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Ca242 as a potential prognostic marker in colorectal cancer Iraqi patients

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Abstract---Background: Colorectal cancer is the third most common cancer-related mortality worldwide, and its prevalence is increasing among many nations. Aim of the study: Investigate the predictive value of carbohydrate antigen 242 (CA242) in comparison to the CEA biomarker and to estimate the significance of CA242 as prognosis maker in colorectal cancer patients. Methods: a case-control study with a total of 150 individuals, 100 patients (59 males, 41 females) and 50 healthy controls (26 males, 24 females). using an enzyme-linked immunosorbent (ELISA) to determine the serum levels of CA242 and CEA. The study was carried out at the gastroenterology consultation clinic of the oncology teaching hospital between November 2020 and February 2021 in Baghdad, Iraq. Result: Patients with colorectal cancer had significantly higher CA242 levels than healthy controls ($p < 0.001$) with a significant positive correlation between CA242 and CEA ($r = 0.866$, $p < 0.001$). The CA242 ROC curve study revealed an AUC of 0.933, a sensitivity of 89%, a specificity of 88%, and a cutoff value of 45 U/ml. CA242 can serve as a potential prognostic biomarker for colorectal cancer.

Keywords---Serum CEA, serum CA242, colorectal cancer, prognostic biomarker, oncology.

Introduction

Colorectal cancer (CRC) is a huge worldwide health concern and one of the most frequent cancers. CRC is the third most common cancer worldwide and the second deadliest, with 1.8 million new cancer cases and 881,000 mortalities in

2018 (Bray et al., 2018), CRC is estimated to rise to 2.2 million new cancer cases and 1.1 million mortalities by 2030 (Arnold et al., 2017), since of expanded colonoscopy screenings, CRC mortality rates have gradually declined in recent times among individuals aged 65 years; unfortunately, the reverse has happened in individuals younger than 50 years (Siegel et al., 2017), this upward tendency in younger individuals, together with the total burden, is concerning; novel measures for early identification and prevention of CRC are desperately needed. CRC epidemiology is complex, as is the case with several diseases, and includes both hereditary and environmental elements (Louis et al., 2014), Only a small percentage of CRCs, are genetically predisposed, such as familial adenomatous polyposis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), Peutz-Jeghers syndrome, as well as other rare illnesses, according to evidence from family studies (Foulkes, 2008), Furthermore, 10%–20% among all CRC patients have a relevant family history of cancer (Dekker et al., 2019), the majority of CRCs are sporadic and non-inherited (Drewes et al., 2016), Sporadic CRC is caused by environmental factors such as food habits, smoking, body weight and obesity, diabetic, and excessive alcohol intake (Coker et al., 2019).

Gold et al. in 1965 discovered carcinoembryonic antigen (CEA), and it is now one of the most commonly investigated cancer markers. It's an onco-fetal antigen that's generally found in fetal period but it can also be found in healthy individuals in low concentrations. It is a glycoprotein with a molecular weight of 200 kDa that is present on the endo-luminal side of the cell of normal epithelial cells as part of the glycocalyx. CEA is a member of the family of CEA-related cell adhesion molecules (Hammarström, 1999), Colorectal, breast, gastric, lung, ovarian, and pancreatic cancers all have elevated CEA levels in the blood (Sisik et al., 2013), However, several non-malignant conditions, such as smoking cigarettes, alcoholism, chronic inflammatory bowel disease, ulcerative colitis, pancreatitis, and liver disease, can cause an increase in CEA (Tan et al., 2009).

CA242 (sialylated carbohydrate antigen 242) is a sialylated carbohydrate antigen located at the surface of cells and in serum. CA242 production was found to be highly linked to the clinical and pathological characteristics of a variety of intestinal malignant tumors, including gastric cancer and colorectal cancer (CRC) (Dong et al., 2018), the combination of CEA and CA242 exhibited a markedly better sensitivity in CRC than each test alone, indicating that CA242 measurement is important for cancer patients, particularly those with gastrointestinal tumors (Zhang et al., 2019).

