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The Relevance between Fecal Tumor M2 Pyruvate Kinase and Colonoscopy for the Detection of Cancer Colon

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Colorectal cancer (CRC) determination is focused on clinical, serological and endoscopic observations These methods are considered as non-invasive, cost-effective and convenient clinical examination methods. A direct association between M2 Pyruvate Kinase (M2-PK) and separate oncoprotein is the product of dissociation of tetrameric form from dimeric structure in tumor cells. The aim of this analysis is to assess the sensitivity in high risk or symptomatic populations of fecal tumor M2-PK.
Methods: This study is a cross sectional study carried out on 50 patients who were categorized into two groups: 25 patients with colorectal neoplasms (group 1). 25 patients symptomatizing of: diarrhea, persistent abdominal discomfort or bleeding per rectum, without colorectal neoplasms (group 2).
Results: The median value of stool M2-PK showed statistically significance**.** At cut-off ≥ 70 of stool M2-PK to predict activity, sensitivity was 88%, specificity was 84%, PPV was 84.6% and NPV was 87.5%. AUC was 0.907 and P value was <0.001.

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Conclusions: Fecal M2-PK can be used as a pre colonoscopy screening test for CRC patients and is superior to other tumor markers (CEA and CA19.9) as it is more sensitive and specific. As a result of its low cost and ease of use, it is a viable tool for pre-selecting individuals who undergo colonoscopy.

Keywords: Fecal; M2 pyruvate kinase; colonoscopy; cancer colon.

1. INTRODUCTION

Colorectal cancer (CRC) is a malignant disease that constitutes a serious health care problem.

Thus, Routine screening is effective for detecting CRC because it may be present for an extended period before clinical symptoms become evident. This provides clinicians with a window of opportunity for screening, effective intervention, and prevention [1-5].

The fecal occult blood test (FOBT) is the most frequently used screening technique for colorectal cancer. A meta-analysis in which data from three studies and a Swedish trial were pooled estimated that FOBT screening could reduce CRC mortality by as much as 16%–23% [6]. CRC screening using the FOBT is associated with a high probability of false-positive results. Lieberman *et al.* [7] reported that among 3,121 asymptomatic people who underwent colonoscopy, the FOBT was positive for only 23.9% of cases of advanced neoplasia; thus, FOBT failed to detect 76.1% cases of advanced neoplasia [8]. These findings stimulated work on the development of a more reliable CRC screening tool that is not affected by the presence of hemoglobin and detects metabolic changes in CRCs cells directly.

The aim of this study was to assess the use of fecal tumor M2 pyruvate kinase (M2-PK) as a diagnostic biomarker for colorectal cancer (CRC) screening in high-risk or symptomatic individuals. Pyruvate kinase is a critical enzyme in glucose metabolism that transforms phosphoenolpyruvate to pyruvate. It exists in organ-specific isoforms (the L, R, M1, and M2 isoforms). M2-PK is mostly tetrameric in normal proliferating cells and has a strong affinity for phosphoenolpyruvate. In comparison, the M2PK isoenzyme identified in tumor cells is often dimeric and exhibits a poor affinity for phosphoenolpyruvate. In tumor cells, dissociation of M2-PK from the tetrameric form to the dimeric form is promoted by direct contact with different oncoproteins. As a result, the dimeric form of M2-PK is referred to as tumor M2-PK. Tumor M2-PK is easily secreted from tumor cells and is quantitatively detectable in bodily fluids due to its poor affinity for phosphoenolpyruvate. Tumor M2-PK may also be identified and quantified in feces samples using an enzyme-linked immunosorbent assay (ELISA) [9-11].

The aim of this study was to evaluate the sensitivity of fecal tumor M2-PK as a diagnostic biomarker for CRC screening in high-risk or symptomatic populations.

2. PATIENTS AND METHODS

This study is a cross sectional study carried on fifty patients of high-risk or symptomatic patients underwent colonoscopy for various indications such as CRC screening, investigation of colonic symptoms, CRC high risk subject examination, a family history of colorectal neoplasia (CRN), and clinically suspected CRC. Informed written consent was obtained from all patients after full explanation of benefits and risk. Privacy of all patients' data is granted and there was code number for every patient file that included all investigations.

