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Comparative Assessment of Tumor Marker Profiles in Colon Cancer and Benign Neoplasms: A Clinical Study in Nineveh Province

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ABSTRACT

Background: Colon cancer is one of the deadliest forms of cancer spread worldwide. it often begins without symptoms, its symptoms in the early stages are similar to those of intestinal disorders and other diseases. And spreads to organs like the liver and pancreas. Also, there is a difference in the incidence of tumors in males compared to females. Detecting it early can make a significant difference in how well patients respond to treatment and survival. Objectives: This study seeks to identify tumor parameters that help differentiate between benign and malignant tumors, detect the different stages of malignant tumors, and distinguish between male and female tumors.

Methods: Blood samples were gathered from 128 individuals undergoing colonoscopies in hospitals across Mosul. And healthy persons too. Based on biopsy results, the tumors were categorized as benign or malignant. and After colectomy, the malignant tumor samples were divided into three groups depending on the tumor stages. Blood was taken before the procedure and tested using the ELISA method. with comparison groups including healthy individuals.

Results: The findings showed Clear differences between the sexes. Males had significantly lower blood counts. and weakened immunity. the ratios such as L/M and P/L showed meaningful differences between men and women, Which provides differences in the immune system response of patients according to gender. In women had higher levels of tumor markers—especially in early-stage cancer. Markers like Septin-9, HIF-1α, and cf-DNA showed significant differences by tumor stage in women, while they were more accurate in men in identifying colon cancer progression. The benign tumor groups showed moderate levels of tumor markers.

Conclusion: The diagnosis and development of colon cancer can be understood with the help of VCAM-1, Septin-9, HIF-1α, CDH-17, cf-DNA, and CRP. cf-DNA and HIF-1α are capable of differentiating between various forms of malignancies and benign tumors, distinguishing factors such as sex and tumor stages.

Keywords: *adenoma, colon cancer, CBC, biopsy, VCAM-1, Septin-9, HIF-1α, CDH-17, cf-DNA, colectomy*

1. INTRODUCTION

Tumors are classified as either benign or malignant and are defined as an abnormal growth of cells. Each one its own characteristics and behavior (1).

Benign tumors arise in any tissue type and are composed of cells that closely resemble the original, healthy tissue. Typically, they are enclosed in a capsule, which Prevents it from invading adjacent tissues or spreading to distant organs. Unlike malignant tumors, benign growths do not invade surrounding structures or metastasize (2). As a result, they are generally considered less dangerous and can often be surgically excised with a low risk of recurrence or harm to the patient (3). Nevertheless, some certain benign tumors possess the potential to undergo malignant transformation over time (4).

The word "malignancy" is used to describe uncontrolled cell growth that has the potential to invade nearby tissues or spread to distant organs (5). it arises as a result of a series of complex genetic changes that enable cells to evade programmed cell death (apoptosis), continue to multiply, and invade neighboring tissues and organs.Which is called metastasis, which spreads the disease to neighboring tissues and organs These are key factors in the development of cancer (6). That the term "malignancy" is used synonymously with cancer (7).

Colon cancer (CCA) ranks as the third most frequently diagnosed cancer and the fourth leading cause of cancer-related mortality globally in both males and females (8). Colon cancer (CCA) ranks as the third most frequently diagnosed cancer

and the fourth leading cause of cancer-related mortality globally in both males and females (8). Early detection of the disease is difficult (9). Colon cancer often develops gradually, starting with benign polyps and progressing to metastatic stages that affect organs of the gastrointestinal tract (10, 11).

Variations in white blood cell (WBC) counts may be attributed to the immune system's response and defense mechanisms. This activation may stimulate the production of monocytes and lymphocytes, leading to an increase in total white blood cells (12, 13).

That some biochemical markers in colon cancer patients were significantly higher than in the control group, Biomarkers are essential for detecting malignant diseases. It can be used to track the growth and spread of tumors. Patients' reactions to treatment are occasionally reflected in it (14).

VCAM-1 is a glycoprotein found on the surface. In 1989, it was found. It dissolves in cancer sufferers' serum. It spreads from the tumor surroundings, where endothelial cells express it in reaction to inflammatory circumstances. It has a crucial role in angiogenesis and the development of colon cancer (15).

VCAM-1 expression may be a biomarker because of linked to cancer stage. lymph node involvement, and tumor development (16).

Hartwell discovered septins in 1971. Septin-9 is as a P-loop GTPase. It is essential for cytoskeletal structure, and cell cycle regulation. It is encoded by the Septin-9 gene on chromosome 17p25. Septin-9 controls unchecked and fast cell division, In malignant tissues. Septin-9 is methylated in the blood of patients with colorectal cancer, that has become a biomarker for cancer monitoring and detection (17, 18).

HIF-1α reacts to low oxygen levels, which are frequently present in solid tumors like colon cancer. It is a component of the heterodimeric HIF-1 complex, which also contains the HIF-1β and oxygen-sensitive HIF-1α subunits. HIF-1α is essential for controlling gene expression linked to cancer cell proliferation, and resistance mechanisms (19). This enables HIF-1α to stabilize, migrate to the nucleus, and then attach to HIF-1β under hypoxic conditions. When the active HIF-1 complex binds to hypoxia response regions in target genes The transcription of genes involved in angiogenesis, metabolism, and cell survival is then started (20).

In colon cancer case HIF-1α is often overexpressed, and this overexpression is connected to bad prognosis and more progresive stages of the colon cancer (21). By controlling vascular endothelial growth factor (VEGF), it support cancer cell survival, proliferation, and metastasis.Its function in linking inflammation to cancer progresive, through the connection between HIF-1α and inflammatory pathways like NF-kB. it thus may becomes a possible target for therapeutic in colon cancer in future.

