(85)	Palliative Gastectomy-1(10)
D2 Total Gastrectomy	6(15)	Palliative Gastrojejunostomy-3(30)

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	Feeding jejunomstomy-5(50)
	Staging lap and Biopsy-1(10)

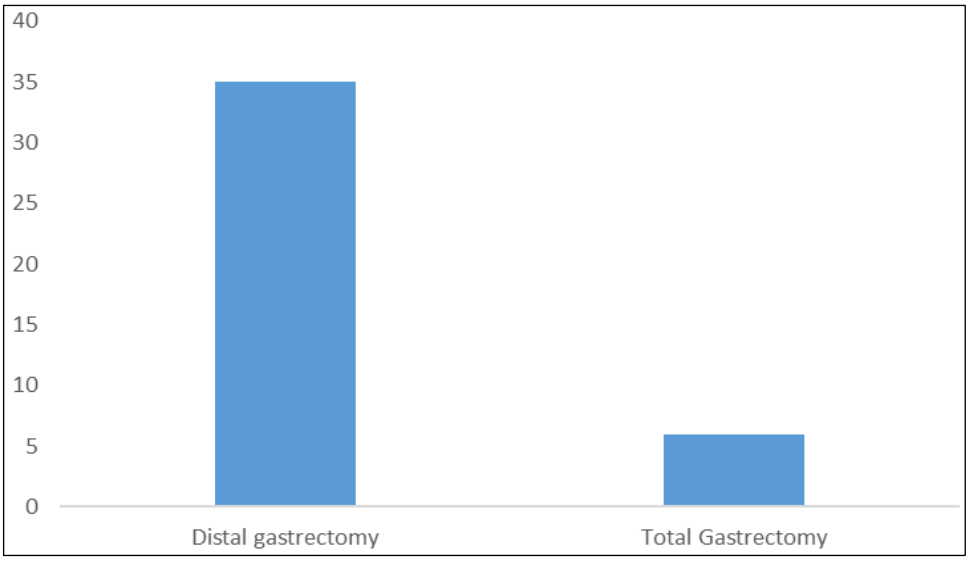

Fig 3a**:** Numbers of Elective Surgery

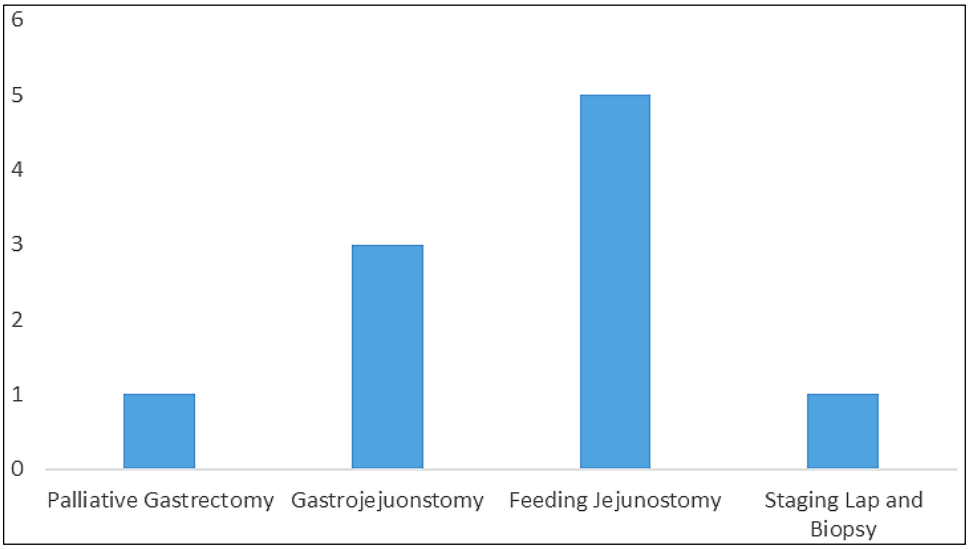

Fig 3b**:** Emergency Surgery

Histopathological charateristics

On complete histopathological examination of formalin fixed specimens, 8 patients had early T-stage i.e., T1, T2 and 33 patients had advanced T-stage i.e., T3, T4. 34 patients had node positive disease, and 10 patients had metastatic disease. 6 patients belong to Stage I amounting to 12 %. Whereas 8 (15 %) and 27 (53 %) patients had stage II and III cancer respectively. 10 patients amounting to 20% had stage IV cancer. Coming to grade and morphology, 10(20%) and 17(33%) patient had well and moderately differentiated adenocarcinoma respectively. 9 (18 %) patients had poorly differentiated adenocarcinoma. 2(4%) patients had mucinous variety of adenocarcinoma and 13(25%) patients had signet ring cell variety of adenocarcinoma. All the patients had proximal and distal margins negative.

