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Assessment of IL-12 and Liver Enzymes Levels in Serum of Some Iraqi Patients with Colon Cancer

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Abstract

Background: Interleukin-12 has extensively studied in colorectal cancer, but its correlation with liver enzymes is still limit.

Objective: the present study aimed to assess the serum levels of Interleukin-12 and liver enzymes in Iraqi patients with colon cancer.

Methods: Serum samples (90) were collected divided to 50 samples of colorectal cancer CRC patients and 40 of healthy subjects, interleukin-12 was measured using ELISA, while liver enzymes were measured spectrophotometrically and statistically analyzed.

Results: The study showed significant increase ($P<0.0001$) in concentration of IL-12 (304.6±26.91) pg/ml, ALP (309.9±66.84) IU/L, AST (323.5±109.9) IU/L and ALT (37.4±7.78) IU/L compared to healthy subjects (142.3±14.71 pg/ml, 165.5±38.8 IU/L, 152.6±55.34 IU/L, and 18.28±6.14 IU/L) respectively for all biomarkers. .

Conclusion: Iraqi patients with CRC show elevated serum IL-12 and elevated lever enzymes, however, liver enzymes work independently and not affected by IL-12.

تقييم مستويات IL-12 وإنزيمات الكبد في مصل بعض المرضى العراقيين المصابين بسرطان القولون

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الخلاصة

دُرِسَ الإنترلوكين-12 على نطاق واسع في سرطان القولون والمستقيم، إلا أن ارتباطه بإنزيمات الكبد لا يزال محدودًا. لذا، هدفت هذه الدراسة إلى تقييم مستويات الإنترلوكين-12 وإنزيمات الكبد في مصل الدم لدى مرضى سرطان القولون والمستقيم العراقيين. جُمِعَت عينات مصل الدم (90 عينة) مُقسّمة إلى 50 عينة من مرضى سرطان القولون والمستقيم و40 عينة من الأصحاء. قُيسَ الإنترلوكين-12 باستخدام تقنيةELISA ، بينما قيست إنزيمات الكبد طيفيًا وحُلّلت إحصائيًا. تظهر نتائج الدراسة الحالية زيادة كبيرة (P<0.0001)في تركيز IL-12 (304.6 ± 26.91) بيكوغرام/مل، و ALP (309.9 ± 66.84)وحدة دولية/لتر، و AST (323.5 ± 109.9)وحدة دولية/لتر، و ALT (37.4 ± 7.78)وحدة دولية/لتر مقارنة بالأشخاص الأصحاء (142.3 ± 14.71 بيكوغرام/مل، و165.5 ± 38.8 وحدة دولية/لتر، و152.6 ± 55.34 وحدة دولية/لتر، و18.28 ± 6.14 وحدة دولية/لتر) على التوالي لجميع المؤشرات الحيوية. وفي الختام، يُظهر المرضى العراقيون المصابون بسرطان القولون والمستقيم ارتفاعًا في مستوى IL-12في المصل وارتفاعًا في إنزيمات الرافعة، ومع ذلك، تعمل إنزيمات الكبد بشكل مستقل ولا تتأثر بـ.IL-12

Introduction

One of the most worldwide distributed cancers is colorectal cancer (CRC), as well as one of most common cancer leads to high rate of mortality [(1)], and both men and women are highly affects, and depending on previous data, CRC is the third leading cause of death [(2,3)]. CRC starts at the inner lining of the colon, rectum, and appendix [(4)]. Over 10,000 new cases were recorded until 2020, with a growing number of young individuals [(5)]. Many factors like environmental, epigenetics, and genetic factors affect the development of CRC [(1)], as well as immunological factors like proinflammatory cytokines can also impact the growth of CRC, as an inflammation is considering a significant risk factor for start of colon cancer, as well as several physiological and biochemical factors are also implicated in the pathophysiology of CRC [(6)].Previous studies shows that proinflammatory cytokines as IL-12 to be a promoter of CRC initiation and progression and involvement of in CRC metastasis and prognosis and it is strongly associated with poor outcomes of this malignancy [(6,7)], as well as increase in biochemical biomarkers like liver enzymes also related with poor outcomes of CRC [(8)]. Previous findings indicate that many types of tumors contribute to elevated serum levels of biochemical biomarkers like aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP)[(9,10,11)], despite that how these liver enzymes affected by levels of interleukins like IL-12 is still unknown, however, recent study of Najmuddin *et al.*[12] shows that the IL-12 levels in mice with CRC were not correlated with liver enzymes like ALP, AST, and ALT, while these findings were not well studied in human, and to our best knowledge, locally in Iraq, there are no data rely the correlation between liver enzymes and IL-12, so the present study aimed to assess serum levels of IL-12, ALP, AST, and ALT and if there a correlation between them in Iraqi patients with CRC.

