Original Article

The Value of Serum Carcinoembryonic Antigen in the Diagnosis of Malignant Colonic Tumor and its Prognosis

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ABSTRACT

Objective: To assess the diagnostic value of serum carcinoembryonic antigen in the detection and prognosis of colorectal malignant epithelial tumors.

Study Design: Case-control study

Place and Duration of Study: This study was conducted at the Department of Pathology & Forensic Medicine, College of Medicine, University of Al-Qadisiyah, Iraq from 1st June 2023 to 31st December 2023.

Methods: Thirty-one patients with colorectal cancer and 36 controls. The serum level of carcinoembryonic antigens was collected from both groups. In addition, information about the age of the patients, sex of patients, tumor stage, and tumor grade was collected.

Results: Serum carcinoembryonic antigen levels were higher significantly in patients who have colorectal cancer patients in comparison to control (2.70 (2.20) vs.1.85 (1.28) ng/ml, respectively). The cut-off value of serum carcinoembryonic antigen was >2.5 ng/ml with a sensitivity level of 58.1 %, a specificity level of 83.3 %, and an accuracy level of 73.1, with the area under the curve of 0.731 indicating a fair ability to differentiate.

Conclusion: Serum carcinoembryonic antigen is the fair marker to differentiate between colorectal carcinoma and healthy control, it has good specificity but poor sensitivity and has no significant correlation to age, sex, grade of disease, and stage of disease.

Key Words: Serum, Carcinoembryonic antigen, Colorectal cancer, Malignant colonic tumor, Prognosis, Diagnosis

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INTRODUCTION

Cancer of colorectal tissue is one of the most frequently encountered malignancies worldwide in adults, and around one to two million cases are diagnosed yearly.[1] It is regarded as the third most frequent malignancy and ranks fourth most frequent reason of cancer-associated mortality, with 700,000 mortalities rate each annum, being late in the list following cancers of lung tissue, hepatic tissue, and gastric region.[2] Concerningsex, this malignant tumor is the second most frequent malignancy in females and the third one in males.[3] The risk factors for colorectal carcinoma can be non-modifiable, such as increasing age.[4]

The usual predisposing factor is the presence of inflammatory bowel disease (Crohn's disease and ulcerative colitis)[5,6] and a family history of colonic tumors or can be modifiable, such as dietary habits and lifestyle.[7]

The diagnosis of colorectal cancer is based on clinical presentation, imaging techniques and tissue diagnosis of biopsy, and detecting the pathognomonic histological changes in these tissue specimens.[8] However, the utilization of markers of tumors in cancer of the colon can aid in the diagnosis and can be utilized to predict therapeutic response and follow-up of patients in addition as a prognostic indicator.[9]

Freedman and Gold were the first to isolate Carcinoembryonic antigen (CEA) from tissues obtained from human malignant colonic tumors. CEA antigen is a fetal glycoprotein often postnatally not synthesized substantially.[10] This glycoprotein has a 200 kDa molecular weight and is naturally produced by the epithelium of endodermin the growing embryo and regulated by the oncogenes of the fetus. It is often not detected in serum following birth, but some amounts may persist in the colon's tissue. The antigen and associated genes (twenty-nine in number and 18 of them are expressed naturally) make up the family of CEA in humans and are found on chromosome 19q13.2.[11]

The CEA level increases in several malignant or non-malignant diseases.[12] The most frequent use of this marker as a diagnostic and prognostic indicator of

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colonic and rectal cancer.[13,14] Other malignant disorders that are associated with elevated CEA are medullary thyroid cancer, mucinous ovarian cancer, breast cancer, gastrointestinal, prostate, pancreas, and cervix.[15] Because the elevation of this serum marker is not specific to a particular type of malignant tumor, it has been used primarily in the follow-up of such tumors and not in the primary diagnosis.[16]

CEA is enrolled within the family of immunoglobulins known as CEA-related cell adhesion molecules (CEACaMs).[17] It is intimately included with various endothelial cell functions, such as proliferation, adhesion, and migration of cells both in vitro and in vivo.[18] It is located on the cell wall of natural cells, on the endoluminal side, and is believed to prevent programmed cell death and, therefore, is enrolled in the pathogenesis of tumors.[12]

Despite the availability of studies in several countries about the use of CEA as a diagnostic, prognostic biomarker and a predictor for relapse for colorectal malignancy, there is a lack of studies to examine the Iraqi population; this is important to ascertain the proper use of CEA in such Ethnic groups. The current research aimed to assess the value of carcinoembryonic antigen serum level in the detection and prognosis of colorectal malignant epithelial tumors in group of Iraqi patients.

