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Roles of IL-6, TNF-α and β-catenin in patients with colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) occurs when cells in the colon or rectum grow uncontrollably. In most cases, polyps form on the inner lining of the colon or rectum and progressively expand into a malignant polypy that causes colorectal cancer. The present work was aimed to investigate role some biomarkers, including IL-6, TNF-α and β-catenin in CRC disease. Fifty-six tissue specimens, including 31 colorectal tissue specimens and 25 healthy normal tissue specimens were collected from individuals, with different ages (ranged between 26 and 85 years) and sexes (males and females), were attained different hospitals in Baghdad city during the period of March 2021 and September 2022. The age of CRC patients was ranged between 38 and 85 years and the age of health controls was ranged between 26 and 85 years. 4 groups of age (50≤ years) and (50-59 years) and (60-69 years) and (≥69 years) were included. was significantly variation in the mean ± SD of age (60.68±12.69 vs. 51.12±14.53 year; p<0.01) among patients with CRC and healthy controls, respectively. Majority of individuals was males (64.3%; n=36), while females were 35.7% (n=20), whereas 61.3% (n=19) males and 38.7% (n=12) females diagnosed with CRC were involved. Also, 32.0% (n=8) women and 68.0% (n=17) men healthy controls were involved. According to results, these was no significantly variation between gender of CRC patients and healthy controls with p-value (<0.5). In order to study some biomarkers, including β-catenin, IL-6 and TNF-α, immunohistochemistry assay was utilized. There was a highly significantly variation in β-catenin, IL-6 and TNF-α in tissue specimens between CRC cases and HCs with p-value <0.05, <0.001 and <0.001. In addition, the study indicated that these were significantly variations in β-catenin and both TNF-alpha and IL-6, in addition to IL-6 and TNF-alpha among CRC patients and controls.

Keywords: Isoxazolidines, breast cancer

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INTRODUCTION

Colorectal Cancer (CRC) is the third most frequent cancer overall and the fourth leading cause of cancer-related mortality, accounting for around 700,000 yearly deaths worldwide. Cancers of the lung, liver, and stomach have greater mortality rates than any others. For males, CRC is the third most frequent kind of cancer (10%), whereas for women, it is the second most common (9.2%). It is influenced by many risk factors associated with it including; heredity, lifestyle, gut microbiota, diet, obesity, and other factors [1].

Biomarkers are molecular patterns that can be utilized to diagnose cancer at an early stage and to tailor treatment for colorectal cancer. Each one has diagnostic, prognostic, and predictive uses. Thus, biomarkers are helpful at various points in the illness process, allowing for the prediction of disease development and recurrence and the provision of a tailored indicator of therapy efficacy [2]. Interleukin-6 (IL-6) is a key inflammatory cytokine, and STAT3 (signal transducer and activator of transcription 3) is involved in CRC proliferation, epithelial-to-mesenchymal transition (EMT), tumorigenesis, and stemness [3]. Another member of the tumor necrosis factor family, tumor necrosis factor-alpha (TNF-α), has been shown to elicit inflammatory responses in CRC cells at a comparable level of potency as TNF-α [4]. This signaling cascade is critical to carcinogenesis [5], and aberrant Wnt/β-catenin signaling has been identified in a variety of malignancies, most notably Colorectal Cancer (CRC). The Wnt/β-catenin signalling cascade includes the β-catenin protein as a potential co-factor. Cell-cell adhesion and signal transduction are the two main biological processes in which β-catenin is involved. Recent studies have shown that certain cancers are caused by a mismatch in the structural and signalling characteristics of β-catenin [6].

Hence, the present work was aimed to investigate role some biomarkers, including IL-6, TNF-α and β-catenin in CRC disease.