The study population was categorized into two groups: 25 patients with colorectal neoplasms (group 1). 25 patients symptomatizing of: diarrhea, persistent abdominal discomfort or bleeding per rectum, without colorectal neoplasms (group 2).

The exclusion criteria: patients who underwent removal surgery or chemotherapy for CRC or polyps.

All patients included in this study were subjected to: history taking: (age, gender, onset of the disease.), complete clinical examination, laboratory evaluation: (Stool M2-PK -CBC-ESR-CRP-CEA-CA19.9) and colonoscopy.

All patients received a toilet hat for stool collection and were instructed to collect a single walnut-size stool sample 1 day before the laxative administration in preparation for colonoscopy. No special diet was recommended

before giving the sample. The pre-colonoscopy stool samples were stored at − 20°C. Repeated freezing and thawing were prevented, and samples were thawed directly before analysis.

2.1 Stool M2-PK Estimation using ELISA Technique

Principle of the assay: ELISA "Sandwich technique": Solid phase M2-PK antibodies are fixed on the microtiter plate bottom. Samples positives with M2-PK antigen are added to the wells so that antigen (Ag) bind with the antibody (Ab) forming Ag-Ab complex. Enzyme-labeled Ab then added to bind the Ag-Ab complex. incubation followed by washing then take place to remove non-specific antigens and antibodies. Substrate of the enzyme then added to the mixture and incubated to start the reaction with the labelled enzyme giving blue color. Addition of stop solution after incubation to stop the reaction and change the color to yellow. Measure the concentration of M2-PK spectrophotometrically at 340nm. M2-PK concentrations in fecal tumors were measured using a sandwich ELISA technique specific for the dimeric form of M2-PK (ScheBo® Biotech AG, Giessen, Germany). A positive test result was defined as a concentration more than 90 ng/ml.

Colonoscopy: By high-definition videoscope epk i.scan 5000 was used in all examinations (Pentax medical. Japan). Colonoscopic criteria of CRC were finding mass, polyp, ulceration, or stricture affecting the colon, so colonoscopy is gold standard to evaluate sensitivity and specificity of compared to other test.

2.2 Statistical Analysis

The data are evaluated in version 26 (IBM ®, USA) of SPSS. Shapiro-Wilks normality test was used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Quantitative parametric data (e.g., age) were presented as range, mean and standard deviation (SD) and were compared by unpaired Student t-test if two groups and by ANOVA test if 3 groups (with post hoc test (LSD) to compare each two groups). Quantitative non-parametric data (e.g., M2-PK) were presented as median and interquartile range (IQR) and were analyzed using Kruskal-Wallis test; further analysis was performed by Mann–Whitney (U) test to compare each two groups. Categorical data (e.g. sex) were presented as number and percentage and were compared by chi-square (X^2) test. Pearson correlation (r) was used to measure the association between two quantitative variables. The ROC (receiver operating characteristic) curve were used to show the sensitivity and specificity for a diagnostic test at various cutoff points. A P-value of < 0.05 was considered statistically significant.

3. RESULTS

In patients' characteristics (age and sex) there were statistically insignificant difference between both groups (P = 0.058 and 0.145 respectively). In bleeding pre rectum there was statistically significant difference between group (1) and group (2) (P <0.001), chronic abdominal pain was statistically significantly decreased in group (1) than group (2) (P <0.001) and regarding chronic diarrhea, weight loss, hematemesis, anemia and appetite loss there were statistically insignificant difference between both groups (P = 1, 0.490, 1, 0.490 and 0.235 respectively) Table 1.

As regard hemoglobin there was statistically significant difference in group (1) than group (2) (P <0.001). In CRP, first hour ESR and second hour ESR there were statistically significant difference in group (1) than group (2) (P = 0.004, <0.001 and <0.001 respectively). Regarding platelets and TLC there were statistically insignificant difference between both groups (P = 0.259 and 0.356 respectively) Table 2.

