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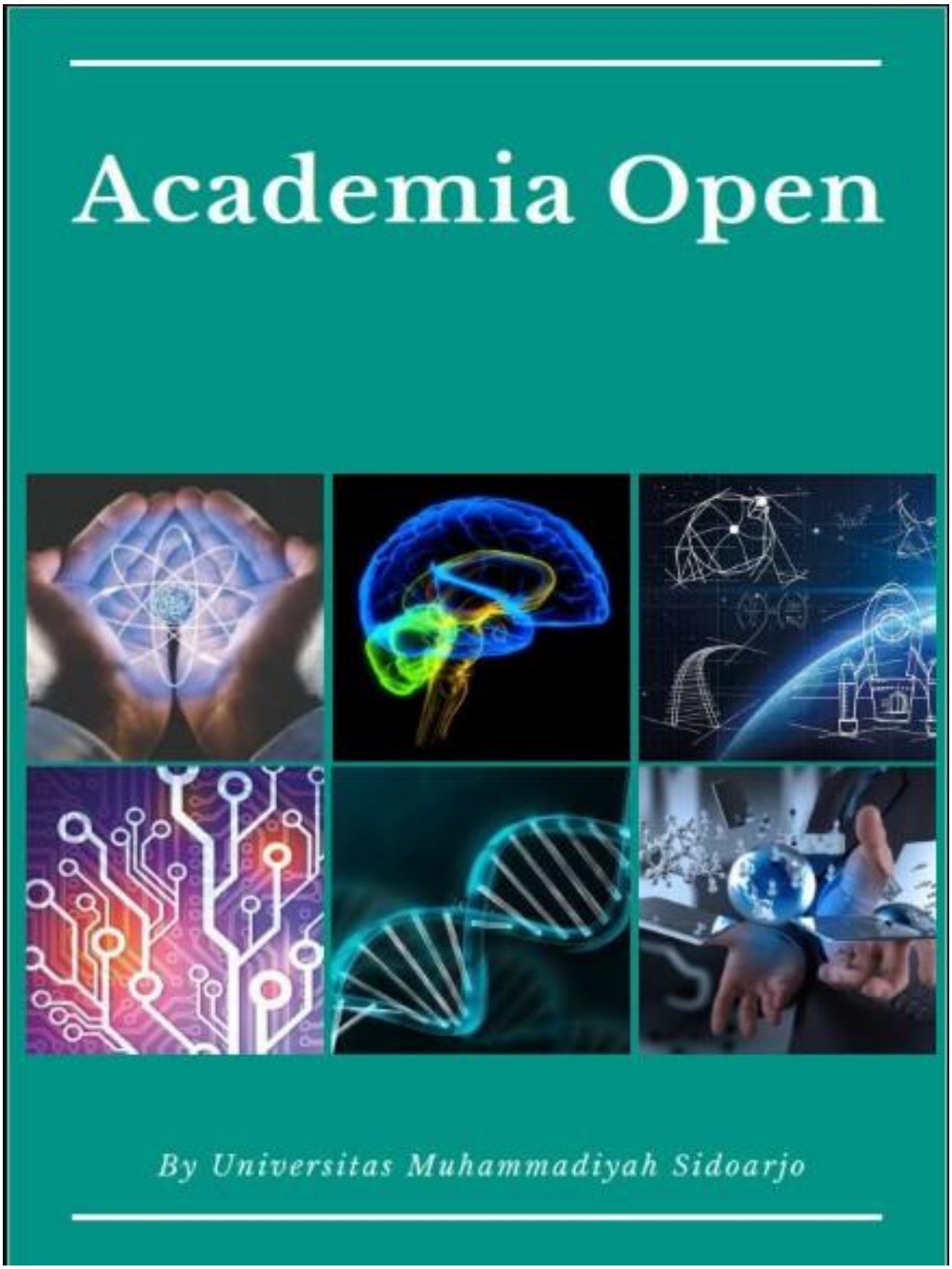

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Immunological Profile of Postoperative Colorectal Cancer Patients: Evaluation of TNF-?, IL-12, , IL-4, and IFN-?