MATERIAL AND METHOD

Specimens' collection

Fifty-six tissue specimens, including 31 colorectal tissue specimens and 25 healthy normal tissue specimens were collected from individuals, with different ages (ranged between 26 and 85 years) and sexes (males and females), were attained different hospitals in Baghdad city during the period of March 2021 and September 2022. The age of CRC patients was ranged between 38 and 85 years and the age of health controls was ranged between 26 and 85 years.

Histopathological Examination

The method followed the protocol established by [7], which included fixing, sectioning, staining, and Immunohistostaining of colon tissues taken from CRC patients. This was done in the Educational Laboratories of the City of Medicine.

Immunohistochemical examination

Specimen preparation for IHC staining: On 5-mm section from each one of the submitted paraffin blocks has been initially stained with H&E for the purpose of verifying that suitable number of adenomatous tissues have been present, also the fixation's quality has been enough for the immunohistochemical analysis.

Antibody dilutions

The TNF-α, IL-6 and β-Catenin are concentrated antibodies, hence diluted with antibodies diluent according to company (Pathinsitu) sheet enclosed with them: The TNF-α and β-Catenin was diluted by ratio of 1:50-1:100 (according to the sheet between 50 -100), by taking 1% (BSA) as well as of 0.05% (NaN3). Antibody dilution as well as protocol might be different on the basis of specimen preparation, also specific applications. IL-6 was diluted by ratio of 1:100-1:1000 (according to the sheet between 100-1000), by taking 1xPBS, 20% Glycerol (pH 7), 0.025% ProClin 300 that has been added as preservative.

Positive Control of markers: Sample biopsies of Tonsil or Follicular Lymphoma, Burkitt lymphomas, Colon Ca, Gastric Ca which were known to be positive for the immune marker we intended to use, were prepared and used as positive control for the TNF-α, IL-6 and Catenin, respectively.

Negative Control of markers: For the negative control, primary antibody has been replaced with PBS.

Immunohistostaining

This was accomplished according to [8], whereas evaluation of slides was made by pathologists blinded to patient's characteristics. The showing brown staining indicate DAB chromogen, then the slides were scored: Staining intensity was rated on a scale from 0 (-) to 3, where 0 denoted no staining, 1 denoted faint staining, 2 denoted moderate staining, and 3 denoted very strong staining. Staining intensity was rated on a scale from 0 (no staining) to 3 (extensive staining) based on the proportion of positive cells in relation to the total tumour area. The total staining score was determined by combining the staining intensity and the total area stained.

Statistical analysis

An unpaired t-test in GraphPad Prism 6 was used for statistical analysis of the data. Measurements were done in triplicate, and the data were reported as the mean ± SD [9].

RESULTS AND DISCUSSION

Collection of samples

In this study, a total of 65 specimens were collected from individuals, with different ages (ranged between 26 and 85 years) and sexes (males and females), were attained several Baghdad hospitals during the period of March 2021 and September 2022. Patients were diagnosed with different adenocarcinoma grade of CRC.

These samples were distributed to groups (patients diagnosed with CRC and controls), as described in table (1), whereas 55.34% (n=31) of specimens were collected from patients diagnosed with CRC and 44.64% (n=25)

Tab 1. Distribution of specimens (n = 56; 100%) in this study.

Group	Patients No.	%	Controls No.	%
Colon tissue specimens (n=56)	31	55.34	25	44.64

Ten percent of all new cancer cases are caused by colon cancer [10]. Although the rate of CRC in Iraq is very low (6.12 per 100,000 people), it has been steadily increasing over the last two decades [11]. While the overall cancer mortality rate has decreased somewhat in Iraq over the last decade, which is encouraging, the CRC mortality rate has risen dramatically over this time, and as a result, the proportion of deaths attributable to CRC has nearly doubled [12].

