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Muthanna Medical Journal
2022; **6**(1):29-40

http://dx.doi.org/10.52113/1/1/2022-29-40

The role of tumor associated glycoprotein CA 72-4 in patients with gastric adenocarcinoma

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Abstract

Gastric cancer is a multifactorial disease with dietary and infection (especially with H. Pylori) being the most important factors; it shows a remarkable variation in distribution worldwide and the incidence have fallen dramatically in past decades, nevertheless it ranks fourth among the commonest cancer and second leading cause of cancer related death, and so global health problem. The aim of the study is measurement of the serum level of CA 72-4 to determine its effectiveness in patients with gastric cancer. The serum level of CA 72-4 was measured in 35 patients with gastric adenocarcinoma preoperative and 8 patients postoperatively, compared with 25 patients control (chronic gastritis) and 18 health control by using immunoenzymatic assay (ELISA) kit. X. In this study the median age of patients with gastric cancer was (53.4 ± 13.9) years, with male to female ratio about 1:1.15. Serological data revealed that the elevated level of serum CA 72-4 was detected in about 48% with 100% specificity, and about 60% sensitivity for advanced disease, the elevated level of serum CA 72-4 correlate significantly with lymph node involvement, extra-nodal metastasis, and tumor invasion, (the P value was < 0.01, 0.028, 0.016 respectively), consequently with disease extension and preoperative stage prediction, the best relationship was with metastasis (80%) sensitivity. In conclusion, according to the present data, CA 72-4 is a useful marker in detecting advanced gastric cancer, and non-invasive tool in predicting stage cancer.

Keywords: Tumor associated glycoprotein, CA 72-4, Gastric adenocarcinoma

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Received 11 April 2022, Accepted 18 June 2022, Available online 26 June 2022

Introduction

Gastric cancer has been described as early as 3000B.C in hieroglyphic inscription and papyri manuscripts from ancient Egypt, nowadays the gastric cancer is one of the commonest malignancies worlds wide [1, 2]. Neoplasm of the stomach consist of benign

and malignant tumors, benign tumors are in general rare and the malignant are common, with about 95% of the latter consisting of adenocarcinoma [3, 4], and in general, the term gastric carcinoma represent adenocarcinoma of stomach [5].

At histological level, adenocarcinoma of stomach is a malignant epithelial tumor of gastric mucosa arising from mucus secreting cell at the base of gastric crypt with glandular differentiation [6]. Overall, gastric incidence and mortality have been fallen dramatically over the past century; part of decline may be due to the recognition of certain risk factors such as dietary and environmental factors and helicobacter pylori infection [7, 8].

The other major classification is the WHO classification, usually divides gastric adenocarcinoma into one of four patterns, despite their histological variability, and the diagnosis is based on the predominant histological pattern: 1- Tubular adenocarcinoma. 2- Papillary adenocarcinoma. 3- Mucinous adenocarcinoma. 4- Signet – ring carcinoma. The WHO classification offers more information which allows Finer division [9]. Gastric carcinoma is a multifactorial disease; the marked geographical variation, time trends, the migratory effect and other variations in incidence suggest that environmental or lifestyle factors are contributors to the etiology of this disease [10,11].

Apart from patients with early gastric cancer, over all prognosis is poor, although the mortality rate has been dramatically decreasing since 1930 it remains a disease with poor prognosis and high mortality rate due to advanced disease at time of diagnosis, in the United State the overall 5 years relative survival rate is about 23%, prognosis in early gastric cancer for any tumor which is limited to the mucosa is good (90%), but if there is penetration of sub-mucosa or muscularis layers the prognosis is intermediate [12, 13]. The aim of the study is to measurement of the serum level of CA 72-4 to determine its effectiveness in patients with gastric cancer.