Table 4: Histopathological charateristics

Variable	**Number**
T stage	
T1	5
T2	3
T2	26
T4	7
N stage	
N0	7
N1	8

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N2	7
N3	19
M Stage	
M 0	41
>M 0	10
Stage	
I	6(12)
II	8(15)
III	27(53)
IV	10(20)
Grade and Morphology	
G1 (WDAC)	10(20)
G2 (MDAC)	17(33)
G3 (PDAC)	9(18)
Mucinous	2(4)
Signet	13(25)

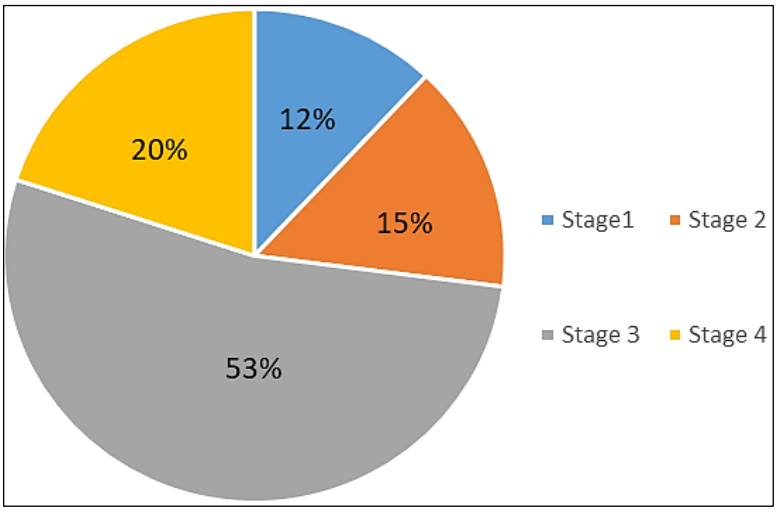

Fig 4a: Proportion of patients in each stage

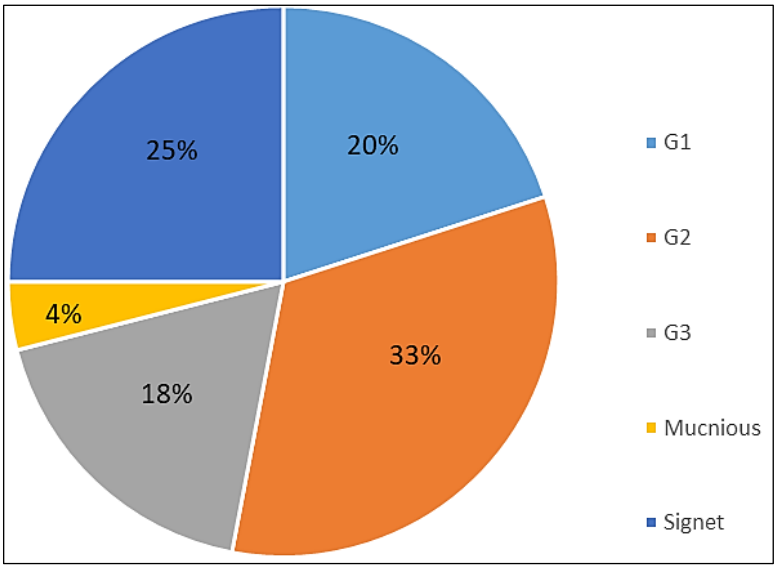

Fig 4b: Proportion of patients in each grade

Correlation of presurgical TAG-72, Ca 19-9 and CEA serum levels and clinical stage in gastric cancer patients.

10(19.6) Patients had elevated CEA out of 51 in which 2 belong to stage I, 1 belong to stage II, 4 belong to stage III and 3 belong to stage I, 36 (70.5) patient had elevated CA19-9 out of 51 in which 1 belong to stage I, 3 belong to stage II, 24 belong to stage III and 8 belong to stage IV. 4 patients had elevated CA72-4 out of 51 in which 1each belong to stage II and IV and 2 in stage III.