CDH17 is crucial in the formation of colorectal cancer. Influencing intestinal cell differentiation, adhesion, and proliferation. Structurally, it attaches to α2β1 integrin, which effect on cancer cell adhesion and encourages metastasis. It also works with desmocollin-1 (DSC1) to effect on p120-catenin a protein in charge of actin polymerization. that being so controlling cancer cell movement and invasion. Moreover, CDH17 may help to start theWNT/β-catenin pathway, which supports cancer spread and metastasis (22).

It increased in colon cancer tissues . It can be identified by immunohistochemistry (IHC), that offering useful diagnosis. Higher CDH17 levels are linked to more advanced tumor stages and metastases. Its importance in patient classification and treatment planning (23).

A cf-DNA is a complicated combination of DNA fragments reflecting a tumor's genomic traits. Released into the circulation by cancer cells. these fragments can be used for cancer detection and surveillance (24). The patterns of 5-hydroxymethylcytosines (5hmC) in cf-DNA have shown great specificity colon cancer. So suggesting that this method is a good for diagnosis (25). Raman spectroscopy has also offered insightful analysis of the chemical makeup of cf-DNA. Including those with colon cancer, this method can differentiate between the cf-DNA of healthy people and cancer patients (26).

C-reactive protein Serving as a diagnostic biomarker, and participant in inflammatory processes linked to tumor formation. CRP plays several roles in the genesis and progression of colon cancer. It controls the function of signaling molecules in monocytes and macrophages, that supporting cancer development and immunological reaction. Through several mechanisms, it has a complicated impact on colon cancer incidence, progression, and clinical consequences (27, 28). Higher protein levels indicate continuous tissue damage linked to cancer growth by means of the acute-phase inflammatory response (29).

2. MATERIALS AND METHODS

128 samples were collected from patients visiting different endoscopy units in Mosul city was as 46 cases of tumor and 44 cases without tumor and 38 healthy individuals. The participants' ages ranged from 17 to 84 years, and the samples included individuals of both sexes. of colonoscopy units in Ibn Sina Teaching Hospital, Aljumhuriy Hospital, Mosul General Hospital,

Al-Salam Hospital, and Research Hospitals at Mosul University, as well as from the private clinic of Dr. Abdullah Zuhair Al-Yuzbaki in Mosul City. between March 14, 2023, and March 12, 2024. Venous blood samples were collected from the study participants before colonoscopy at the above-mentioned hospitals. Each sample size was 5 ml, distributed into two types of tubes: 3 ml in gel tubes for tumor marker analysis and 2 ml in EDTA tubes for complete blood count (CBC) analysis using the MicroCC-20Plus device on the same day of the collection. Complete blood counts were performed within one hour of sample collection to ensure accurate results and were not affected by subsequent time changes. After serum separation, samples were classified into two main categories based on histopathological biopsy reports: benign tumors and malignant tumors.For the malignant tumor groups, according to the colon cancer staging system, these groups was classified into tumor stages based on histopathological results: Stages II, III, and IV (The serum was stored in deep freeze until the histopathological report of the patients' colectomy was obtained, and the groups were divided into Biopsies II, III, and IV), Then the serum was used to measure tumor biomarkers.

In addition, 5 ml blood samples were collected from patients whose colonoscopies showed no evidence of tumors or polyps. This group was considered a positive control group; ultimately, and healthy people without any disease symptoms formed the healthy control group.

Tumor markers

This aspect of the study involved estimating six tumor markers in the serum using ELISA technology, Labtech Microplate Reader LT-4000, East Sussex, UK. The markers included Vascular Cell Adhesion Molecule 1 (VCAM-1), Septin-9, Hypoxia-Inducible Factor 1 Alpha (HIF-1α), Cadherin-17 (CDH-17), cf-DNA, and C-Reactive Protein (CRP), following the guidelines provided by Shanghai Ideal Medical Technology Co., Ltd., China.

Statistical Analysis

All data are presented as means ± SD, differences between groups were analyzed by using the Duncan test, one-way ANOVA at the level of statistical significance $P \leq 0.05$ by SPSS version 26 (30).

3. RESULT

The results showed significant differences between the biopsy groups and the control groups of males in each of white blood cell (WBC), lymphocyte counts (LYM), red blood cell (RBC), hemoglobin (Hb), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Volume (MCV), Hematocrit (HCT), and Mean Platelet Volume (MPV). However, in Granulocytes (GRA), the significant difference was limited to biopsy II only. There was no significant difference in platelet count except for the adenoma group. The lack of substantial difference between the two control groups is worth noting, as shown in Table 1.

Table 1. Complete blood count of male biopsy groups

Groups / Variables	Control he. Mean± SD	Control + Mean± SD	Biopsy II Mean± SD	Biopsy III Mean± SD	Biopsy IV Mean± SD	Adenoma Mean± SD
WBC	7.29 a ± 0.65	7.30 a ± 0.62	7.50 a ± 1.14	6.02 b ± 0.57	6.82 b ± 0.15	6.56 b ± 0.65
LYM	2.80 a ± 0.42	2.23 b ± 0.30	1.53 c ± 0.17	1.50 c ± 0.618	1.67 c ± 0.54	2.01 c ± 1.23
MID	0.561 c ± 0.07	0.51 c ± 0.13	0.625 b ± 0.07	0.403 c ± 0.11	0.467 c ± 0.13	0.640 a ± 0.12
GRA	3.92 b ± 0.39	4.57 b ± 0.72	5.35 a ± 0.91	4.11 b ± 0.30	4.68 b ± 0.55	3.91 b ± 0.29
RBC	5.23 a ± 0.11	5.32 a ± 0.16	4.02 c ± 0.72	4.33 c ± 0.18	4.52 b ± 0.17	3.43 d ± 1.13
Hb	14.57 a ± 0.44	14.03 a ± 1.91	9.62 c ± 1.45	9.20 c ± 2.08	10.00 b ± 0.20	7.90 c ± 0.56
MCHC	33.20 a ± 0.7	32.21 b ± 2.46	31.50 b ± 0.50	29.70 b ± 2.48	30.43 b ± 0.65	31.85 b ± 1.82
MCH	27.94 a ± 0.76	26.32 b ± 3.55	24.10 c ± 0.83	21.17 c ± 3.95	22.10 c ± 1.30	23.20 c ± 1.97
MCV	84.26 a ± 1.76	81.16 b ±	76.52 c ± 2.08	70.83 c ± 7.91	72.6 c ± 2.70	72.70 c ± 9.61

