



## Relationship between distress and inflammatory biomarkers in patients with colorectal cancer

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### Abstract

**Background:** Some studies show that pro-inflammatory cytokines are involved in the pathophysiology of anxiety and depression in cancer patients. **Objective:** To evaluate the levels and relationship of psychological variables (distress and optimism) and physiological markers [pro-inflammatory cytokines interleukin (IL)-1, IL-6, IL-8, C-reactive protein (CRP), and cortisol] in patients with colorectal cancer. **Methods:** Seventeen patients with colorectal cancer participated. **Results:** 35-41% of the patients' present distress and 29.40% anxiety and depression. In the physiological markers, most of the patients present elevated levels of IL CRP, compared to IL-1, IL-6, IL-8, and cortisol. Only positive and significant relationships were found between IL-6 and distress measured by HADS ( $r_s = 0.724$ ) and by the thermometer ( $r_s = 0.625$ ), depression ( $r_s = 0.877$ ), and physical problems ( $r_s = 0.747$ ). **Conclusion:** It is suggested to continue with the research on the relationship between psychological variables and physiological markers to provide information that will allow comprehensive care for the cancer patient.

**Keywords:** Colorectal cancer. Distress. Anxiety. Depression. Proinflammatory cytokines.

### Relación entre el malestar psicológico y los biomarcadores inflamatorios en pacientes con cáncer colorrectal

### Resumen

**Antecedentes:** Algunos estudios muestran que las citocinas proinflamatorias están involucradas en la fisiopatología de la ansiedad y la depresión en los pacientes con cáncer. **Objetivo:** Evaluar los niveles y la relación de variables psicológicas (malestar psicológico y optimismo) y marcadores fisiológicos [citocinas proinflamatorias, interleucina (IL) 1, IL-6, IL-8, proteína C reactiva (PCR) y cortisol] en pacientes con enfermedad colorrectal. **Método:** Participaron 17 pacientes con cáncer colorrectal. **Resultados:** Entre el 35 y el 41% de los pacientes presentaron malestar psicológico y el 29.40% ansiedad y depresión. En los marcadores fisiológicos, la mayoría de los pacientes presenta niveles elevados de IL PCR, en comparación con IL-1, IL-6, IL-8 y cortisol. Solo se encontraron relaciones positivas y significativas entre IL-6 y el malestar psicológico medido por el HADS ( $r_s = 0.724$ ) y por el termómetro ( $r_s = 0.625$ ), depresión ( $r_s = 0.877$ ) y problemas físicos ( $r_s = 0.747$ ). **Conclusión:** Se sugiere continuar con la investigación sobre la relación entre variables psicológicas y marcadores fisiológicos para brindar información que permita una atención integral del paciente con cáncer.

**Palabras clave:** Cáncer colorrectal. Malestar psicológico. Ansiedad. Depresión. Citocinas proinflamatorias.

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## Introduction

Some studies show pro-inflammatory cytokines are involved in the physiopathology of anxiety and depression in cancer patients. Oliveira Miranda et al.<sup>1</sup> observed in colorectal cancer patients' diagnosis and treatment increased serum levels of interleukins (IL)-1, IL-6, IL-8, and tumor necrosis factor alpha (TNF- $\alpha$ ), but low concentrations of IL-10. Correlation analysis between hospital anxiety and depression scale (HADS) and cytokine levels shared a positive association of anxiety and depression with IL-1, IL-6, IL-8, and TNF- $\alpha$  and a negative correlation with IL-10. This correlation was studied on colorectal cancer patients at distinct stages of the treatment: the highest levels of pro-inflammatory cytokines and the lowest levels of IL-10 were found in the pre-chemotherapy group<sup>2</sup>. Other pro-inflammatory markers, like C-reactive protein (CRP), are related to post-surgery depression symptoms in colorectal cancer patients<sup>3</sup>.

Also, stress and TNF- $\alpha$  were positively related to distress symptoms. The authors suggest to explore factors with a potential role in inflammatory biomarkers in cancer diagnosis<sup>4</sup>.

In terms of optimism, it is related to less severe anxiety symptoms in advanced gastrointestinal and colorectal cancer<sup>5</sup>. In breast cancer patients, it is seen that optimism moderates the relationship between stress and natural killer cells<sup>6</sup>. At the same time, it has been reported an inverse relationship between optimism and CRP, where optimism predicts a lower inflammation of a year after the evaluation<sup>7</sup>.