Method

Materials and methods:

The study was authorized by the Baghdad University College of Medicine's ethics committee as well as the Ministry of Health's Training and Development Section in Baghdad, Iraq, all patients were informed about the study's significance via a written and spoken information page, and all patients gave their permission before the samples were taken, this is a case control study prospective study carried out between November 2020 and February 2021. The CRC group included 59 men and 41 women ranging in age from 26 to 75 years old (mean \pm SD, 50.58

± 11.38 years), The patient CRC group consisted of 100 patients who were diagnosed by oncology consultant after a clinical, laboratory & radiographic examination, with CRC of the rectum (n=16) and colon (n=84). The control group consist of 50 healthy volunteers (ages 34 – 68; mean ± SD, 49.9 ± 8.45 years, 26 men and 24 women) who were free of any critical infections or gastrointestinal disorders, Inclusion criteria, histopathological diagnosis of colorectal cancer, full clinical histopathologic report and post - operative follow-up data, complete information of preoperative serum oncologic biomarker, Patient received admission evaluations, such as abdominal CT or MR, and postsurgical tissue biopsy confirmed the diagnostic test, Exclusion criteria, all patients with ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease, hypothyroidism.

Patients group was subdivided into 3 sub-groups, (on chemotherapy only) subgroup (40) like (XELODA, OXALIPLATIN, XELOX, OXALIPLATIN, IRINOTECAN, LEUCOVORIN, FOLFIRI), (on chemotherapy and immunotherapy) subgroup (32) same chemotherapy above with AVASTIN, (follow up) subgroup (28), and apparently healthy people (50).

Teaching Laboratories/Medical City used the Enzyme Linked Immunosorbent Assay (ELISA) method (CEA kit: BT LAB/ China) and (CA242 kit: BT LAB/ China), 5 mL intravenous blood samples were taken from each patient with colorectal cancer and a control subjects. For our parameters under research, we used plain tubes (5ml) with each blood sample, allow the serum to clot for 10-20 minutes at room temperature. Centrifuge (at 2000-3000 RPM) for 20 minutes. Collect the supernatants carefully, Storage: the kit kept at the temperature of 2-8°C. Each individual was given a questionnaire that contained the information about the case, age, gender, medical history, smoking, family history of cancer and surgical treatment, depending on the American Joint Committee on Cancer Staging's Tumor-Node-Metastasis (TNM) classification (eighth edition) (Amin et al., 2017).

Statistical analysis:

The SPSS 26 statistical software program was used for the statistical analysis. Standard descriptive statistics, tabulation of categorical variables, and histograms of numerical variables were used to describe basic data, the data is presented as a mean ± standard deviation. The difference in median among two groups was analyzed using the nonparametric test (Mann-Whitney), Statistical differences between the groups were determined using the ANOVA test, and student t-test results were found to be significant if $P < \text{value } 0.05$.

Results

The study design is case control study which is comprised of (150) individuals, age Mean ± SD for the patients group (50.58 ± 11.38) years and for the control group (49.9 ± 8.45) years, The age of the patients subdivided into two categories involves (age ≥ 50) include (58) subjects and (age > 50) include (42) subjects, the age range from (26 to 75) years in patients group, Compared to (50) apparently healthy person with an age range from (34 to 68) years, The gender of the patients group consists of (59) males & (41) females with colorectal cancer patients, while

the control group include (26) male (52 %) and (24) female (48%), in total of both groups the male consists (56.6%) and female (43.4%), as in table 1.

Table 1
The Demographic Distribution Of Study

Factors	Patients N=100	Control N=50
Male	59 (59%)	26 (52%)
Female	41 (41%)	24 (48%)
Age Mean \pm SD	50.58 \pm 11.38 years	49.9 \pm 8.45 years
Age \geq 50	58	26
Age < 50	42	24
Rang of age	26-75	34-68

Serum concentration of Carcinoembryonic antigen (CEA)

The mean of concentration of serum CEA in patients' groups is (19.24 ng/ml), while in control group it was (3.45 ng/ml), there was statistical significant when compare patients group with control group ($p < 0.001$), Furthermore the mean of concentration in subgroups of the patients (on chemotherapy only, on chemotherapy and immunotherapy, on follow up) was (19.88 ng/ml), (19.79 ng/ml), (16.99 ng/ml) respectively, with on statistical significant in compare between the subgroups of patients, all explain in table 2.

Table 2
serum level of (CEA) in different groups

CEA (ng/ml)	Serum level	P value (Sig. \leq 0.05)		
Group	M \pm SD	Chemotherapy P value	Follow up P value	Control P value
Chemo/Immunotherapy	19.79 \pm 6.57	0.95	0.1	<0.001
Chemotherapy	19.88 \pm 7.62		0.07	<0.001
Follow up	16.99 \pm 6.89			<0.001
Control	3.45 \pm 2.21			
Patients	19.24 \pm 8.28			<0.001

Serum concentration of carbohydrate antigen-242 (CA-242)

The mean of serum concentration of CA 242 was (64.36 U/ml) patients group, the mean of serum concentration in control group was (18.66 U/ml), there was a statistical significance among patient's group and control group ($p < 0.001$), The mean of serum concentration of CA 242 in the subgroups of the patients was (64.96 U/ml), (66.39U/ml), (60.71 U/ml) in (on chemotherapy only, on chemo/immunotherapy, on follow up) respectively, and there was no statistical significance between the subgroups of patients, as in table 3.