		6.71				
RDW_CV	12.13 c ± 0.29	12.73 c ± 1.13	13.15 c ± 0.19	13.83 b ± 1.10	13.26 c ± 0.45	14.20 a ± 1.69
RDW_SD	42.25 a ± 1.23	40.05 c ± 3.4	40.07 c ± 1.92	38.23 c ± 2.87	37.13 c ± 0.35	41.80 b ± 1.56
HCT	44.62 a ± 2.32	43.24 a ± 3.79	30.55 b ± 4.79	30.76 b ± 4.6	32.80 b ± 1.10	24.90 c ± 1.97
PLT	220 b ± 11	222 b ± 30.4	209 b ± 39	198 b ± 3.51	195 b ± 5.0	278 a ± 9.89
MPV	7.92 c ± 0.25	8.42 b ± 0.66	7.55 d ± 0.58	7.83 d ± 0.85	8.70 a ± 0.40	7.10 d ± 1.13
PDW	12.70 b ± 0.56	14.14 b ± 1.58	12.90 b ± 1.89	14.63 b ± 2.05	16.70 a ± 0.60	13.20 b ± 1.69
PCT	0.17 b ± 0.007	0.186 a ± 0.03	0.161 b ± 0.04	0.149 b ± 0.049	0.10 c ± 0.009	0.196 a ± 0.007

RBC (×106/µl) - Hb (g/dl)- PCV and PDW (%) - MCV (϶l) - MCH (pg) - MCHC (g/L) – WBC, Lymph, MID, GRA and PLT (×103/µl). SD (Standard deviation) ; control + (positive control); control he (Healthy control), biopsy II (colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV). Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

Furthermore, when comparing the biopsy and adenoma groups with the control groups, the results showed significant differences in WBC and LYM counts for Biopsy II; monocytes (MID) for Biopsy IV; RBC counts, Hb levels, HCT, PLT, and platelet critical value or Plateletcrit (PCT)when comparing the biopsy and adenoma groups with the control groups.

No significant differences were observed in the following parameters: (GRA), mean corpuscular hemoglobin concentration (MCHC), (MCH), (MCV), red blood cell distribution width (RDW-SD), mean platelet volume (MPV), and red blood cell distribution width (RDW-CV). As well significant differences were observed between the control groups, as shown in Table 2.

Table 2. Complete blood count of female biopsy groups

Groups / **Variable**	**Control he.** **Mean± SD**	**Control +** **Mean± SD**	**Biopsy II** **Mean± SD**	**Biopsy III** **Mean± SD**	**Biopsy IV** **Mean± SD**	**Adenoma** **Mean± SD**
WBC	6.93 b ± 1.09	7.04 b ± 2.24	10.12 a ± 1.88	6.48 b ± 0.54	8.50 ab ± 0.54	8.01 ab ± 0.01
LYM	2.37 b ± 0.53	2.19 b ± 0.86	3.54 a ± 1.46	2.45 ab ± 0.943	2.75 ab ± 0.451	2.04 b ± 0.05
MID	0.476 b ± 0.1	0.479 b ± 0.27	0.68 ab ± 0.31	0.6 b ± 0.06	0.813 a ± 0.11	0.630 ab ± 0.14
GRA	4.09 ab ± 0.87	4.37 ab ± 1.74	5.90 a ± 3.65	3.42 b ± 0.330	4.95 ab ± 0.26	5.34 ab ± 1.35
RBC	4.66 ab ± 0.20	4.67 ab ± 0.28	4.32 ab ± 1.78	3.39 d ± 0.11	3.84 cd ± 0.20	5.08 a ± 1.52
Hb	13.04 ab ± 0.61	13.07 ab ± 1.30	11.6 ab ± 1.40	8.42 d ± 1.26	10.53 c ± 0.33	13.80 a ± 1.13
MCHC	32.91 a ± 0.75	33.61 a ± 2.16	32.10 a ± 1.9	31.55 a ± 1.6	32.5 a ± 0.56	32.91 a ± 2.11
MCH	27.96 a ± 0.88	27.92 a ± 3.10	26.9 a ± 2.2	24.72 a ± 3.5	27.43 a ± 0.82	27.20 a ± 1.69
MCV	85.01 a ± 1.68	82.82 a ± 5.02	84.0 a ± 15	78.02 a ± 7.18	84.4 a ± 2.83	82.50 a ± 2.82
RDW_CV	12.36 b ± 0.28	12.69 ab ± 1.41	12.3 b ± 2.7	14.1 a ± 0.93	12.56 ab ± 0.42	12.00 b ± 0.28

RDW_SD	42.61 a ± 0.90	40.99 a ± 2.77	41.2 a ± 3.1	43.85 a ± 7.83	43.13 a ± 2.79	40.30 a ± 0.99
HCT	39.66 a ± 1.58	38.86 ab ± 2.35	36.30 b ± 6.2	26.5 d ± 2.78	32.4 c ± 0.712	41.80 a ± 1.13
PLT	239 b ± 25	250 b ± 44	393 a ± 8	274 b ± 33.6	184 c ± 21.7	107 d ± 3.2
MPV	7.54 bc ± 0.26	8.24 ab ± 0.82	7.20 c ± 1.30	7.50 bc ± 0.44	7.44 bc ± 0.18	9.10 a ± 1.56
PDW	12.53 b ± 0.70	14.41 a ± 1.6	12.2 b ± 1.30	13.2 ab ± 0.66	11.84 b ± 0.54	13.60 ab ± 1.13
PCT	0.18 b ± 0.02	0.2 b ± 0.03	0.3 a ± 0.03	0.21 b ± 0.03	0.138 c ± 0.02	0.09 d ± 0.001