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Table 5

			Serum Antigen Levels	
Stage	**No. of patients**	**CEA**	**CA19-9**	**CA72-4**
>5ng/ml	**>37units/ml**	**>6units/ml**		
I	6	2(33.3)	1(16.6)	0
II	8	1(12.5)	3(37.5)	1(12.5)
III	27	4 (14.8)	24(88.8)	2(7.4)
IV	10	3(30)	8(80)	1(10)
Total	51	10(19.6)	36(70.5)	4(7.8)

Table 5 Numbers in parentheses, percentage of patients within each stage of malignant gastric cancer in which their serum samples contain positive titers of the indicated tumour antigen.
CEA levels >5ng/ml is considered significant. 2 patients in stage I, 1 patient in stage II, 4 patient in stage III and 3 patients in stage 4 had raised CEA Levels as shown in graph below.

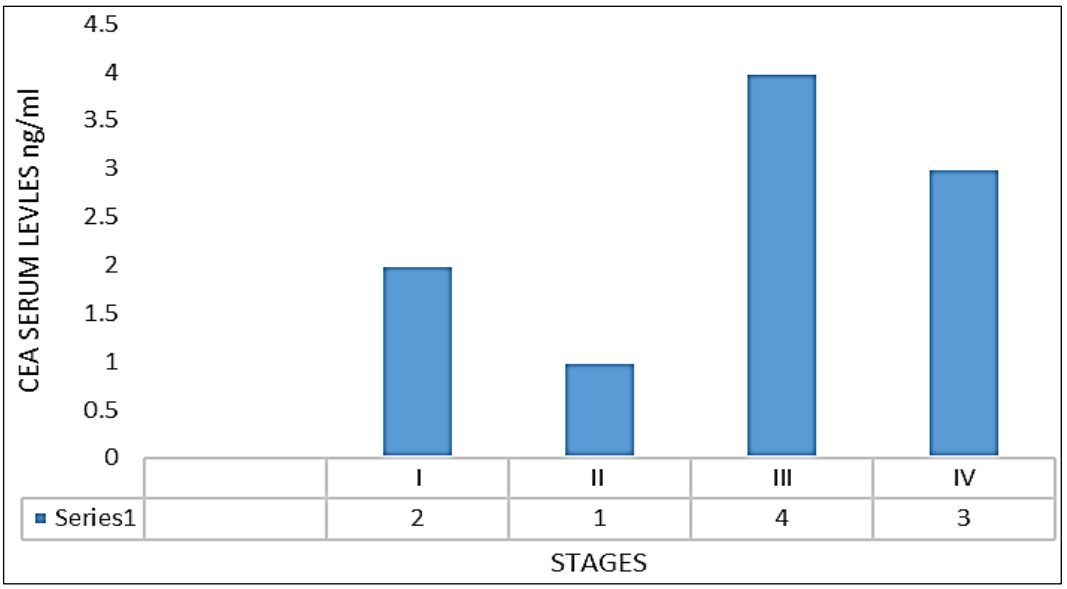

Fig 5a: Serum CEA levels according to stage of disease

CA19-9 levels >37U/ml is considered significant. 1 patients in stage I, 3 patient in stage II, 24 patient in stage III and 8 patients in stage 4 had raised CA19-9 Levels as shown in graph below

