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RESEARCH ARTICLE

Comparative Evaluation of Colon Cancer Specific Antigen-2 Test and Chromocolonoscopy for Early Detection of Egyptian Patients with Colorectal Cancer

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Abstract: ***Background*:** Effective screening of colorectal cancer (CRC) in early stage could reduce the advancement of CRC and therefore mortality. Effective screening is based on either stool dependent tests or colon dependent examination.

***Aims*:** The aim of the study was a comparative evaluation of chromocolonoscopy and Colon Cancer-Specific Antigen-2 test for early detection of colorectal cancer in Egyptian patients.

***Methods*:** This case control study was carried out on 55 patients classified into 3 groups: Group I consisted of twenty patients with precancerous lesions detected by colonoscopy, Group II consisted of twenty patients diagnosed with colorectal cancer and Group III consisted of fifteen individuals (who underwent colonoscopy for other indications) as a control group. All the subjects were subjected to measure occult blood in the stool, measurement of Colon Cancer-Specific Antigen-2 level in serum and tissue and chromo colonoscopy using Indigo Carmine stain.

***Results*:** In group II**,** there was a statistically significant increase in CCSA2 in serum as compared to the other 2 groups. Cutoff >11.3 CCSA2 in serum showed 65% sensitivity, 85% specificity, 81.2% PPV, 70.8% NPV and 70.3% accuracy in the differentiation of group II with cancer colon from group I with premalignant colonic lesions. A cutoff > 9.1 CCSA2 in serum showed 95% sensitivity, 46.67% specificity, 70.4% PPV, 87.5% NPV and 73.5% accuracy in differentiating group II with cancer colon from normal controls (group III).

***Conclusion*:** CCSA-2 level in serum was significantly higher in cancer colon. Chromoendoscopy has a role in the detection of polyps, both neoplastic and non-neoplastic.

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1. INTRODUCTION

Colorectal cancer (CRC) is the second most common diagnosed cancer in females and the third most diagnosed cancer in males worldwide with 694,000 deaths and 1.4 million new cases. The incidence of colorectal cancer (CRC) and mortality rates differ markedly around the world [1]. In Egypt, CRC is the 7th commonest cancer, and it represents 3.47% of male cancers and 3% of female cancers [2].

The effective screening of CRC at the early stage could reduce the progress of cancer and

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therefore decrease mortality rates. The screening tests for CRC are stool dependent tests (*e.g*. guaiac fecal occult blood testing or testing exfoliated DNA stool), the fecal immunochemical test, or colon dependent examination (flexible sigmoidoscopy, double-contrast barium enema, colonoscopy, and virtual colonoscopy) [3, 4].

Colonoscopy is the standard method to detect adenomas and colorectal cancers. The start of early, regular screening is the main strategy for the prevention of colorectal cancer at the age of 45. The American Cancer Society recommends colon and rectal cancer screening by colonoscopy or other methods starting at the age of 45 years and continuing to 75 years. People at risk of colorectal cancer should begin screening at a younger age and may need frequent testing [5]. Chromoendoscopy includes the usage of special stains to help recognize and distinguish lesions in the gastrointestinal tract. The diagnostic value of colonoscopy for the diagnosis of flat and depressed colorectal neoplasms in patients with ulcerative colitis, in high-risk patients who have either a personal or family history of colorectal cancer, and in patients with disease symptoms has been improved by chromo-endoscopy [6].

An ideal screening test should be safe, low cost, none or minimally invasive with high sensitivity and specificity. In 2002, Brunagel and his colleagues recognized the colon cancer-specific nuclear matrix proteins that were not present in normal colonic tissue but were present in cancer tissue [7]. One of these proteins is colon cancer-specific antigen (CCSA)-2 protein that is not found in normal adjacent tissue or the normal colon but it is associated with colon cancer tissue [8]. The aim of the study was a comparative evaluation of chromo-colonoscopy and Colon Cancer-Specific Antigen-2 test for early detection of colorectal cancer in Egyptian patients.

2. METHODS

All the patients had been enrolled in this prospective study who underwent colonoscopy at the Tropical medicine department of the Tanta University during the period between July 2015 to July 2017. All the patients undergoing colonoscopic examination who were known to have colorectal carcinoma or patients with clinical suspicion of colorectal carcinoma (abdominal pain, rectal bleeding, altered bowel habits or weight loss), with the exclusion of patients with metastatic colorectal cancer or known to have other malignancies were enrolled. A total of fifty-five subjects were enrolled. Informed consent was taken from every subject. The study was approved by the Ethical Committee of Faculty of Medicine, Tanta University.

These subjects were classified into three groups according to colonoscopic findings:

- Group I consisted of twenty patients with Precancerous lesions detected by colonoscopy.
- Group II consisted of twenty patients diagnosed with colorectal cancer.
- Group III consisted of fifteen individuals (who underwent colonoscopy for other indications) as a control group.

All the subjects were subjected to full history taking and thorough clinical examination in addition to routine laboratory investigations. Moreover, specific tests were performed: occult blood in stool with three consecutive samples was obtained for identifying hemoglobin by the presence of a peroxidase reaction, which turned the guaiac-impregnated paper into blue colour.