Distribution of biopsy samples among age, gender of studied groups

In this study, the age of CRC patients was ranged between 38 and 85 years and the age of health controls was ranged between 26 and 85 years. Four age groups (50≤, 50-59, 60-69 and ≥69 years) were included. The majority of specimens (n=14; 56.0%) was obtained from controls. According to the results, there was significant difference in the mean ± SD of age (60.68±12.69 vs. 51.12±14.53 year; $p < 0.01$) among patients with CRC and healthy controls, respectively. The results in this study was indicated the incidence of CRC was observed in age group (50-59) years by 29.0%.

Tab 2. The distribution of biopsy specimens (n=56) among age and gender.

Parameter		Patient (n=31)	Control (n=25)	*p*-value
(Mean±SD) Years		60.68±12.69	51.12±14.53	0.01*
Age range (Years)	≤50	6 (19.4%)	14 (56.0%)	0.02*
	(50-59)	9 (29.0%)	5 (20.0%)	
	60-69)	8 (25.8%)	2 (8.0%)	
	≥69	8 (25.8%)	4 (16.0%)	

* Significant difference.

Injuries and tumour incidence were estimated at increasing rates in age groups above the age of 45, and that is less than it was of great value 41.7% much more than the age groups less than 45 years old [13] in a study conducted at the General Teaching Hospital in Karbala Governorate using data recorded between 2009 and 2017. While high rates of sickness were noted for individuals under the age of 40, this investigation found an increase in the incidence of colorectal cancer. This is supported by data from previous years in Najaf, where many victims were younger than 50 [14]. Because the old in Iraq have a shorter life expectancy and make up a smaller proportion of the population, research have shown that the prevalence of the disease is greater among adults than among the elderly.

Majority of individuals was males (64.3%; n=36), while females were 35.7% (n=20), whereas 61.3% (n=19) males and 38.7% (n=12) females diagnosed with CRC were involved. Also, 68.0% (n=17) male and 32.0% (n=8) female healthy controls were involved. According to results in figure 1, these was no significant difference between gender of CRC patients and healthy controls with p-value (<0.5).

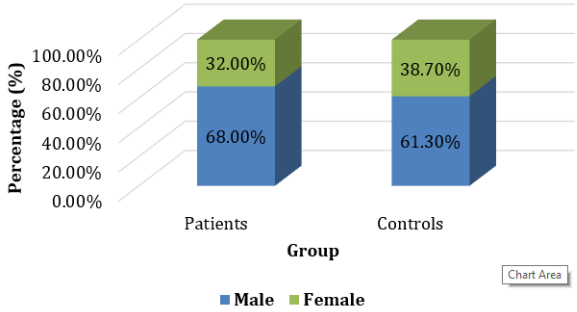

Fig 1. The distribution of specimens among genders

In corresponding with the findings of this study, Alrubaiaee and Al-taee [15] indicated that revealed a higher frequency of CRC among males than females. However, a meta-analysis of studies from Australia and Europe detected that screening uptake of CRC was significantly lower (16%) in males aged 40–75 years than females [16]. Almuttairi reported that 33 (55%) of CRC were males, while the rest 27 patients (45 %) were females, While, it was found that 30 (75%) of benign colorectal tumor were males, and the rest 10 Patients (25%) were females [17]. Whereas, the gender distribution in apparently healthy control was found that 8 (40%) were males and 12(60%).

Immunological study of biomarkers using immunohistochemistry and their association with CRC :In order to study some biomarkers, including β-catenin, IL-6 and TNF-α, immunohistochemistry assay was utilized. The histological sections of different CRC tissue specimens were represented in Figure 2 with different differentiation stage.

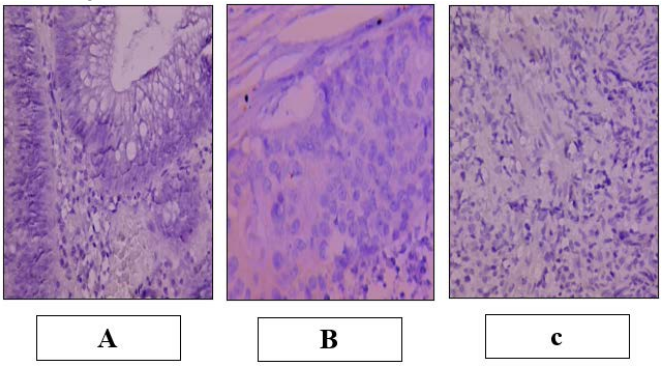

Fig 2. Histological sections of colonic cancer tissue biopsy show (A: poorly, B: moderate and C: high) differentiation, H&E stain (40x).