Materials and Methods

Ethical approval

All design of the present study was ethically approved by Medical City Department / Baghdad in letter No. 28797 dated 21-8-2024.

Study Samples

This study included 50 patients with CRC and 40 healthy subjects, their ages between (28-75), for both sexes. Inclusion criteria included newly diagnosed colon cancer. The exclusion criteria were children and those receiving chemotherapy.

Measuring serum concentrations of interleukin-12

The serum concentrations were assessed using the ELISA method with a commercial kit from SunLong, China. The plate was pre-coated with an antibody specific to human interleukin-12. The concentration of IL-12 in the sample is presented. The content of human IL-12 shown a positive association with the development of color in the substrate solution. The procedure is terminated by the addition of an acidic stop solution, following which the absorbance is measured at a wavelength of 450 nm.

Measuring serum Liver Enzymes

All liver enzymes were measured spectrophotometric ally using commercial kits (GIESSE/Italy). Typically, the enzymatic method involves coupling the AST and ALT reaction with other enzymatic reactions to produce a detectable color change. Measure the absorbance of the reaction product using a spectrophotometer [13].

Statistical analysis

GraphPad prism was used to calculate the Mean Standard deviation followed by independent sample t-test, and Pearson correlation was done using SPSS (v.23) to assess correlation between all biomarkers [14].

Results and Discussion

Serum levels of IL-12 in CRC patients were evaluated in the present study, and figure (1) shows significantly increased ($P<0.05$) compared to IL-12 concentration in healthy subjects. Serum concentration of IL-12 in CRC patients were (304.6±26.91) pg/ml while in healthy subjects were (142.3±14.71) pg/ml. as shown in table (1). Figure (2) and table (1) show a significant ($P<0.05$) increased levels of serum ALP in the present study among patients with CRC compared to healthy subjects, as a concentration of ALP in CRC patients reached (309.9±66.84) IU/L while healthy subject was in normal range (165.5±38.80) IU/L. Serum levels of aspartate transaminase was significantly high ($P<0.05$) in patients compared to healthy subjects, as shown in figure (3). The level of AST were (323.5±109.9) and (152.6±55.34) in patients and control groups respectively, as shown in table (1).The result of this study showed a significant elevation ($P<0.05$) in serum level of ALT in patients with CRC compared to control group (as shown in figure 4), and table (1) shows that ALT level was (37.4±7.78) IU/L in patients' group while in healthy subjects was (18,28±6.14) IU/Statistical analysis of the present study shows a non-significant ($P>0.05$) correlation between IL-12 and ALP, AST and ALT levels, as shown in figures (5) (6) (7) and table (2).