- Measurement of Colon Cancer-Specific Antigen-2 level in serum and tissue homogenate was done by sandwich enzyme-linked immunesorbent assay technology ELISA (CCA-2 ELISA kits) (MyBioSource, USA); chromocolonoscopy was performed using Indigo Carmine stain. Indigo carmine is a contrast dye that does not react with and is not absorbed by the mucosa, but simply pools in the mucosal grooves and crevices, allowing better topographic definition. During continuous extubation, indigo carmine (0.4%) was gently applied to achieve diffuse coverage of the entire mucosal surface. Only a small volume of dye was applied to avoid excess dye accumulation, followed by re-examination after excess dye was aspirated. The location and shape of detected colonic lesions were recorded.

Table 1. Age, sex and smoking among the studied groups.

		Groups						ANOVA Or Chi-Square		TUKEY'S Test		
		Group I		Group II		Group III		F or X2	P-value	I&II	I&III	II&III
Age	Range	18-75		22-74		28-65		4.165	0.021*	0.022*	0.863	0.114
	Mean ± SD	47.3 ± 13.77		58.65 ± 13.91		49.60 ± 10.487						
Sex	Male	15	75%	9	45%	10	66.67%	4.018	0.134			
	Female	5	25%	11	55%	5	33.33%					
Smoking	Yes	9	45%	2	10%	3	20%	6.779	0.034*	0.013*	0.123	0.403
	No	11	55%	18	90%	12	80%					
		Groups						Chi-Square		TUKEY'S Test		
		Group I		Group II		Group III		X2	P-value	I&II	I&III	II&III
DM	Yes	7	35%	14	70%	3	20%	9.666	0.008*	0.027*	0.331	0.003*
	No	13	65%	6	30%	12	80%					
Hyper-tension	Yes	3	15%	8	40%	2	13.33%	4.676	0.097			
	No	17	85%	12	60%	13	86.66%					

- Multiple mucosal biopsies from visible abnormalities and quadrantic, non-targeted areas (every 10 cm) were obtained from colonic mucosa using standard pinch forceps. The specimen was preserved directly in formalin (10%) till paraffin block was done for histopathological examination.

2.1. Statistical Analysis

Statistical presentation and analysis of the present study were conducted using the mean and standard deviation in order to show the distribution of data. Student t-test, Chi-square and analysis of variance [ANOVA] tests by SPSS V17 were done. P-value ≤ 0.05 was considered as significant and p-value < 0.01 was considered as highly significant. ROC (Receiver Operating Characteristic) curve analysis was used to assess sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and Accuracy of the tests.

3. RESULTS

As regards patients characteristics (age, sex, smoking, DM and HTN), (Table **1**) age, smoking index and DM showed a statistically significant difference between studied groups as age and DM were higher in group II compared to the other 2 groups, while smoking was higher in group I compared to group II. As regards history, patients in group I showed a statistically significant increase with respect to previous colonoscopy and inflammatory bowel disease while colorectal polyps and family history showed no significant difference between studied groups. Regarding the symptoms, abdominal pain, diarrhea, constipation, bleeding per rectum and weight loss showed non-significant difference among the studied groups except for bleeding per rectum, that was positive in 18 patients (90%) in group I, 11 patients (55%) in group II and 1 control (6.67%) in group III with a statistically significant increase in group I compared to the other 2 groups. As regards the laboratory investigations, there was a statistically significant decrease in hemoglobin, serum albumin and ESR in group II compared to the other 2 groups. There was no statistically significant difference between the studied groups as regards color, consistency, microscopic examination of the stool. But there was a statistically significant difference among the studied groups as regards the occult blood in the stool.

In group II, there was a statistically significant increase in CCSA2 in serum as compared to the

Table 2. Colon cancer-specific antigen-2 (CCSA2) in the serum among the studied groups.

Groups	CCSA2 Serum						ANOVA	
	Range			Mean	±	SD	F	P-value
Group I	7.1	-	15.3	10.350	±	1.506	7.735	0.001*
Group II	8.9	-	24.9	14.450	±	6.035		
Group III	5.9	-	14.6	9.613	±	2.862		
TUKEY'S Test								
I&II				I&III			II&III	
0.006*				0.855			0.003*	

Table 3. Colon cancer-specific antigen-2 (CCSA2) in tissue homogenate among the studied groups.

Groups	CCSA2 Tissue						T-Test	
	Range			Mean	±	SD	T	P-value
Group I	6.2	-	17.7	10.725	±	3.173	-2.040	0.048*
Group II	6.8	-	22.8	13.685	±	5.661		

CCSA2 in the tissue homogenate among the studied groups; in group I, it ranges between (6.2-17.7) with mean (10.725 ± 3.173), group II ranges between (6.8-22.8) with mean (13.685 ± 5.661). There is a statistically significant increase in CCSA2 in group II compared to group I.

Table 4. Receiver operator characteristic (ROC) curve results for the level of Colon cancer-specific antigen-2 (CCSA2) in serum in group II compared to group III.

ROC Curve between Group II and Group III					
Cutoff	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
>9.1	95%	46.67%	70.4%	87.5%	73.5%

Table 5. ROC curve results for the level of Colon cancer-specific antigen-2 (CCSA2) in serum in group II compared to group I.

