HHS Public Access

Author manuscript

Psychooncology. Author manuscript; available in PMC 2023 June 19.

Published in final edited form as:

Psychooncology. 2022 September ; 31(9): 1536–1544. doi:10.1002/pon.5986.

Depression and anxiety in colorectal cancer patients: Ties to pain, fatigue, and inflammation

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Abstract

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Megan Renna. The first draft of the manuscript was written by Megan Renna, M. Rosie Shrout, and Annelise Madison. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

CONSENT TO PARTICIPATE

Participants were explained the details of the study and, if interested in the study, signed informed consent in compliance with ethical standards.

CONSENT TO PUBLISH

Participants gave consent to publish de-identified study findings through informed consent.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ohio State University Institutional Review Board Approval Number 2007C0079) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Objective: Colorectal cancer poses a significant threat to both psychological and physical health. This study examined relationships between anxiety and depressive symptoms with pain, fatigue, and inflammation among colorectal patients.

Methods: Colorectal cancer patients (n = 88, stages 0-IV) completed a laboratory-based study visit before undergoing adjuvant cancer treatment. Patients completed questionnaires assessing depressive, anxiety, pain, and fatigue symptoms. A blood sample was also collected to measure c-reactive protein (CRP). Analyses controlled for age, sex, cancer stage, body mass index (BMI), and menopause status.

Results: Multiple linear regression analyses showed colorectal patients with higher depressive and anxiety symptoms had greater pain, fatigue, and CRP (ps < 0.03). Approximately one-third of patients with clinically significant depressive (CESD >16) and anxiety symptoms (BAI >16) also had clinically-elevated levels of CRP (>3 mg/L) (ps = 0.02).

Conclusion: These results extend findings from other cancer subgroups showing heightened symptom burden among patients with depression and anxiety. They also highlight the detrimental role that elevated anxiety and depressive symptoms may play in the physical and biological side effects associated with colorectal cancer.

Keywords

anxiety; colorectal cancer; depression; fatigue; inflammation; pain

1 | BACKGROUND

Colorectal cancer is the third most common cancer and fourth deadliest worldwide.[1] Colorectal cancer diagnosis and treatment often co-occurs with burdensome physical effects including pain and fatigue.[2] Inflammation also contributes to increased pain, fatigue, and reduced quality of life among cancer patients.[3–5] Alongside these physical symptoms, cancer diagnosis and treatment present several uncertainties: fears of the disease progression, recurrence, treatment side effects, changes in physical health, and early mortality. Each of these uncertainties can contribute to heightened anxiety and depression both prior to treatment and throughout survivorship. This study tested relationships between depressive and anxiety symptoms with pain, fatigue, and inflammation among recently diagnosed colorectal cancer patients.

Prevalence rates of pain severity and duration in colorectal patients are estimated at over 70% depending on stage of disease.[6] Although treatment carries its own side effects, colorectal patients may experience significant physical symptoms even prior to treatment: Following a diagnosis of colorectal cancer, approximately 51% of patients already reported at least one moderately bothersome symptom related to pain or fatigue.[7] In fact, pain and fatigue may be highest among newly diagnosed colorectal cancer patients compared to other points in the cancer trajectory.[2] In terms of inflammation, a proinflammatory environment promotes tumor initiation, growth, and metastases, contributing to poorer prognoses, risk for recurrence, and reduced survival among cancer patients.[8–10] High inflammation among colorectal cancer patients corresponds to reduced survival time and risk for recurrence.[11–13] Further, heightened inflammation increases the risks of comorbid disease development that

is common among colorectal cancer patients including cardiovascular disease, osteoporosis, and diabetes.[9,14,15] Overall, inflammation and its associated consequences pose significant threats to colorectal cancer patients' long-term health and physical functioning.

