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Levels of Interleukin-6 in Colorectal Carcinoma Patients in Relation to Metastasis degree

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ABSTRACT

Background: Colorectal cancer is the third most common form of cancer and the second leading cause of death among cancers in the Western World. Adenocarcinoma represents 98% of colorectal cancer. In Iraq, It is the 7th most common malignant tumor according to the commonest ten cancers by site in 2005. the 7th commonest in male , while the 4th commonest in female

Materials and Methods: This cross-sectional study was done in Kirkuk city from the beginning of March 2017 to the end of April 2018. The study include 50 patient (27 male and 23 female) with different degree of CRC (from new diagnosis to metastasis), their age were 27-77 years, these patients were attended to Kirkuk oncology center evaluating the role of interleukin-6 in progression and prognosis of colorectal carcinoma. This study also included 40 healthy blood donors as control group. Five ml blood was collected from each patient and control enrolled in the study for determination of serum IL-6 level.

Results: The study found that highest rate (56%) of CRC patient of admitted to Kirkuk oncology center were above 50 years old and 20% were below 30 years, Table 1. The study showed that 60% of CRC patient were in the first grade of the cancer (without metastasis), 30% in the grade 2 and only 20% were in the grade 3 of progression of the cancer, Table 1. In this study, IL- 6 was significantly elevated in CRC patient comparing with healthy control ($P<0.05$), Table 3 show mean and standard deviation of IL-6 which recorded 33.79±6.22 pg/ml on CRC patients versus 6.6±0.91 pg/ml in the control group. Interleukin- 6 showed significant elevated level ($P<0.05$) in CRC patients who in the grade 3 (i.e: who with advanced stage of metastasis) (37.19±7.12 pg/ml), followed by CRC patients in grade 2 (28.24±5.59 pg/ml) and the lowest mean of IL- 6 was found in CRC patients who didn't suffer from metastasis (20.27±3.21 pg/ml.(

It was concluded that the there was a significant relation of interleukin elevation with promote colorectal cancer.

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Introduction

Colorectal cancer is the third most common form of cancer and the second leading cause of death among cancers in the Western World [1]. Adenocarcinoma represents 98% of colorectal cancer. In Iraq, It is the 7th most common malignant tumor according to the commonest ten cancers by site in 2005. the 7th commonest in male , while the 4th commonest in female [2]. The importance of CRC comes from the fact that in spite of its high incidence but it's a complete treatable disease if caught early .It represents a challenge to the medical profession because they almost always arise in adenomatous polyps that are generally curable by resection [3]. Early in their growth, most human tumors do not induce angiogenesis. They remain small or in situ for years until the angiogenic switch terminates the stage of vascular quiescenc so tumors can not enlarge beyond 1-2 mm in diameter or thickness ,unless they are vascularized [4]. Therefore, development of noninvasive diagnostic and prognostic biomarkers is critical for CRC early detection and curative treatment interventions, which can significantly reduce its morbidity and mortality [5.[

It has been reported that cancer-associated inflammation is a key determinant of disease progression and survival in CRC, which can contribute to tumor angiogenesis, invasion, and metastatic spread [6,7]. As an inflammatory cytokine, IL-6 can be involved in immune regulation, hematopoiesis, and carcinogenesis [5]. It can act as a tumor promoter in colorectal neoplasms by activating the downstream oncogenic transcription factors in epithelial cells, such as NF-κB and STAT3 [6]. Several meta-analyses and systematic reviews have assessed the association between serum IL-6 and risk of CRC, whereas these pooled results were insignificant with positive association between the serum IL-6 level and risk of colon cancer, but the results were opposite for rectal cancer [7-9]. This study aimed at evaluating the role of interleukin-6 in progression and prognosis of colorectal carcinoma.

Material and methods

This cross-sectional study was done in Kirkuk city from the beginning of March 2017 to the end of April 2018. The study include 50 patient (27 male and 23 female) with different degree of CRC (from new diagnosis to metastasis), their age were 27-77 years, these patients were attended to Kirkuk oncology center. This study also included 40 healthy blood donors as control group. Five

ml blood was collected from each patient and control enrolled in the study for determination of serum IL-6 level.

