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Comparting study of *cytokeratin* 18 fragment M65 with CA19-9 and CEA as a biomarker in Iraqi colon cancer patients

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ABSTRACT

Cytokeratin 18-M65 (CK18-M65), Carbohydrate Antigen 19-9 (CA 19-9), and Carcinoembryonic Antigen (CEA) in stage II, III, and IV colon cancer patients. The stages were classified according to TNM classification.

Methods: CK18-M65, CA19-9, and CEA were measured in serum samples of 27 patients who had stage II, 28 patients who had stage III, and 45 patients had stage IV colon cancer and 30 healthy subjects to show the correlation between the different stages and the change in the three markers.

Results: Plasma CK18-M65 levels were significantly high in all study stages of colon cancer patients but their mean ± SEM was higher in stage II than stages III and IV, while the mean ± SEM of plasma levels of both CA19-9 and CEA levels were significantly associated with tumor stage. The area under receiver operating characteristics curve (AUC) of CK18-M65, CA19-9, and CEA were (0.96, 0.7, and 0.8) in stage II, (0.88, 1, and 1) in stage III, and (0.89, 1, and 1) in stage IV. However, AUCs of CK18-M65 are higher in stage II than in stages III and IV. Moreover, the AUCs of CA19-9 and CEA were raised when the stage was raised and they were higher in the metastatic stage.

Conclusion: CK18-M65 exhibited the highest sensitivity for early stages than the advanced stage, contrariwise CA19-9 and CEA which were the highest sensitivity in advanced stages. This study suggests that CK18-M65 can be used as a tumor marker in screening examinations and detection for early stages of colon cancer and that can reduce mortality and morbidity of this cancer.

Keywords: CK18-M65, CA19-9, CEA, colon cancer, TNM stages

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INTRODUCTION

Cancer is the second-leading cause of mortality worldwide [1]. Colon cancer is a disease of the large intestine that begins in the cecum and spreads across the abdomen until it meets the rectum [2]. It develops during a lifetime as a result of either inherited or somatic genetic changes. The mucosa, or the inner layer of the gut, is made up of a single layer of columnar epithelial cells; this is the primary site for the initial genetic alterations that can contribute to cancer cell progression. In industrialized countries, it is the fourth most prevalent cancer [3]. Colo-Rectal Cancer (CRC) is a kind of gastrointestinal cancer that affects many people. Patients would experience changes in their bowel habits as the tumor became larger, such as hematochezia, diarrhea, diarrhea alternating with constipation, and local abdominal discomfort. Anemia, weight loss, and other systemic symptoms appear in the late stage [4].

According to the Iraqi Cancer Registry 2018, there were 1391 CRC cases in both sexes, accounting for 5.5 % of all newly diagnosed tumor cases. There were 763 male cases and 628 female cases among them [5].

The TNM classification of cancer stages describes the extent of primary Tumor invasion (T), regional lymph Node involvement (N), and distal site (M) Metastasis. The three classes are combined into staging groups 1 to 4, with stage I tumors usually confined to the submucosal layer or muscle layer of the colon and stage IV presenting with distant metastasis [6].

Cytokeratin (CK-18) is a significant cytoplasm intermediate filament protein that is released into the bloodstream as a result of cell necrosis and apoptosis. CK-18 is a mostly insoluble, intracellular protein that is widely expressed by epithelial cells of diverse; cytokeratin 18 fragments (M65) generated by human cancer cells light be used as biomarkers in colorectal cancer with a high rate of metastatic spreading [7-9]. In adult epithelial organs such as the liver, lung, kidney, pancreas, gastrointestinal tract, and mammary gland, CK18, is expressed stably, and is usually expressed during malignant transformation [10].

Carbohydrate Antigen 19-9 (CA 19-9), is a complex of *Glycoprotein* found on the cell surface. CA 19-9 is generated from cells of pancreatic ductal, the biliary system, stomach, colon, uterus, and salivary gland epithelial cells. CA 19-9 is overexpressed in a wide range of benign and malignant, gastrointestinal, and extra gastrointestinal disorders, these malignancies have a serum level that is 10 to 100 times greater than that of colorectal and gastric cancers [11, 12].