ROC Curve between Group II and Group I					
Cutoff	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
>11.3	65%	85%	81.2%	70.8%	70.3%

other 2 groups (Tables **2** and **3**), as in group I, it ranged between (7.1-15.3), in group II it ranged between (8.9-24.9), and in group III it ranged between (5.9-14.6). At cutoff > 9.1 CCSA2 in serum showed 95% sensitivity, 46.67% specificity, 70.4% PPV, 87.5% NPV and 73.5% accuracy in differentiating group II with cancer colon from normal controls (group III) (Table **4** and Fig. **1**). In order to set cutoff value of CCSA2 in serum for detection of cancer colon we found that at a cutoff >11.3 CCSA2 in serum showed 65% sensitivity, 85% specificity, 81.2% PPV, 70.8% NPV and 70.3% accuracy in differentiating group II with cancer colon from group I with premalignant colonic lesions (Table **5** and Fig. **2**).

There was a statistically significant increase in CCSA2 in the tissue homogenate in group II compared to group I; in group I, it ranged between (6.2-17.7) while in group II, it ranged between (6.8-22.8) (Table **3**). In order to set a cutoff value of CCSA2 in tissue homogenate for the detection

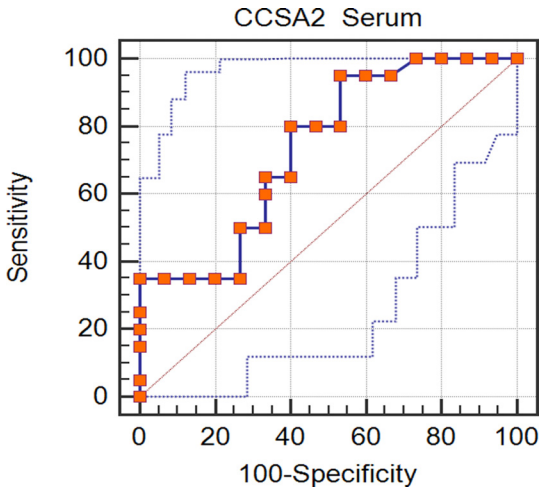

Fig. (1). ROC curve results for CCSA2 in serum in group II compared to group III.

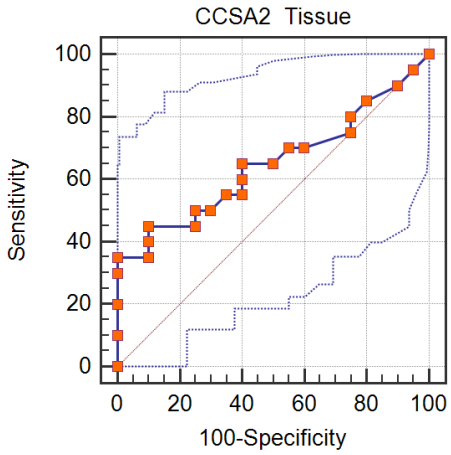

Fig. (3). ROC curve for CCSA2 in tissue homogenate.

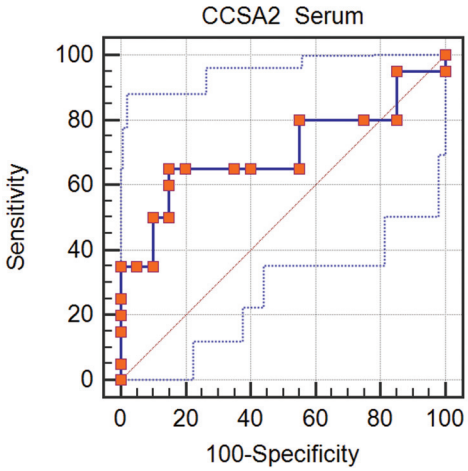

Fig. (2). ROC curve for CCSA2 in serum in group II compared to group I.

of colon cancer, we found that at a cutoff >13.6 CCSA2 in tissue homogenate showed 45% sensitivity, 90% specificity 81.8% PPV 62.1% NPV and 64.7% accuracy in differentiating patients with cancer colon (group II) from patients with premalignant colonic lesions (group I) (Table **6** and Fig. **3**).

Fig. (**4**) shows chromoendoscopy in different patients and the difference in tissue appearance was detected.

Table **7** shows colonoscopic findings in group I, 18 cases (90%) had ulcerative colitis, 1 had Crohn's disease (5%) and 1 had adenomatous polyp (5%). Table **8** shows colonoscopic findings in group II, 14 cases (70%) had colonic mass, 4 cases had malignant ulcers (20%) and 2 cases had rectal mass (10%).

4. DISCUSSION

Early detection of CRC by screening and progress in treatment techniques had led to decreased mortality of CRC [9]. There are different options for screening and surveillance of CRC with each of them having distinctive advantages, cost-effectiveness, limitations and risks [10, 11].

In this cross-sectional study, we assessed the value of chromocolonoscopy and colon cancer-specific antigen-2 test for early detection of colorectal cancer in Egyptian patients.

There was a significant increase in age in group II compared to group I. This result coincided with

Table 6. ROC curve results for the level of Colon cancer-specific antigen-2 (CCSA2) in tissue homogenate in group II compared to group I.