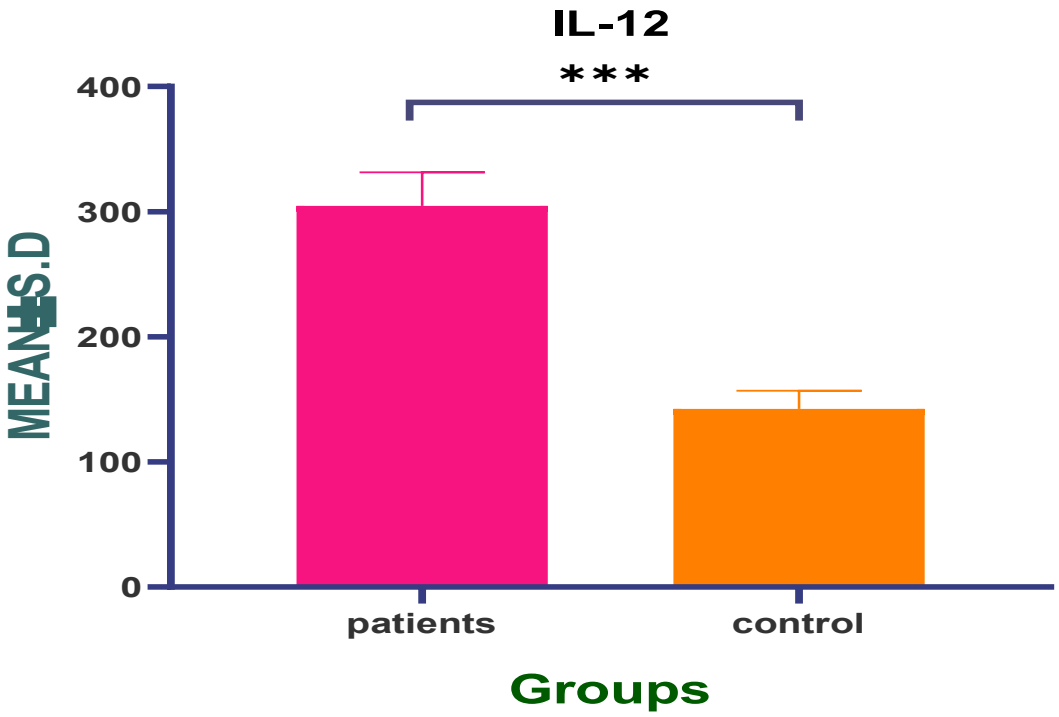

Figure 1: Serum levels of IL-12 in CRC patients and healthy subjects.

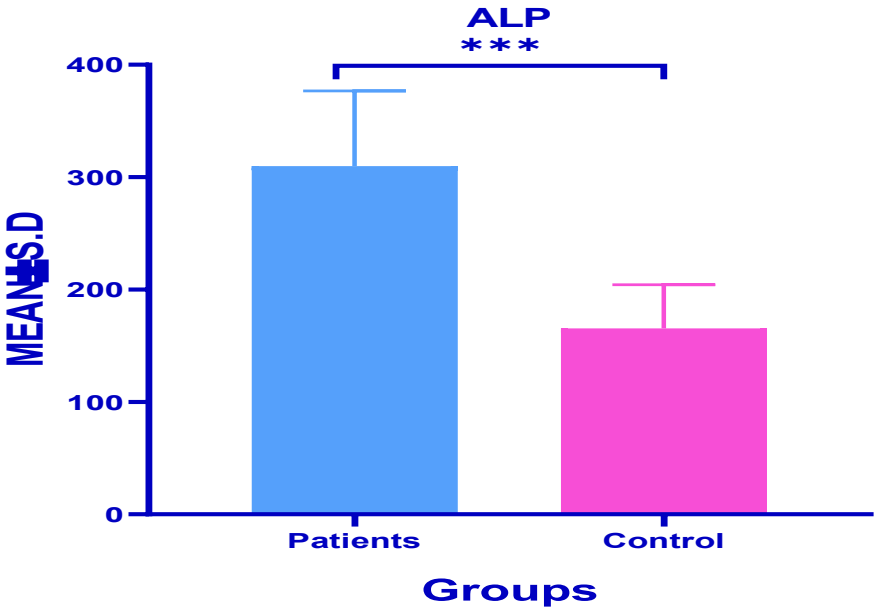

Figure 2: Serum levels of Alkaline phosphatase in CRC patients and healthy subjects.