Tab 3. Distribution the B-catenin score between patients and control groups a (n=56) for samples collected from biopsy

B-catenin	Studied groups (N,%)			
	Patient (n=31)	Control (n=25)	Total	P-value
Negative	6 (19.4%)	17 (68.0%)	23 (41.1%)	0.02 H.S.
+Ve	8 (25.8%)	7 (28.0%)	15 (26.8%)	
++Ve	3 (9.7%)	0 (0.0%)	3 (5.4%)	
+++Ve	14 (45.2%)	1 (4.0%)	15 (26.8%)	
Total	31 (100.0%)	25 (100.0%)	56 (100.0%)	

The β-Catenin is a crucial component of the Wingless-related integration site (Wnt) transmission of signals. Aberrant activation of the β-catenin signalling system, shown by high β-catenin expression, is believed to enhance tumour development, in particular CRC progression [18].

High -catenin nuclear expression was strongly connected with overall survival of CRC patients (P=0.009), as reported by Kim et al. [19] who conducted an immunohistochemical investigation of 101 CRCs and found high (14.9%), low (52.5%), and undetectable (32.6%) β-catenin nuclear expression. Nie [20] found that human colon cancer cells have significantly active β-catenin signalling in in vitro assays. According to research by Li et al. (18), serum β-catenin levels in CRC patients were statistically substantially higher than those in the Healthy Control (HC) group (p<0.05). Compared to normal mucosa, β-catenin was shown to be much more abundant in colon cancer tissues, suggesting that this dysregulation may play a role in the aetiology of human colon cancer.

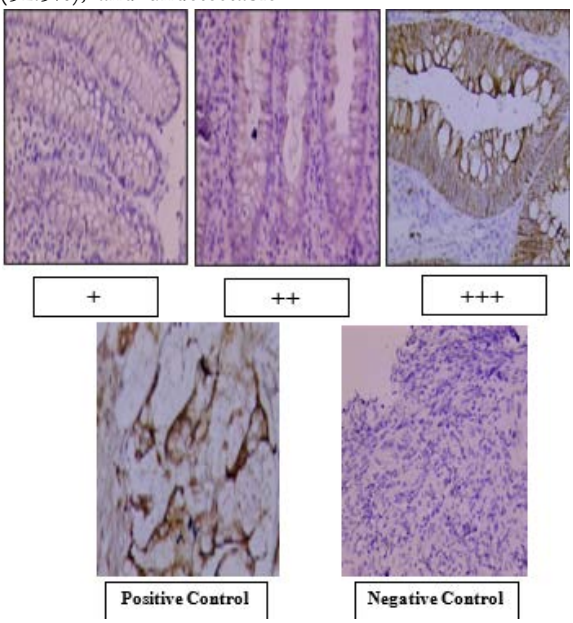

Fig 3. Histological sections of β-catenin IHC score (40X).

The results in table 4 indicated that there were highly significant differences in levels of IL-6 among CRC patients and controls with p-value <0.001. The majority of specimens, which collected from CRC patients, were given positive (+) for IL-6 by 51.6%, while the majority of controls were given negative for IL-6. while the histological sections of these specimens were represented in figure 4.