Carcino-Embryonic Antigen (CEA) is a glycosylphosphatidylinositol-anchored cell surface glycoprotein with specific sialofucosylated glycoforms that operate as usable colon cancer markers [13, 14]. It's a fetal glycoprotein that's seldom generated in large amounts after birth. CEA is a colorectal cancer antigen that should not be utilized for cancer screening since it is nonspecific and not sensitive enough to detect early tumors. CEA should revert to normal within one month of cancer surgery if it was raised earlier. CEA is an I ncrease in very suggestive of recurrent malignancy. CEA can also be utilized as a chemoprophylaxis response marker [15].

SUBJECTS AND METHODS

Subjects

This case-control study included 130 participants aged between (27-80) years, 100 patients with colon cancer, divided equally into 3 groups, 27 patients having stage II colon cancer (G1), 28 patients having stage III colon cancer (G2), and 45 patients with metastatic stage IV colon cancer (G3), in addition to 30 healthy control subjects were selected as healthy people with ages ranging between (27-80) years (G4); during the period from December 2020 to May 2021, permission to conduct the research was obtained in the Cancer Advisory Unit in the Biochemistry Laboratory at the Oncology Teaching Hospital in Medical City in Baghdad/Iraq.

Blood sample collection

All individuals had five milliliters of blood drawn from their peripheral veins in simple tubes. After allowing blood samples to coagulate, they were centrifuged for 15 minutes at 3000 rpm to extract serum, which was kept at (-20˚C) until needed for the measurement of additional parameters such as CK18-M65, CA19-9, and CEA.

The diagnosis of each case was identified by a clinical examination by a specialist oncologist Asst. Prof. Dr. Munawar Abduilah Al-Naqash and verified by a colonoscopic biopsy following histopathological diagnosis and laboratory investigation.

The concentration of M65 was measured by using an Enzyme-Linked Immunosorbent Assay (ELISA) kit, according to the manufacturer (Yangpu Dist. Shanghai, China). The sample is added to the wells and binds to the antibodies that have been coated on them. The biotinylated human M65 antibody is then added to the sample and binds to M65. The biotinylated M65 antibody is then bound by Streptavidin-HRP. During a washing step after incubation, unbound Streptavidin-HRP has washed away. After that, the substrate solution is added, and the color develops in proportion to the amount of human M65 present. The process is stopped by adding an acidic stop solution and measuring the absorbance at 450 nm. Elevated levels were defined as values ≥ 300 U/l [16].

The concentrations of CA 19-9 and CEA were quantitatively measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits, according to the manufacturer's instructions (Human Gesellschaft für Biochemica und Diagnostica mbH, Germany). Normal reference range for CA 19-9 and CEA were assumed to be 0-37 U/ml and 0-4.7 ng/ml respectively [17, 18].

Statistical analyses

The CK18-M65, CA 19-9, and CEA area under the curve (AUC), the sensitivity, specificity, and the cut-off values were identified by Receiver Operating Characteristic (ROC) analysis. The results were expressed as mean ± standard error of mean SEM. The significance of the difference between the groups was compared using the students t-test. p-values less than 0.05 were regarded statistically significant. All statistics were performed using GraphPad Prism 5 (La Jolla, USA).

RESULTS AND DISCUSSION

The percentage of age was (20 years-40 years) 17%, (41 years-60 years) 73% and (61 years-80 years) 10% in patients' groups. Of the 27 (20.8%) patients who had stage II colon cancer, 28 (21.5%) patients had stage III colon cancer and 45 (34.6%) patients had metastatic stage IV colon cancer, in addition to 30 (23.1) healthy control subjects.

Serum concentrations of M65 and ROC analysis

The mean ± SEM of CK18-M65 of stage II group (G1) was 1288.3 ± 1 44.20, stage III group (G2) was 1095.08 ± 139.36, metastatic group IV was 977.12 ± 91.17 (G3) while the control was 317.88 ± 26.56 (G4), a high statistically significant difference in mean between G1 group, G2 group and G3 group, which is statically higher than the control group (G4), with p-value < 0.0001 for each group, as presented in Table 1.

Tab. 1. Mean ± SEM of CK18-M65 among all partcipants

Group		Mean ± SEM	p-value
G1	Stage II	1288.3 ± 144.20	<0.0001
G2	Stage III	1095.08 ± 139.36	<0.0001
G3	Stage IV	977.12 ± 91.17	<0.0001
G4	Control	317.88 ± 26.56	-

To evaluate the accuracy of M65 in detecting the colon cancer in each patient group, ROC test was done, as presented in Table 2. Stage II group has cut off >579.5, AUC (0.96), with sensitivity (90%), specificity (100%) and p-value <0.0001, figure 1. Stage III group has cut off > 514.5, AUC (0.88), with lowest sensitivity (78.26%), specificity (92%) and p-value < 0.0001, figure 2. Stage IV group has cut off > 528.5, AUC (0.89), with lowest sensitivity (77.78%), specificity (96%) and p-value < 0.0001(Figure 3).