ROC Curve between Group II and Group I					
Cutoff	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
>13.6	45%	90%	81.8%	62.1%	64.7%

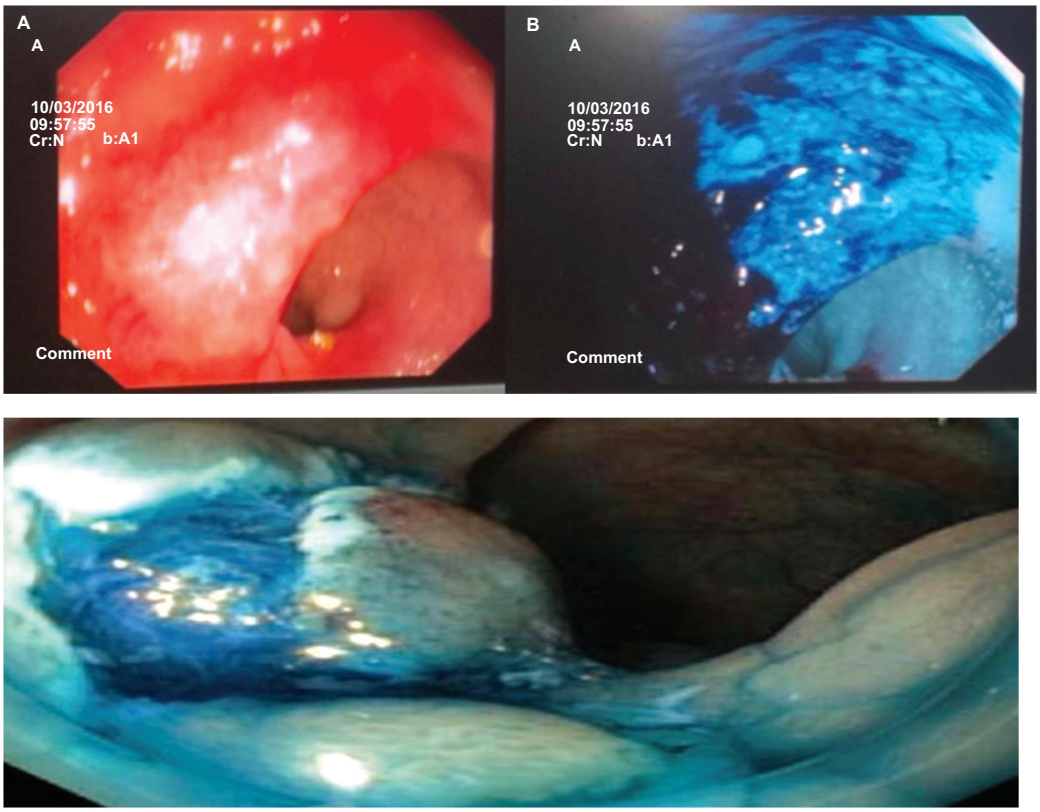

Fig. (4). (**a**) Shows ulcerative colitis lesions by colonoscopy (**b**) shows uc lesions highlighted after application of indigo carmine dye (**c**) shows colonic mass highlighted by chromocolonoscopy.

Table 7. Colonoscopic findings in group I.

Group I	Chromocolonoscopy	
	N	%
Ulcerative colitis	18	90
Crohn`s disease	1	5
Adenomatous Polyps	1	5
Total	20	100

Table 8. Colonoscopic findings in group II.

Group II	Chromocolonoscopy	
	N	%
Malignant Ulcers	4	20
Colonic Mass	14	70
Rectal mass	2	10
Total	20	100

the result of the study done by Kemppainen *et al*. (1993) [12] who concluded that the risk of developing colorectal cancer development increased with advancing age as > 90% of the people diagnosed with CRC were older than 50 and that CRC is the commonest cancer in the population older than 75 years in the United States [12].

Also, there was a significant increase in smoking prevalence in group I compared to group II. Although the association between smoking and cancer colon development is still not clear, several trials studied the rule of smoking in CRC development as Zisman *et al*. (2008) concluded that 12% of the colorectal cancer deaths were attributed to smoking [13]. In addition, Buchanan *et al*. (2010) described smoking as the main risk factor for serrated polyps of the colon including hyperplastic and adenomatous polyps [14].

Diabetes mellitus was significantly higher in group II compared to the other 2 groups. This can be explained by the fact that insulin resistance or compensatory hyperinsulinemia leads to hormonal and metabolic alterations, and is involved in the formation of the microenvironment for tumorigenesis and tumor progression [15]. This finding was similar to other studies [16-18].

As regards symptoms, abdominal pain and bowel habits were insignificantly associated with the presence of cancer colon which coincided with a meta-analysis of 15 studies done by Ford *et al*. (2008) and systematic review done by Adelstein *et al*. (2011) which concluded no significant association of colorectal cancer or polyps with a change in bowel habit, constipation, diarrhea or abdominal pain [19, 20]. On the other hand, bleeding per rectum was found to be significantly higher in group II compared to the control group. This result agreed with that obtained by Jones *et al.* (2007), Hamilton *et al*. (2008), and Viborg *et al.* (2016) [21-23] who found an increased short-term risk of CRC after lower GI bleeding in primary care settings and that it was a strong clinical symptom of widespread GI cancer. As regards weight loss, we found no significant difference between the studied groups. In agreement with our results, Adelstein *et al*. (2011) described weight loss as a common reason for seeking a referral for colonoscopy but it was not a common single symptom presenting in CRC [20].

On the other hand, unintentional weight loss was found to be of bad prognostic value as it was found significantly associated with decreased long-term survival [24].

In addition, Kuo *et al*. (2018) described weight loss in colon cancer patients as not onlya symptom, but was found to be correlated with tumor location, size and depth, and considered as a prognostic factor for poor outcomes including overall survival and tumor recurrence [25].