Tab 4. Distribution the IL-6 score between patients and control groups a (n=56) for samples collected from biopsy

IL-6	Studied groups (N,%)			
	Patient (n=31)	Control (n=25)	Total	P-value
Negative	3 (9.7%)	16 (64.0%)	19 (33.9%)	0.001 H.S
+Ve	16 (51.6%)	7 (28.0%)	23 (41.1%)	
++Ve	4 (12.9%)	2 (8.0%)	6 (10.7%)	
+++Ve	8 (25.8%)	0 (0.0%)	8 (14.3%)	
Total	31 (100.0%)	25 (100.0%)	56 (100.0%)	

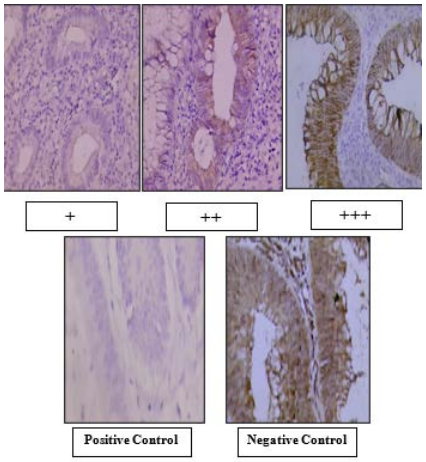

Fig 4. Histological sections of IL-6 IHC score (40X).

In vivo, interleukin-6 (IL-6) is involved in inflammatory responses, immune responses, and wound healing [21]. Increased expression of IL-6 in CRC tissues relative to non-cancerous cells is related with an increased risk of recurrence [22], suggesting a major role for IL-6 in the development of colonic cancer. Circulating IL-6 in plasma is also raised in patients with CRC [23], and many meta-analyses have shown that serum IL-6 may be a possible biomarker for the detection of CRC.

Chen et al. (24) detected an increase in IL-6 release in the interstitial fluid of the colorectal tissues during the progression of colorectal cancer in C57BL/6J-ApcMin/+ mice. Interleukin (IL)-1, IL-4, and IL-6 levels were found to be significantly higher in colon cancer patients (17.26 2.49 pg/ml, 32.18 1.45 pg/ml, 28.26 1.88 pg/ml) than in controls (6.35 1.07 pg/ml, 21.25 2.18 pg/ml, 9.58 3.33 pg/ml [25].

Evaluation of TNF-α was also performed and the results in table 5 indicated that there were highly significant differences in TNF-α among the studied groups with $p<0.001$. The majority of CRC patients' specimens was given highly positive (+++) for TNF-α by 64.5% (n=20), while 68.0% (n=17) of specimens' control group was given negative for TNF-α as well as 55.0% (n=11) of adjacent tissues' specimens were given positive (+) for TNF-α.

Tab 5. Distribution the TNF-α score between patients and control groups a (n=56) for samples collected from biopsy

TNF-α	**Studied groups (N,%)**			
	Patient (n=31)	**Control (n=25)**	**Total**	**P-value**
Negative	2 (6.5%)	17 (68.0%)	19 (33.9%)	≤0.001 H.S
+Ve	-	-	-	
++Ve	9 (29.0%)	7 (28.0%)	16 (28.6%)	
+++Ve	20 (64.5%)	1 (4.0%)	21 (37.5%)	
Total	31(100.0%)	25 (100.0%)	56 (100.0%)	