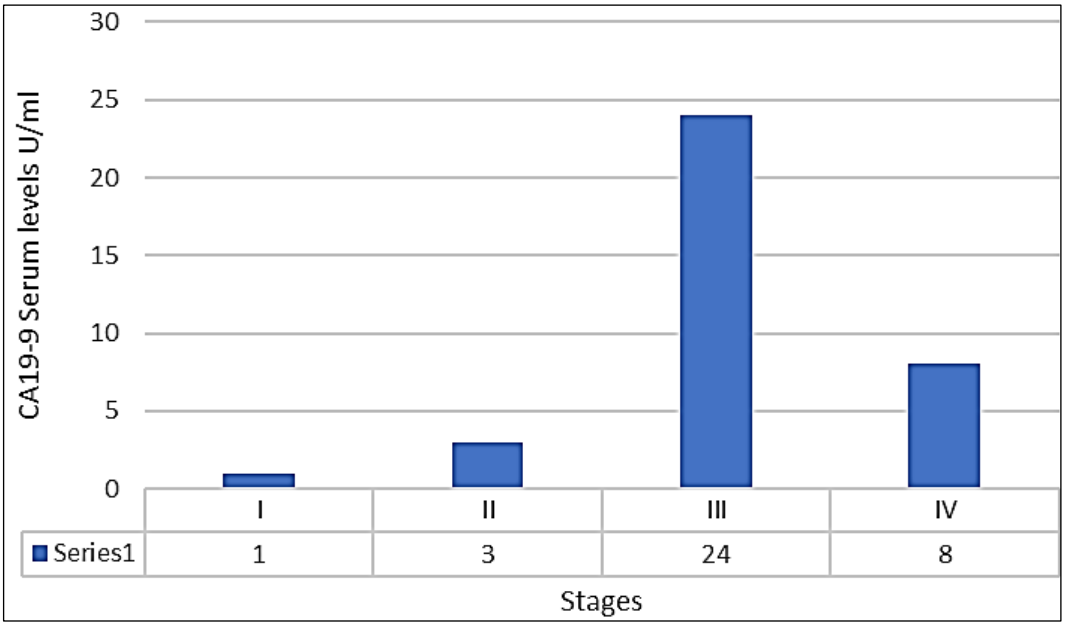

Fig 5b: Serum CA 19-9 levels according to stage of disease

CA72-4 levels >6U/ml is considered significant. None patients in stage I, 1 patient in stage II, 2 patient

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in stage III and 1 patient in stage 4 had raised CA72-4 Levels as shown in graph below.

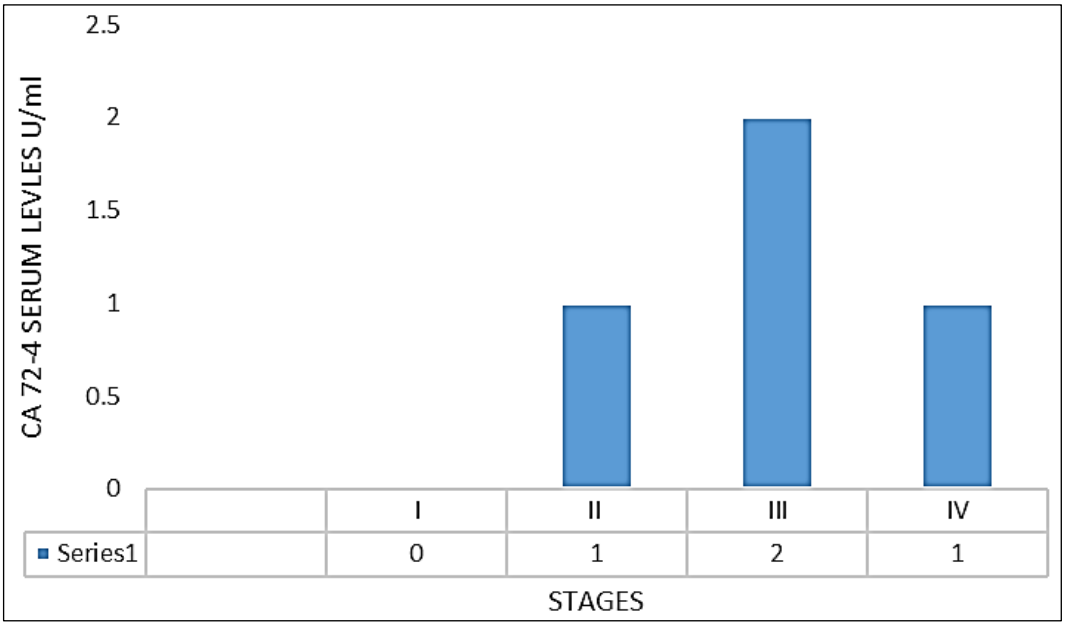

Fig 5C: Serum CA 72-4 levels according to stage of disease

Preoperative analysis of CEA

- CEA was considered positive when it was more than 5.0ng/ml. It was raised in 10 patients (n=51, 19.6%) and within normal limits in 41 patients (80.4%) preoperatively.
- Of the 6 patients in Stage 1 (AJCC), 2 patients had raised CEA levels preoperatively (34%).
- Of the 8 patients in Stage 2 (AJCC), 1 patient had elevated CEA levels preoperatively (12%).
- Of the 27 patients in Stage 3 (AJCC), 4 patients had elevated CEA levels preoperatively (15%).
- Of the 10 patients in Stage 4 (AJCC), 3 patients had elevated CEA levels preoperatively (30%).