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Abstract

General Background: Colorectal cancer is a prevalent malignancy associated with complex immune responses that persist after surgical intervention. **Specific Background:** Cytokines such as TNF-α, IFN-γ, IL-12, and IL-4 regulate tumor immunity and reflect postoperative immunological status. **Knowledge Gap:** Limited data exist regarding the cytokine profile and immune balance in postoperative colorectal cancer patients, particularly in relation to inflammatory and regulatory responses. **Aims:** This study aimed to evaluate serum levels of TNF-α, IFN-γ, IL-12, and IL-4 in postoperative colorectal cancer patients and characterize their immunological profile. **Results:** In a cross-sectional study of 67 patients, mean cytokine levels were TNF-α (137.64 ± 38.15 pg/mL), IFN-γ (30.47 ± 5.75 pg/mL), IL-12 (23.76 ± 12.07 pg/mL), and IL-4 (5.21 ± 2.07 pg/mL). Elevated TNF-α and IFN-γ indicated persistent pro-inflammatory and cell-mediated immune activation, while lower IL-4 levels suggested limited anti-inflammatory regulation. Significant correlations were observed between postoperative duration and TNF-α, IL-12, and IL-4, as well as a negative correlation between IL-12 and IFN-γ. **Novelty:** This study provides a defined cytokine pattern demonstrating Th1-dominant immune response in postoperative colorectal cancer patients. **Implications:** Cytokine profiling may serve as a valuable approach for immune monitoring and understanding postoperative immune dysregulation in colorectal cancer management.

Highlights:
- Elevated pro-inflammatory mediators indicate sustained immune activation after surgery
- Reduced anti-inflammatory response reflects imbalance in immune regulation
- Cytokine correlations reveal interaction between postoperative duration and immune markers

Keywords: Colorectal Cancer, Cytokine Profile, TNF-Alpha, Interferon Gamma, Interleukin-12

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Introduction

Colorectal cancer (CRC) is one of the leading contributors to morbidity and mortality associated with cancer in the world [1-3]. The last global cancer data indicates that colorectal cancer is one of the most prevalent tumors that have been diagnosed and it is a leading cause of cancer-related mortality [4-5]. The immune system plays an important role in tumor surveillance and progression even with the current developments in targeted therapies, chemotherapy and surgical methods [6-7]. The interaction between tumor cells and host immune responses determines the disease progression and possibly the long-term survival and postoperative recovery [8].Cytokines are the key mediators of immune communication, which regulate tumor immunity, inflammation, and immune activation [9-11]. Interleukin-12 (IL-12), among the cytokines implicated in tumor immunology is an important modulator of cell-mediated immunity, which induces T helper 1(Th1) lymphocyte differentiation [12]. Moreover, IL-12 stimulates the production of interferon-g (IFN-g) which is an antitumor cytokine by the natural killer cells and cytotoxic T lymphocytes [13-15]. Tumor necrosis factor-alpha (TNF-α) is another key pro-inflammatory cytokine that is used in immunity against cancerous cells [16]. Th2 immune responses are also associated with interleukin-4 (IL-4), which is essential in the regulation of humoral immunity and anti-inflammatory responses despite its role in the destruction of tumor cells [17-19]. The changes in the immune of patients with colorectal cancer after surgery can significantly influence the prognosis of the disease and its recurrence [20]. Consequently, the determination of the cytokine profile of such patients can provide valuable data regarding their immunological condition and potential areas of treatment [21]. This research was aimed at assessing TNF-α, IFN-γ, IL-4, and IL-12 serum concentration of postoperative patients with colorectal cancer and determining whether they could play a role in immune regulation in the postoperative period.

Materials and Methods

Study Design

The cross-sectional / observational study was done to compare the chosen parameters of immunology in the postoperative colorectal cancer patients.

Study Population

The study involved 67 patients who had colorectal cancer that had been operated at the surgical wards of Nasiriyah General Hospital. The age interval of the sample population was 38-79. The parameters that were used to gather samples and data included age, sex, and the number of hours that the patient had been in the post-operative period. Blood samples were taken on average 14 days following the procedure. All the samples were taken in a sterile manner so that the results were accurate. TNF- α interleukin-12 (IL-12), interleukin-4 (IL-4), (IFN-γ) cytokines were determined with (Fine Test)® ELISA kits. pg/mL was the unit of measurement of cytokines.