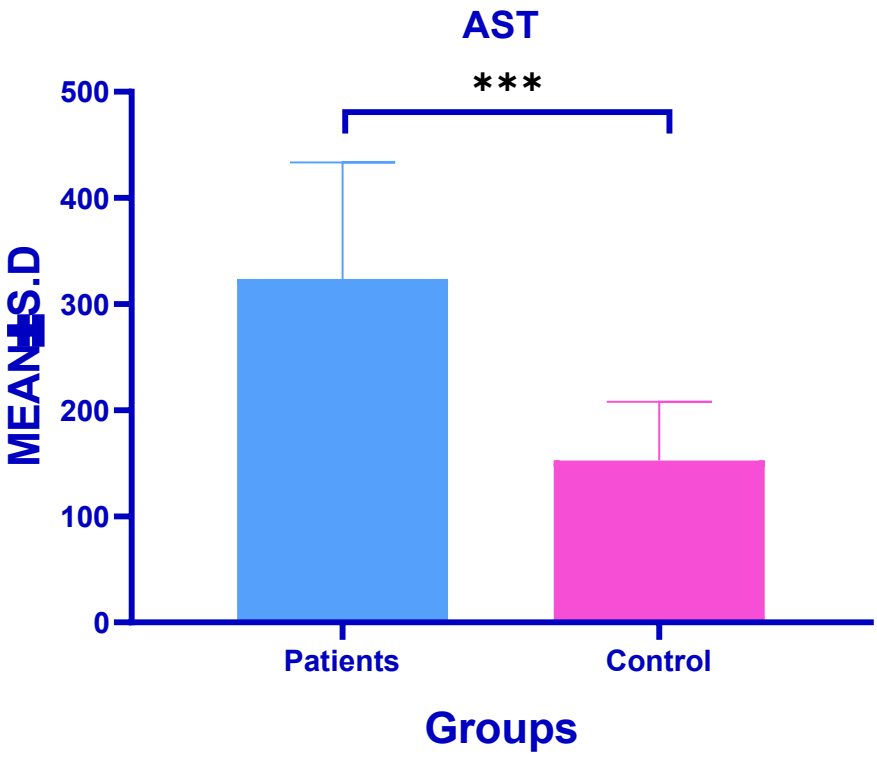

Figure 3: Serum levels of Aspartate transaminase in CRC patients and healthy subjects.

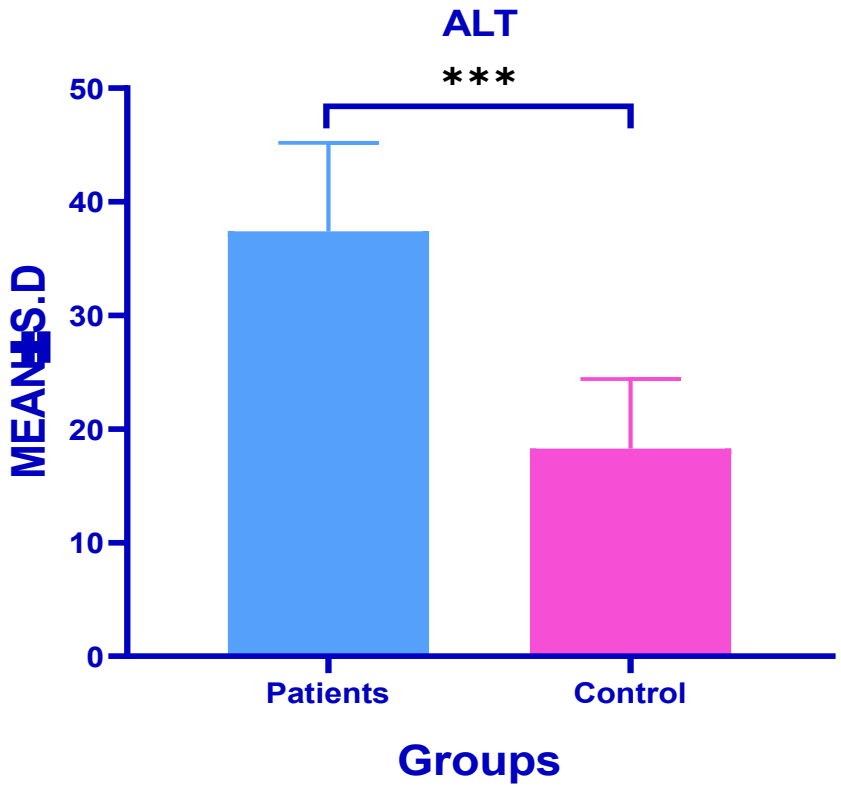

Figure 4: Serum levels of Alanine aminotransferase in CRC patients and healthy subjects.