The Self-Regulatory Model of Illness Behavior highlights the importance of emotional responses when managing a health threat such as cancer.[16] Within this model, poor self-regulation leads to increased anxiety and depression along with maladaptive coping behaviors. Considerable research has addressed the impact of depression and anxiety on health and well-being in a cancer context.[17] Clinically significant depressive and anxiety symptoms are common among colorectal cancer patients. Ranges of anxiety and depressive symptoms differ across samples, with rates of anxiety can ranging from 1.0% to 47.2% of patients across studies, while depression rates range from 1.6%–57.0%.[18] Rates of depressive and anxiety symptoms are approximately 10% higher in colorectal cancer patients compared to physically healthy peers.[19] Although distress persists throughout survivorship, psychological symptoms are typically highest following diagnosis.[2] Within the Self-Regulatory model, difficulty regulating one's thoughts and emotions can evoke psychological symptoms, and, in turn, decreases overall physical health. This model, in part, helps explain why depressive and anxiety symptoms may be high around the time of cancer diagnosis. The current study tests one piece of the Self-Regulatory Model of Illness Behavior by examining anxiety and depressive symptoms along with their biological and physical correlates among colorectal cancer patients prior to undergoing adjuvant therapy.

The Perseverative Cognition Hypothesis (PCH) builds from The Self-Regulatory Model of Illness Behavior. Specifically, worry and rumination, common among people who feel anxious and depressed, prolong physiological activation and increase the likelihood for heightened inflammation and associated physical symptoms such as pain and fatigue.[20,21] Perseveration also provokes anxiety and depression, respectively, among both healthy individuals and cancer patients. Consequently, depression and anxiety are associated with cognitive risk factors that may influence physical health and biological dysfunction throughout diagnosis and treatment. The PCH therefore highlights how psychological symptoms can increase biological dysfunction and heighten physical symptoms, thus prolonging or worsening symptoms associated with diagnosis and treatment among cancer patients and individuals with other chronic illnesses.

Inflammation, pain, and fatigue commonly cooccur with depressive and anxiety symptoms among physically healthy individuals and cancer patients.[22–24] Among colorectal cancer patients awaiting chemotherapy treatment, depressive and anxiety symptoms were positively associated with increased levels of interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α).[25,26] However, other studies have not found associations between depression and inflammation, highlighting a need to better understand these relationships within a cancer context.[27] Depressive symptoms also contribute to increased pain and fatigue among colorectal cancer patients across stages.[28,29] Longitudinal research links anxiety and depressive symptoms to physical health across time in colorectal patients.[19] Collectively, depression and anxiety may contribute to increased mortality risk among colorectal cancer patients. In fact, a one standard deviation increase in anxiety or depressive symptoms in one sample corresponded to a 16% higher mortality risk.[30]

1.1 | The current study

Despite relationships between inflammation and depressive/anxiety symptoms, research has not examined whether clinically significant levels of anxiety and depressive symptoms may correspond to heightened inflammation among colorectal patients. Further, prior correlational studies did not control for known influencers of physical symptoms and inflammation, therefore limiting our overall understanding of the relationship between psychological and physical health among colorectal patients. Further, no prior research has looked at both inflammation and physical symptoms as consequences of anxiety and depression among colorectal cancer patients or inflammatory mediators of the relationship between pain/fatigue and depression/anxiety. Better understanding the relationships among these variables in the context of colorectal cancer would allow for a more comprehensive understanding of the relationship between psychological and physical health in this population, providing insight into potential future intervention targets. Subsequently, this study tested how anxiety and depressive symptoms were associated with pain, fatigue, and inflammation among newly diagnosed colorectal cancer patients awaiting treatment. We predicted that higher anxiety and depressive symptoms would be associated with greater c-reactive protein (CRP) and higher self-reported pain and fatigue. To better understand how clinically significant levels of anxiety and depressive symptoms relate to inflammation, we used clinical cutoffs to test whether clinically significant depressive and anxiety symptoms corresponded to health-relevant CRP elevations (>3 mg/L). Finally, given that inflammation has ties to fatigue and pain in cancer patients[3–5] as well as depression and anxiety,[24,31] an exploratory aim of this study tested the indirect effect of depression and anxiety symptoms on pain and fatigue through CRP.