RBC (×106/µl) - Hb (g/dl)- PCV and PDW (%) - MCV (ϑl) - MCH (pg) - MCHC (g/L) – WBC, Lymph, MID, GRA and PLT (×103/µl). SD (Standard deviation) ; control + (positive control); control he (Healthy control), biopsy II (colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV). Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

Table 3. The percentage of lymphocytes to monocytes and platelets to lymphocytes in both sexes

Percentage / Groups	**Sex**	**% L/M**	**% P/L**
Control he.	males	5.6	78.6
	females	5	101
Control +	males	4.4	99.6
	females	4.6	114
Biopsy II	males	2.5	136.6
	females	5.2	111
Biopsy III	males	3.7	132
	females	4.1	110
Biopsy IV	males	3.6	117
	females	3.4	67
Adenoma	males	3.1	134.3
	females	3.2	52.5

L/M (lymphocyte to monocyte ratio) ; P/L (platelets to lymphocyte ratio). ; control + (positive control) ; control he (Healthy control), biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV)

Regarding to tumor markers, the results demonstrate that males and females had significant increase in all parameters compared to the control groups, as shown in Table 4. The readings for CDH-17 were relatively high in the biopsy II group, while

VCAM-1 and cf-DNA, along with HIF-1α, were significantly elevated in Biopsy III and IV exhibited a notable increase in Septin-9. but CRP showed an increase in stage III over stage II, while it was not statistically significant. A significant difference was observed in HIF-1α and cf-DNA across the three biopsy groups. The VCAM-1 indicate significant differences only in the biopsy IV group. Additionally, CDH-17 has a direct decrease as the disease stage progressed.

Table 4. Male tumor markers

Groups / Variables	Control he. Mean± SD	Control + Mean± SD	Biopsy II Mean± SD	Biopsy III Mean± SD	Biopsy IV Mean± SD
VCAM_1	62.5 d ± 2	64.3 d ± 1.8	72.2 b ± 2	75.3 a ± 1.9	68 c ± 2
Septin_9	1.04 d ± 0.02	1.07 d ± 0.02	1.48 c ± 0.31	1.88 b ± 0.6	2.28 a ± 0.4
HIF_1_alpha	4.3 d ± 0.5	4.5 d ± 1.3	9.4 c ± 1.3	13.5 a ± 1.2	11.7 b ± 0.4
CDH_17	217 b ± 14	221 b ± 11	262 a ± 20	254 a ± 19	250 a ± 22
cf_DNA	53 d ± 8	67 c ± 12	96 b ± 4	105 a ± 8	88 b ± 2
CRP	1.74 b ± 0.03	1.81 b ± 0.14	2.10 a ± 0.05	2.11 a ± 0.07	2.05 a ± 0.04

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation) ; control + (positive control) ; control he (Healthy control), biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV) . Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

It is worth to mention that patients tumor parameters in stage were highest, significant differences were found in VCAM-1, HIF-1α, and cf-DNA among the three groups. Also direct increase was observed with the progression of the disease stage, except for VCAM-1, as detailed in Table 5.

Table 5. Female tumor markers

Groups / Variables	Control he. Mean± SD	Control + Mean± SD	Biopsy II Mean± SD	Biopsy III Mean± SD	Biopsy IV Mean± SD
VCAM_1	60.1 c ± 2.0	61.8 c ± 2.0	74.5 b ± 1.5	76.2 b ± 2.0	81.4 a ± 4.3
Septin_9	1.05 d ± 0.7	1.07 d ± 0.3	1.5 c ± 0.23	1.99 b ± 0.41	2.48 a ± 0.5
HIF_1_alpha	6.0 d ± 0.9	6.2 d ± 0.8	9.7 c ± 0.7	11.8 ± 1.6	13.8 a ± 0.9
CDH_17	214 c ± 18	219 c ± 18	260 b ± 18	272 ab ± 9	285 a ± 23
cf_DNA	47 e ± 3	59 d ± 10	85 c ± 9	97 b ± 5	117 a ± 11
CRP	1.84 c ± 0.07	1.93 c ± 0.14	1.99 b ± 0.01	2.01 a ± 0.06	2.13 a ± 0.03

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation); control + (positive control) ; control he (Healthy control), biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV). Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

Table 6. Differences in tumor parameters between the sexes

Groups / Variables	Males			Females		
	Biopsy II Mean± SD	Biopsy III Mean± SD	Biopsy IV Mean± SD	Biopsy II Mean± SD	Biopsy III Mean± SD	Biopsy IV Mean± SD

VCAM_1	72.2 c ± 2	75.3 b ± 1.9	68.0 d ± 2.0	74.5 c ± 1.5	76.2b ± 2.0	81.4 a ± 4.3
Septin_9	1.48 c ± 0.31	1.88c ± 0.6	2.28b ± 0.4	1.5 c ± 0.23	1.99 c ± 0.41	a ± 0.5 2.48
HIF_1_alpha	9.4c ± 1.3	13.5a ± 1.2	11.7b ± 0.4	9.7c ± 0.7	11.8b ± 1.6	13.8a ± 0.9
CDH_17	262b ± 20	254b ± 19	250b ± 22	260b ± 18	272b ± 9	a ± 23285
cf_DNA	96b ± 4	105a ± 8	88c ± 2	85c ± 9	97b ± 5	117a ± 11
CRP	2.10 a ± 0.05	2.11 a ± 0.07	2.05 a ± 0.04	1.99 b ± 0.01	2.01 a ± 0.06	2.13 a ± 0.03

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation) ; biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV). Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

Compared to the biopsies, the benign tumor group demonstrated a significant reduction in all parameters, in both sexes, as presented in Table 7.