Table 1: Concentrations of serum IL-12, ALP, AST, and ALT in Iraqi patients with CRC compared to healthy subjects.

Groups	IL-12 pg/ml	ALP IU/L	AST IU/L	ALT IU/L
		Mean±S.D		
Healthy subjects	142.3±14.71	165.5±38.8	152.6±55.34	18.28±6.14
CRC patients	304.6±26.91	309.9±66.84	323.5±109.9	37.4±7.78
P-value	<0.0001	<0.0001	<0.0001	<0.0001

Table 2: Pearson correlation between serum IL-12, ALP, AST, and ALT in Iraqi patients with CRC.

Biomarkers	**ALP**	**AST**	**ALT**
IL-12	**0.09**	**-0.15**	**-0.01**
P-value	**0.552**	**0.3**	**0.934**

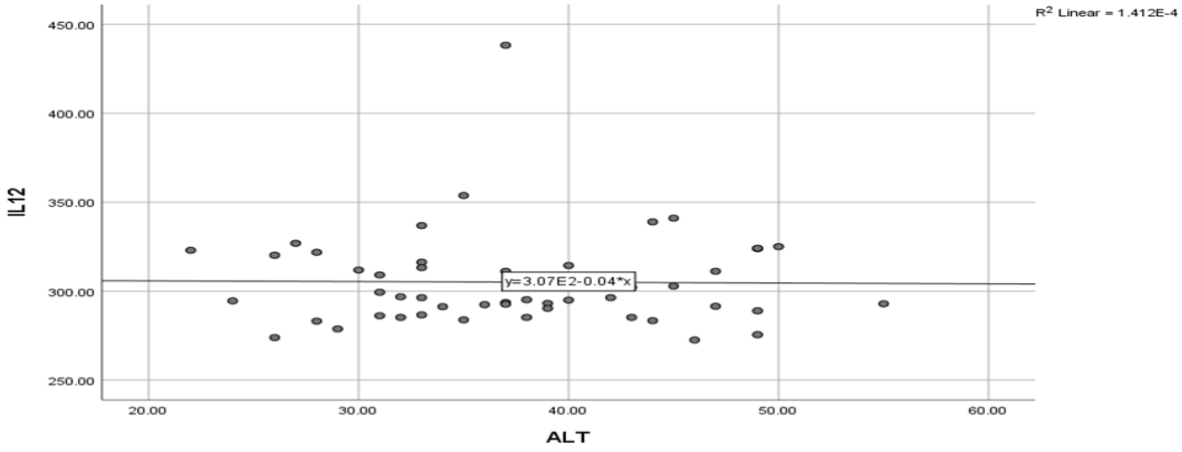

Figure 5: Pearson correlation between IL-12 and ALT in CRC patients.