Tab. 2. ROC test of CK18-M65 as valid tests to differentiate patients' groups from controls

Stage	Cut off	AUC	SE	Sensitivity	Specificity	p-value
II	>579.5	0.96	0.027	90%	100%	<0.0001
III	>514.5	0.88	0.053	78.26%	92%	<0.0001
IV	>528.5	0.89	0.04	77.78%	96%	<0.0001

AUC=Area Under Curve; SE=Standard Error

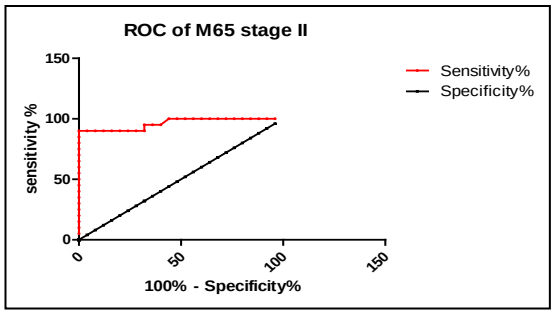

Fig. 1. ROC diagram of M65 in stage II group

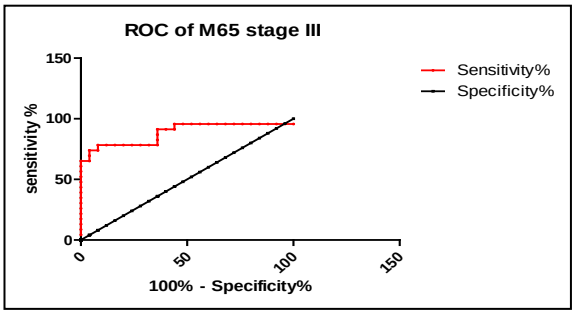

Fig. 2. ROC diagram of M65 in stage III group

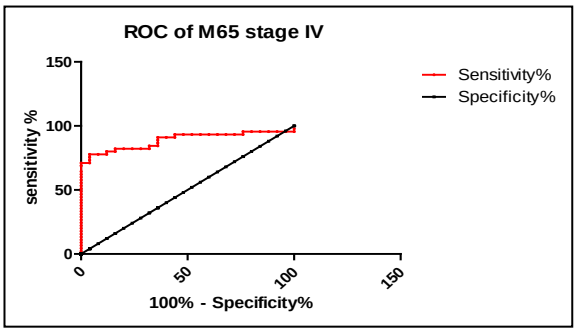

Fig. 3. ROC diagram of M65 in stage IV group

These results agree with a study of 62 colorectal cancer patients with 27 healthy subjects. M65 serum concentrations were considerably higher in patients with International Union against Cancer stage I and IIA tumors compared to controls, although M65 serum concentrations in stages IIB–III cancers were equivalent to healthy controls [19]. In cancerous epithelial cells, protein analysis indicated a high abundance of CK8 and CK18 fragments truncated at the N-terminus. Increased CK serum levels in early-stage tumors could be linked to increased rates of cell death or other factors related to the production, degradation, release, and peripheral elimination of these cytokeratin fragments [20].

Another study performed on 26 women with stage I endometrial cancer found that serum M65 levels were considerably greater in women with Early-Stage (EC) compared to 26 healthy women. In the physiology of the menstrual cycle, apoptosis is critical. Furthermore, enhanced cellular death is typically observed as endometrial hyperplasia progresses to adenocarcinoma via atypia. Furthermore, increased apoptosis has been suggested as a possible early morphological sign of continuous aberrant endometrial development. EC may arise as a result of abnormal alterations in pro- or anti-apoptotic proteins. M65 antibodies, which detect caspase-cleaved CK-18 activation products in circulation, can be used to examine the morphology of tissue samples as well as to determine apoptotic activity [21].