2 | METHODS

2.1 | Participants and procedure

Participants were patients with a colorectal cancer diagnosis ($N = 88$, stages I-IV) recruited from cancer clinics for a parent study on fatigue and immune dysregulation. Recruitment occurred within 1–3 months after diagnosis. The colorectal patients in this study had not yet begun adjuvant treatment (e.g., radiation, chemotherapy, or immune therapy). Table 1 presents the sample characteristics. During their study visit, participants completed questionnaires and a blood draw to measure inflammation. Exclusion criteria included a history of cancer except basal or squamous cell skin carcinomas and significant visual, auditory, or cognitive impairments. The Ohio State University Institutional Review Board approved the project (Approval Number 2007C0079) and all participants provided written informed consent. Data collection occurred between July 2008 and July 2011.

2.2 | Depression and anxiety measures

2.2.1 | Depression—The Center for Epidemiologic Studies Depression Scale (CES-D), commonly used in cancer patients, provided data on participants' depressive symptoms.[32] The CES-D is a 20-item scale that asks participants to indicate the frequency at which they experienced depressive symptoms over the past week. Scores on the CES-D range from 0 to 60 with higher scores representing greater depressive symptoms. A score of 16 or above

on the CESD is consistent with clinically significant depressive symptoms consistent with a diagnosis of major depressive disorder.[32] Reliability of the CESD was excellent (a = 0.91).

2.2.2 | Anxiety—The 21-item Beck Anxiety Inventory (BAI) asked participants to rate how frequently they experienced anxiety symptoms over the last month.[33] Scores on the BAI range from 0 to 63 with higher scores reflecting greater anxiety symptoms. BAI score groups indicate minimal anxiety (0–7), mild anxiety,[8–15] moderate anxiety,[16–15] or severe anxiety (16–63), with scores of 16 or above indicating clinically significant anxiety.[34] The BAI showed excellent reliability in this study (a = 0.91).

2.3 | Pain and fatigue measures

2.3.1 | Fatigue—The Multidimensional Fatigue Symptom Inventory (MFSI) measured fatigue.[35] The total score on MFSI reflects behavioral, cognitive, physical, and affective expressions of fatigue in the last week with higher scores corresponding to more fatigue. Reliability for the MFSI in this study was excellent (a = 0.96).

2.3.2 | Pain—Pain was assessed using a 10-point rating scale from 1 (no pain) to 10 (intense pain). Similar numerical rating scales have been widely used for pain measurement and have demonstrated reliability and validity for assessing pain intensity.[36]

2.4 | Covariates

All analyses controlled for cancer stage, physical comorbidities, body mass index (BMI), age, and sex. The Charlson comorbidity index provided data on physical comorbidities.[37] The Charlson, originally designed for cancer patients, assigns weights to 19 medical conditions with higher scores representing more physical comorbidities.

2.5 | Inflammation assays

The collection of fasting blood samples occurred between 7:00 and 9:00 AM to control for diurnal variation. Serum C-reactive protein (CRP) was measured using a chemilluminescence method via the Immulite 1000 (Siemens Healthcare Diagnostics, Inc., Deerfield, IL). Sensitivity for the assay was 0.3 mg/L. The intra-assay coefficient of variation (CV) was 3.1%, and the inter-assay CV was 7.3%. CRP levels greater than 3 mg/L indicate increased risk of cardiovascular disease, even when other markers such as blood pressure are low.[38,39] CRP data was natural log transformed to better approximate normality of residuals.

2.6 | Analytic plan

A post hoc power analysis using G*Power (Faul et al., 2007) revealed that using an alpha of 0.10, a sample size of at least 73 participants was required to detect at least a medium effect ($f^2 \geq 0.15$) for hierarchical linear regressions (described below). SPSS Version 27 was used to conduct all analyses. Preliminary bivariate correlations examined relationships between and among study variables. Hierarchical linear regressions addressed the hypotheses that depression and anxiety would predict greater fatigue, pain, and CRP. Separate models were run with depression and anxiety as predictors. All models were tested using a two-step approach; covariates were entered into the first step, and depressive or anxiety symptoms

were entered into the second step to quantify additional variance explained. To reduce the likelihood of Type I error due to multiple comparisons, *p*-values underwent a Bonferroni correction separately for anxiety and depression. This correction indicated a *p* value of < 0.02 to be considered statistically significant.