Table 7. Results of tumor parameters for biopsies and Adenoma tumors in males

Groups / Variables	**Biopsy II Mean± SD**	**Biopsy III Mean± SD**	**Biopsy IV Mean± SD**	**Adenoma Mean± SD**
VCAM_1	72.2 b ± 2	75.3 a ± 1.9	68 c ± 2	38.2 d ± 3.5
Septin_9	1.48 b ± 0.31	1.88 b ± 0.6	2.28 a ± 0.4	0.65 c ± 0.04
HIF-1_alpha	9.4 c ± 1.3	13.5 a ± 1.0	11.7 b ± 0.4	3.6 d ± 0.6
CDH_17	262 a ± 20	254 a ± 19	250 a ± 22	170 b ± 49
cf_DNA	96 b ± 4	105 a ± 8	88 c ± 2	51 d ± 9
CRP	2.10 a ± 0.05	2.11 a ± 0.07	2.05 a ± 0.04	1.38 b ± 0.11

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation), biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV) . Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

Table 8. Results of tumor parameters for biopsies and Adenoma tumors in females

Groups / Variables	**Biopsy II Mean± SD**	**Biopsy III Mean± SD**	**Biopsy IV Mean± SD**	**Adenoma Mean± SD**
VCAM_1	74.5 b ± 1.5	76.2 b ± 2	81.4 a ± 4.3	51.7 c ± 7.7
Septin_9	1.5 b ± 0.23	1.99 b ± 0.41	2.48 a ± 0.5	0.88 c ± 0.1
HIF_1_alpha	9.7 c ± 0.7	11.8 b ± 1.6	13.8 a ± 0.9	4.9 d ± 0.1
CDH_17	260 a ± 18	272 a ± 9	285 a ± 23	201 b ± 12
cf_DNA	85 c ± 9	97 b ± 5	117 a ± 11	49 d ± 4

CRP	1.99 b ± 0.01	2.01 a ± 0.06	2.13 a ± 0.03	1.72 c ± 0.13

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation) , biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV) . Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

On the other hand, the comparison of the biopsy with the benign tumor and control groups in males, the results indicate a significant difference only in circulating cell-free DNA (cf-DNA). When comparing the two control groups with biopsy and the adenoma group, there were notable differences in Septin-9 and C-reactive protein (CRP). The adenoma group exhibited a relative decrease in hypoxia-inducible factor 1-alpha (HIF-1α) compared to both control groups and a decrease in cf-DNA compared to the healthy control group. Furthermore, there were no significant differences between the control groups regarding cadherin-17 (CDH-17) compared to biopsies III and IV. Overall, the adenoma group demonstrated a decrease in all parameter readings compared to the two control groups, as summarized in Table 9.

Table 9. Differences in tumor markers among control, biopsy, and benign tumor groups in males.

Groups / **Variables**	**Control he.** **Mean± SD**	**Control +** **Mean± SD**	**Biopsy II** **Mean± SD**	**Biopsy III** **Mean± SD**	**Biopsy IV** **Mean± SD**	**Adenoma** **Mean± SD**
VCAM_1	62.5 d ± 2	64.3 d ± 1.8	72.2 b ± 2	75.3 a ± 1.9	68 c ± 2	38.2 e ± 3.5
Septin_9	1.04 d ± 0.02	1.07 d ± 0.02	1.48 c ± 0.31	1.88 b ± 0.6	2.28 a ± 0.4	0.65 e ± 0.05
HIF-1_alpha	4.3 d ± 0.5	4.5 d ± 1.3	9.4 c ± 1.3	13.5 a ± 1.2	11.7 b ± 0.4	3.6 d ± 0.6
CDH_17	217 b ± 14	221 b ± 11	262 a ± 20	254 b ± 19	250 b ± 22	170 c ± 49
cf_DNA	53 d ± 8	67 c ± 12	96 b ± 4	105 a ± 8	88 b ± 2	51 d ± 9
CRP	1.74 b ± 0.03	1.81 b ± 0.14	2.10 a ± 0.05	2.11 a ± 0.07	2.05 a ± 0.04	1.38 b ± 0.11

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation) ; control + (positive control) ; control he (Healthy control), biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV(colon cancer stage IV)

Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

Additionally, female groups demonstrate no significant difference between the control groups in any of the measurements, except for cf-DNA. Additionally, when comparing the control group to the adenoma group, there were no significant differences in Septin-9, HIF-1α, CDH-17, and cf-DNA levels. Similarly, no significant differences were observed in the CRP levels between the adenoma and healthy control groups. The adenoma group showed a significant decrease in all tumor parameters compared to the biopsy groups and a significant decrease compared to both control groups, except cf-DNA, as presented in Table 10.

Table 10. Comparison of tumor markers among control, biopsy, and benign tumor groups in females.

Groups / **Variables**	**Control he.** **Mean± SD**	**Control +** **Mean± SD**	**Biopsy II** **Mean± SD**	**Biopsy III** **Mean± SD**	**Biopsy IV** **Mean± SD**	**Adenoma** **Mean± SD**
VCAM_1	60.1 c ± 2	61.8 c ± 2	74.5 b ± 1.5	76.2 b ± 2	81.4 a ± 4.3	51.7 d ± 7.7
Septin_9	1.05 d ± 0.7	1.07 d ± 0.3	1.5 c ± 0.23	1.99 b ± 0.41	2.48 a ± 0.5	0.88 d ± 0.1
HIF_1_alpha	6.0 d ± 0.9	6.2 d ± 0.8	9.7 c ± 0.	11.8 b ± 1.6	3.8 a ± 0.9	4.9 d ± 0.1

CDH_17	214 b ± 18	219 b ± 18	260 a ± 18	272 a ± 9	285 a ± 23	201 b ± 12
cf_DNA	47 e ± 3	59 d ± 10	85 c ± 9	97 b ± 5	117 a ± 11	49 e ± 4
CRP	1.84 c ± 0.07	1.93 c ± 0.14	1.99 b ± 0.01	2.01 a ± 0.06	2.13 a ± 0.03	1.72 c ± 0.13

VCAM-1(ng/ml) ; Septin-9(ng/ml) ; HIF-1α (pg/ml) ; CDH-17 (ng/ml) ; cfDNA (nmol/L) ; CRP (mg/ml). SD (Standard deviation) ; control + (positive control); control he (Healthy control), biopsy II(colon cancer stage II), biopsy III (colon cancer stage III), biopsy IV (colon cancer stage IV). Using the Dun can' test, the different letter indicates the significant difference at the probability level ($P \leq 0.05$)

4. DISCUSSION

A CBC is a standard blood test that reveals a patient's general health and can find anomalies suggesting cancer development or presence. The link between colon cancer and a complete blood count (CBC) is may includes both diagnostic and prognostic components and complicated. Though not a direct diagnostic for colon cancer, but it can show indirect indicators like anemia that prompt more tests. Hematological paired with biochemical markers can offer helpful prognostic data. Generally, differences in WBCs among colon cancer patients show a complicated between the immune response to the malignancy, And tumor inflammatory environment . Also the physiological alterations brought about by the disease itself.