Table 6a: Correlation of preoperative CEA with AJCC staging system

Preoperative		AJCC			P value
CEA	I	II	III	IV	
0-5	4(66)	7(88)	23(85)	7(70)	0.549
>5	2 (34)	1(12)	4(15)	3(30)	
	6 (100)	8(100)	27(100)	10(100)	

No significant association could be demonstrated between preoperative CEA levels and AJCC staging system for Gastric cancer.

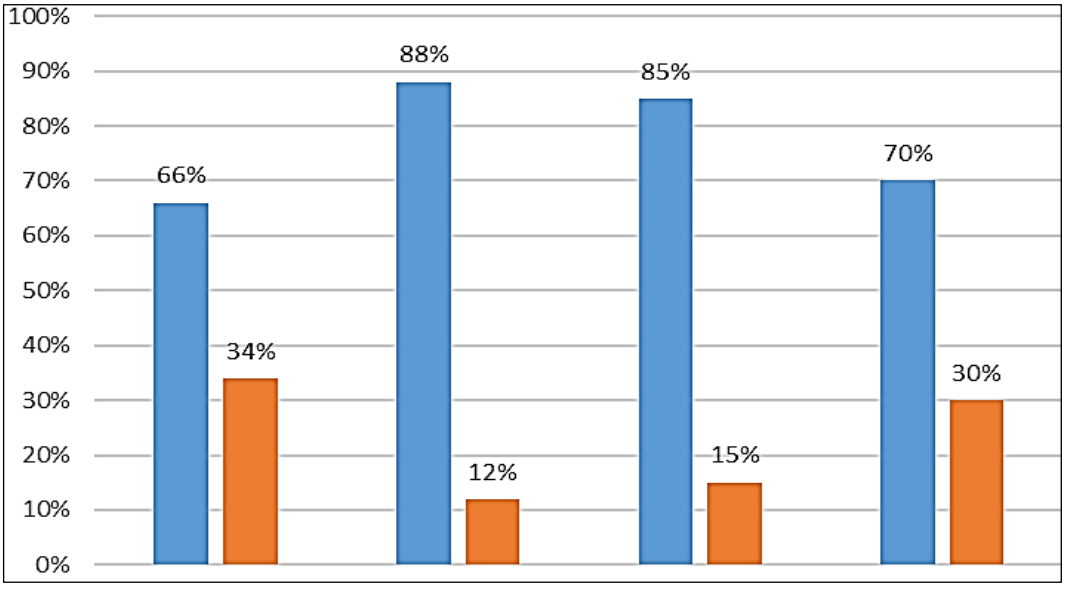

Fig 6a: Correlation of preoperative CEA with AJCC staging system

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Table 6b: Correlation of preoperative CEA with tumour Grade

	0-5 (n=42)	>5 (n=9)	P value
WDAC	9 (21)	3(30)	0.843
MDAC	14 (33)	2(20)	
PDAC	7 (17)	3(30)	
SC	10 (24)	2(20)	
MC	2 (5)	0	

No significant association could be demonstrated between preoperative CEA levels and tumour grade.

Preoperative analysis of CA19-9

- CA19-9 was considered positive when it was more than 37U/ml. It was raised in 36 patients (n=51, 70.5%) and within normal limits in 15 patients (29.5%) preoperatively.
- Of the 6 patients in Stage 1 (AJCC), 1 patient had raised CA19-9 levels preoperatively (17%).
- Of the 8 patients in Stage 2 (AJCC), 3 patient had elevated CA19-9 levels preoperatively (37%).
- Of the 27 patients in Stage 3 (AJCC), 24 patients had elevated CA19-9 levels preoperatively (89%).
- Of the 10 patients in Stage 4 (AJCC), 8 patients had elevated CA19-9 levels preoperatively (80%).

Table 7a: Correlation of preoperative CA19-9 with AJCC staging system

Preoperative	AJCC				P value
CA19-9	I	II	Ill	IV	
0-37	5(83)	5(63)	3(11)	2(20)	0.002
>37	1(17)	3(37)	24(89)	8(80)	
Total	6 (100)	8(100)	27(100)	10(100)	

Significant association could be demonstrated between preoperative CA19-9 levels and AJCC staging system for Gastric Carcinoma.
Elevated preoperative CA19-9 was more commonly associated with Stage III(89%) and Stage IV(80%) of Gastric Carcinoma suggestive of association of elevated CA19-9 with advanced and metastatic GC .