To test the relationship between clinically significant depressive/anxiety symptoms with high CRP, we categorized each variable based on clinical cut points.[32,33,38,39] We then conducted chi-square tests to assess relationships between depression and anxiety cutoffs with high CRP. The hypothesis that CRP would have an indirect effect on the relationship between anxiety and depressive symptoms with pain and fatigue was tested using Hayes' SPSS PROCESS macro.[40] Indirect effects were tested with 95% bias-corrected confidence intervals and 5000 bootstrapped samples.

All models adjusted for physical comorbidities, BMI, age, menopause status, and cancer stage (I; II; III; IV). Continuous covariates were grand mean centered to improve interpretability of the intercepts.

3 | RESULTS

3.1 | Descriptive statistics

Table 1 presents the sample demographics. Zero-order correlations among study variables are presented in Table 2. Patients, on average, were middle-aged (M = 58.60, SD = 14.63) and identified as White (N = 79, 89.8%). The average BMI for patients fell into the obese category (M = 30.91, SD = 8.28) and rates of physical comorbidities were low (M = 1.41, SD = 2.19). The distribution of patients across stages I-IV was also relatively equal, showing variability in disease severity across the sample.

3.2 | Effects of depression on pain, fatigue, and CRP

Consistent with study hypotheses, even after adjusting for relevant covariates, depressive symptoms predicted higher pain, fatigue, and CRP (See Table 3). Depressive symptoms explained an additional 23% of variance in CRP (R^2 = 0.23, F[6, 69] = 3.30, p < 0.01) and 69% of the variance in fatigue (R^2 = 0.69, F[6, 72] = 26.45, p < 0.001).

3.3 | Effects of anxiety on pain, fatigue, and CRP

Consistent with study hypotheses, independent of covariates, anxiety predicted higher pain, fatigue, and CRP. Anxiety symptoms explained an additional 24% of variance in CRP (R^2 = 0.24, F[6, 69] = 3.66, p < 0.01), 66% of the variance in fatigue (R^2 = 0.66, F[6, 72] = 22.87, p < 0.001), and 18% of variance in pain (R^2 = 0.18, F[6, 72] = 2.55, p = 0.03) (See Table 4).

3.4 | Clinical depression and anxiety symptoms predicting CRP

Patients' mean CESD score was 15.96, indicating near-clinical levels of depressive symptoms. A total of 38 patients (43.2%) reported CESD scores above 16. Of these patients, 26 of them (68.4%) also had CRP levels >3 mg/L. The remaining participants had both low depression and low CRP levels (n = 26; 29.5%) or were low on either depression or CRP, but

not both (n = 28, 31.8%). The relationship between these variables was significant, X^2 (1, N = 77) = 5.33, p = 0.02. Patients with CESD scores ≥16 were more likely to have CRP values ≥ 3 mg/L. The remaining 8 patients had missing CESD (n = 8) or CRP (n = 3) data.

Mean BAI scores in this sample were 11.75, suggesting mild anxiety.[34] A total of 31 participants endorsed minimal anxiety (35.2%), 26 (29.5%) mild anxiety, 15 (17.0%) moderate anxiety, and 11 (12.5%) severe anxiety. There were 20 (22.7%) participants who endorsed moderate or severe anxiety and had CRP levels >3 mg/L. The remaining patients either had low BAI scores and CRP levels <3 (n = 31, 35.2%) or were low on the either anxiety or CRP, but not both (n = 29, 33.0%). Consistent with the depression findings, the relationship between these variables was significant, X^2 (1, N = 80) = 5.94, p = 0.02. There were 8 patients with missing BAI data.