To this day, few studies in Mexico and Latin America have determined the association between psychological and biochemical factors in colorectal cancer. On a continental scale, studies by authors like Miranda et al.<sup>1,2</sup> can be found, as well as a systematic revision in pancreas cancer where IL and other molecules might have been related to the physiopathogenesis of the affective symptoms<sup>8</sup>. Based on the previous information, the aim of this study was to evaluate the levels and relationship of psychological variables (distress and optimism) and physiological markers (pro-inflammatory cytokines IL-1, IL-6, IL-8, CRP, and cortisol) in colorectal cancer patients.

## Participants and procedure

A transversal, descriptive, and correlational design was used. A non-probability sample was used, and people with diagnosed colorectal cancer participated.

These people attended the hospital and complied with the following inclusion criteria: not oncological treatment received (surgery or chemotherapy/radiotherapy) in the moment of psychological and physiological evaluation, I-III stage disease, ages 25-80, and willingness to participate. Patients with any type of cancer previously diagnosed, metastatic cancer, autoimmune disease background, chronic inflammatory disease, active infectious disease, kidney disease, uncontrolled diabetes mellitus (glycated hemoglobin > 7%), liver failure, previous chemotherapy or radiotherapy, psychiatric disorder, or previous or current neurological disease were excluded from the study.

## Measurements

### DISTRESS

HADS the Spanish 14-item version for the population of oncological patients was used. It is composed of two subscales (depression and anxiety) of seven questions each. Each question has four possible answers that score from 0 to 3, to get a final score from 0 to 21. Cronbach's alpha with 14 questions was 0.85, whereas the subscale for anxiety and depression was 0.77, respectively<sup>9</sup>.

### DISTRESS THERMOMETER

The translated version was used. It is also adapted to the Mexican population<sup>10</sup>. This thermometer is composed of two parts: the first is the following instruction: "please circle the number (0-10) that best describes how much distress you have been experiencing in the past week, including today." The second part requires point out the existence or inexistence of problems from a determined list. The distress thermometer counts with an area under the curve of 0.631, a sensitivity of 93%, and a specificity of 76.

### OPTIMISM

The life orientation test was revised. This study used the Spanish version by Otero et al.<sup>11</sup>, which consists of 10 items: six of them measure dispositional optimism, and four decrease the impact of the test's content. This scale has a reliability of  $\alpha = 0.79$ . Out of the six items for dispositional optimism measuring, three of them are redacted in a positive way (optimism) and three in a negative way (pessimism). A total score range goes from 5 to 30; the highest score indicates the greatest optimism.

## CYTOKINES

ILs IL-1, IL-6, and IL-8 blood levels were measured through chemiluminescence from the collected samples and following the enzyme-linked immunosorbent assay (ELISA) method in the proper fasting period. The results were consigned by a written report in the hospital laboratory.

## CRP AND CORTISOL

CRP blood levels were measured through turbidimetry from the collected samples during the proper fasting period. The results were consigned by a written report in the hospital laboratory.

## Procedure

This study counts with the approval of the hospital's Research and Bioethics Committee (R-2019-1901-025). Data were collected from January 2019 to December 2021. Potential participants were identified by checking their daily files. 513 candidates were identified to participate, of which 496 were excluded for not meeting the criteria and 11 refused to participate. Then, patients who complied with the inclusion criteria were invited to the study. Finally, those who accepted signed the informed consent and answered the questionnaires after diagnosed and before oncological treatment (surgery, chemotherapy, or radiotherapy). To get the sample, specialist doctors, nurses, and social workers were consulted. They collaborated by referring patients who complied with the inclusion criteria of the study.

## Statistical analysis

The collected data were captured in version 22 of the Statistical Package for the Social Sciences (IBM SPSS). Descriptive statistics of frequency and percentage were used to categorical variables, and mean and standard deviation were used for continuous variables. For the distress variable, a cutoff point of  $\geq 13$  in the total HADS scale,  $\geq 5$  in the depression subscale (HADS-D) were used, as well as  $\geq 7$  in the anxiety subscale (HADS-A) was suggested by Singer et al.<sup>12</sup>. For the distress thermometer, it was used the optimal cutoff point  $\geq 4$ , with a positive predictive value of 82% and a negative predictive value of 90%<sup>10</sup>.