Based on the in-depth analysis of high-density Tissue Microarrays (TMAs). Depending on the histological type of the tumor, partial or full deletion of CK18 expression was detected in 25% of the cases. As a result of the observed down-regulation of this protein, using individual luminal CK18 as a diagnostic marker for breast cancer cells may result in false-negative results. This result is backed up by studies showing that a subpopulation of micro metastatic tumor cells in the bone marrow, which is the most common location of metastatic recurrence in breast cancer, lacks CK18 expression [22]. These findings support the use of a combination of nonspecific antibodies or a broad range anti-CK antibody directed against a common epitope found on numerous distinct CKs for diagnostic reasons, particularly for the identification of occult metastatic cells [23, 24].

Serum concentrations of CA19-9 and CEA and their ROC results

The mean ± SEM of CA19-9 of stage II (G1) was 11.58 ± 1.69, stage III (G2) was 136.38 ± 19.97, stage IV (G3) was 152.74 ± 15.72 while the control (G4) was 7.61 ± 0.30, a statistically significant difference in mean between the stage II group and control group, with a p-value 0.03, a high statistically significant difference in mean between stage III group and stage IV group, which is statically higher than the control group, with p-value <0.0001 for each group, as presented in Table 3.

Tab. 3. Mean of CA19-9 among all participants

Group		Mean ± SEM	p-value
G1	Stage II	11.58 ± 1.69	0.03
G2	Stage III	136.38 ± 19.97	<0.0001
G3	Stage IV	152.74 ± 15.72	<0.0001
G4	Control	7.61 ± 0.30	-

To evaluate the accuracy of CA19-9 in detecting the colon cancer in each patient group, a ROC test was done, as presented in Table 4. Stage II group has cut off >9.930, AUC (0.7), with lowest sensitivity (63.16%), high specificity (100%) and p-value 0.02, figure 4. Stage III group has cut off >31.21, AUC (1), with high sensitivity (100%), high specificity (100%) and p-value <0.0001, figure 5. Metastatic stage IV group has cut off >15.11, AUC (1), with high sensitivity (100%), high specificity (100%) and p-value <0.0001 (Figure 6).

Tab. 4. ROC test of CA19-9 as valid tests to differentiate patient groups from controls

Stage	Cut off	AUC	SE	Sensitivity	Specificity	p-value
II	>9.930	0.7	0.096	63.16%	100%	0.02
III	>31.21	1	0	100%	100%	<0.0001
IV	>15.11	1	0	100%	100%	<0.0001

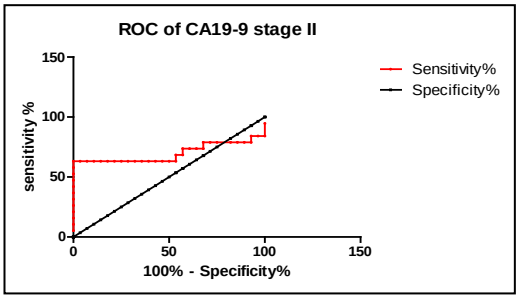

Fig. 4. ROC diagram of CA19-9 in stage II group

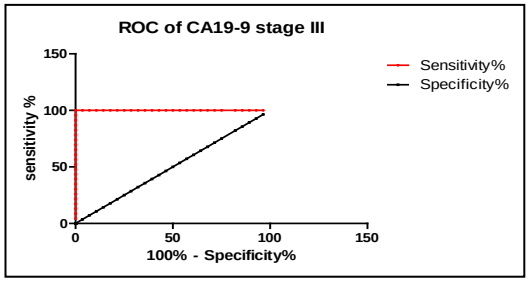

Fig. 5. ROC diagram of CA19-9 in stage III group

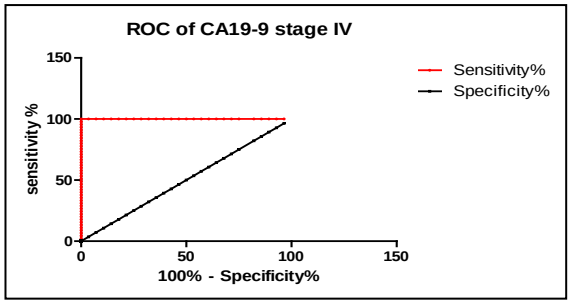

Fig. 6. ROC diagram of CA19-9 in stage IV group

The mean ± SEM of CEA of stage II (G1) was 2.31 ± 0.25, stage III (G2) was 8.29 ± 1.0 and stage IV (G3) was 72.09 ± 10.37 while the control (G4) was 1.2 ± 0.11, a statistically significant difference in mean between stage II group, stage III group and metastatic group, which is statically higher than the control group, with p-value 0.0005, 0.0001 and 0.0001 consequently, as presented in Table 5.