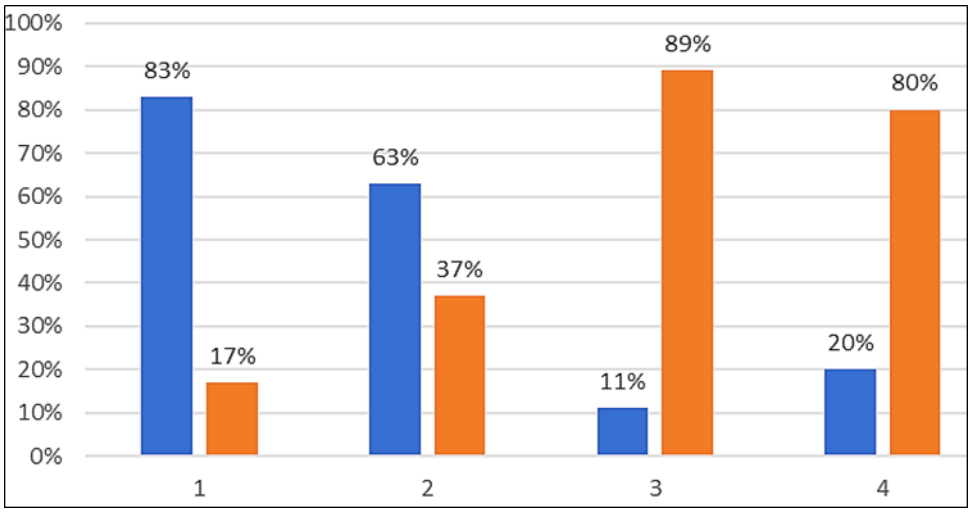

Fig 7a: Correlation of preoperative CA19-9 with AJCC staging system

Table 7b: Correlation of preoperative CA19-9 with tumour Grade

	0-37(n=15)	>37(n=36)	P value
WRAC	3 (20)	8(22)	0.742
MDAC	5(33)	12(33)	
PDAC	1 (7)	8(22)	
SC	6 (40)	6(17)	
MC	0 (0)	2((6)	

No significant association could be demonstrated between preoperative CA19-9 levels and tumour grade

Preoperative analysis of CA72-4

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- CA72-4 was considered positive when it was more than 6U/ml. It was raised in 4 patients (n=51, 7.8%) and within normal limits in 47 patients (92.2%) preoperatively.
- Of the 6 patients in Stage 1 (AJCC), none patient had raised CA72-4 levels preoperatively.
- Of the 8 patients in Stage 2 (AJCC), 1 patient had elevated CA72-4 levels preoperatively (12%).
- Of the 27 patients in Stage 3 (AJCC), 2 patients had elevated CA72-4 levels preoperatively (7%).
- Of the 10 patients in Stage 4 (AJCC), 1 patient had elevated C72-4 levels preoperatively (10%).

No significant association could be demonstrated between preoperative CA72-4 levels and AJCC staging system for Gastric cancer.

Table 8a: Correlation of preoperative CA72-4 with AJCC staging system

Preoperative	AJCC				P value
CA72-4	I	II	III	IV	
0-6	6(100)	7(88)	25(93)	9(90)	0.942
>6	0	1(12)	2(7)	1(10)	
Total	6 (100)	8(100)	27(100)	10(100)	