Statistical Analysis :

Computerized statistically analysis was performed for obtaining of P. value (P<0.05=significant.(

Results:

The study found that highest rate (56%) of CRC patient of admitted to Kirkuk oncology center were above 50 years old and 20% were below 30 years, Table 1. The study showed that 60% of CRC patient were in the first grade of the cancer (without metastasis), 30% in the grade 2 and only 20% were in the grade 3 of progression of the cancer, Table 1. In this study, IL- 6 was significantly elevated in CRC patient comparing with healthy control (P<0.05), Table 3 show mean and standard deviation of IL-6 which recorded 33.79±6.22 pg/ml on CRC patients versus 6.6±0.91 pg/ml in the control group. Interleukin- 6 showed significant elevated level (P<0.05) in CRC patients who in the grade 3 (i.e: who with advanced stage of metastasis) (37.19±7.12 pg/ml), followed by CRC patients in grade 2 (28.24±5.59 pg/ml) and the lowest mean of IL- 6 was found in CRC patients who didn't suffer from metastasis (20.27±3.21 pg/ml), as shown in Table 4.

Table 1: Distribution of CRC patient according to age

Age groups (years)	Number	Percentage
< 30	10	20
30-50	22	44
>50	28	56
Total	50	100

Table 2: Distribution of CRC patient according to grade of metastasis

Age groups (years)	Number	Percentage
Grade 1	25	50
Grade 2	15	30
Grade 3	10	20
Total	50	100

Table 3: determination the level of IL-6 in the studied group

Estimated IL-6 (pg/ml)	Study groups	
	CRC patient	Blood donors (control)
No.	50	40
Mean±SD	33.79±6.22	6.6±0.91

P <0.05

Table 4: Estimation the level of IL-6 in CRC patients as their distribution of metastasis grades

Estimated IL-6 (pg/ml)	CRC patients		
	Grade 1	Grade 2	Grade 3
No.	25	15	10
Mean±SD	20.27±3.21	28.24±5.59	37.19±7.12

P<0.05

Discussion:

Colorectal cancer (CRC) is persistently presenting a major health probelm and it is the sixth among the most common 10 cancers in Iraq [2]. According to our finding, patients above 50 years were more frequently to have the disease, ALSafi et al [11] found incidence of colorectal was estimated to be generally increased in patient than 45 years. Our finding also agreed with study done by AL-Janabi [12] at 2016 in Karbala who stated that colorectal carcinoma wer more occurred in aged patients. Another Iraqi studies concerning the trend, the early diagnosis and managements of colorectal cancer were recorded that 35.5% and 17.5% of patients included in these studies were under the age of 40 years respectively [13,14]. Many influences can explain this prevalence in young. High body mass index and obesity, absence of physical activities and sedentary life and bad nutritional habits like loss of dietary fibers and consumption of heavy fatty meals. However; It is evident that the ecological and genetic influences can raise the probability of acquiring colorectal carcinoma [1,12]. ALSafi et al [11] found that most CRC patients presented with grade I (61.5%) and the frequency of CRC with Grade 3 was higher among patients > 45 years. In relation of IL-6 with CRC, and in agreements with our investigations, Median IL-6 level was significantly higher in patients with colorectal cancer than in normal controls. Chung et al [8] indicated that IL-6 level was significantly higher in patients with colorectal

cancer than in normal controls and IL-6 levels also increased in a stage-related manner ($P < 0.01$). Ueda et al [5] also found that levels of IL-6 was significantly higher in CRC patients with metastasis than in those without metastasis. Xu et al [16] in results of meta-analysis indicated that serum IL-6 may be a potential noninvasive biomarker for CRC diagnosis. Additionally, Wang et al [17] showed that serum IL-6 expression was highly correlated with CRC comparing with healthy control and found that serum IL-6 expression was associated with certain clinical parameters of CRC, such as tumor invasion. Because of its low molecular weight, IL-6 can freely diffuse through intercellular junction and appear in the tumor microenvironment rapidly, which is the basis for IL-6 to function [18]. IL-6 can promote cancer cell entry into the cell cycle through activating STAT3 which increases the expression of cyclin D1, D2, B1, and c-Myc, and decrease the expression of the cyclin-dependent kinase (Cdk) inhibitor p21[19]. IL-6 can also increase telomerase activity, thus preventing cellular senescence[20]. Besides, IL-6 can promote noncancer cells conversion into cancer stem cells, which possess properties of self-renewal and repopulation potential[21]. Furthermore, IL-6 can regulate tumor cell proliferation by interacting with growth factor signaling, including epidermal growth factor family members and hepatocyte growth factor[21]. IL-6 also provides a key regulatory signal in the T-cell differentiation pathway, downregulating T-lymphocytic function and impairing adaptive immune response, thus allowing tumor cells to escape immune surveillance[22]. All of these discoveries illustrated the protumor function of IL-6 via promoting tumor cell growth inordinately and inhibiting apoptosis [23]

Conclusions**:**

It was concluded that the there was a significant relation of interleukin elevation with promote colorectal cancer**.**

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