Tab. 5. Mean ± SEM of CEA among all participants

Group		Mean ± SEM	p-value
G1	Stage II	2.31 ± 0.25	0.0005
G2	Stage III	8.29 ± 1.0	0.0001
G3	Stage IV	72.09 ± 10.37	0.0001
G4	Control	1.2 ± 0.11	-

To evaluate the accuracy of CEA in detecting colon cancer in each patient group, a ROC test was done, as presented in Table 6. Stage II group has cut off >1.950, AUC (0.8), with lowest sensitivity (60%), specificity (89.66%) and p-value 0.0004 (Figure 7). Stage III group has cut off >3.515, AUC (1), with high sensitivity (100%), high specificity (100%) and p-value <0.0001 (Figure 8). Stage IV group has cut off >6.535, AUC (1), with high sensitivity (100%), high specificity (100%) and p-value <0.0001 (Figure 9).

Tab. 6. Distribution the IL-6 score between patients and control groups a (n=56) for samples collected from biopsy

Stage	Cut off	AUC	SE	Sensitivity	Specificity	p-value
II	>1.950	0.8	0.066	60%	89.66%	0.0004
III	>3.515	1	0	100%	100%	0.0001
IV	>6.535	1	0	100%	100%	0.0001

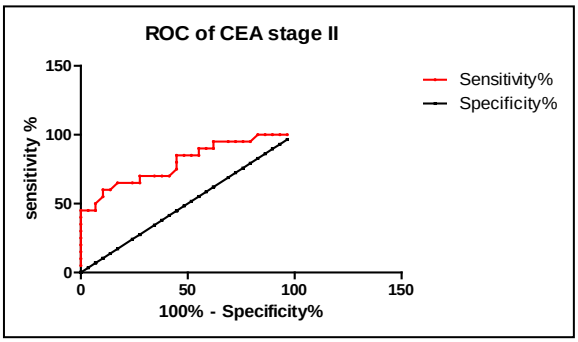

Fig. 7. ROC diagram of CEA in stage II group

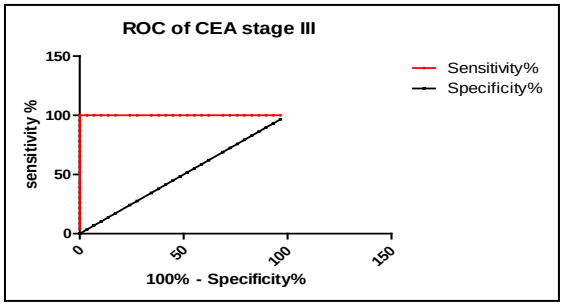

Fig. 8. ROC diagram of CEA in stage III group

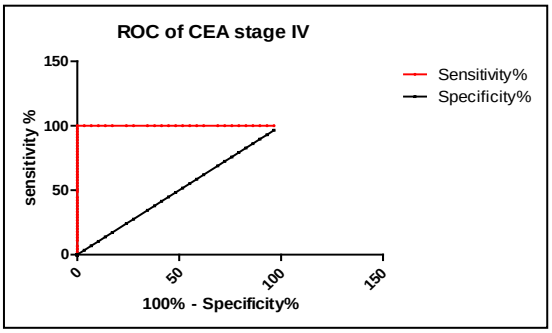

Fig. 9. ROC diagram of CEA in stage IV group

The combination of more than one marker in the diagnosis of disease

To improve the diagnostic value of markers, it appears that determining at least two or more markers at the same time is the optimum method. Multimodal diagnostics, unique patient profiles, disease-specific biomarker patterns, and person-specific therapy might all be part of an integrated medical strategy that includes circulating tumor cells investigation. Scientific biomarker research has recently benefited from technical and analytical advancements [25].

A total of 150 patients with esophageal, stomach, and colon cancer who had not previously received any anticancer therapy were included in the study. In esophageal and gastric cancer, the combination of CEA and CA19-9 has greater diagnostic effectiveness than either tumor marker alone. The results of both markers together give superior prediction results and a more accurate clinical picture for these two cancer types than either CEA or CA19-9 alone. High levels of CEA and CA19-9 at the time of diagnosis have a stronger predictive value and can help clinical practice. More advancements in cancer screening, diagnostics, and tailored therapies may improve cancer survival rates [26].