Statistical Analysis

The statistical analysis was done through descriptive and inferential analysis. Continuous variables were expressed in the mean standard deviation (SD). To describe the postoperative immunological landscape in patients with colorectal cancer, serum levels of IFN-γ, TNF-α,IL-4, and IL-12 were examined. Inter-cytokine connections were evaluated using Pearson's correlation coefficient, which sheds light on how Th1-, Th2-, and inflammation-associated immune responses interact.

Results

The study population consisted of 67 postoperative colorectal cancer patients of both sexes. Their age were between 38-79 years (Mean 58.3± 10.6 years). The cytokine levels of the tested population is presented in Table 1.

Table 1: cytokine levels according to sex of the patients.

Parameter	Male	Female	Significance
Age	57.1	63.1	X^2 =0.38
IL-12	23.96	23.02	
IFN-γ	30.94	28.68	
IL-4	5.26	5.06	
TNF-α	136.7	141.0	p>0.05

In postoperative patients, TNF-α had the highest average levels, suggesting a robust inflammatory response (Figure 1). despite the fact that male and female cytokine levels did not show statistically significant differences (p>0.05).

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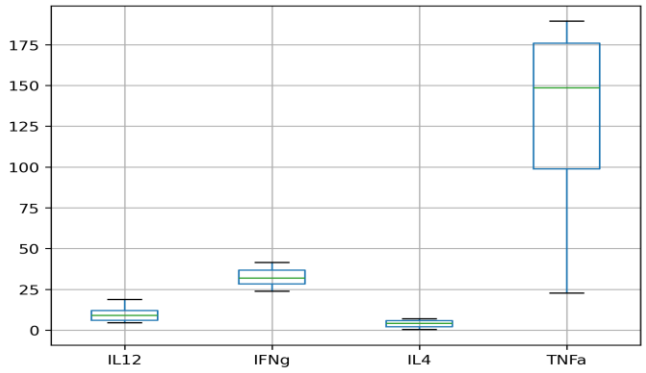
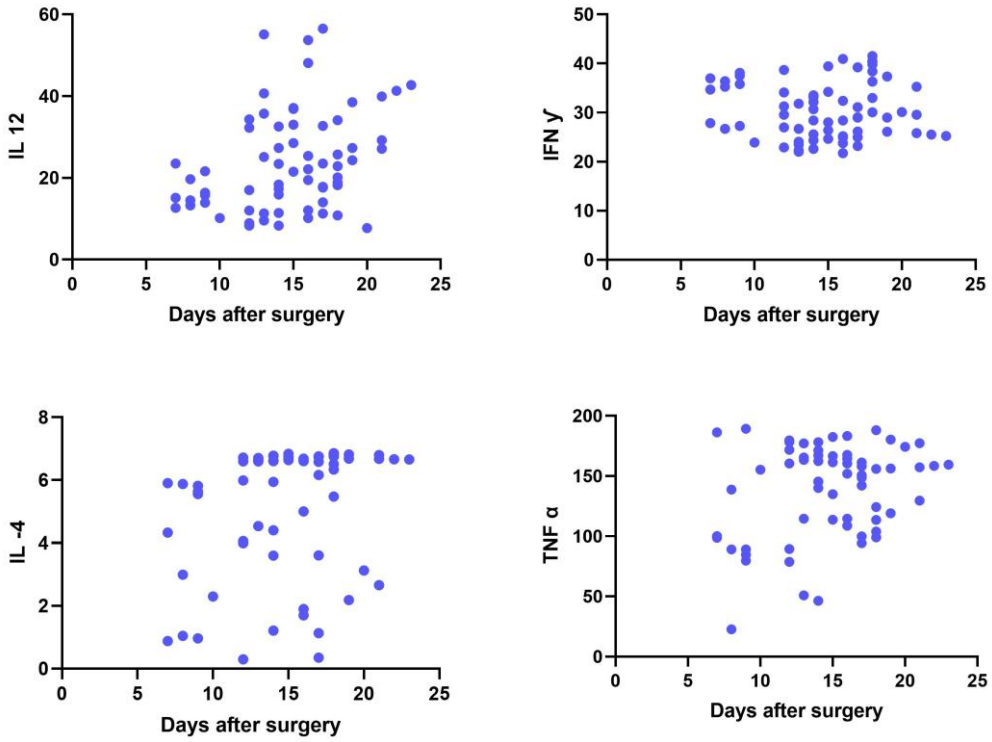
Figure1. Distribution of cytokine concentrations.