As regards the laboratory investigations hemoglobin level, albumin and ESR were significantly affected in group II. There was a significant decrease in hemoglobin level in group II compared to the other two groups. This decrease can be explained by the development of iron-deficiency anemia which has long been recognized as a feature of colorectal cancer [26], as it was found in 11–57% of cancers [27-30], and was particularly suggestive of caecal tumors [31]. In addition, patients with anemia as their presenting sign of cancer had worse staging [32], and mortality [33].

ESR was found significantly higher in group II compared to the other 2 groups. Several studies have discussed the association between chronic inflammation and carcinogenesis, and found that subclinical or even undetectable inflammation may be as significant as chronic inflammation in increased cancer risk, development and progression as chronic inflammation may promote excessive cell proliferation and activate a cascade of cellular events, promoting tumor cell growth [34]. Additionally, Ananthakrishnan *et al*. (2016) stated that CRP and ESR in patients with inflammatory bowel disease are associated with a consequent risk of CRC [35].

Lastly, albumin was found significantly lower in group II. This can be explained by the fact that cancer patients suffer inflammation along with inadequate protein and caloric intake leading to hypoalbuminemia [36], due to a decreasing rate of albumin synthesis [37]. Also, albumin levels among patients with preoperative metastatic disease appeared to be lower as compared to those

who are metastasis-free. In addition, albumin levels were more reflective of the tumor size rather than the tumor stage, with larger tumors having lower serum albumin levels. Larger volume of tumor cells causes a higher production of proinflammatory cytokines, which in turn decreases hepatic production of albumin [38, 39].

While Lai *et al.* (2011) added the role of hypoalbuminemia in the prediction of postoperative mortality for both localized (stage I and II) and regionally advanced cancer. The impact was significant for 30 days and 5 years after surgery, and remained significant on multivariate analysis [40].

In order to increase the accuracy of the results of a biopsy taken from colon we used Indigo carmine contrast as chromoendoscopy has a benefit for the detection of polyps, both neoplastic and non-neoplastic [41].

Moreover, it has a superior benefit over ordinary random biopsy technique in detecting dysplasia for long-term surveillance [42].

Even though chromoendoscopy has some limitations that appeared during our work, it can be time-consuming and interpretation of the staining patterns requires trained endoscopist as it is not always direct. It is also liable to interobserver variability. Finally, its classification lacks standardization.

In our study, we analyzed the variables for CCSA-2 both in serum and tissue homogenate. We found that its level in serum was significantly higher in group II compared to group I and group III. Its level in tissue homogenate in group II was found significantly higher compared to group I.

In agreement with our results, the study conducted by Walgenbach-Brunagel *et al*. (2008) showed that CCSA-2 in serum was 88.8% sensitive and 84.2% specific for distinguishing cancer colon [43]; and Xue *et al*. (2014) concluded that serum CCSA-2 concentration had a sensitivity of 98.10% and a specificity of 97.90% in distinguishing individuals with CRC from other contributor population [44].

Additionally, Knychalski and Łukieńczuk, 2012 compared both CEA and CCSA-2 as diagnostic and prognostic parameters and stated that there was a positive correlation between markers in patients with colorectal cancer but the accuracy of CCSA was slightly lower than that of CEA [45]. The lower sensitivity of CCSA-2 for detecting cancer colon may be attributed to small sample size and different population included in our study.

On the contrary Xue *et al*., (2014) concluded that the CCSA-2 assay was significantly more sensitive than CEA and CA19-9 assay in CRC detection, moreover, the serum CCSA-2 level in CRC patients had declined significantly after curative resection, but it rebounded to a high level when recurrences occurred. They also stated that patients with higher pre-operative serum CCSA-2 level had a higher relapse rate compared to patients who had no relapse [44-46].

One of the limitations of our study was the small sample size. In addition, we did not compare CCSA-2 results with CA19-9 and CEA which are considered as markers for CRC. So, further investigations on a larger cohort of patients need to be done.

CONCLUSION

In conclusion, CCSA-2 level in serum was significantly higher in cancer colon and can be used as a new marker for screening of colorectal cancer. Chromoendoscopy has a role in the detection of polyps, both neoplastic and non-neoplastic and it has a superior benefit over ordinary random biopsy technique in detecting dysplasia for long-term surveillance.

AUTHOR'S CONTRIBUTION

All authors contributed equally to this work. All the authors participated sufficiently in the work and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethical Committee of Faculty of Medicine, Tanta University, Egypt (approval number 30123/05/31).

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are basis of this research. The study protocol on humans

conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approval by the institution's Human Research Committee.

CONSENT FOR PUBLICATION

Informed consent was taken from every subject.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available from the corresponding author [S.A.-E] upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

REFERENCES

[1] Torre, L.A.; Bray, F.; Siegel, R.L.; Ferlay, J.; Lortet-Tieulent, J.; Jemal, A. Global cancer statistics, 2012. *CA Cancer J. Clin.,* **2015**, *65*(2), 87-108. http://dx.doi.org/10.3322/caac.21262 PMID: 25651787

[2] Ibrahim, AS; Khaled, HM; Mikhail, NN; Baraka, H; Kamel, H. Cancer incidence in Egypt: results of the national population-based cancer registry program. *J. Cancer Epidemiol.,* **2014**, *2014*, 437971. PMID: 25328522