Often, a CBC will detect anemia, which can suggest colon cancer from persistent blood loss because tumor growth. For patients showing symptoms like rectal bleeding or unexplained lethargy, which need additional diagnostic tests, such as colonoscopy or computed tomography (CT) colonography (31).

The high LMR is linked to improved survival rates in cancer patients. However, survival results showed no correlation with LMR following treatment. LMR is derived from lymphocyte and monocyte counts, as measure of antitumor immunity. A lack of LYM is linked to a failure the tumor immune response, which results in bad clinical results in many different kinds of cancer. Conversely, tumor-infiltrating lymphocytes (TILs) are lymphocytes that travel within tumor settings and significantly contribute to antitumor immunity via their capacity to kill cancer cells (32).

In study of 1,674 colorectal cancer surgery patients, found that WBCs values rise as surgery drew near, although lymphocyte levels decrease. After surgery, those with the highest WBC and low lymphocyte values had worse cancer-related survival (CRS) results. Although the relationship between inflammation and cancer is well-studied, there is little data on prediagnostic inflammatory and their association with higher cancer risk. They also found low hemoglobin levels, high platelet counts, and rising inflammatory markers seen as early as nine months before diagnosis colon cancer, that could help diagnosis cancer (33). These findings are consistent with our present result, which indicated that female WBC levels in the IV and II biopsy groups increase by 1.5 to 3.2 times when compared to the control group.

Our findings show that the lymphocyte-to-monocyte (L/M) and platelet-to-lymphocyte (P/L) ratios decreased in the biopsy groups across all three disease stages (II, III, and IV) for both males and females. The lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) as significant prognostic markers in colon cancer, indicating a heightened inflammatory state. A low lymphocyte ratio is linked to reduced overall survival (OS) and disease-free survival (DFS) in patients with colon cancer (34).

Complete blood count components, such as the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), are significantly higher in patients with colorectal cancer compared to those without the disease. These ratios possible cancer screening indicators. and Red blood cell distribution width (RDW) and other CBC parameters, referred to higher colorectal cancer risk (35).

Patients with colorectal cancer have more (RDW), which indicates the variation in size of RBC. This rise points in abnormal circulation and generation of red blood cells. Research show that RDW is 1.4% greater in colorectal cancer patients than in healthy individuals, thus underlining the effect of cancer on red blood cell traits (36).

A study of 272 stage I - III colon cancer patients who had surgical removal, among these individuals, that variations in hemoglobin levels may given to many factors including tumor site. Often connected to bleeding, right-sided colon cancer (RCC) might cause lower hemoglobin levels than left-sided colon cancer (LCC). Over time, LCC is more likely to induce chronic, less obvious blood loss, which might develop to anemia (37).

The discovery of occult blood in the stool is notably more common in colorectal cancer patients than in those with benign tumor and control groups. This means continuous bleeding, which may be resulting in decreases hemoglobin concentrations (38). Lymphocytes are involved in anti-tumor immunity, while monocytes contribute to inflammation that promotes tumors (39, 40).

Cell adhesion molecules are the components of cell contacts and the extracellular matrix (ECM). Over 100 of these molecules have been categorized into five families: selectins, integrins, cadherins, and others. These adhesion molecules are essential

in deciding the right course of key activities including cell development, differentiation, migration and critical for signal transmission to cells. They also help tumors to grow. Moreover, their involvement in intracellular signal transduction pathways influences the capacity of cancer cells to move through blood artery walls, hence promoting metastasis (41).

Biological molecules known as colon cancer biomarkers can be detected in blood, various body fluids, or tissues, that indicating the presence or advancement of colon cancer. That certain crucial compounds can rise by as much as 50% or more in malignant tumors when compared to benign tumors (42, 43). Elevated levels of tumor marker tests, including CEA, were noted in the blood serum of patients across different stages of colon cancer when compared to the control group (44).

Tables 4 and 5 indicate a rise in VCAM-1 levels in both males and females in biopsy samples when compared to control groups. In patients with colon cancer, heightened expression could be associated with its involvement in tumor advancement and spread. VCAM-1 serves as a cell adhesion molecule that enhances the interaction between cancer cells and their microenvironment, thereby facilitating processes such as cell migration, invasion, and metastasis. It is frequently elevated in multiple cancer types, such as colon cancer, and correlates with unfavorable outcomes and treatment resistance (15).

That VCAM-1 is crucial in initiating the epithelial-mesenchymal transition (EMT) program, a vital mechanism in the progression of cancer metastasis. EMT facilitates the transition of cancer cells from epithelial characteristics to mesenchymal, therefore increase their migratory and invasive abilities. This process enables cancer cells to adhere to endothelial cells, which is essential and necessary for their migration and the progression of metastasis. The study revealed that heightened expression of VCAM-1 correlated with inadequate differentiation and greater distant metastases in colorectal cancer patients, suggesting a more aggressive tumor phenotype. Additionally, it was confirmed that patients exhibiting elevated levels of VCAM-1 experienced shorter survival durations in contrast to those with reduced levels, underscoring its importance as a prognostic indicator in colon cancer (45).