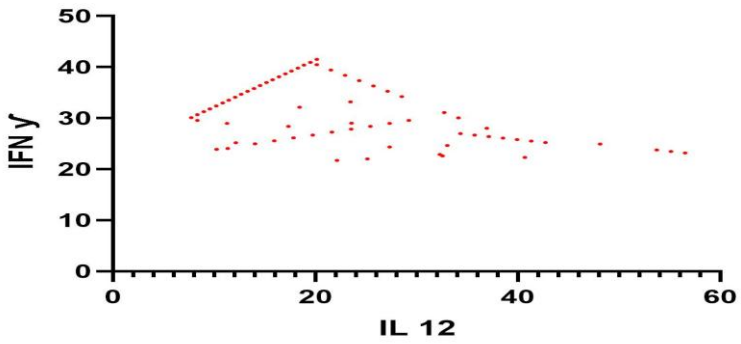
IFN-γ was also elevated, indicating the activation of cell-mediated immune responses. Patients' inflammatory responses vary, as seen by the diversity in TNF-α levels. A significant ($p<0.05$) mild positive association ($r=0.33$, 0.27, and 0.27) was found in the data between the postoperative duration and TNFα, IL-12, and IL-4, respectively. In contrast, there was no discernible relationship between IFN-γ and the length of time following surgery(Figure 2).

Figure 2: cytokine correlation with postoperative duration



A highly significant negative moderate correlation ($r =0.46$, $p<0.01$) was revealed between IL12 and IFN-γ, (Figure 3).

Figure 3: IFN-γ and IL-12 correlation



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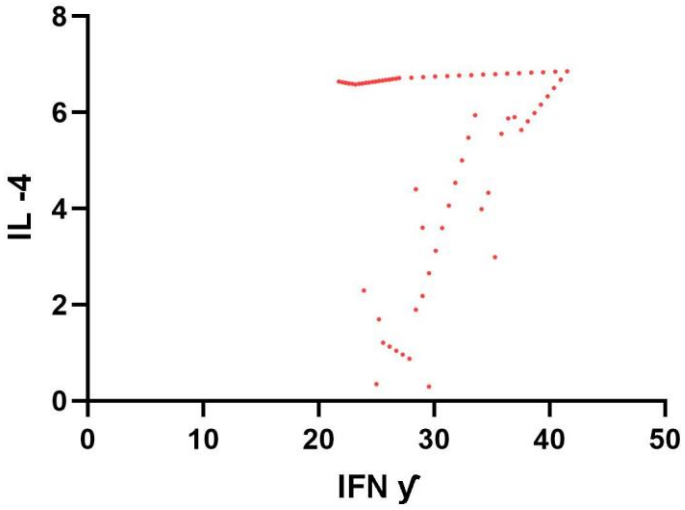
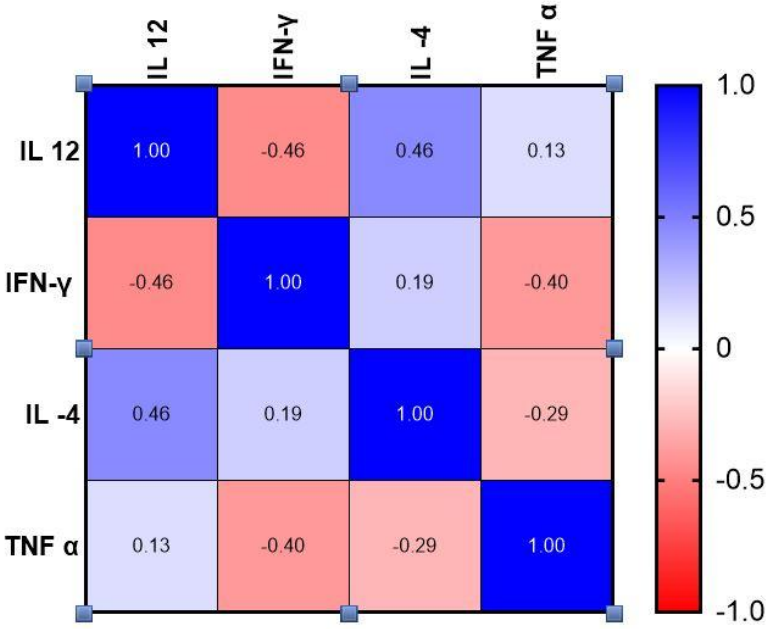
nonetheless , no statistically significant correlation was find between IFN-γ and IL-4(r=0.19, p>0.05), which indicate no clear cut was maintained between humoral and cell mediated immune response(Figure 4).