Method and Patients

A prospective study was conducted in the period between Decembers 2010 and June 2011, a total of 86 individuals were subjected to the assay, and they were subdivided into the following main groups. Patients study group: It included (43) patients with histologically diagnosed stomach cancer. Patient control group: Includes a total of 25 patients with chronic gastritis and they were endoscopic ally and histologically considered a benign condition. Healthy control group: Includes 18 healthy subjects who had no manifestations of gastric diseases as volunteer.

Three to five ml of venous blood was obtained from each subject included in this study and placed in a sterile plane tube, centrifuged and then the serum is divided into adequate amount and stored at (-2C) for further processing, and all the sera were thawed when

used. It's a solid phase ELISA based on the sandwich principle, the microwells walls are coated with a monoclonal (mouse) antibody directed towards a unique antigenic site on a CA72-4 Molecule.

The aliquot of patient sample is incubated in the coated wall with enzyme conjugate which is an anti-CA72-4 antibody conjugate with horseradish peroxidase, if sample is positive, then the Antigen-Antibody reaction will result with subsequent interaction with the enzyme conjugate, after incubation the unbound conjugate is washed off. The amount of bound peroxides is proportional to the concentration of CA72-4 in the sample, having added the substrate solution, the intensity of color developed is proportional to the concentration of CA72-4 in the patient sample.

The results have been calculated automatically using a 4 Parameter logistic curve fit (4PL) the concentration of sample can be read directly from the curve. A sample was considered to be elevated if the concertation value was equal or higher than the normal value which is in this assay is 3U/dL, and those lower than the normal value was considered normal. Data were translated to codes using a specially coding sheet, and then into computerized database structure, statistical analysis was done using SPSS (statistical Package for Social Science), P value below 0.05 was considered statistically significance.

Results

The study comprises a total of 43 with established gastric adenocarcinoma of which 35 patients with clinical and histological evidence of active disease and additional of 8 patients in the follow up period with no evidence of active disease, and 25 patients control group (including cases with chronic gastritis), and 18 healthy control individuals. Table (1) shows the distribution of cases according to age, in this study the of age of patients with gastric carcinoma in general ranged between (28-77 years) with mean age (53.4± 13.9 years), the highest percentage (44.1%) of patients is in age group of 60 years and more. The mean age of the patients control group was 49.1± 12.9 years and that for healthy group was (47.16 ± 12.9), with P value about (0.135) which considered not significant.

Table 1.

The distribution of cases according to the age.

Age group (year)*		Carcinoma		Patient control		Healthy control	
		No.	**%**	**No.**	**%**	**No.**	**%**
Ten years ageintervals	20-29 years	2	4	3	12	2	11.11
	30-39 years	4	9.3	3	12	3	16.67
	40-49 years	7	16.6	5	20	5	27.78
	50-59 years	11	25.58	7	28	5	27.78
	≥60 years	19	44.18	7	28	3	16.67
	Total	100	43	100	25	100	18
Mean age		53.4 ± 13.9		49.1 ± 12.9		47.1 ± 12.9	

*P Value 0.135 considered non-significant

Table (2) shows the gender distribution of the cases involved in the study groups with demonstration of the male to female ratio and in carcinoma cases are about 1:1.15.

Table 2.

The distribution of cases in relation to gender

*P= 0.689 / Gender		Carcinoma		Patient control		Healthy control	
		No.	**%**	**No.**	**%**	**No.**	**%**
Gender	Male	20	46.51	14	56	10	55.56
	Female	23	53.48	11	44	8	44.44
	Total	43	100	25	100	18	100
	M:F	1:1.15		1.27:1		1.25:8	

* P: 0.689 considered not significant between the 3 groups

The distribution of elevated and normal level of CA 72-4 (which is 3U/dL) with the frequency in the groups enrolled in the study are demonstrated in table (3), this table shows that 17 patients out of 35 (48.57%) with active disease are positive for the marker, while none of the patients with chronic gastritis and healthy control have a value above the normal level for the tumor marker, also no elevated level noticed in patients during the follow-up period.