3.5 | Indirect effects of CRP on pain and fatigue

We first tested the model with anxiety as the predictor. No covariates had a direct effect on CRP, pain, or fatigue. As expected, anxiety was associated with higher levels of CRP (b = 0.03, SE = 0.01, p = 0.05), higher fatigue (b = 1.62, SE = 0.18, p < 0.0001), and greater pain (b = 0.08, SE = 0.04, p = 0.04). There was no indirect effect of CRP on the relationship between anxiety and fatigue (b = 0.03, SE = 0.05, 95% CI = −0.07, 0.16) or pain (b = −0.16, SE = 0.14, 95% CI = −0.50, 0.01).

When testing depressive symptoms as the predictor in these models, no covariates directly effected CRP, pain, or fatigue. Consistent with the anxiety-related findings, depressive symptoms were associated with higher CRP (b = 0.02, SE = 0.01, p = 0.03) and greater fatigue (b = 1.52, SE = 0.15, p < 0.0001). There was no direct relationship between depressive symptoms and pain (b = 0.04, SE = 0.03, p = 0.24). There was no indirect effect of CRP on the relationship between depressive symptoms and fatigue (b = 0.03, SE = 0.04, 95% CI = −0.04, 0.14) or pain (b = −0.16, SE = 0.12, 95% CI = −0.47, 0.01).

4 | DISCUSSION

This study assessed the effects of anxiety and depressive symptoms on several common consequences of colorectal cancer pain, fatigue, and inflammation. The colorectal patients in this study had not yet begun adjuvant treatment (e.g., radiation, chemotherapy, or immune therapy). This period is particularly important because psychological health prior to adjuvant treatment can set the stage for future psychological and physical distress throughout treatment and survivorship.[41–44] Results showed that higher anxiety and depressive symptoms were related to higher pain, fatigue, and CRP among colorectal cancer patients prior to undergoing treatment.

Notably, our results held while controlling for several covariates including BMI, physical comorbidities, age, gender, and cancer stage highlighting robust relationships between anxiety symptoms with pain, fatigue, and inflammation. Significant relationships also emerged between depressive symptoms with fatigue and inflammation. Findings from this study extend earlier research on relationships between anxiety and depressive symptoms with physical symptoms among colorectal cancer patients in several important ways.[18,19]

First, most of the earlier cross-sectional research did not adjust for known influencers of pain, fatigue, and inflammation among these patients. Further, our findings highlighted the clinical significance of these relationships: nearly one-third of patients who reported clinically significant levels of depressive symptoms also had high CRP levels (defined as levels >3 mg/L). A similar pattern of relationships emerged for anxiety symptoms: 29.5% of patients who reported moderate or high anxiety also had CRP levels >3 mg/L. This study is therefore among the first to show relationships between depressive and anxiety symptom severity and heightened inflammation among colorectal patients. High inflammation among colorectal cancer patients corresponds to reduced survival time and risk for recurrence[11–13] along with increasing the risk of comorbid disease development.[9,14,15] Within the limitations of cross-sectional data, understanding how psychological factors may relate to inflammation in this population provides a basis for further research that addresses the interplay between biological and psychological health as colorectal cancer patients navigate the cancer trajectory. Lastly, no prior research has tested potential mechanisms in the link between psychological health and pain or fatigue. Although the indirect effects of CRP on the relationship between anxiety and depression with pain or fatigue were not significant, it highlights important considerations for future research in studying biological mechanisms linking psychological and physical health among colorectal cancer patients.

Depression is closely tied to increased mortality risk among colorectal cancer patients,[19,45,46] but research tying anxiety symptoms to mortality risk in this population is limited. Given inflammation's correlates with both psychological symptoms and morbidity and mortality,[11–13] inflammation may play a crucial role in the link between depressive and anxiety symptoms with increased mortality in this population. Contrary to study hypotheses, inflammation did not partially explain the relationship between psychological symptoms and pain or fatigue. This study was not able to test mortality given its cross-sectional design, but future research should examine whether inflammation helps to explain relationships between psychological or physical distress and mortality among colorectal cancer patients.