Regarding the mass, there was statistically significant difference between group (1) and group (2) (P <0.001). In Polyp, ulcer and non-specific colitis there were statistically insignificant difference between both groups Table 3.

As regard stool M2-PK there was statistically significant difference in group (1) than group (2) (P <0.001). In CEA and CA19.9 there were statistically insignificant difference between both groups (P = 0.234 and 0.082) respectively Table 4.

Diagnostic accuracy of stool M2-PK, serum CEA and serum CA19.9 for prediction of colon cancer are shown in Table 5 and Figs. 1-3.

Table 1. Patients' characteristics and clinical presentation in both studied groups

Patients' characteristics		Group (1) (n = 25)	Group (2) (n = 25)	P value
Age	Range	40-70	45-63	0.058
(years)	Mean ± SD	56.12 ± 8.85	52.12 ± 5.29	
Sex	Male	18 (72%)	13 (52%)	0.145
	Female	7 (28%)	12 (48%)	
Onset of disease (mon)	Range	1-18	----	----
	Mean ± SD	8.48 ± 5.16	----	
Clinical presentation				
Chronic diarrhea	0 (0%)	1 (4%)	1	Chronic diarrhea
Chronic abdominal pain	1 (4%)	20 (80%)	<0.001*	Chronic abdominal pain
Bleeding per rectum	20 (80%)	0 (0%)	<0.001*	Bleeding per rectum
Weight loss	2 (8%)	0 (0%)	0.490	Weight loss
Hematemesis	1 (4%)	0 (0%)	1	Hematemesis
Anemia	2 (8%)	0 (0%)	0.490	Anemia
Appetite loss	3 (12%)	0 (0%)	0.235	Appetite loss
Chronic diarrhea	0 (0%)	1 (4%)	1	Chronic diarrhea
Chronic abdominal pain	1 (4%)	20 (80%)	<0.001*	Chronic abdominal pain
Bleeding per rectum	20 (80%)	0 (0%)	<0.001*	Bleeding per rectum

Table 2. Laboratory investigations in both studied groups

		Group (1) (n = 25)	Group (2) (n = 25)	P value
Hemoglobin	Range	8-13	10.2-14.4	<0.001*
(g/dl)	Mean ± SD	10.42 ± 1.54	12.30 ± 1.43	
Platelets	Range	130-370	160-380	0.259
(*103/cc)	Mean ± SD	249.6 ± 84.19	274.8 ± 71.19	
TLC	Range	4.8-10	4.9-10.4	0.356
(*103/cc)	Mean ± SD	7.31 ± 1.73	7.76 ± 1.67	
CRP	Range	0-23	1-12	0.004*
(*103/cc)	Mean ± SD	11.68 ± 7.47	6.88 ± 3.0	
First hour ESR	Range	6-96	4-16	<0.001*
(mm/h)	Mean ± SD	51.64 ± 25.55	9.68 ± 4.36	
Second hour ESR	Range	12-116	10-26	<0.001*
(mm/h)	Mean ± SD	69.28 ± 28.17	17 ± 4.93	

*TLC: total leucocytic count, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate. *significant as p value <0.05*

Table 3. Colonoscopic findings and laboratory markers in both studied groups

Colonoscopic findings	Group (1) (n = 25)	Group (2) (n = 25)	P value
Mass	23 (92%)	0 (0%)	<0.001*
Polyp	2 (8%)	0 (0%)	0.490
Ulcer	0 (0%)	0 (0%)	---
Non-specific colitis	0 (0%)	2 (8%)	0.490

Table 4. Colonoscopic findings and laboratory markers in both studied groups

Laboratory markers		Group (1) (n = 25)	Group (2) (n = 25)	P value
Stool M2-PK	Range	13.8-190	0.25-97.9	<0.001*
(mg/ml)	Mean ± SD	102.01 ± 37.87	35.19 ± 32.87	
CEA	Range	0-16	0-5	0.234
(ng/ml)	Mean ± SD	5.76 ± 5.60	2.64 ± 1.58	
CA19.9	Range	8-55	1-55	0.082
(U/ml)	Mean ± SD	34.28 ± 14.54	26.48 ± 15.86	