A study of 279 colorectal cancer patients looked at the sensitivity and reliability of single/multiple serum indicators not only for diagnosis but also for their relationship with pathological characteristics. CEA >Cancer Antigen 72-4 (CA72-4) >Cancer Antigen 19-9 9 (CA19-9) >ferritin >Cancer Antigen 125 (CA125), according to the study, while the most sensitive combined-markers for two to five were CEA+CA72-4; CEA+CA72-4+CA125; CEA+CA19-9+CA72-4+CA125; and CEA+CA19-9+CA72-4+CA125+ferritin, respectively. Patients with positive preoperative blood CEA, CA19-9, or CA72-4 were more likely to have lymph node invasion, high CA125 was more likely to have a vascular invasion, and positive CEA or CA125 was linked to perineural invasion, according to the same study. Furthermore, positive CA19-9, CA72-4, or CA125 levels were positively connected with pathological tumor-node-metastasis stages, whereas CEA, CA19-9, CA72-4, and CA125 levels were negatively correlated with pathological tumor-node-metastasis stages. According to the results, combined serum markers can be utilized to not only detect colorectal cancer, but also to assess tumor status for treatment guidance, evaluation of curative impact, and patient prognosis [27].

In a study of the sera levels of TK1, CEA, CA19-9, and CA72-4 in 513 patients with stomach, colon, and rectum cancer patients. The positive frequencies of the four tumor markers rose with the clinic stage, and there were statistically significant differences between stage I+II and stage III+IV for TK1, CA 19-9, CA 72-4, and CEA (p-0.05). Four indicators are linked to growth, and the level of TK1 may represent the pace of tumor development in patients. The AUCs for CA 19-9 and CA 72-4 in the gastric, colon, and rectal cancer ranged from 0.682 to 0.826 in this study, indicating that CA 19-9 and CA 72-4 had limited use in GC and CRC diagnosis. The four tumor markers (TK1, CEA, CA 19-9, and CA 72-4) were integrated with the logistic regression model in this study to improve the accuracy of GC and CRC identification. The four tumor markers integrated into the logistic regression model, on the other hand, exhibited a stronger diagnostic performance for GC and CRC, which is in line with prior study findings [28].

In 60 patients with esophageal squamous cell carcinoma or gastric adenocarcinoma, a comparative study was conducted to investigate the clinical usefulness of serum CK-18, CEA, and CA19-9 alone and in combination. Patients with esophageal squamous cell carcinoma or gastric adenocarcinoma had their serum tumor markers tested. Serum CK-18 values were found to be 53% of the patients with esophageal squamous cell carcinoma, 70% of the patients with gastric adenocarcinoma, and 43% of the controls. Serum CEA values were found to be in 70% of the patients with esophageal squamous cell carcinoma, 70% of the patients with gastric adenocarcinoma, and 36% of the controls. Serum CA 19-9 values were found to be in 66% of the patients with esophageal squamous cell carcinoma, 70% of the patients with gastric adenocarcinoma, and 40 % of healthy subjects. The results of this study indicated that serum CK-18 is not a much more sensitive marker than CEA and CA19-9 in esophageal and gastric carcinomas. The combination of CK-18 and any other tumor marker would be more predictive since the different markers may act in a complementary fashion and provide a better clinical picture. In general, terms, although most tumor markers are not satisfactory in the diagnosis of malignancy so far, tumor markers of esophageal

and gastric cancer are more helpful in prognosis or recurrence, less so in early diagnosis [29].

In conclusion, the serum M65 levels in patients with colon cancer were higher compared to healthy subjects. It's significantly higher early stages than advanced stages, therefore; M65 could serve as a tumor marker in screening examinations and detection for early stages of colon cancer and could not use as a prognostic marker. The serum levels of CA19-9 and CEA showed a significant correlation with the stages of the patient's tumor, therefore; they could serve as prognostic and follow-up tumor markers.

The compensation of the three markers might be beneficial in detecting colon cancer and its stages.

CONCLUSIONS

In conclusion, the serum M65 levels in patients with colon cancer were higher compared to healthy subjects. It's significantly higher early stages than advanced stages, therefore; M65 could serve as a tumor marker in screening examinations and detection for early stages of colon cancer and could not use as a prognostic marker. The serum levels of CA19-9 and CEA showed a significant correlation with the stages of the patient's tumor, therefore; they could serve as prognostic and follow-up tumor markers.

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