This study has several notable strengths. Assessing if anxiety and depression symptom severity correspond to inflammation, pain, and fatigue advances our understanding of not only of how psychological symptoms influence health in this population, but also if more severe symptoms are related to cancer-related symptoms and inflammation. Our sample included colorectal cancer patients who had undergone surgery but had not yet begun adjuvant treatment. The assessment of patients at this stage in cancer treatment provides novel insights into their psychological and physical health that can predict cancer-related symptoms and inflammation both prior to and following adjuvant treatment.

4.1 | Study limitations

The cross-sectional nature of these data precludes causal claims about the impact of anxiety and depressive symptoms on somatic symptoms and inflammation. Given the racial, ethnic, and socioeconomic homogeneity of the current sample, replication of this study in more diverse populations is important to increase generalizability of these results. These results should also be replicated in a larger sample of colorectal cancer patients, as well as among those with currently diagnosed anxiety and depressive disorders. An added limitation is

that we did not assess depression and anxiety symptoms prior to diagnosis, which limited our ability to understand pre-morbid psychological functioning. Lastly, other inflammatory markers aside from CRP may be important to examine in relation to anxiety and depression in this population.

4.2 | Clinical implications

Given inflammation's correlates to cancer recurrence, tumor growth, and increased symptom burden, understanding both psychological and physical factors contributing to a proinflammatory environment in colorectal cancer patients can aid in improving health throughout treatment and survivorship.[8,9] If inflammation proves to be high for a cancer patient, anti-inflammatory targeted treatments may prove beneficial for reducing corresponding physical symptoms such as pain and fatigue. Further, these data can be used to understand how, if someone has high anxiety or depressive symptoms, they may also be at risk for experiencing worse physical symptoms as they navigate the cancer trajectory. Results from the current study also underscore the need for screening for and treating anxiety and depression in colorectal patients, in line with recommendations from the American Society of Clinical Oncology and accreditation standards for cancer facilities set forth by the American College of Surgeons Commission on Cancer.[47,48] Intervening on depressive and anxiety symptoms early in the cancer trajectory among colorectal cancer patients is critical in improving psychological health and quality of life. Such interventions have the potential to reduce symptom burden across treatment and survivorship and improve the quality of life and extend the longevity and overall health of colorectal cancer survivors. Importantly, the benefits of these interventions extend to both psychological and physical health.

5 | CONCLUSION

As survival rates for colorectal cancer improve, understanding the potential physical and psychological side effects of diagnosis and treatment, and how these symptoms interact with one another, is critical. Results from this study underscore the important relationship between anxiety and depressive symptoms with several notable physical symptoms associated with colorectal cancer and highlights important avenues for future research.

ACKNOWLEDGEMENTS

This work was supported in part by National Institute of Health grants CA131029, UL1TR0000090, CA016058, K05 CA172296, and T32 CA229114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding information

National Institutes of Health, Grant/Award Numbers: CA131029, UL1TR0000090, CA016058, K05 CA172296, T32 CA229114

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLE 1

Sample characteristics ($N = 88$)

	Mean (SD)	Number (%)
Age	58.60 (14.63)	
% Female		42 (47.7%)
BMI	30.91 (8.28)	-
Physical comorbidities	1.41 (2.19)	-
Race		
White	-	79 (89.8%)
Black	-	6 (6.8%)
Native American	-	3 (3.4%)
Cancer stage		
I	-	23 (26.1%)
II	-	16 (18.1%)
III	-	20 (22.7%)
IV	-	26 (29.5%)
No longer menstruating	-	26 (61.9%)
Depression	15.96 (10.41)	-
Anxiety	11.75 (9.42)	-
Pain	2.63 (2.71)	-
Fatigue	15.20 (20.80)	-
CRP	8.23 (16.52)	-

Note: CRP data represents non-log transformed values.

Abbreviations: Anxiety, Anxiety symptoms assessed via the Beck Anxiety Inventory; BMI, body mass index; CRP, C-reactive protein; Depression, Depressive symptoms as measured by the Center for Epidemiological Studies Depression Scale; SD, standard deviation.