Table 5. Diagnostic accuracy of stool M2-PK, serum CEA and serum CA19.9 for prediction of colon cancer

	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC	P value
Stool M2-PK Eliza	>70	88.00	84.00	84.6	87.5	0.907	<0.001*
CEA	>3	48.00	64.00	57.1	55.2	0.600	0.234
CA19.9	>37	40.00	76.00	62.5	55.9	0.638	0.082

**Significant as p value <0.05*

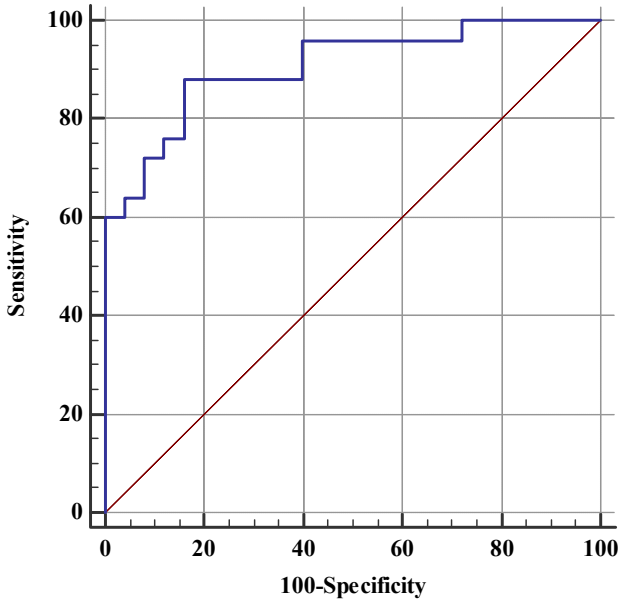

Fig. 1. ROC curve of M2-PK Eliza for prediction of colon cancer

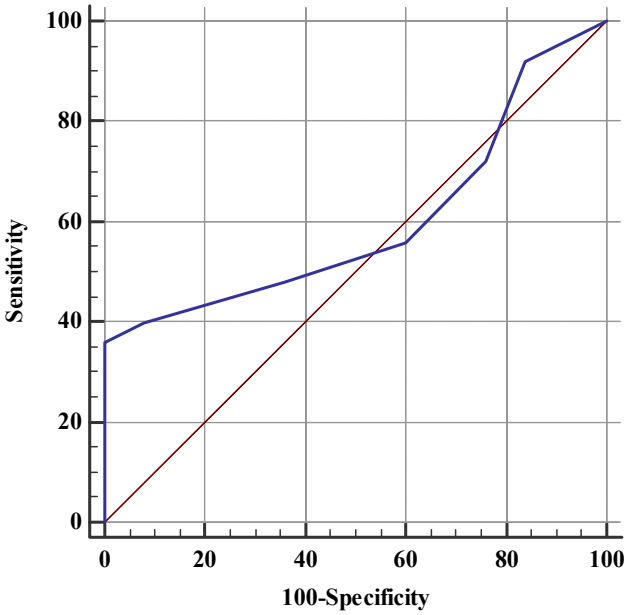

Fig. 2. ROC curve of CEA for prediction of colon cancer

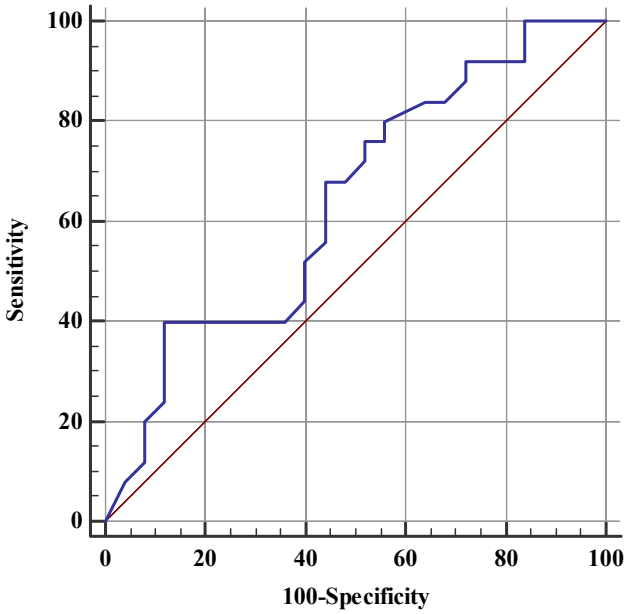

Fig. 3. ROC curve of CA19.9 for prediction of colon cancer

4. DISCUSSION

Diagnosis and monitoring of CRC course are based on clinical assessment, fecal or serological biomarkers and colonoscopy, which is the "gold standard" method.

Colonoscopy though is an invasive procedure with risk of complications. On the opposite, non-invasive biomarkers are readily employed for the task by being convenient, easily reproducible, objective and less invasive methods and with no risk of complications. The non-invasive biomarkers currently include both fecal and serological markers. The new immunochemical fecal test (FIT) has been shown to be more acceptable and more accurate than the previous guaiac version of FOBT. Thus, FIT is now adopted as the preferred test by several countries.

Our result comes in agreement with Gado et al. [12] and Sakr et al. [13] who found that the mean age of their assessed Egyptian patients was 51ys and 44.8ys respectively.

Moreover, Sakr et al. [13], and El Attar [14], found that the median age of CRC patients in Egypt was 48 and 51.2 ys respectively.

As well as, Basu et al. [15] found the mean age of their assessed Indian patients was 52.8 ± 13.5 years and Nataraj et al. [16] found the mean age of their assessed Indian patients 49.31 years.

On the other hand; Yi M et al. [17] found that the mean age of their assessed American Non-Hispanic white and American Asian patients was 70.3ys and 66.3ys respectively.

While Tonus et al. [11] found that the median age of CRC cases was 70 years in Germany.

Less than 1/4 of the assessed cases in group (1) in the current study were below the age of 40 yrs.