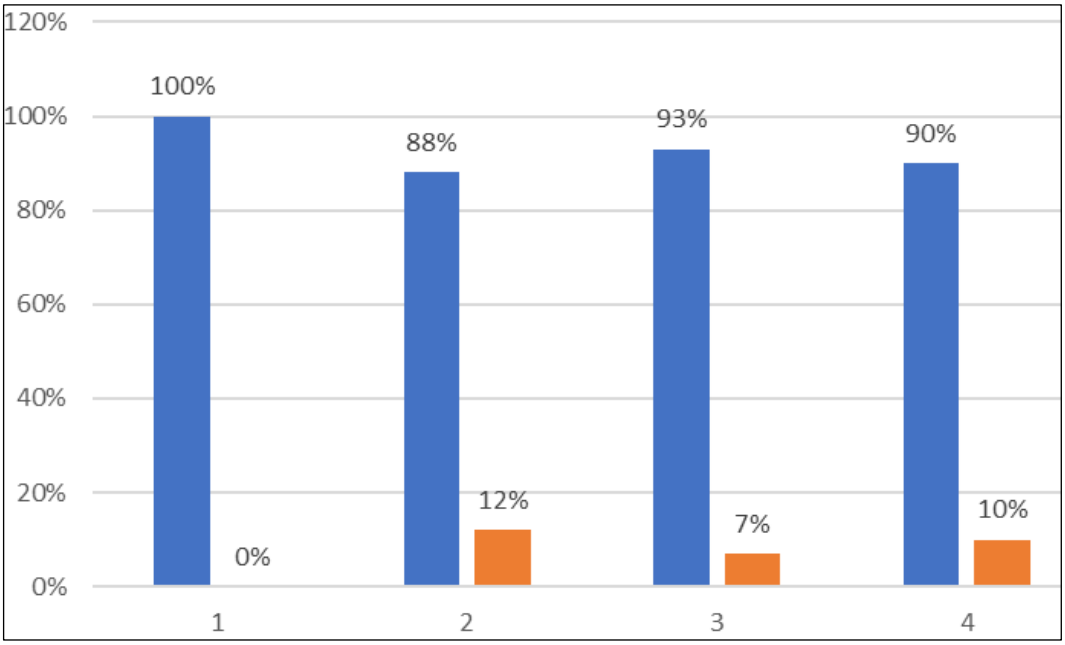

Fig 8a: Correlation of serum CA72-4 with stage of disease

Table 8b: Correlation of preoperative CA72-4 with Tumour Grade (8c)

	0-6(n=47)	>6(n=4)	P value
WDAC	9(19)	1(25)	0.5^2
MDAC	17(36)	0	
PDAC	8(17)	1(25)	
SC	11(23)	2(50)	
MC	2(5)	0	

No significant association could be demonstrated between preoperative CA72-4 levels and tumour grade. Out of all the parameters (pre-operative CEA, CA19-9 and CA72-4), elevated CA19-9 was the most sensitive marker associated with advanced stage and none of above tumour markers are correlate with grade of tumour. CA72-4 is least sensitive marker associated with advanced stage of tumour.

Discussion

The increased levels of tumour markers such as CEA, CA 19-9 and CA72-4 are proposed to be correlated with clinic and pathological features of gastric cancer. In clinical practice; the tumour markers CEA, CA 19-9 and CA72-4 are used to assess the efficacy of adjuvant treatment as a supplementary evidence for response. Despite numerous reports on the usefulness of preoperative and periodic postoperative measurements to predict stage, tumour progression, recurrence and prognosis in patients with gastric cancer, already tumour markers have limited clinical utility due to their low sensitivity and specificity [61]. Although there are no specific tumour-associated antigens in GC.

CEA and CA 19-9 are increased in the sera of many patients with advanced GC. Some studies have

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suggested their relevance to monitoring recurrence especially in patients with high preoperative levels [5]. CONVERSELY, few reports have studied their value as predictive factors for tumoral pathological staging, and they have also used different combinations of markers, making drawing of definitive conclusions difficultly. Tumour markers are primarily used in preoperative staging of neoplasms, postoperative monitoring of the treatment's effectiveness, and early diagnosis of recurrence. Furthermore, the possibility of using tumour markers as an aid in establishing the prognosis of patients who have undergone radical surgery has become a point of ever-increasing interest.

The markers routinely used to date in gastric cancer are CEA and CA 19-9; several authors, however, have shown the greater sensitivity of the recently identified CA72-4 with respect to these markers.

Marrelli D *et al*. [62] studied Preoperative levels of CEA, CA 19-9 and CA 72-4 were above the cut-off levels in 20.9, 34.6 and 28.1% of cases, respectively. Positivity rates of CEA, CA 19-9 and CA 72-4 were significantly higher when large tumour size, deep invasion in the gastric wall, and lymph node involvement were present. CEA and CA 19-9 were more frequently positive in the presence of distant metastasis and the same tendency was shown by CEA and CA 72-4 in cases with tumour residuals.

Our study showed preoperative levels of CEA, CA19-9 and CA72-4 were 19.6, 70.5 and 7.8% respectively. In comparison to above study CA19-9 was significantly associated with depth of invasion, lymph node status and associated with higher stage. The correlation between the preoperative level of tumour markers and the progression of the neoplasm explains, in part, the worse prognosis in patients with positive values. Of primary interest is whether tumour marker assays can provide useful information on clinical outcome of patients, in addition to the common prognostic factors.