Table 3
Serum level of (CA-242) in different groups

CA242 Group	Serum level (U/ml) M±SD	P value (Sig≤0.05)		
		Chemotherapy p value	Follow up p value	Control p value
Chemo/Immunotherapy	66.39±13.42	0.64	0.09	<0.001
Chemotherapy	64.96±12.58		0.18	<0.001
Follow up	60.71±18.27			<0.001
Control	18.61±8.21			
Patients	64.36±11.3			<0.001

Correlation between the markers:

The correlation between both of makers that use in this study, the correlation of CEA with CA 242 was (0.866), with statistical significance ($p < 0.05$), Linear regression was mad between the maker's dependent on CEA as predict value to CA-242 makers to determine the relationship's strength and character, with R^2 was (0.75), as in figure 1.

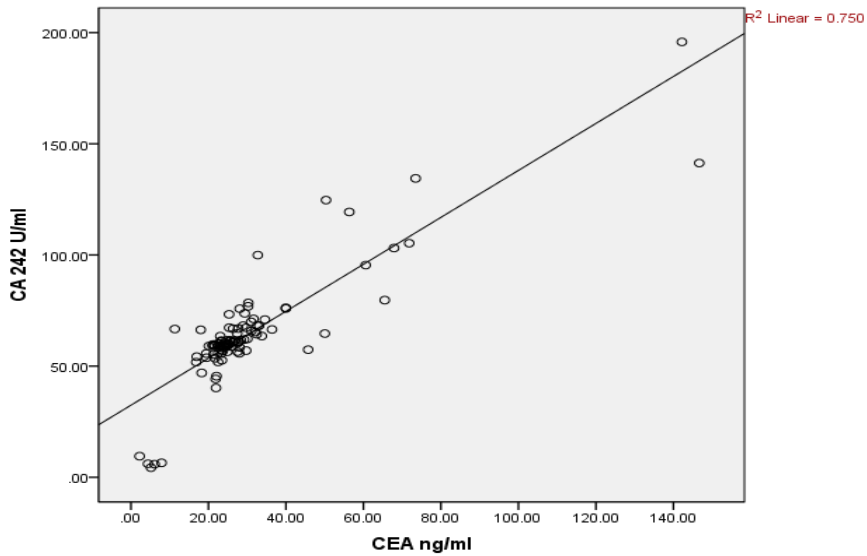


Figure 1: Linear regression between CEA and CA-242.

Receiver operator characteristic curve (ROC) for markers of the study

The ROC curve of serum makers (CEA) has area under the curve (0.91) which is strong correlation between disease and markers as prognosis value, the sensitivity of maker (91%) and the specificity (80%) with cut off (5 ng/ml), and for (CA242) marker the cut off (45 U/ml) and the sensitivity (89%), the specificity (88%) and the area under the curve was (0.93) which is strong correlation with the disease as prognosis value, as in table 4,5, and figure 2,3.

Table 4
The Area Under The Curve For Markers

Area Under the Curve						
Test Variable(s)	Result	Area	Std. Error	Asymptotic Sig.*	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
CEA (ng/ml)		.919	.026	.000	.868	.970
CA242 (U/ml)		.933	.025	.000	.885	.981
*. Null hypothesis: true area = 0.05						

Table 5
Cut-Off, Sensitivity, Specificity For Makers

makers	Cut-of	sensitivity	specificity
CEA	5 ng/ml	91%	80%
CA 242	45 U/ml	89%	88%

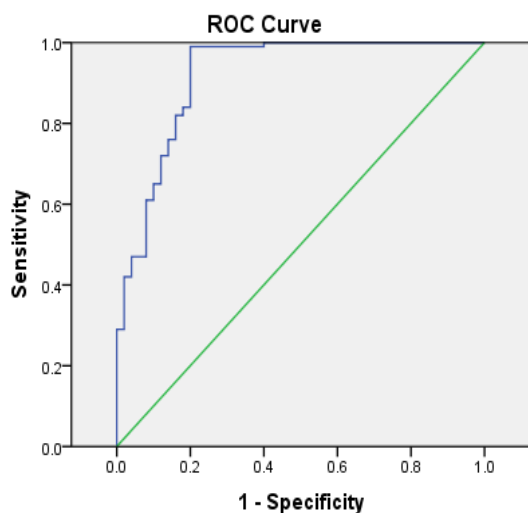


Figure 2: the (ROC) curve of CEA.