It is important to highlight that Septin-9 levels have also risen in both males and females; these findings align with the results (46), regarding the various molecular mechanisms that contribute to increased Septin-9 in colon cancer patients. The mechanisms are mainly linked to their roles in cellular structures and signaling pathways. Moreover, the tumor-causing variant stimulates the development of invadopodia, which aid in the invasion of cancer cells by breaking down the extracellular matrix (ECM).

That the suppression of Septin-9 expression enhances cell migration and modifies Rho A signaling, without influencing cell proliferation. Hypermethylation could be associated with the inhibition of gene expression, subsequently playing a role in the migration of cancer cells and their resistance to chemotherapy (47).

Hypermethylation of the SEPT-9 gene is a prevalent genetic alteration in colorectal cancer that contributes to disease progression (17). Furthermore, the hypermethylation of the SEPT9 gene represents a crucial molecular mechanism in the progression of colon cancer. This genetic modification is linked to the repression of tumor suppressor genes, which play a important role in the advancement of cancer. This marker can be identified in both tissues and the peripheral blood of patients, showing its significance as a biomarker for the detection and monitoring of colorectal cancer. Hypermethylated SEPT9 found in plasma signifies the release of tumor DNA from dead colorectal cancer cells. This discovery support the link between methylation and reduced levels of Septin-9 throughout the progression of cancer (48, 49). our findings also align with the work who indicated that septin-9 levels rise as the disease progresses, particularly in stages III and IV (50).

That tracking protein levels post-surgery can serve as a predictor for tumor recurrence, offering valuable insights for the management of colorectal cancer patients (51), that assessing this protein in patients with colorectal cancer, both prior to and three months post-surgery, resulted in a sensitivity of 96.7% and a specificity of 95.5% for differentiating between colorectal cancer cases and non-malignant conditions (52). This is consistent with observations made when analyzing protein levels in biopsy samples versus adenomas, as outlined in Tables 6, 7, 9, and 10.

Similar to other findings, the hypoxia factor HIF-1α shows increased levels in both male and female colon cancer patients when compared to control subjects. HIF-1α functions as a key regulator of the cellular response to low oxygen levels, which is a prevalent feature of solid tumors. This factor is linked to uncontrolled cell growth, processes that prevent cell death, as well as migration and invasion, all of which play a role in tumor development and spread. HIF-1α is activated in response to low oxygen levels and is essential in cancer progression by turning on genes that help cancer cells adjust to the hypoxic conditions present in the tumor microenvironment (53).

Malignant colon cancer generally presents a more intense hypoxic environment, leading to a significant increase in HIF-1α levels. This is attributed to the rapid proliferation of cancer cells outpacing the development of new blood vessels (54).

That the activation of the hypoxia-inducible factor (HIF) pathway by roxadustat results in an increase in glycolysis, which is intricately associated with the metabolic alterations frequently seen in cancer cells (55). That the overexpression of HIF-1α is markedly increased in colon cancer cells when subjected to hypoxic conditions (56).

The microenvironment of solid tumors is marked by hypoxia, a phenomenon resulting from the swift growth of cancer cells coupled with inadequate blood vessel formation within the tumor. This indicates that the blood supply might be insufficient

to satisfy the tumor's requirements. It was observed that under hypoxic conditions, the HIF-1α subunit accumulates and translocates to the cell nucleus, where it forms an asymmetric dimer with HIF-1β. This process plays a vital role in allowing cancer cells to adjust to anaerobic environments, as it governs the expression of genes that are key to various adaptive mechanisms, such as angiogenesis and metabolism (57).

That the expression rate of HIF-1α in colon cancer tissues was 80%, compared to just 14% in normal colon tissues. The findings are illustrated in tables 4, 5, and 6 (21).

Our findings indicate elevated levels of cadherin-17 (CDH-17) present in both male and female colon cancer patients (22), CDH-17 is generally found in normal intestinal cells, but its expression is reactivated in several cancer types, including colon cancer. It has the potential to interact with desmocollin (DSC1) and p120-catenin, leading to the formation of complexes that are essential for the regulation of cell adhesion, migration, and invasion. The interactions play a crucial role in the metastatic potential of colon cancer cells. Moreover, the heightened expression of CDH-17 significantly boosts cell adhesion, migration, and invasion in colorectal cancer cells by engaging with integrins and catenins, thereby aiding in actin polymerization and the development of structures that encourage migration. The observations presented in Table 5 align with this, indicating a gradual increase in these processes.

That the overexpression of CDH17 in colorectal cancer correlates with advanced tumor stages and the occurrence of distant metastasis. This indicates that it contributes to the development of an aggressive cancer phenotype. Furthermore, CDH17 is present in higher quantities in colorectal cancer patients who have advanced tumor stages in comparison to those with early-stage disease (23).

The hypermethylation of CDH-17 is associated with the activation of KRAS and other oncogenic signaling pathways that play a significant role in facilitating tumor growth and progression in colon cancer patients. This activation may result in enhanced cell proliferation and survival. The study observed that increased CDH-17 methylation correlates with reduced antitumor immune responses, potentially contributing to the tumor's aggressiveness. Furthermore, the overexpression of CDH-17 shows a correlation with the infiltration of exhausted T-cells, suggesting a compromised immune surveillance in the tumor microenvironment. Moreover, this overexpression is associated with an increased risk of colon cancer recurrence in stage II, indicating its possible involvement in tumor progression. The results align with the current data presented in Tables 4 and 5 (58).

That the silencing of CDH-17 diminishes the tumorigenic characteristics of cells (22). Overexpression correlates with the advanced stages of colon cancer, suggesting a progressive escalation in the disease's development. This observation corresponds with the information outlined in Table 5, demonstrating a steady rise in disease progression. Nonetheless, it stands in opposition to the findings presented in Table 4, which indicated a relative decline in stage progression among males. The expression of CDH-17 varies between genders, showing higher levels in females compared to males during stages III and IV of the disease, as demonstrated in Table 6. This observation aligns with findings by Bujko et al., (59), indicating that a decrease in CDH-17 expression may result in diminished cell adhesion. This reduction enhances cell movement and invasion, which are critical features of cancer progression.