This comes in agreement with Howlader et al. [18] in USA which mentioned that CRC is rare before age 40 yrs in both men and women.

Moreover, Khuhaprema et al. [19] highlighted that CRC is uncommon before the age of 40, save in individuals with a genetic predisposition or other risk factors.

On the contrary, Soliman et al. [20] Abou-Zeid et al. [21] Veruttipong et al. [20] and Gado et al. [12] observed that CRC cases under the age of 40yrs were 35.6%, 25%, 22%, 38% and respectively in their studied Egyptian patients.

The disparity in mean ages might be because different cultures and communities have varying risk factors, food habits, lifestyles, and life expectancies.

This data may emphasise the need of early CRC screening in the Egyptian population.

Sakr et al. [13] Abotchie et al. [22] El-Bolkainy et al. [23] and Zakaria et al., found that CRC affects men and women almost equally.

In disagreement with our study, Murphy et al. [24] and Rim et al. [25] emphasized that men have more incidence of CRC than women.

This may be attributed to larger numbers of included patients in these studies, different risk factors, dietary patterns and life style.

In our study, bleeding per rectum was the commonest presenting symptom (80%) which is concomitant with the local reports of Zakaria e al. [26] show bleeding via rectum as the primary presenting symptom in the patients they examined. This was associated with weight loss and cachexia in patients with CRC. Although no significant differences were identified in the prevalence of anemia and cachexia among the two groups, it was more prevalent in our group (1) patients, similarly to Fletcher et al. [27].

In disagreement with our study, Dabbous et al. [28] found that weight loss and anemic manifestations are the main presenting symptoms.

Zakaria et al. [26] who found that In 86.2 percent of patients, the primary colonoscopy finding was a fungating tumor in the colon.

Morikawa., et al. [29] concluded that the FIT relies on the antibodies that bind to the globin, the decomposition of the hemoglobin influences the tool's detection ability, and it is possible that bleeding from proximal colon may lead to an underestimation of the hemoglobin level.

Various studies have investigated anemia in patients with CRC, but the incidence of anemia varies because the criteria for anemia differed.