TABLE 2

Correlations among study variables

	1	2	3	4	5	6	7	8	9	10	11
1. CESD	-										
2. BAI	0.82**	-									
3. Pain	0.31**	0.35**	-								
4. Fatigue	0.79**	0.79**	0.34**	-							
5. CRP	0.31**	0.31**	0.31**	0.27*	-						
6. Age	−0.35**	−0.28**	−0.12	−0.24*	−0.13	-					
7. Sex	0.04	0.01	0.13	−0.04	0.03	−0.15	-				
8. BMI	0.29**	0.34**	0.08	0.27*	0.26*	−0.14	−0.15	-			
9. Comorbidities	0.04	0.18	0.11	0.29**	−0.03	0.39**	−0.26*	0.23*	-		
10. Menopause	−0.40*	−0.28	0.18	−0.44**	0.06	0.73**	−0.14	−0.29	−0.02	-	
11. Stage	−0.06	−0.05	−0.05	−0.01	0.25*	0.06	0.06	−0.10	0.16	−0.19	-

Abbreviations: BAI, Beck Anxiety Inventory; BMI, body mass index; CESD, Center for Epidemiological Studies Depression Scale; CRP, C-reactive protein; Stag, cancer stage.

* $p < 0.05$,

** $p < 0.001$.

TABLE 3

Effects of depression on pain, fatigue, and c-reactive protein (CRP)

	B	SE	β	R^2	ΔR^2
Pain					
Block 1				0.06	
Age	−0.03	0.02	−0.16		
Sex	0.75	0.62	0.14		
BMI	0.004	0.04	0.01		
Stage	−0.06	0.12	−0.06		
Comorbidities					
Block 2				0.12	0.06
Depression	0.07	0.03	0.27*		
Fatigue					
Block 1				0.24	
Age	−0.54	0.17	−0.38**		
Sex	1.02	4.48	0.02		
BMI	0.29	0.27	0.12		
Stage	−0.35	0.86	−0.04		
Comorbidities	3.76	1.12	0.41**		
Block 2				0.69	0.45**
Depression	1.51	0.15	0.75***		
CRP					
Block 1				0.17	
Age	−0.002	0.01	−0.02		
Sex	−0.02	0.24	−0.10		
BMI	0.04	0.02	0.32*		
Stage	0.13	0.05	0.30**		
Comorbidities	0.23	0.15	0.20		
Block 2				0.23	0.07*
Depression	0.03	0.01	0.29*		

Abbreviations: ΔR^2 = change in R2; B = standardized beta; SE = standard error; b = unstandardized beta.

*$p < 0.05$,

**$p < 0.01$.

TABLE 4

Effects of anxiety on pain, fatigue, and c-reactive protein (CRP)

	B	SE	β	R^2	ΔR^2
Pain					
Block 1				0.06	
Age	−0.03	0.02	−0.16		
Sex	0.75	0.62	0.14		
BMI	0.004	0.04	0.01		
Stage	−0.06	0.12	−0.06		
Comorbidities	0.28	0.15	0.24		
Block 2				0.18	0.11 *
Anxiety	0.10	0.03	0.38 **		
Fatigue					
Block 1				0.24	
Age	−0.54	0.17	−0.38 **		
Sex	1.02	4.48	0.02		
BMI	0.29	0.27	0.12		
Stage	−0.35	0.86	−0.04		
Comorbidities	3.76	1.12	0.41 **		
Block 2				0.66	0.42 **
Anxiety	1.62	0.17	0.73***		
CRP					
Block 1				0.17	
Age	−0.002	0.01	−0.02		
Sex	−0.02	0.24	−0.01		
BMI	0.04	0.02	0.32 *		
Stage	0.13	0.05	0.30 **		
Comorbidities	−0.07	0.06	−0.16		
Block 2				0.24	0.08 **
Anxiety	0.04	0.01	0.31 *		

Abbreviations: ΔR^2, change in R2; B, standardized beta; SE, standard error; b, unstandardized beta.

* $p < 0.05$,

** $p < 0.01$.