According to the ELISA method, the reference values for a normal range in cytokines were IL-1 of  $< 36$  pg/mL, IL-6 of 0.0-15.5 pg/mL, and IL-8 of 0.0-66.1 pg/mL. For CRP, the reference values for a normal range were 0.0-5.0 mg/L

while the blood levels of cortisol were 8.70-22.40 ug/dL, according to the written report by the hospital laboratory.

Non-parametrical tests were used. For continuous variables, the Spearman correlation was carried out.

## Results

The participants were 17 patients, most of whom were colon cancer patients in II and III clinical stages, with no complications in their surgery treatment. Their age range was 30-80 years old, most of them men, and they were married (Table 1).

Table 2 shows psychological variable levels: most participants did not show distress, anxiety, or depression according to the cutoff points. Nevertheless, 41.20% of patients showed moderate to severe distress in thermometer scale. It is possible to see high levels of CRP in most participants.

The correlation analysis showed a positive correlation and significant between IL-6 and distress, depression, thermometer-measured distress, and physical problems (Table 3).

## Discussion

In this study, it was found that 35-41% of patient's present distress and 29.40% have anxiety and depression. Results are similar to those reported in other studies, which found that depression ranges between 1.6 and 57% and anxiety ranges between 1-47.2%<sup>13,14</sup>. These results were obtained even under different conditions, like the end of treatment. No matter the percentage of patients with high distress levels, these must be detected and provided with psychological care<sup>13</sup>.

In terms of optimism, in this research, it is possible to see that the punctuation mean was 23.06, which is higher than other studies<sup>5,15</sup>. The highest levels of optimism in the sample of these studies may be due to the fact that they have not started treatment.

In relation to physiological markers, most of patients present high levels of IL IL-8 and CRP, compared to IL-1, IL-6, and cortisol. High IL IL-8 levels are similar to those obtained in studies on colorectal cancer patients in different treatment conditions, like pre-surgery and post-surgery or after chemotherapy<sup>2,16,17</sup>. This fact is important, as IL-8 is a cytokine involved in colon cancer progression, and its level increases hand in hand with the disease and an eventual metastasis<sup>17</sup>. In this study, most of the participants had a locally advanced disease, and more than half of them had complications due to the COVID treatment, which can be related to the obtained data.

**Table 1.** Medical and sociodemographic characteristics of the participants

Variables	F (%)
Diagnosis	
Colon cancer	10 (58.8)
Rectal cancer	7 (41.2)
Stage	
I	2 (22.2)
II	7 (41.2)
III	8 (47.0)
Treatment	
Surgery	12 (70.6)
Chemotherapy/radiotherapy	5 (29.4)
Treatment complications	
Yes	6 (35.3)
No	7 (41.2)
Others (COVID-19)	4 (23.5)
Sex	
Man	11 (64.7)
Woman	6 (35.3)
Civil status	
Married/common law	13 (76.5)
Widower	1 (5.9)
Divorced	3 (17.6)
M (SD)	
Age	62.47 (11.4)
Scholarship	8.41 (4.75)
Number of children	2.88 (1.47)

This is also the case of CRP and its high levels in this study ( $> 5.00 \text{ mg/mL}$ ). It has been discovered that the pre-surgery level of this protein is an independent prognostic factor. This means increasing values are associated with worse survival<sup>18</sup>. In the same way, Kim et al.<sup>19</sup> found that high CRP levels have a major correlation with cancer recurrence. Besides, survival was noticeably lower on this group of patients, which suggests that pre-surgery CRP level has a prognostic importance in rectal cancer patients with previous chemoradiation.

On the other hand, values of IL-1 and IL-6 were in the proper range, in contrast to that reported by Oliveira Miranda et al.<sup>1</sup> in which patients with colorectal cancer had elevated serum levels of IL-1  $\beta$  and IL-6, the same condition shared by patients prior to chemotherapy<sup>2</sup>.

In the correlation analysis between psychological variables and physiological markers, results show that distress, depression, distress thermometer, and physical problems are all related to high cytokine IL-6 levels. This is similar to the results obtained by Miranda et al.<sup>1,2</sup>, who also resorted to the HADS. This study also counted with

**Table 2.** Levels of psychological and physiological variables (n = 17)

Psychological variables	F (%)
Distress	6 (35.30)
Anxiety	5 (29.40)
Depression	5 (29.40)
Distress thermometer moderate to severe	7 (41.20)
M (SD)	
Optimism	23.06 (4.44)
IL-1 $> 36 \text{ pg/mL}$	0 (0)
IL-6 $> 15.5 \text{ pg/mL}$	5 (29.40)
IL-8 $> 61.1 \text{ pg/mL}$	8 (47.10)
CPR $> 5.00 \text{ mg/L}$	13 (76.50)
Cortisol $> 22.40 \text{ ug/dL}$	2 (11.80)

F: frequency; M: mean; SD: standard deviation; IL-1: interleukin 1; IL-6: interleukin 6; IL-8: interleukin 8; PCR: C reactive protein.

the distress thermometer, which confirms the findings with a second instrument.

