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Determinants of health – related quality of life in patients with inflammatory bowel diseases

Odrednice kvalitete života kod oboljelih od upalnih bolesti crijeva

Barbara Stamenković Tadić, Meri Tadinac[*]

─────────── **Summary** ───────────

The aim is to examine the contribution of socio-demographic, medical, and psychological factors in predicting health related quality of life (HRQoL) in patients with inflammatory bowel diseases (IBD) and to examine the differences between those with Crohn's disease and ulcerative colitis, regarding psychosocial factors and quality of life.

Methods. Data from 90 participants with Crohn's disease and 63 participants with ulcerative colitis were collected using HBI, SCCAI, HADS, and shortened versions of SIBDQ, SS – A, and COPE, and the measure of self-evaluated disease activity. Data were analyzed by multiple hierarchical regression and discriminant analysis.

The results of socio-demographic, medical and psychological factors accounted for 66% of variance of HRQoL in participants with IBD, with disease activity, and levels of anxiety and depression being the strongest independent predictors. Higher disease activity and higher level of psychological disturbances were related to lower HRQoL. Differences between the two diagnostic groups were found in disease activity assessments and disengagement, with participants suffering from Crohn's disease indicating lower levels of disease activity, using disengagement as a coping strategy less often.

Conclusion. The findings on independent contribution of psychological disturbances in predicting the HRQoL, positive correlation of anxiety and depression with disease activity, and high representation of clinically relevant anxiety (27.5%) and depression (10.5%) in the sample with a low representation of participants with severe, active phase of disease point towards a need for routine screening for anxiety and depression in IBD patients and inclusion of specific psychological support in IBD treatment.

Key words: inflammatory bowel diseases, quality of life, disease activity, anxiety, depression

─────────── **Sažetak** ───────────

Cilj. Ispitati doprinos sociodemografskih, medicinskih i psiholoških čimbenika u predviđanju kvalitete života povezane sa zdravljem kod oboljelih od upalnih bolesti crijeva, te ispitati razlike u psihosocijalnim čimbenicima i kvaliteti života između oboljelih od Crohnove bolesti i ulceroznog kolitisa.

Metode. Prikupljeni su podaci od 90 sudionika s Crohnovom bolešću i 63 sudionika s ulceroznim kolitisom, pomoću upitnika HBI, SCCAI, HADS; skraćenih verzija upitnika SIBDQ, SS – A i COPE, te mjere samoprocjene aktivnosti bolesti. Podaci su analizirani pomoću multiple hijerarhijske regresijske analize i diskriminacijske analize.

Rezultati. Ispitani sociodemografski, medicinski i psihološki čimbenici objasnili su 66% varijance kvalitete života povezane sa zdravljem kod oboljelih od upalnih bolesti crijeva, pri čemu su se aktivnost bolesti, te stupanj anksioznosti i depresivnosti pokazali najsnažnijim nezavisnim prediktorima. Kvaliteta života oboljelih pokazala se manjom, što su aktivnost upalnih bolesti crijeva i razina psiholoških smetnji veće. Razlike između dviju dijagnostičkih skupina nađene su u samoprocjeni aktivnosti bolesti i dezangažmanu, pri čemu su oboljeli od Crohnove bolesti izvještavali o nižim razinama aktivnosti bolesti i rjeđem korištenju dezangažmana kao strategije suočavanja sa stresom.

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Zaključak. Nalazi o nezavisnom doprinosu psiholoških smetnji u predviđanju kvalitete života, pozitivnoj povezanosti anksioznosti (27.5%) i depresivnosti s aktivnošću bolesti, te visokoj zastupljenosti klinički značajne anksioznosti i depresivnosti (10.5%) u uzorku s niskim udjelom sudionika u teškoj aktivnoj fazi bolesti, ukazuju na potrebu za rutinskim probirom za anksioznost i depresivnost, te sustavnim pružanjem psihološke podrške oboljelima od upalnih bolesti crijeva.