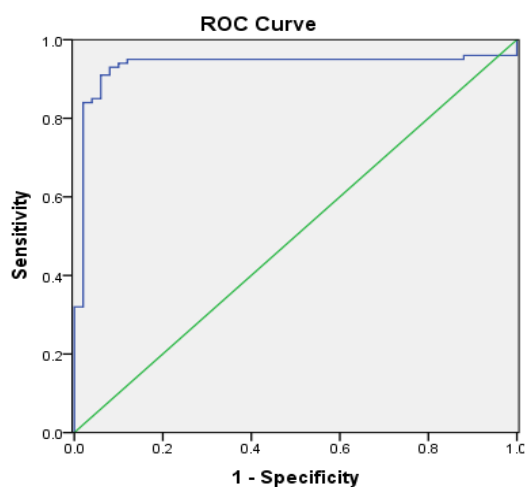


Figure 3: the (ROC) curve of CA242.

Discussion:

Demographic distribution

The age in this study groups ranged between (26 to 75) yeas in patients group, with a mean age \pm SD (50.58 ± 11.38), (49.9 ± 8.45) for the patients, which agrees with other studies that indicating colorectal cancer can affect people of various ages (Siegel et al., 2020).

Most incidence of colorectal cancer in age ≥ 50 years about (58%) in the patients group, while about (42%) in age > 50 years, the incidence of colorectal cancer has increased among people aged (20 to 49), in recent years, there has been a rise in the incidence of CRC in young adults in several parts of the world, according to other study as shown in (Vuik et al., 2019).

Notice in this study that young age with colorectal cancer has family history of cancer about (48%) of the patients group, in this study which may due to

Transmission of genetic information (mutations) responsible for cancer from parents to offspring, that agrees with the study (Pesola et al., 2020), discovered that colorectal cancer is caused by gene alterations (also known as mutations or alterations), or may due to other different factors like habits of feeding, smoking and past medical history.

This study showed that the majority of males in patient groups was (59%) more than females (41%), men are more likely than women to acquire CRC, which could be attributable to a variety of biological and gender-related conditions, that agree with study (Abancens et al., 2020), which declare that men are more likely than women to eat a diet high in red and processed meat, consume more alcohol, and smoke, men are also more likely to store visceral fat, which has been linked to an increased risk of CRC and these findings matched those of other study (White et al., 2018) that found that males were more impacted than females, and also in other study in Iraq (Hussein et al., 2017).

In this study Non-smoking were (79%) of the patients in compare with smokers (21%), smoking one of the risk factor for colorectal cancer, this agreed with other study that demonstrate smoking was associated with colorectal cancer because smoking was linked to the mutation-positive colorectal cancer, suggesting that epigenetic alteration may have a functional role in the development of colorectal cancer as a result of smoking (Limsui et al., 2010). Family history of cancer was (19%) in patients group while (71%) with no family history, the majority of colorectal cancers are detected in adults who have no family history of the disease, may be due different risk factors that Contribute to the development of cancer, which agrees with other study (Kastrinos et al., 2020), a family history of colorectal cancer (CRC) caused by genetic factors, environmental exposures, or both affects about 35% of people with the disease. Only 5 to 10 % of CRC cases are attributable to some families with a history of cancer having genetic variations with high or moderate incidence that cause CRC.

Carcinoembryonic Antigen (CEA):

Carcinoembryonic antigen (CEA) is a group of strongly linked glycoproteins that are expressed in intestinal tissue from the human's embryonic stage to the fetus. CEA is mostly produced by colon mucosal cells in adults, with a little amount produced by other cells. There is a little quantity of spread into the blood. It has a two-day half-life in blood. as an embryonic tumor antigen CEA is employed as a diagnostic marker in clinical practice since it is highly expressed in colorectal cancer (Fang et al., 2022).

In this study, the mean level of serum CEA was (19.24ng/ml) in the colorectal cancer patients group, which has a significant statistical difference ($p < 0.001$) with control groups which was (3.45 ng/ml), this was agreed with (Zhai et al., 2018), which demonstrate that high level of CEA in colorectal cancer patients.