[3] Labianca, R.; Merelli, B. Screening and diagnosis for colorectal cancer: present and future. *Tumori,* **2010**, *96*(6), 889-901. http://dx.doi.org/10.1177/548.6506 PMID: 21388049

[4] Smith, R.A.; Cokkinides, V.; Brooks, D.; Saslow, D.; Shah, M.; Brawley, O.W. Cancer screening in the United States, 2011: A review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J. Clin.,* **2011**, *61*(1), 8-30. http://dx.doi.org/10.3322/caac.20096 PMID: 21205832

[5] Smith, R.A.; Cokkinides, V.; Brooks, D.; Saslow, D.; Shah, M.; Brawley, O.W. Cancer screening in the United States, 2011: A review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J. Clin.,* **2011**, *61*(1), 8-30. http://dx.doi.org/10.3322/caac.20096 PMID: 21205832

[6] Kahi, C.J. Chromocolonoscopy for colorectal cancer screening: Dive into the Big Blue. *J. Interv. Gastroenterol.,* **2012**, *2*(3), 112-113. http://dx.doi.org/10.4161/jig.23729 PMID: 23805388

[7] Brünagel, G.; Vietmeier, B.N.; Bauer, A.J.; Schoen, R.E.; Getzenberg, R.H. Identification of nuclear matrix protein alterations associated with human colon cancer. *Cancer Res.,* **2002**, *62*(8), 2437-2442. PMID: 11956108

[8] Knychalski, B.; Lukieńczuk, T. The evaluation of diagnostic value of the tumor markers: CCSA-2 and CEA in colorectal cancer. *Pol. Przegl. Chir.,* **2012**, *84*(2), 86-92. http://dx.doi.org/10.2478/v10035-012-0014-3 PMID: 22487741

[9] Espey, D.K.; Wu, X.C.; Swan, J.; Wiggins, C.; Jim, M.A.; Ward, E.; Wingo, P.A.; Howe, H.L.; Ries, L.A.; Miller, B.A.; Jemal, A.; Ahmed, F.; Cobb, N.; Kaur, J.S.; Edwards, B.K. Annual report to the nation on the status of cancer, 1975-2004, featuring cancer in American Indians and Alaska Natives. *Cancer,* **2007**, *110*(10), 2119-2152. http://dx.doi.org/10.1002/cncr.23044 PMID: 17939129

[10] Mandel, J.S. Which colorectal cancer screening test is best? *J. Natl. Cancer Inst.,* **2007**, *99*(19), 1424-1425. http://dx.doi.org/10.1093/jnci/djm166 PMID: 17895471

[11] Di Cristofaro, L.; Scarpa, M.; Angriman, I.; Perissinotto, E.; Ruffolo, C.; Frego, M.; Erroi, F. Cost-effectiveness analysis of postoperative surveillance protocols following radical surgery for colorectal cancer. *Acta Chir. Belg.,* **2012**, *112*(1), 24-32. http://dx.doi.org/10.1080/00015458.2012.11680791 PMID: 22442906

[12] Kemppainen, M.; Räihä, I.; Rajala, T.; Sourander, L. Characteristics of colorectal cancer in elderly patients. *Gerontology,* **1993**, *39*(4), 222-227. http://dx.doi.org/10.1159/000213537 PMID: 8244050

[13] Zisman, T.L.; Rubin, D.T. Colorectal cancer and dysplasia in inflammatory bowel disease. *World J. Gastroenterol.,* **2008**, *14*(17), 2662-2669. http://dx.doi.org/10.3748/wjg.14.2662 PMID: 18461651

[14] Buchanan, D.D.; Sweet, K.; Drini, M.; Jenkins, M.A.; Win, A.K.; English, D.R.; Walsh, M.D.; Clendenning, M.; McKeone, D.M.; Walters, R.J.; Roberts, A.; Pearson, S.A.; Pavluk, E.; Hopper, J.L.; Gattas, M.R.; Goldblatt, J.; George, J.; Suthers, G.K.; Phillips, K.D.; Woodall, S.; Arnold, J.; Tucker, K.; Muir, A.; Field, M.; Greening, S.; Gallinger, S.; Perrier, R.; Baron, J.A.; Potter, J.D.; Haile, R.; Frankel, W.; de la Chapelle, A.; Macrae, F.; Rosty, C.; Walker, N.I.; Parry, S.; Young, J.P. Risk factors for colorectal cancer in patients with multiple serrated polyps: a cross-sectional case series from genetics clinics. *PLoS One,* **2010**, *5*(7), e11636.

http://dx.doi.org/10.1371/journal.pone.0011636
PMID: 20661287

[15] Zhu, B.; Wu, X.; Wu, B.; Pei, D.; Zhang, L.; Wei, L. The relationship between diabetes and colorectal cancer prognosis: a meta-analysis based on the cohort studies. *PLoS One,* **2017**, *12*(4), e0176068.
http://dx.doi.org/10.1371/journal.pone.0176068
PMID: 28423026

[16] Yuhara, H.; Steinmaus, C.; Cohen, S.E.; Corley, D.A.; Tei, Y.; Buffler, P.A. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? *Am. J. Gastroenterol.,* **2011**, *106*(11), 1911-1921.
http://dx.doi.org/10.1038/ajg.2011.301
PMID: 21912438

[17] Deng, L.; Gui, Z.; Zhao, L.; Wang, J.; Shen, L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. *Dig. Dis. Sci.,* **2012**, *57*(6), 1576-1585.
http://dx.doi.org/10.1007/s10620-012-2055-1 PMID: 22350783