Figure 4: IL-4 and IFN-γ correlation



Furthermore ,no considerable correlation was found between the cytokines levels and age (p>0.05). Significant correlation patterns were noticed in the levels of the tested cytokines as presented in(Figure 5).

Figure 5: Correlation matrix of tested cytokines.



Discussion

Significant immunological dysregulation is linked to colorectal cancer and may continue even after the tumor is surgically removed[22]. Tumor suppression and tumor development are both influenced by cytokines, which are important immune response mediators [23].

TNF-α levels were significantly higher in postoperative colorectal cancer patients in the current investigation. TNF-α is a powerful pro-inflammatory cytokine that contributes to inflammatory signaling, immunological activation, and tumor necrosis. On the other hand, persistent TNF-α increase may affect the remodeling of the tumor microenvironment and lead to chronic inflammation [24].TNF-α is also implicated in NF-κB signaling activation, Inflammatory cascade promotion and Tumor microenvironment modification[25-27]. Despite the fact that TNF-α can cause tumor cell death, persistent increase may paradoxically as it encourage the growth of angiogenesis ,improve the survival of tumors and Promote metastasis[28]. Therefore, continuous TNF-α levels in postoperative patients may symbolize a double-edged sword, reflecting both antitumor activity and likely tumor-promoting inflammation[25].

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The population under study also had higher levels of IFN-γ. IFN-γ is a key component of antitumor immunity and is mostly produced by natural killer cells and activated T lymphocytes. This study's elevated IFN-γ levels could be the result of continued immune surveillance after tumor excision[29].IFN-γ is essential for cytotoxic T lymphocyte (CTL) activation ,improving the presentation of antigens and tumor proliferation inhibition[30].The idea of a functional IL-12-IFN-γ axis, which is essential to antitumor immunity, is supported by the positive correlation between IFN-γand IL-12 .

The moderately higher levels of IL-12 indicate that Th1-mediated immune mechanisms have been activated. It is well established that IL-12 contributes to antitumor immunity by boosting cytotoxic immune responses and IFN-γ production. As ,IL-12 stimulates the production of IFN-γ ,it is a crucial regulator of Th1 differentiation. The observed mild elevation implies immune activation that persists after surgery constant cellular immunity stimulation .Although prolonged activation may add to systemic inflammation, it is helpful in preventing recurrence[31].

IL-4 levels, however, were significantly lower. Th2 immune responses and the control of inflammation are linked to IL-4. The study's comparatively low IL-4 levels may suggest that Th1-mediated immune responses predominate in patients with colorectal cancer who have undergone surgery.This implies a restricted control of inflammation ,an imbalance between the Th1 and Th2 pathways .Patients with cancer frequently experience this imbalance, which may lead to prolonged inflammation ,damage to tissue and a weakened immunological response[32].

All of these results point to a pro-inflammatory cytokine profile dominated by Th1 immune responses in postoperative colorectal cancer patients. Although prolonged inflammation may also be a factor in postoperative problems, such immune activation may help prevent tumor recurrence[33].The idea of inflammaging, in which older people show altered baseline inflammation and changed immune regulation, is supported by the weak association between measured cytokines and age. This may help to explain some of the diversity in postoperative immunological responses. To determine the clinical importance of cytokine changes in patients with colorectal cancer, more research with bigger sample numbers and control groups is required.

Conclusion

Patients with colorectal cancer who have undergone surgery have a unique immunological profile that includes lower levels of IL-4, intermediate amounts of IL-12, and higher levels of TNF-α and IFN-γ. This trend suggests an ongoing inflammatory system with Th1 predomination that can be used in chronic inflammation and in tumor prevention. Cytokine profiling is a promising tool in the evaluation of immunological activity and the provision of postoperative treatment in patients with colorectal cancer.

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Conflict of Interest

No conflicts of interest.

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