Benign tumors typically show reduced levels of CDH-17 expression. Consequently, they do not exhibit the metastatic potential typically linked to elevated CDH-17 levels. Additionally, benign tumors typically exhibit well-differentiated characteristics, which are associated with low levels of CDH-17. This distinction aids in maintaining the non-threatening characteristics of the tumor, thereby averting its advancement to a malignant state (60). The data presented corresponds with the findings illustrated in Tables 7 and 8, applicable to both males and females.

In related with circulating cell free DNA (cf-DNA), elevated levels have been observed in colon cancer patients. these may result from various biological mechanisms related to tumor presence and activity. Factors such as increased tumor cell turnover, genetic alterations, and fragmentation of cf-DNA contribute collectively to the detectable levels of cf-DNA found in the bloodstream.

The cf-DNA consists of small, fragmented pieces of DNA that circulate freely in the bloodstream, as opposed to being enclosed within cells. These fragments can be considered as signals that cells release into the bloodstream. cf-DNA can be derived from both healthy and malignant cells. This substance, derived from cancer cells, has the potential to aid medical professionals in identifying cancer in its initial stages. The terminal regions of these DNA fragments generally feature CC or GC base pairs. The significance of methylation and embryonic expression is crucial for comprehending the characteristics of these fragments. Increased methylation at CpG sites leads to the presence of larger and more abundant cf-DNA fragments, suggesting a higher quantity of genetic material in the bloodstream (61).

The cf-DNA includes circulating tumor DNA (ct-DNA) derived from cancer cells. During the process of apoptosis, tumor cells release fragments of DNA into the circulation. The blood's level of cf-DNA is a measure of the tumor The blood's level of cf-DNA is a measure of the size of the tumor. Useually increased level of it correlate with advance stages of colon cancer, also a elevated chance of recurrence. so that cf-DNA as a significant biomarker for tracking colon cancer. Moreover, elevated blood levels may indicate the presence of cancer cells, highlighting its potential utility as a biomarker for early detection of

cancer. Moreover, the increased levels observed post-surgery are associated with a greater likelihood of cancer recurrence, aligning with the findings (62), shown in Tables 4 and 5.

The reduction in cf-DNA levels following colectomy is mainly due to the excision of tumors. When tumor cells release DNA into the bloodstream, that leade to a increase levels of cf-DNA as a result of surgical trauma and inflammation. usually decrease cf-DNA levels after the body recovers and inflammation goes down. In addition to use for tracking cancer and medical treatment, this decrease is a positive indication of surgical success. Also, an increase in cf-DNA levels could refere to of residual or recurrent cancer (62, 63).

The ct-DNA levels rose by 62.2% in stage II patients exhibiting high-risk factors, including T4 adenomas or lympho vascular invasion, in contrast to a 28.2% increase observed in patients without such risk factors (64). The findings revealed an increased probability of cancer recurrence among patients exhibiting high-risk factors, showing rates of 39% compared to 19% for those lacking such factors. This data could provide insight into the rise in stage II and III male patients, as illustrated in Table 4.

Benign tumors show less aggressive growth and Cellular transformation, which decrease the concentration of cf-DNA in bloodstream. This result support the findings presented in Tables 7, 8, 9, and 10. Also the findings indicated a direct relationship between elevated serum cf-DNA concentration and cancer stage tumor size in individuals with colon cancer. This observation could elucidate the reason behind the elevated cf-DNA concentrations in male patients with stage III colon cancer when compared to other biopsy groups, as shown in Table 4. The study indicated that this significant distinction between benign tumors and colon cancer might serve as a biomarker to aid physicians in differentiating between colon cancer and benign lesions (65).

It is worth noting that the levels of C-reactive protein (CRP) have also risen (66), major inflammatory cytokines can influence various processes, including survival and tumor invasion. These cytokines are part of the body's immune response to cancer. The increase in CRP levels among colon cancer patients prior to surgery is primarily due to the systemic inflammatory response triggered by the cancer itself and the body's reaction to it.

The systemic inflammation plays a crucial role in disease progression and assists in assessing risk factors associated with distant metastases in colon cancer(9, 67). These findings are consistent with our current results, as shown in Tables 4 and 5.

Demonstrated a significant increase in CRP levels in breast cancer patients compared to those with benign breast tumors (68). This difference is attributed to the nature of the tumors: benign tumors are less aggressive, do not invade surrounding tissues, and do not spread to other parts of the body, leading to a lower inflammatory response. In contrast, malignant tumors are more aggressive and induce a stronger inflammatory response as they invade nearby tissues and cause greater tissue damage. Our findings support this observation regarding benign tumors, as illustrated in Tables 7, 8, 9, and 10. Additionally, we observed a significant decrease in CRP levels in males compared to females, as shown in. This aligns with (69), which found that female gender was associated with higher CRP levels in benign cases.

C-reactive protein is part of a broader profile used to assess colon cancer patients' prognoses. For example, the C-reactive protein/albumin ratio (CAR) is an inflammatory marker assessed alongside other markers, such as the platelet/lymphocyte ratio (PLR), which differs between right- and left-sided colon cancers. Studies have shown that right-sided colon cancer (RCC) is associated with elevated CAR (37).

In conclusion, the involvement of VCAM-1, Septin-9, HIF-1α, CDH-17, cf-DNA, and CRP, both inflammatory cell infiltration and cancer cells metastasis, owes their marked functional versatility as a target for colon cancer disease. Some may also be used to observe the patients' post-surgical response to predict the occurrence of complete remission or relapses. cf-DNA can be used as a biomarker for assessing tumor progression and metastasis in addition to differentiating between benign and malignant tumors. Finally, the differences between the values obtained for males and females may reflect a biological indicator of gender discrimination.

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Conflict of Interest Disclosure

Every author affirms that they have no conflicts of interest.

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