METHODS

The present case-control research was conducted in Diwaniyah Province, Iraq, in the Oncology Department of the Teaching Hospital from 1st June 2023 to 31st December 2023. A total of 31 patients with colorectal cancer and 36 healthy control subjects of comparable age range were included. The patients with colon cancer relapse or those treated with chemotherapy or radiotherapy were excluded from the study. Information about the age and sex of patients, tumor stage, and tumor grade was collected. Colonic cancer was confirmed by obtaining tissue samples from tumor masses, paraffin blocks were processed, and microscopical slides were stained with conventional hematoxylin and eosin stains and examined by two independent pathologists.

A sufficient amount of venous blood samples wastaken from each patient and was sent to the central laboratory of the Teaching Hospital to measure serum CEA. Venous samples were also obtained from each control subject for the same purpose. The level of CEA was measured using a Biomrieux kit (North Carolina, USA) and the samples were inserted in VEDAS (lab equipment used to measure tumor marker level by ELFA; enzyme-linked fluorescent assay). Briefly, the serum was diluted and incubated with a solid phase receptacle, and then inserted into the machine. Then, the samples were incubated with ALP-labelled anti-CEA polyclonal antibodies (derived from goat). The samples were washed thereafter to remove the unbound antibodies, followed by the final step of fluorescence detection after adding 4-methyl-umbelliferone (the fluorescent material. The concentration of the tumor marker will be proportional to the fluorescence intensity measured at 450 nm.

Data were analyzed using SPSS-16. A comparison of the level of serum CEA between the control group and the patients' group was done using the Whitney U test. An unpaired *t*-test was used to see the variation in average age between patients and control categories. The association between categorical variables was based on a Chi-square test. The Spearman correlation test assessed the correlation between serum CEA and other variables. The point of significance was considered when the *p*-value was equal to or less than 0.05.

RESULTS

There was no substantial variation in average age between control subjects and patients with colorectal carcinoma, 60.31±8.73 years versus 59.32±11.00 years (p=0.685). There was also no significant variation in the frequency distribution of individuals based on gender between study and control groups (p=0.605); however, the frequency of male patients was more than the frequency of females, 64.5% versus 35.5%, respectively, and the male to female ratio was 1.81:1 (Table 1).

According to stage patients were categorized into 2 (6.5%) as Stage I, 13 (41.9%) as Stage II, 7 (22.6%) as Stage III, and 9 (29.0%) as Stage IV. According to grade patients were categorized into 3 (9.7%) as grade I, 20 (64.5%) as grade II, and 8 (25.8%) as grade III (Table 2).

The median level in the patients' group was 2.70 (2.20) ng/ml and the range was 0.23-201.00 ng/ml; whereas the median level in the control group was 1.85 (1.28) ng/ml and the range was 0.50-7.20 ng/ml. Therefore, the serum level of CEA in patients with colorectal carcinoma was higher than that of the control category in a significant manner (p< 0.001) [Table 3].

Table No. 1: Demographic characteristics

Characteristics	Patients group (n=31)	Control Group (n=36)	P value
Age (years)			
Mean±SD	59.32 ±11.00	60.31±8.73	0.685[I]
Range	43-81	41-71	
Sex			
Male, *n* (%)	20 (64.5%)	21 (58.3%)	0.605[C]
Female, *n* (%)	11 (35.5%)	15 (41.7%)	

C: Chi-square test**; SD**: standard deviation; ***n***: number of cases; **I**: independent samples *t*-test

Table No.2: Pathological characteristics of patients

Characteristics	No.	%
Stage		
I	2	6.5
II	13	41.9
III	7	22.6
IV	9	29.0
Grade		
I	3	9.7
II	20	64.5
III	8	25.8

Table No. 3: Comparison of serum level of carcinoembryonic antigen between patients with colorectal cancer and control group

Characteristics	Patients group (n=31)	Control Group (n=36)	P value
CEA (ng/ml)			
Median (IQR)	2.70 (2.20)	1.85 (1.28)	<0.001M***
Range	0.23 - 201.00	0.50 -7.20	

IQR: interquartile range; **M**: Mann Whitney U test; ***significant at $p \leq 0.001$

Table No. 4: The characteristics of ROC curve analysis

Cutoff	> 2.5 ng/ml
AUC	0.731
95 % CI	0.608 to 0.832
p-value	< 0.001
Sensitivity %	58.1
Specificity %	83.3
Accuracy %	73.1

AUC: area under curve; **CI**: confidence interval

Table No. 5: Correlations of serum CEA to other patients' characteristics

Characteristic	*r*	*P*
Age	-0.232	0.209
Gender	-0.057	0.763
Stage	-0.048	0.797
Grade	-0.255	0.166

Figure 1 and Table 4 show receiver operating characteristic (ROC) curve analysis to detect the cutoff value of carcinoembryonic antigen serum level that can segregate between colorectal cancer cases and control cases. The cutoff value was >2.5 ng/ml, with a sensitivity level of 58.1 %, a specificity level of 83.3 %, and an accuracy level of 73.1%. There has been no substantial correlation between serum CEA and other clinicopathological characteristics of patients with colorectal carcinoma (Table 5).