Ključne riječi: upalne bolesti crijeva, kvaliteta života, aktivnost bolesti, anksioznost, depresivnost

Introduction

Inflammatory Bowel Diseases (IBD) are heterogeneous disorders resulting from the combination of genetic factors, disorders of intestinal motility, visceral oversensitivity, disrupted regulation of mucosal immune response, changes in bacterial flora and disrupted regulation of the axis between the central nervous system (CNS) and the enteric nervous system (ENS), the so called "second brain".[1-2] The assumed important role of psychosocial factors in the development and course of IBD, as well as the perceived imbalance between the clinical presentations of the disease and real disease activity confirmed by laboratory and the endoscopic tests,[3] are all behind the growing interest for measuring health related quality of life (HRQoL) in IBD. This should supplement the information on physical symptoms with social, emotional, systematic and functional characteristics, leading to better comparability with overall self-evaluation of participants' health.[4]

The role of psychological factors in development and course of the IBD is very complex and still not fully clarified.[5] The general opinion is that psychological factors (personality, psychological stress, depression and anxiety) contribute to exacerbation of IBD, but not to their etiology or development,[5-8] with the exception of the finding of Kurina et al., that depression and anxiety antecede the development of ulcerative colitis (UC), but not Crohn's disease (CD),[9] and contrary findings of Ananthakrishnan et al. on depression[10] as the antecedent psychological disorders in CD, but not in UC. Research on contribution of biopsychosocial factors to the prediction of HRQoL in participants with IBD showed that disease activity,[11,12-16] intake of systemic corticosteroids and immunosuppressants, disease relapses, presence of extraintestinal manifestations of disease,[17] presence of symptoms resembling irritable bowel syndrome (IBS),[18-21] anxiety and depression,[11,12,22-23] depressive coping with stress[24-26] and emotion focused coping with stress[27] were all negatively correlated, while social support[23,27-28] was positively correlated, with the quality of life (QoL). On the other hand, findings on relations between illness duration, level of education, gender, problem focused coping with stress, chronic psychological stress, and acute everyday stress with QoL in patients with IBD are contradictory. Some studies found longer illness duration,[13-14] higher level of education[13,29] and male gender[13,23,29-30] to be related with better HRQoL, while other found no correlation of illness duration[22,31] and level of education with quality of life,[11,30-31] and higher general satisfaction and HRQoL in females.[11] There are findings of the positive correlation of problem focused coping with the quality of life,[27] but also those of the positive correlation of active coping with stress and intense concerns, as well as higher number of somatic complaints, which is explained by inadequacy of active coping in uncontrollable and unpredictable diseases as are IBD or by the possibility that participants with a higher amount of concerns are more frequently involved in active information seeking.[32] Some studies show a correlation between stressful life events and a higher risk of later relapse of IBD,[33-35] while in others this relation was not significant.[36-41] Similarly, a positive correlation of acute everyday stress and self-evaluated activity of IBD, even after controlling for major life events, was established in some studies,[42-43] while in some no such relation was found.[38] In addition, one study shows that exacerbation was not associated with stressful life events or short-term perceived stress, but that long-term perceived stress increases the risk of later exacerbation,[38] in line with other studies showing the association between perceived stress and disease activity assessed both by presence of symptoms[44] and presence of inflammation.[45] Furthermore, a most recent study found prospective bidirectional relationships between perceived stress and IBD symptom reporting but no relationship between perceived stress and presence of inflammatory disease activity as assessed by fecal calprotectin,[46] raising further questions in debates over the role of stress in IBD. Finally, several studies found early adverse life events to be a major risk factor for the adult onset and severity of IBD and IBS.[47-50]

Analyses of the differences in biopsychosocial factors between patients with CD and UC also show contradictory findings. While some studies found no differences in levels of anxiety[19,22] and depression[12,19,22] between the two diagnostic groups, other studies point towards a higher level of depression[3,51] and

anxiety[3,26,51-52] in CD. Furthermore, some found an equally disrupted quality of life in both diagnostic groups,[12,13,15,22] and other the poorer quality of life in the CD group[14,51,53] attributed to more severe disease type.[54]

With the purpose of further clarification of the complex role of biopsychosocial factors of IBD, the aim of this research was to examine the relative contribution of socio-demographic (gender, age, socio-economic status), medical (diagnosis, disease activity, illness duration) and psychological factors (anxiety, depression, strategies of coping with stress, perceived social support) to the prediction of HRQoL in patients with IBD.