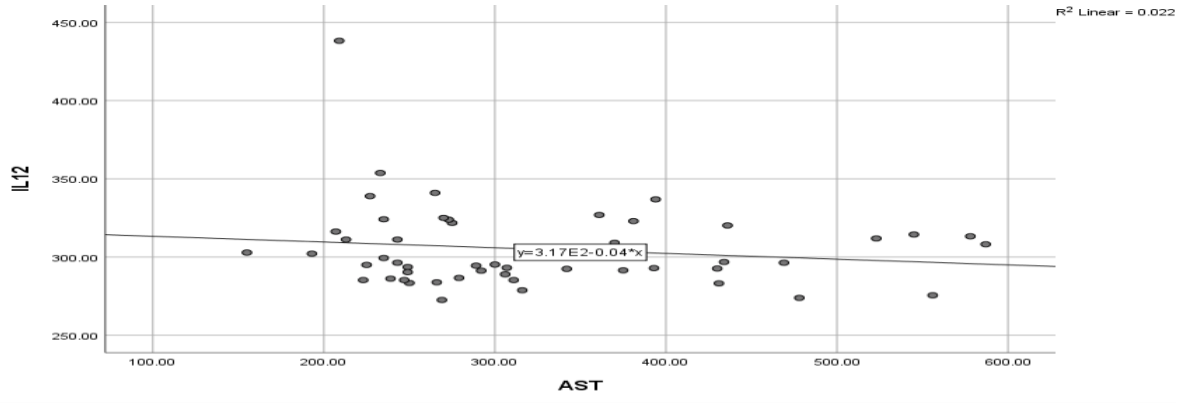

Figure 6: Pearson correlation between IL-12 and AST in CRC patients.

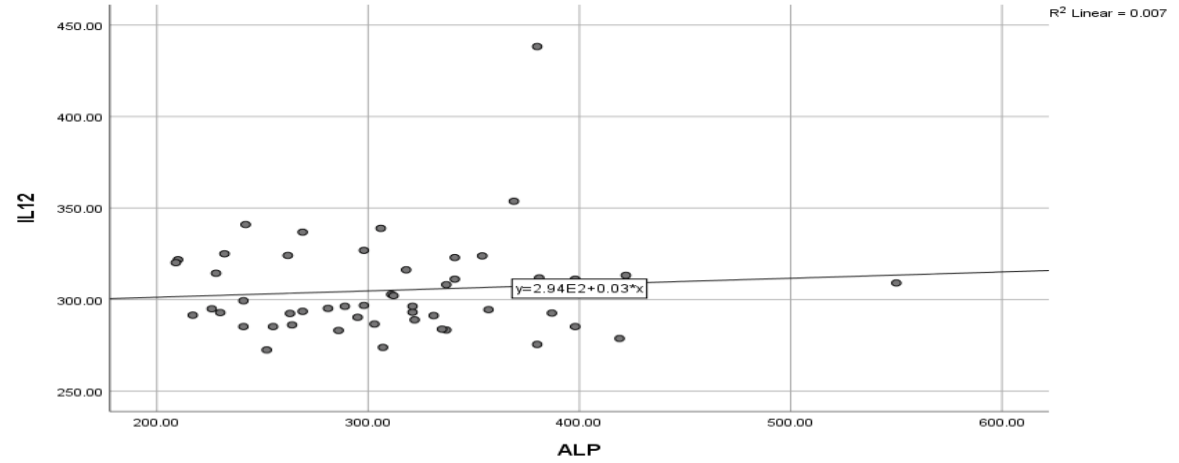

Figure 7: Pearson correlation between IL-12 and ALP in CRC patients

Discussion

Present study shows a significant increase in the serum concentration of IL-12 in CRC patients compared to healthy subjects. This finding is in accordance with the previous recent article of Czajka-Francuz *et* al [15] which indicates a significant increased levels of cocktails of cytokines including IL-12 in CRC patients compared to control group, as well as same finding showed by a study of Yamaguchi *et al* [16]. Other previous work shows increased levels of IL-12 and other several cytokines in CRC patients with metastasis [17]. Increased levels of serum IL-12 in the present study could interpreted with anti-tumor mechanisms of IL-12. As several previous findings suggest shift of cytokines production towards Th1 secreted immunosuppressive cytokines during the development of CRC [18,19]. Th2 mainly secretes immunosuppressive cytokines like IL-4 and IL-10, while Th1 mainly enhances production of anti-tumor effective cytokines like IL-2, INF-gamma, and IL-5, as mentioned in many previous findings by (O'Hara *et al.*[20] and Heriot *et al.*[21]; Lyratzopoulos *et al.*[22]. previous work by Nastala *et al.*[23], shows that IL-12 enhances production of INF-gamma in CRC patients, as well as Silva-Pilipich *et al.*[24] and Tian *et al.*[25], which reveal the anti-tumor role of IL-12. Interleukins-12 family cytokines comprise several types of interleukins such as IL-12, IL-23, and IL-27, and all of them have critical roles in shaping both innate and adaptive immune responses in cancers, and all of them need to activate Th1 response in order to activate both cytotoxic T cells and NK cells as antitumor effector cells [26]. Despite its nature as a liver specific enzyme where it rises in many liver disorders like hepatitis [27], recent