Moreover, McSherry et al. [30] reported that 27% of 1654 patients with CRC had anemia when the criterion was a hemoglobin of less than 11 g/dl.

As well as, Cappell et al. [31] reported that 58.2% of 315 patients with CRC had anemia when the criteria were a hemoglobin of less than 14.1 g/ dl for men and less than 12.3 g/dl for women.

Moreover, Speights et al. [32] reported that 40% of men and 48% of women with CRC had anemia when the criteria were a hemoglobin of less than 14 g/dl for men and less than 12 g/dl for women.

Jessica Watson et al. [33] who declared that Cancer risk is greater with higher inflammatory marker levels, with older age and in men.

The fecal levels of tumor M2-PK in the current study were significantly higher ($P < 0.001$) in group (1) ranged from (13.8-190 ng/ml) with a mean value (102.01 ± 37.97 ng/ml) and ranged from (0.25-97.9 ng/ml) with a mean value (35.19 ± 32.87 ng/ml) in group (2). This was in agreement with Tonus et al. [11] Hardt et al. [9] Koss et al., and Parente et al. [34].

In our study, the cut-off value for fecal tumor M2-PK levels was 70 ng/ml, as recommended by the manufacturer and other similar studies. Fecal tumor M2-PK was 88% sensitive and 84% specific for diagnosis of CRC with an AUROC = 0.907. This comes in agreement with Sithambaram et al. [35] who reported that M2-PK had a sensitivity ranging from (73 - 97%) and specificity from (78.6 - 100 %) [(337)].

Tonus et al. [11] found that the high sensitivity of the tumor M2-PK test is due to its ability to detect bleeding and non-bleeding tumors. From a practical point of view, the use of a single random formed stool sample for tumor M2-PK analysis, without requiring dietary restrictions, might be of greater patient convenience.

Also this agrees with Jesús-Miguel et al. [36] who revealed that Concerning the diagnostic performance of tumor markers in differentiating the study groups, M2-PK has a good diagnostic performance in differentiating CRC from control group. We verified the role of M2-PK as a sensitive marker for early diagnosis of colorectal cancer in Egyptian patients in the current investigation.

Also, this is in agreement with JOHANN KARL et al. [37] who concluded that M2-PK, a tumor-associated dimeric form of enzyme pyruvate kinase, is commonly elevated in CRC and several studies have found that it is always over expression in the stool of patients with CRC.

On the other hand, Vogel et al. [38] decalred that M2-PK sensitivity was (77.3%) and specificity was (71.8%).

This could be explained by higher number of patients included in his study.

In our study, At cut-off >3 of serum CEA for prediction of colon cancer, sensitivity was 48%, specificity was 64%, PPV was 57.1%, NPV was 55.2%, AUC was 0.600 and P value was 0.234 and at cut-off >37 of serum.

CA19.9 for prediction of colon cancer, sensitivity was 40%, specificity was 76%, PPV was 62.5%, NPV was 55.9%, AUC was 0.907 and P value was (0.082).

This come in agreement with Gao et al. [39] who found that CEA sensitivity was (46.59%) and specificity (80%) and CA19.9 sensitivity was (14.39%) and specificity (89%).

Also, this come in agreement with Liu Z et al. [40] Xi Wang et al. [41] Gupta V et al. [42] and El-Badry et al. [43] who found that the pooled sensitivity of CEA for diagnosis of CRC was only (46 %) and the specificity was (89 %).

On the other hand, Wang et al. [41] CA19-9 has been shown to have a sensitivity of 69% and a specificity of 61% in CRC.

5. CONCLUSION

Fecal M2-PK can be used as a precolonoscopy screening test for CRC patients and is superior to other tumor markers (CEA and CA19.9). Thus, being cost-effective and easy-to-perform test, it is a feasible tool to preselect patients who require colonoscopy.

Stool M2-PK cut-off >70 ng/ml of for prediction of colon cancer, sensitivity was 88%, specificity was 84%, PPV was 84.6%, NPV was 87.5%, AUC was 0.907 and P value was <0.001.

CONSENT

Informed written consent was obtained from all patients after full explanation of benefits and risk.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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