Methods

Participants and procedure

The questionnaires were filled out by 202 participants. However, 49 were excluded due to missing data and further 7 due to their diagnosis of intermediate colitis. Therefore, analyses were performed on the results of 153 participants, 90 of them with CD and 63 with UC. The majority of the participants were members of the Croatian Crohn's and Ulcerative Colitis Association (HUCUK). Participants were invited to join the research via written invitation sent to their home address, the invite published on HUCUK's website, or an e–mail invitation by using the method of snowball sampling. The questionnaires were filled out online, using the services of Survey Monkey platform. The description of the socio-demographic characteristics of the sample is presented in Table 1.

The overall sample, as well as both subsamples, were well balanced regarding gender, age, education and income. As can be seen from medical data for both subsamples (Table 2), they are also comparable in illness duration. However, they differ in the distribution of self-evaluated disease activity: the largest proportion of participants with CD reported being in remission, and significantly more participants with UC being in the moderate active phase of the disease.

Table 1 Socio-demographic data for the overall sample of patients with inflammatory bowel diseases (*N* = 153) and for subsamples of patients with Crohn's disease (*n* = 90) and ulcerative colitis (*n* = 63)
Tablica 1. Socio-demografski podaci za ukupni uzorak bolesnika s upalnim bolestima crijeva (N = 153) i za podvrste bolesnika s Crohnovom bolešću (n = 90) i ulceroznim kolitisom (n = 63)

			Inflammatory bowel diseases *Upalne bolesti crijeva*	Crohn's disease *Crohnova bolest*	Ulcerative colitis *Ulcerozni kolitis*
Gender/*Spol*	Male/*Muško*	*n*	70	44	26
		%	45.8	48.9	41.3
	Female/*Žensko*	*n*	83	46	37
		%	54.2	51.1	58.7
Age/*Dob*		*M*	35.07	35.28	34.76
		SD	10.635	11.651	9.069
		Min	15	15	17
		Max	87	87	60
Education *Obrazovanje*	Primary school *Osnovna škola*	*%*	2.6	3.3	1.6
	High school *Srednja škola*	*%*	55.6	58.9	50.8
	College/Undergraduate *Viša škola/dodiplomski*	*%*	12.4	14.4	9.5
	Graduate/*diplomirani*	*%*	23.5	17.8	31.7
	Postgraduate *Poslijediplomski*	*%*	5.9	5.6	6.4
Average monthly income per household member in HRK *Prosječan prihod po članu obitelji u HRK*		*M*	2792	2831	2738
		SD	1746	1651	1885

Table 2 Medical data for patients with Crohn's disease (n = 90) and ulcerative colitis (n = 63)
Tablica 2. Medicinski podaci za pacijente s Crohnovom bolešću (n = 90) i ulceroznim kolitisom (n = 63)

			Crohn's disease *Crohnova bolest*	Ulcerative colitis *Ulcerozni colitis*
HBI		*M*	4.01	
		SD	3.636	
SCCAI		*M*		5.26
		SD		1.825
Self-evaluated disease activity *Samoprocijenjena aktivnost bolesti*		*n*	90	63
		M	2.03	2.56
		SD	1.086	1.215
		K-S	2.23**	1.46*
	Remission / *Remisija*	*%*	41.1	25.4
	Remission with some IBS symptoms *Remisija s ponekim IBS simptomima*	*%*	27.8	25.4
	Mild active phase *Blago aktivna faza*	*%*	20	20.6
	Moderate active phase *Umjereno aktivna faza*	*%*	8.9	25.4
	Severe active phase *Teška aktivna faza*	*%*	2.2	3.2
Illness duration *Trajanje bolesti*		*M*	9.66	9.27
		SD	7.594	8.999

HBI: *Harvey-Bradshaw Index of Crohn's Disease Activity/* Harvey-Bradshaw Indeks aktivnosti Crohnove bolesti
SCCAI: *Simple Clinical Colitis Activity Index /* Indeks aktivnosti jednostavni klonički colitis
IBS: symptoms resembling irritable bowel syndrome*/simptomi slični simptomima razdražljivih crijeva*
K-S: Kolmogorov-Smirnov test for normality of the distribution, * $p < 0.05$ ** $p < 0.01$
*K-S: Kolmogorov-Smirnov testiranje normalnosti distribucije * $p < 0.05$ ** $p < 0.01$*

Both distributions were significantly positively asymmetric ($K-S = 2.23$; $p < 0.01$ in CD, and $K-S = 1.46$; $p < 0.05$ in UC), with the majority of participants being in remission or very mild phase of the disease, and only 2.2% participants with CD and 3.2% participants with UC evaluating their disease as being in a severe, active phase. This is probably the consequence of lower interest in severely ill patients for participating in the research, due to the intensity of symptoms or hospitalization.