Table 3.

The distribution of elevated concentration among preoperative stomach carcinoma, follow up, chronic gastritis and healthy control groups.

Study group		Carcinoma stomach	Follow up	Patient control	Healthy control
CA-72-4	Elevated	17 (48.57%)	0 (0%)	0 (0%)	0 (0%)
	Normal	18 (51.43%)	8 (100%)	25 (100%)	18 (100%)
	Total	35 (100%)	8 (100%)	25 (100%)	18 (100%)

Table (4) demonstrated the elevated level in patient with pre-operative period in relation to the stage of the disease, which shows that 7 patients out of 14 (50%) with stage III were positive for the presence of the marker, and 8 patients out of 12 (83%) with stage IV werepositive, while patient with stage II were negative.

Table 4.

The distribution of elevated level of CA 72-4 according to the stage ofthe disease in patients with active disease

Disease Stages	CA724		Total
	Normal	Elevated	
Stage II	9	0	9
Stage III	7	7	14
Stage IV	2	10	12
Total	18	17	35
P	**0.001 S**		

P value is <0.001 considered significant

Table (5), show the relation of elevated level with metastasis, and 7 patients from a total of 23 with no evidence of metastasis and 10 from 12 patients with metastasis had elevated level ofCA 72-4, with P value about 0.02.

Table 5.

Distribution of serum level of CA 72-4 according to presence orabsence of metastasis

	CA724		Total
	Normal	Elevated	
No metastasis	16	7	23
Metastasis	2	10	12
Total	18	17	35
P	**0.028 S**		

P value: < 0.028 considered significant

Table (6) reveals the elevated level of CA 72-4 in relation to the depth of invasion, which shows that the sensitivity of the marker increases with deeper invasion , in table (7) the distribution of normal and elevated serum level is demonstrated in relation to lymphatic involvement, which shows increased percentage of positive cases with increase lymphatic involvement, and table (8) shows the positive and to the other groups with sensitivity and specificity in general, in addition to positive predictive value (PPV) and negative predictive value (NPV) respectively.

Table 6.
Elevated and normal level of CA 72-4 according to the depth of invasion

Depth of Invasion	*Serum level of CA724		Total
	Normal	Elevated	
T2	10	3	13
T3	7	7	14
T4	1	7	8
Total	18	17	35
0.016 S P			

*P value is 0.016 is significant
*T= represent the tumor depth, T_2 sub serosa, T_3 serosa, T_4 adjacent structures.

Table 7.
Distribution of normal and elevated serum level of CA 72-4 according to lymph node invasion

	*CA 72-4		TOTAL
	Normal	Elevated	
No	0	0	0
N1	9	2	11
N2	5	9	14
N3	4	6	10
Total	18	17	35

*P value < 0.05

N referred to lymph node, N_0 no regional lymph node metastasis N_1 metastasis to 1-6 regional lymph node, N_2 7-15 lymph node metastasis N_3 more than 15 lymph nodes.

Table 8.

Sensitivity and specificity of CA 72-4 marker in gastric cancer

	CARCINOMA GROUP	OTHER GROUPS	TOTAL
Elevated CA-27-4	17 (TP)	0 (FP)	17
Normal CA-27-4	18 (FN)	51 (TN)	69
Total	35	51	86
Sensitivity	48.57%		
Specificity	100%		
PPV	100%		
NPV	73.91%		

TP = True Positive FP = False Positive TN = True Negative FN = False Negative

PPV = Positive predictive Value NPV = Negative Predictive value.

Discussion

Malignant diseases in most instances are associated with release of various substances into biological fluids and spaces, such substances have been termed biological marker, or more commonly tumor markers, as it's known, cancers still represent a challenging problem worldwide, many issues including tumor markers have received a considerable attention with more increase searches and studies about markers to identify their possible role in cancer management and, in addition to their role in understanding tumor biology in general [14,15].