Kodera *et al*. [63] compared the prognostic value of CEA and CA 19-9, and found positivity rates of CEA and CA19-9 were 16.6% and 16.0%, respectively. They found that positivity of CA19-9 correlated well with various forms of metastases, depths, and tumour size and CA19-9 in the preoperative sera is a good prognostic factor in gastric cancer patients. This study supported CA19-9 as good prognostic marker as same with our study and also Kodera *et al*. showed that none of tumour marker correlated with grade of tumour as same in our study. Another study Victorzon M *et al*. [64] showed similar finding that CEA and CA19-9 have good prognostic valve but limited in diagnostic value. In our study CA 19-9 proved to be a better prognostic indicator with respect to CEA and CA 72-4 and better correlate with stage of disease. Ikeguchi M *et al*. [65] found that elevated levels of CA72-4 were frequently found in patients with peritoneal metastasis at the time of operation and high pre-operative serum levels of CA72-4 and tumours with high proliferative activity. But in our study C72-4 does not corelated with advanced nature of disease.

However, differences in the number of patients, the assay technique used, cut-off levels and the follow-up period can explain the different findings. Due to this reason may our study has not corelating with above study. Guadagni F *et al*. [49] evaluated the correlation between CEA, CA19-9 and CA72-4 in Carcinoma stomach patients found that all elevated in Stage III and IV in following ratio 24%, 32% and 42% respectively. In our study only CA19-9 had elevated more than as compared to CEA and CA72-4 and correlated with higher stage.

This finding can be explained due to heterogenicity of population, mode of assay, laboratory methods and incubation period of blood samples and less number of study population. Jae-Cheol JO *et al*. [66] found elevated serum concentrations of carbohydrate antigen (CA) 19-9, CA 72-4 and carcinoembryonic antigen CEA were observed in 38, 56 and 33% of patients respectively. Jae-Cheol JO *et al*. found that CA19-9 more better predictor of higher and advanced stage of malignancy than CEA and CA72-4. In our study only there was significant elevation of CA19-9 as compared to CEA and CA 72-4 (70.5%, 19.6% and 7.8%) same as that of Jae-Cheol JO *et al*. Cidón EU *et al*. [66] found significant elevation of CA 72-4 as compared to CEA and CA 19-9 in contrast to our study and also this study didn't found any correlation between levels of tumour markers and pathological grade which is correlating with our study.

Ucar E [67] *et al*. done study on the following markers and found percentage of CA 19-9, CA 72-4, CEA, and AFP-positive cases were 41%, 32.6%, 24.2% and 8.4%, respectively and none of tumour marker correlated with grade of tumour as compared with our study only CA 19-9 had significantly increased in advanced stage and correlated with higher depth of invasion and lymph node involvement and none of correlated with grade of tumour.

To summarize, this is one of the very few prospective studies available and the best of our knowledge, this is the only study was done on Indian population, which have prospectively evaluated correlation of CEA, CA19-9 and CA72-4 with staging and grading of carcinoma stomach. We found significant correlation between CA19-9 and stage of disease as compared to CEA and CA 72-4 and none of tumour marker in study correlated with grade of tumour. Results in our study is consistent with some studies done in past. Coming to correlation with CEA and CA72-4 with stage of disease, our results differ with almost all the previous studies available. The reason for the above difference may be due to smaller sample size compared to most of the studies available, different population group (all previous studies being from other than India). It also depends on type of analysis, laboratory methods and incubation period of blood sample. All this reason may explain difference in results.

In our study we found significant correlation between Serum CA19-9 levels and stage of disease and none of tumours marker correlated with grade of tumour). Most of the previous studies correlated

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increased levels of above all three tumours markers with stage of disease more of CA 72-4 and none with grade of tumour. Hence our results substantiate that, increased Serum levels of CA 19-9 is associated with advanced stage of disease and associated with poor prognosis.

Limitations

- Single Centre, Non-randomized, Observational study.
- Limited sample size.
- No follow up analysis.
- No survival analysis.

Conclusion

Preoperative Increased Serum levels of CA 19 -9 is associated with advanced TNM stage of Carcinoma Stomach as compared to CEA and CA 72-4 and none of above tumour markers is associated with grade or histology of malignancy. Considering our results and the evidence available to present day, we can say that, Increased Serum CA 19-9 is perhaps an independent predictor of advanced stage and poor prognostic factor in patients with Gastric carcinoma. Hence, the patients with increased Serum CA 19-9 is associated with advanced stage and may require neoadjuvant therapy unless there is no contraindication for neoadjuvant therapy and not any emergency condition. But this has to be substantiated by long term follow up studies and survival analysis and further randomized control studies.

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