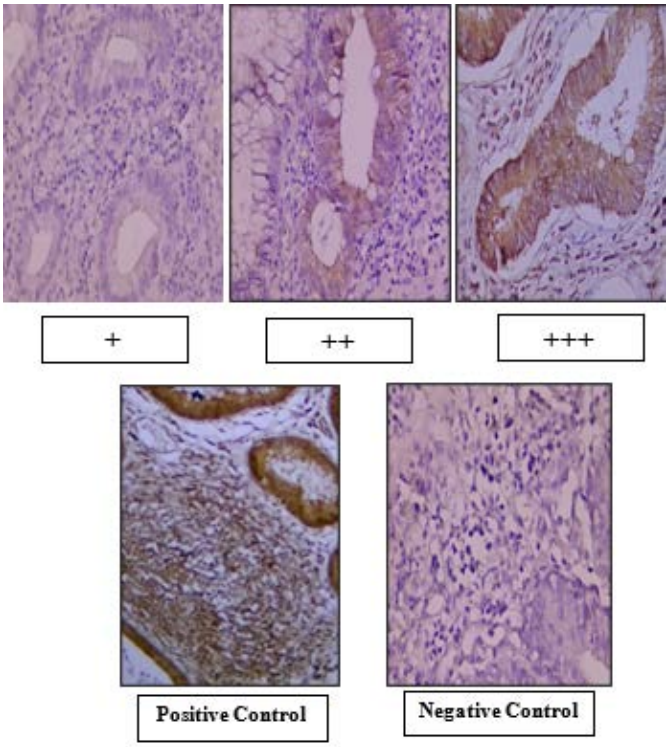

Fig 5. Histological sections of TNF- α IHC score (40X).

In a healthy immune system, TNF-alpha plays an essential function. Like interleukin-1 and interleukin-6, it is a significant pro-inflammatory cytokine. Some neoplasms, such as Non-Hodgkin Lymphoma (NHL), colorectal adenocarcinoma, renal cell carcinoma, and sarcomas, utilise tumour necrosis factor-alpha as a potent prognostic factor and biomarker [26]. Patients with colorectal cancer had higher mean blood levels of IL-6 and TNF-alpha compared to healthy controls ($p<0.001$ and $p<0.0001$, respectively) [27]. Clinical outcomes for several cancer types, including colon cancer, have been linked to serum TNF-alpha levels [28].

Patients with hepatocellular carcinoma who have elevated serum TNF-alpha have a significantly worse chance of survival compared to those who have lower levels of the protein [26]. Increased levels of IL-6 and TNF-alpha in the blood have been linked in several studies to both colorectal cancer and advanced illness. Cancer may be diagnosed with greater accuracy and individuals with a poor prognosis can be singled out for more intensive therapy [29]

Correlation between biomarkers: Based on the results in table 6, these were significant differences in β-catenin and both TNF-alpha and IL-6. Also, there were significant differences between IL-6 and TNF-alpha among CRC patients and controls.

Tab 6. Correlations between biomarkers

		β-catenin score	TNF-α score	IL-6 score
β-catenin score	Pearson Correlation	1	0.348**	0.467**
	Sig. (2-tailed)		0.003	0
TNF-α score	Pearson Correlation		1	0.634**
	Sig. (2-tailed)			0
IL-6 score	Pearson Correlation			1
	Sig. (2-tailed)			

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

The aforementioned functions of various biomarkers in the colorectal colon have been outlined. As Kangwan point out, inflammatory mediators such cytokines and chemokines have a role in all three stages of carcinogenesis (initiation, promotion, and progression) [30]. TNF-alpha was shown to dramatically elevate IL-6 levels in colitis-associated malignancy by Kangwan et al., 2016. Tissue levels of b-catenin rose at the same time as the pro-inflammatory cytokines IL-6 and TNF-a [31].

TNF-induced production of IL-6 and CCL2 in human microvascular endothelial cells was enhanced by lithium or siRNA suppression of GSK-3, whereas -catenin regulated NF-B promoter activity in colorectal cancer cells. Strong expression of -catenin

inhibited IL-6 promoter activity via inhibiting NF-B-dependent interactions with T-cell factor (TCF)/LEF transcription factors. They also demonstrated that beta-catenin increased NF-B and CCAAT/enhancer binding protein expression, which in turn increased IL-6 production [32, 33].

CONCLUSION

Expression of some biomarkers, including IL-6, TNF-α and β-catenin were significant abundance in CRC, suggesting that these biomarkers may play vital roles in treatment of the disease and indicating their uses as predicted markers for CRC detection and regarding new biomarkers-targeted therapies with regard to the treatment of colon cancer.

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