Other authors have confirmed a stronger relationship between IL-6 and depression compared to IL-6 and anxiety Juhn et al.<sup>20</sup> in their study IL-6 correlates significantly with depression symptoms, but anxiety was not associated with an increase in IL-6 in patients with metastatic breast cancer.

Parallelly, the study of Breitbart et al.<sup>21</sup> showed severity of depressive symptoms correlates with high IL-6, but anxiety did not associate neither with IL-6 beta nor IL-6 in patients with pancreas cancer. These results could suggest that the relationship between IL-6 and depression can be exclusive to depression symptoms. Nonetheless, it is recommended to continue with studies to confirm these findings.

IL-6 is also correlated with physical problems. These are sleeping difficulties, diarrhea, constipation, sexual problems, fatigue, feeding, and nausea, among others. Some studies show that the presence and severity of symptoms, such as pain, fatigue, depression, and sleep disorders were associated with higher scores on the Eastern Cooperative Oncology Group Performance Status Scale and higher levels of IL-6<sup>22</sup>. A possible explanation is that IL-6 encourages tumor growth and has an active role in cancer cachexia<sup>23,24</sup>.

Conversely, IL-1, IL-8, CRP, and cortisol did not correlate majorly with distress, anxiety, depression, distress thermometer, practical problems, family problems,

**Table 3.** Correlation analysis between psychological variables and physiological markers (n = 17)

Psychological variables	Physiological markers				
	IL-1	IL-6	IL-8	C reactive protein	Cortisol
Distress	0.000	0.724**	0.084	0.242	0.235
Anxiety	-0.174	0.452	-0.198	0.218	0.316
Depression	-0.093	0.877**	0.564	0.304	0.184
Distress thermometer	-0.076	0.625*	0.018	0.248	0.087
Practical problems	-0.416	0.352	0.275	-0.215	-0.089
Family problems	-0.255	0.337	0.198	0.024	-0.351
Emotional problems	0.052	0.153	-0.291	-0.224	-0.078
Physical problems	0.089	0.747**	0.487	0.015	-0.220
Optimism	-0.471	-0.082	-0.182	0.429	0.386

\*\*p ≤ 0.01, \*p ≤ 0.05,  $r_s$ : spearman correlation; IL-1: interleukin 1; IL-6: interleukin 6; IL-8: interleukin 8.

emotional problems, physical problems, and optimism. Some correlations were likely not significant due to the small sample size of the study. Different works show discrepancies, as in some cases psychological variables do correlate with ILs, CRP, and cortisol<sup>1,2,25,26</sup>, while others do not<sup>27,28</sup>. That is the case of Vukojevic et al.<sup>28</sup> who point out that there was no correlation between morning serum cortisol level and optimism or pessimism in patients with recently diagnosed cancer. One reason for this might be that the study was done in patients with a recent diagnosis and no exposure to the treatment. In consequence, patients had not yet felt exhausted or frustrated by the disease. This stands out the importance of consequently studying the relationship between these variables, seeking to add evidence for the understanding of physiopathological mechanisms potentially influential in the proper clinical care of the oncological patient.

This study has limitations like sampling size and the lack of a control group of healthy population to compare both psychological and physiological results. Despite the last, this study provides important information about the relationship between psychological variables such as distress, depression, and physical problems (symptoms) with the inflammatory marker of IL-6 in patients with colorectal cancer.

## Conclusion

Depression, distress, and physical problems have a positive and strong correlation with the cytokine IL6 in patients with colorectal cancer. It is suggested to

continue with the research on the relationship between psychological variables and physiological markers to provide psychosocial intervention, which, together with oncological treatment, can contribute comprehensive care of the cancer patient.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Ethical disclosures

**Protection of people and animals.** The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

**Data confidentiality.** The authors declare that they have followed their workplace's protocols regarding the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

**Use of artificial intelligence to generate texts.** The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables, or their corresponding captions or legends.

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