[18] Chiu, H.M.; Lee, Y.C.; Tu, C.H. Effects of metabolic syndrome and findings from baseline colonoscopies on occurrence of colorectal neoplasms. *Clin. Gastroenterol. Hepatol.,* **2014**, *10*, 10-22.
PMID: 25445768

[19] Ford, A.C.; Veldhuyzen van Zanten, S.J.; Rodgers, C.C.; Talley, N.J.; Vakil, N.B.; Moayyedi, P. Diagnostic utility of alarm features for colorectal cancer: systematic review and meta-analysis. *Gut,* **2008**, *57*(11), 1545-1553.
http://dx.doi.org/10.1136/gut.2008.159723
PMID: 18676420

[20] Adelstein, B.A.; Macaskill, P.; Chan, S.F.; Katelaris, P.H.; Irwig, L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. *BMC Gastroenterol.,* **2011**, *11*, 65.
http://dx.doi.org/10.1186/1471-230X-11-65
PMID: 21624112

[21] Jones, R.; Latinovic, R.; Charlton, J.; Gulliford, M.C. Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database. *BMJ,* **2007**, *334*(7602), 1040.
http://dx.doi.org/10.1136/bmj.39171.637106.AE
PMID: 17493982

[22] Hamilton, W.; Lancashire, R.; Sharp, D.; Peters, T.J.; Cheng, K.K.; Marshall, T. The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records. *Br. J. Cancer,* **2008**, *98*(2), 323-327.
http://dx.doi.org/10.1038/sj.bjc.6604165
PMID: 18219289

[23] Viborg, S.; Søgaard, K.K.; Farkas, D.K.; Nørrelund, H.; Pedersen, L.; Sørensen, H.T. Lower gastrointestinal bleeding and risk of gastrointestinal cancer. *Clin. Transl. Gastroenterol.,* **2016**, *7*(4), e162.
http://dx.doi.org/10.1038/ctg.2016.16
PMID: 27054580

[24] Kocarnik, J.M.; Hua, X.; Hardikar, S.; Robinson, J.; Lindor, N.M.; Win, A.K.; Hopper, J.L.; Figueiredo, J.C.; Potter, J.D.; Campbell, P.T.; Gallinger, S.; Cotterchio, M.; Adams, S.V.; Cohen, S.A.; Phipps, A.I.; Newcomb, P.A. Long-term weight loss after colorectal cancer diagnosis is associated with lower survival: The Colon Cancer Family Registry. *Cancer,* **2017**, *123*(23), 4701-4708.
http://dx.doi.org/10.1002/cncr.30932
PMID: 28841225

[25] Kuo, C.N.; Pan, J.J.; Huang, Y.W.; Tsai, H.J.; Chang, W.C. Association between nonsteroidal anti-inflammatory drugs and colorectal cancer: a population-based case-control study. *Cancer Epidemiol. Biomarkers Prev.,* **2018**, *27*(7), 737-745.
http://dx.doi.org/10.1158/1055-9965.EPI-17-0876
PMID: 29695380

[26] Goodman, D.; Irvin, T.T. Delay in the diagnosis and prognosis of carcinoma of the right colon. *Br. J. Surg.,* **1993**, *80*(10), 1327-1329.
http://dx.doi.org/10.1002/bjs.1800801037
PMID: 8242314

[27] Curless, R.; French, J.M.; Williams, G.V.; James, O.F. Colorectal carcinoma: do elderly patients present differently? *Age Ageing,* **1994**, *23*(2), 102-107.
http://dx.doi.org/10.1093/ageing/23.2.102
PMID: 8023715

[28] Majumdar, S.R.; Fletcher, R.H.; Evans, A.T. How does colorectal cancer present? Symptoms, duration, and clues to location. *Am. J. Gastroenterol.,* **1999**, *94*(10), 3039-3045.
http://dx.doi.org/10.1111/j.1572-0241.1999.01454.x
PMID: 10520866

[29] Roncoroni, L.; Pietra, N.; Violi, V.; Sarli, L.; Choua, O.; Peracchia, A. Delay in the diagnosis and outcome of colorectal cancer: a prospective study. *Eur. J. Surg. Oncol.,* **1999**, *25*(2), 173-178.
http://dx.doi.org/10.1053/ejso.1998.0622
PMID: 10218461

[30] Young, C.J.; Sweeney, J.L.; Hunter, A. Implications of delayed diagnosis in colorectal cancer. *Aust. N.Z.J. Surg.,* **2000**, *70*(9), 635-638.
http://dx.doi.org/10.1046/j.1440-1622.2000.01916.x
PMID: 10976891

[31] Dunne, J.R.; Gannon, C.J.; Osborn, T.M.; Taylor, M.D.; Malone, D.L.; Napolitano, L.M. Preoperative anemia in colon cancer: assessment of risk factors. *Am. Surg.,* **2002**, *68*(6), 582-587.
PMID: 12079143

[32] Gonzalez-Hermoso, F.; Perez-Palma, J.; Marchena-Gomez, J.; Lorenzo-Rocha, N.; Medina-Arana, V. Can early diagnosis of symptomatic colorectal cancer improve the prognosis? *World J. Surg.,* **2004**, *28*(7), 716-720.
http://dx.doi.org/10.1007/s00268-004-7232-8 PMID: 15383871