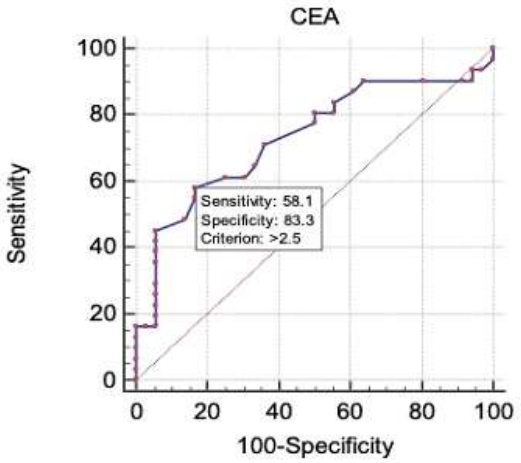

Figure No. 1: "Receiver operating characteristic (ROC)" curve analysis to detect the carcinoembryonic antigen serum level between colorectal cancer and control cases

DISCUSSION

The current study was planned and conducted to see the value of CEA as an aid tool in detecting colorectal carcinoma and its association with prognostic parameters of this malignant tumor, such as stage and grade of the disease. We found significant variation in the serum level of CEA between patients and control subjects, and the level was higher in patients than in the control group. We also found a cutoff value of >2.5 ng to segregate cases from control subjects, but the sensitivity was poor (58.1%). In addition, we find that serum CEA in patients with colorectal carcinoma had no significant correlation to the age of the patient, gender of the patient, stage of disease, and grade of disease.

Therefore, we can suggest that serum CEA above 2.5 ng/ml is important in detecting colorectal cancer in patients with high clinical suspicion; this may be related to tumor mass burden, and the level may not reflect the true prognosis of patients with such malignant tumors, especially if we notice the wide variation in serum levels ranging from 0.23 to 201.00 ng/ml.

In previous Iraqi studies[19-21], serum CEA was evaluated in subjects with colon malignancy. In the research of Al-Saadi et al[19], there was no significant link between serum CEA and the stage of disease, and this observation is consistent with our observation. In the study of Mahmood *et al*[20], there was a significant deviation in average serum CEA between controls and patients, and they found that a cutoff value of >2.65 ng/ml carries 100% sensitivity, which is far more than that reported in our study; they found a significant correlation between stage of disease and serum CEA level in clear contradiction to our observation. In the study of AL-Rubaiawi et al[21], there was no significant link between serum CEA and the stage of disease, and this observation is consistent with our observation.

Patients with colon malignancy who underwent surgical removal and treatment that is adjuvant benefit from the powerful predictive biomarker CEA.[22-24] When colorectal cancer is first diagnosed, elevated CEA levels of >5 g/L are linked to a poor prognosis.[25,26] After surgery, however, stabilization of increased CEA levels is not linked to a bad prognosis. Therefore, routine CEA screening before surgical therapy is not advised, and post-surgical detection is typically more helpful for prognostication and recurrence detection within one year of operation. In the follow-up after colorectal surgery (FACS) trial, it was discovered that following up with a CEA concentration in patients with colon cancer following initial therapy is useful for identifying cancer reappearance that may be managed with the intention of curing them.[27] National recommendations for colorectal cancer in Europe and North America also support measuring CEA in post-surgicalcare.[28] Serial measurement of CEA is advised before treatment begins; then, every three months during active treatment to evaluate the effectiveness of resection and systemic therapy (chemotherapy/ radiotherapy).[29,30]

CONCLUSION

Serum CEA is a fair marker to differentiate between colorectal carcinoma and healthy control, it has good specificity but poor sensitivity and has no significant correlation to age, sex, grade of disease, and stage of disease.

Limitations of the study: We would like to mention, the first limitation is that the study was conducted in a short time in Diwaniyah Province**,** the second is that there is no follow-up for that patient's serum level of CEA, third is that we need to look further for other tumor marker expression in tumor cells in addition to the normal colon tissue near the tumor mass. Additional studies are needed to show the expression of CEA in colon cancer patients all around Iraq, with follow-up for at least 5 years so we can assess the response of the patient to colon cancer therapy and predict the ratio of relapse using serum CEA level.

Author's Contribution:

Concept & Design of Study:	Dina Saleh, Esraah Alharris
Drafting:	Esraah Alharris, Thair Wali Ali
Data Analysis:	Esraah Alharris, Thair Wali Ali, Dina Saleh
Revisiting Critically:	Dina Saleh, Esraah Alharris, Thair Wali Ali
Final Approval of version:	By all above authors

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