In the present study the age of patients with gastric adenocarcinoma ranged between 28-77 years (mean = 53.4 years) this result was agreed compared to other studies in our country [16,17]. The age incidence of gastric cancer rises after the 50 years of age and reaches peak after 60 years of age, its uncommon before the age of 40 years [6].

In this study the peak age incidence was in the age group 60 years and above (44%), the second frequency was in the age group between 50- 59 (25%) years, which comparable with other studies [18,19] however the age group 30-39 years consist about (9.3%) which is younger than mentioned in literatures, and studies [20], this earlier onset of disease is noticed in our country and could be due to geographical variation.

On the other hand, the male to female ration was about 1:1.15 which is nearly equal, and which is disagreed with reported statistics worldwide, as they show that the male to female ratio is nearly 2:1, [21] this may be related to the small population of study in addition to geographical aspects, as it's agreed with some other Iraqi studies [16,17].

It was found that the percentage of elevated serum level of CA 72-4 in patient with established gastric adenocarcinoma is nearly 48.7%, previous literatures and authors reported a percentage of positivity or sensitivity ranging between (16.4-61%), so the present result is within this range [22, 23]. On the other hand, many workers study and reported the sensitivity of markers that currently used in gastric cancer, as CEA (15.9-57%) and CA 19-9 (16.0-44%). In comparing to other markers, CA72-4 has a higher sensitivity than that of CA 19-9 and CEA [24, 25].

When patients were divided into two groups, group 1 (stage I and stage II) and group 2 (stage III and stage IV), the percentage of positivity was elevated to be about (50%-80%) for group 2 (advanced disease) and P value < 0.001, which is agreed with other studies [25, 26].

Furthermore, in other studies that used immune polymerase chain reaction (PCR) method. When ELISA method was applied on the patients control and healthy control individuals, no elevated serum level was observed, which gives 100% specificity of the markers, this is compared with some studies [27].

Other authors reported a percentage of specificity between 90-95% [25] which is although high but lower than the present result, this may be due to the smaller study population and specific selection of control groups. In this study by comparing the serum level of CA 72-4 in correlation to number of lymph node involved, it was found that P value is (< 0.05) which considered statistically significant, and the marker may give a prediction of lymph node involvement, this result is agreed with that documented by previous studies [28, 29].

Regarding the presence or absence of metastasis, the seroimmunological data revealed, that only 7 patients out of 25 without metastasis had elevated serum level (30.9%) while 10 patients out of 12 (81.0%) with metastasis with elevated serum level CA72-4 and P value is < 0.028, which is considered a good indicator for presence of metastasis preoperatively, and consequently in determining prognosis, and therapy selection, this result agreed with most of other studies [30, 31].

When the depth of tumor invasion was considered, the results revealed increase effectiveness with increasing in depth of invasion and a P value of less than 0.016, which is statistically significant, these results are agreed with some other studies [25, 32]. In the present study 8 patient postoperatively in the follow up period have been investigated, all had normal marker level, some of them had undetected serum level of the tumor markers, whereas other have a detectable serum level but not above the cut-off value, some

workers study the CA 72-4 postoperatively, one of these are Guadagni et al (1992), found by 3 years follow up of patient post-surgery.

That 7 patients out of 10 with clinical recurrence have elevated serum level of CA 72-4 either prior or concomitant with clinical diagnosis, while serum level of CA 19-9 was positive in 5 cases and only 2 cases were positive for CEA, and the elevation of CA 72-4 was detected about 297-day s prior to clinical recurrence, furthermore some of these cases were negative for TAG-72 prior to therapy [33].

Conclusion

According to the present data, CA 72-4 is a useful marker in detecting advanced gastric cancer, and non-invasive tool in predicting stage cancer.

Ethical Approval

The study was approved by the Ethical Committee.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

All authors shared in conception, design of the study, acquisition of data, and manuscript writing, the critical revising and final approval of the version to be published.

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