[33] Stapley, S.; Peters, T.J.; Sharp, D. The mortality of colorectal cancer in relation to the initial symptom

and to the duration of symptoms: a cohort study in primary care. *Br. J. Cancer,* **2006**, *95*, 1321-1325. http://dx.doi.org/10.1038/sj.bjc.6603439 PMID: 17060933

[34] Grivennikov, S; Greten, F; Karin, M. Immunity, inflammation, and cancer. *Cell, 19; 140*(6), 883-99. http://dx.doi.org/10.1016/j.cell.2010.01.025

[35] Ananthakrishnan, A.N.; Cagan, A.; Cai, T.; Gainer, V.S.; Shaw, S.Y.; Churchill, S.; Karlson, E.W.; Murphy, S.N.; Liao, K.P.; Kohane, I. Statin use is associated with reduced risk of colorectal cancer in patients with inflammatory bowel diseases. *Clin. Gastroenterol. Hepatol.,* **2016**, *14*(7), 973-979. http://dx.doi.org/10.1016/j.cgh.2016.02.017 PMID: 26905907

[36] Nazha, B.; Moussaly, E.; Zaarour, M.; Weerasinghe, C.; Azab, B. Hypoalbuminemia in colorectal cancer prognosis: Nutritional marker or inflammatory surrogate? *World J. Gastrointest. Surg.,* **2015**, *7*(12), 370-377. http://dx.doi.org/10.4240/wjgs.v7.i12.370 PMID: 26730282

[37] McCutchen, A.S.; Munoz, J.C.; Brenner, L.; Wludyka, P.; Vega, K.J. Lower albumin levels in African Americans at colon cancer diagnosis: a potential explanation for outcome disparities between groups? *Int. J. Colorectal Dis.,* **2011**, *26*(4), 469-472. http://dx.doi.org/10.1007/s00384-011-1134-7 PMID: 21271345

[38] Cengiz, O.; Kocer, B.; Sürmeli, S.; Santicky, M.J.; Soran, A. Are pretreatment serum albumin and cholesterol levels prognostic tools in patients with colorectal carcinoma? *Med. Sci. Monit.,* **2006**, *12*(6), CR240-CR247. PMID: 16733481

[39] Roxburgh, C.S.; Salmond, J.M.; Horgan, P.G.; Oien, K.A.; McMillan, D.C. Tumour inflammatory infiltrate predicts survival following curative resection for node-negative colorectal cancer. *Eur. J. Cancer,* **2009**, *45*(12), 2138-2145. http://dx.doi.org/10.1016/j.ejca.2009.04.011 PMID: 19409772

[40] Lai, C.C.; You, J.F.; Yeh, C.Y.; Chen, J.S.; Tang, R.; Wang, J.Y.; Chin, C.C. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. *Int. J. Colorectal Dis.,* **2011**, *26*(4), 473-481. http://dx.doi.org/10.1007/s00384-010-1113-4 PMID: 21190025

[41] Brown, S.R.; Baraza, W.; Hurlstone, P. Chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum. *Cochrane Database Syst. Rev.,* **2007**, *4*, CD006439. http://dx.doi.org/10.1002/14651858.CD006439.pub2 PMID: 17943910

[42] Marion, J.F.; Waye, J.D.; Israel, Y.; Present, D.H.; Suprun, M.; Bodian, C.; Harpaz, N.; Chapman, M.; Itzkowitz, S.; Abreu, M.T.; Ullman, T.A.; McBride, R.B.; Aisenberg, J.; Mayer, L. Chromoendoscopy study group at mount sinai school of medicine. Chromoendoscopy is more effective than standard colonoscopy in detecting dysplasia during long-term surveillance of patients with colitis. *Clin. Gastroenterol. Hepatol.,* **2016**, *14*(5), 713-719. http://dx.doi.org/10.1016/j.cgh.2015.11.011 PMID: 26656297

[43] Walgenbach-Brunagel, G.; Burger, B.; Leman, E.S.; Walgenbach, K.J.; Tolba, R.; Heukamp, L.; Hirner, A.; Getzenberg, R.H. The use of a colon cancer associated nuclear antigen CCSA-2 for the blood based detection of colon cancer. *J. Cell. Biochem.,* **2008**, *104*(1), 286-294. http://dx.doi.org/10.1002/jcb.21619 PMID: 18044711

[44] Xue, G.; Wang, X.; Yang, Y.; Liu, D.; Cheng, Y.; Zhou, J.; Cao, Y. Colon cancer-specific antigen-2 may be used as a detecting and prognostic marker in colorectal cancer: a preliminary observation. *PLoS One,* **2014**, *9*(4), e94252. http://dx.doi.org/10.1371/journal.pone.0094252 PMID: 24710115

[45] Knychalski, B.; Lukieńczuk, T. The evaluation of diagnostic value of the tumor markers: CCSA-2 and CEA in colorectal cancer. *Pol. Przegl. Chir.,* **2012**, *84*(2), 86-92. http://dx.doi.org/10.2478/v10035-012-0014-3 PMID: 22487741

[46] Marwa, N.A. *Elhossary. Comparative evaluation of chromocolonoscopy and colon cancer specific antigen-2 test for early detection of Egyptian patients with colorectal cancer.* MD degree thesis, Tropical Medicine, Tanta University., **2019**.