findings show that ALP related to CRC, however the role of other liver enzymes remain unclear, so present study aimed to evaluate the serum levels of liver enzymes including ALP in Iraqi patients with CRC. The result indicates significant elevated in serum levels of ALP in CRC patients and this finding agrees with the findings of Saif *et al*.[9] and Maisano *et al*.[28] which show that serum ALP was elevated significantly among CRC patients. Elevation of serum ALP in the present study may correlates with high tumor and metastatic stages of CRC. Several previous studies showed that low serum ALP in patients with newly diagnosed CRC [29,30,31]. A study of Qader *et al*.[29] show that more aggregative tumor in CRC correlates with low ALP but with unclear mechanisms, and a study of Li *et al*.[30] show the same finding using cell-line technique and show that when ALP was inhibited, tumors were promoted. Concerning the second point, a study of Hung *et al*.[32] show that the elevated ALP in CRC not only related with previously liver damages but also significantly related with advances in CRC. Aspartate transaminase is widely used as hepatocellular damage biomarker [33], however it still unclear its correlation with CRC. Present study shows increased levels of serum AST in CRC patients, and this agree with several previous studies, as a study of [34] that show both serum AST and ALT were elevated in CRC and associated with good prognosis, also another recent study of He *et al*. [8] show that higher AST associated with low risk of CRC. It has been known that abnormally elevated liver enzymes related to liver disorder like viral infection, excessive use of medicine and alcoholic consumption [35] , and both AST and ALT are significantly correlated with liver damages, but AST is differ with ALT that mainly found in the liver, it can be found in several other tissues like skeletal muscle, heart, and erythrocytes [36], so many other clinical conditions can cause elevated serum AST, and while this study excludes only known patients with other clinical conditions, it remain chance to presence other conditions that cause elevated serum AST. However, exact elevated AST and other liver enzymes are yet to be understood, many explanations, one of most acceptable reasons for this elevation may rely on glycolysis process, as a study of [37] show that the cancer cells depend on glycolysis as their main source of energy, and while malate-aspartate is a biochemical system during the aerobic glycolysis that leads to formation of many proteins like AST, so the metabolism of tumor itself can cause elevation of AST [38]. Elevated serum levels of ALT in the present study agree with the previous study of He *et al*. [8] which show elevated serum ALT in most patients under the study, however, the study indicated that elevated serum ALT was inversely related with CRC risk, but another study by Scheipner *et al*., [34] showed that elevated serum ALT is significantly correlated with CRC stages, and is more confirmed study with the results of the present study. Also, another previous finding by [39] show that elevated serum ALT give high risk with colorectal adenoma. Several scientific explanations were existed to explore the elevation of serum ALT, such as a result of liver metastasis [40] states that when CRC spread to liver it can causes elevation in serum ALT compared to those without metastasis. Another explanation is a systemic inflammation and tumor microenvironment, as a previous finding show that the CRC overall cause systemic inflammation and cause secretion of lipid mediators so suggesting that CRC cause elevated ALT by liver [41]. Non-alcoholic fatty liver is one of the most important risk factors for CRC spread to liver, which in turns cause elevated serum ALT [42] and this may the cause of elevated serum ALT in the present work. Finally, elevated serum ALT in CRC patients in the present study may be due to gut-liver axis and microbial dysbiosis, the study of De Col *et al*.,[43] showed that during CRC, many microbial will undergoes dysbiosis, and through gut-liver axis it may cause damage and elevation in liver enzymes including ALT.

Conclusions

Patients with CRC present with high serum IL-12, ALP, AST, and ALT and all may contribute to risk in CRC, as well as elevated serum IL-12 not correlated with serum liver enzymes.

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