In this study, the patients divided into three subgroup according the treatment receive (chemotherapy only, chemo/immunotherapy) subgroups the CEA mean was (19.88 ng/ml, 19.79 ng/ml) respectively which consider high level, may be due to short time of receive treatments, within 4 to 6 weeks after a successful surgical removal of colorectal cancer and treatment, the CEA levels should return

to normal, agree with other study (Saito et al., 2017), also may be due to patients undergoing first-line chemotherapy for metastatic colorectal cancer, a temporary rise (surge phenomenon or flare) was linked to a therapeutic benefit which agree with other study (Andrea et al., 2014). And also as a part of immune response the interleukin 6 (IL-6) is secreted during acute and chronic inflammation, many hallmarks of cancer affected by IL-6, including as proliferation, cell growth, and apoptosis suppression, are influenced by IL-6, which can lead to medication resistance in cancer cells, which agree with other study (Lehtomäki et al., 2021). The subgroup (follow up) serum CEA mean was (16.99 ng/ml), recurrence following successful surgery is one of the most important factors affecting long-term survival, with a frequency of 22.5% at five years, this is agree with other study (Farhat et al., 2019). CEA has a high specificity and sensitivity for CRC screening and is a useful tool for determining the prognosis of CRC patients. The knowledge of human cancers and how to treat it. their linked serum indicators have risen in recent years. biomarkers in the last few years, and this has shown the promise of biomarkers in assistance in the development of the diagnosis and evaluation of effects of therapy and prognosis (Luo et al., 2020).

The ROC findings indicate that the optimal serum CEA cutoff value for the patients group was 5ng/ml, with sensitivity of maker (91%) and the specificity (80%), which agree with (Sørensen et al., 2016), study that demonstrate CEA had a high sensitivity reach (100 %), and specificity (98.4 %).

Carbohydrate antigen 242 (CA242)

Is a novel tumor marker based on the monoclonal antibody C 242 (C 242 antibody), which was discovered after mice were immunized with a human colorectal cancer cell line, the serum level of CA242 has been discovered to be higher in cancer patients, and CA242 has been found to be overexpressed very strongly in cancer cells than in neighboring tissues, so serum CA242 is assumed to be a product of cancer cells (Dou et al., 2019).

In this study, the mean of serum concentration of CA-242 was (64.36 U/ml) in the colorectal cancer patients group, which has a significant statistical difference ($p < 0.001$) with control groups which was (18.66 U/ml), CA242 levels were observed to be increased in colorectal cancer patients, and CA242 was also demonstrated to be able to identify colorectal cancer patients compared with healthy controls, which is agree with other study (Shen et al., 2020).

The subgroups of patients (chemotherapy only, chemo/immunotherapy) mean of serum concentration was (64.96 U/ml), (66.39U/ml) respectively, while the mean of serum concentration of follow up subgroup was (60.71 U/ml), there is no significant statistical difference between the subgroups.

The CA242 could be used to track the progress of colorectal cancer patients, and it could help distinguish between metastatic and non-metastatic cancer, linked with the risk of metastatic disease caused by e-selectin, is a vascular adhesion molecule that is mostly found on endothelium, and its major function is to accelerate up the movement of leukocyte cells by detecting ligand surface molecules, Since it was shown that E-selectin was involved in the movement of cancer cells, it was given a new function. only endothelial cells stimulated by

cytokines generate this cell adhesion molecule, it like other selectins, plays a key role in inflammation, this led to the theory that cancer cells produced inflammatory cytokines like IL-1 or TNF at distant metastatic locations to trigger E-selectin. This activation would allow tumor cells to circulate through the blood to different site, as state in other study (Muz et al., 2021).

According to ROC data, the optimal serum CA-242 cutoff value for patients was 45U/ml, with a sensitivity of 89 % and specificity of 88 %, and an area under curve of (0.93). The correlation between (CA-242) and (CEA) as a classical marker was strong (0.86), and the leaner regression between both makers was ($R^2 = 0.75$).

Conclusions

The serum concentration of CEA was significantly higher in patients with colorectal cancer group when comperere with control group, at cutoff value 5 ng/ml which support previous studies of role of CEA in prognosis of colorectal cancer. The serum CA 242 level were increased markedly in colorectal cancer group compering with control group at cutoff 45 U/ml, and can be used as prognostic biomarker specially with advanced colorectal cancer.

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Availability of data and materials

he datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

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