Instruments

The Short Inflammatory Bowel Disease Questionnaire (SIBDQ)[55] is a health-related quality of life (HRQoL) tool, measuring physical, social, and emotional status (score 10-70, poor to good HRQoL).

Harvey-Bradshaw Index of Crohn's Disease Activity (HBI)[56] is a simpler version of *Crohn's Disease Activity Index (CDAI),* the research tool for quantification of symptoms in subjects with CD, with higher total score indicating a higher disease activity.

Simple Clinical Colitis Activity Index (SCCAI)[57] is the shortened version of *Powell-Tuck Index*, a tool for quantification of symptoms in patients with UC, with higher overall score indicating a higher disease activity.

Self-evaluation of disease activity. Participants were asked to evaluate the activity of their disease during the previous two weeks on a 5-point scale: 1 - in remission/ inactive; 2 - in remission/inactive, with some symptoms resembling irritable bowel syndrome (stomach aches, constipation, diarrhea, mucus in excrement, bloating, heavy feeling in the stomach after a meal, heartburn, but without signs of inflammation or degenerative changes); 3 – in the mild active phase (the disease symptoms did not interfere with my everyday activities); 4 - in the moderate active phase (the disease symptoms interfered with my everyday activities); 5 - in the severe active phase (the disease symptoms disabled me from performing my everyday activities and forced me to take a sick leave or be hospitalized).

Hospital Anxiety and Depression Scale (HADS)[58] is a self-assessment scale for detecting states of anxiety

and depression in patients with physical ailments, by measuring exclusively emotional states, but not somatic symptoms. The result is expressed in two scores: anxiety (HADS-A) and depression (HADS-D), on a scale from 0 (low levels of anxiety/depression) up to 21 (extremely high levels of anxiety/depression). Scores ≥ 11 on both subscales are considered clinically relevant.

Scale of Perceived Social Support (Hudek-Knežević, 1994)[59] is a shortened and adapted version of the *Social Support Appraisals Scale (SS-A)*. The scale measures the participants' experienced level of love, respect and involvement received from their family and friends. The total score can range from 0 (very low level of perceived social support) up to 56 (very high level of perceived social support).

Questionnaire for evaluating coping as disposition (Hudek-Knežević and Kardum, 1993)[60] is a shortened and adapted version of *Coping Orientation to Problems Experienced (COPE)*. The scores can range from 0 to 24 for problem-focused coping, from 0 to 12 for emotion-focused coping, and from 0 to 24 for disengagement. A high score in each of the subscales indicates a more frequent usage of that coping style.

The socio-demographic data on gender, age, level of education, average monthly income per household member, and medical data on the type of the diagnosis (CD vs. UC) and duration of illness (in years) were collected.

Statistics

Data were analyzed by SPSS (*Statistical Package for the Social Sciences*), version 17. In order to determine the biopsychosocial status of the patients with IBD, a descriptive statistical analysis was performed for both all participants with IBD, and subgroups with CD and UC. Discriminant analysis was used to determine whether participants with CD and UC differed in socio-demographic, medical and psychological variables, and in their HRQoL. A multiple hierarchical regression analysis was performed to examine the contribution of socio-demographic, medical and psychological factors to the prediction of HRQoL in patients with IBD. As the discriminant analysis had shown only minimal differences in predictor variables between those with CD and UC, the regression analysis was performed for the whole sample, with diagnosis entered into the regression as a predictor. Before conducting the regression analysis, inter-correlations of predictors and the criterion were examined (Table 4). Self-evaluated disease activity was used as a measure of disease activity for both subsamples, as it was highly positively correlated with both HBI in the subsample with CD ($r = .70$; $p < 0.01$) and SCCAI in the subsample with UC ($r = .66$; $p < 0.01$).

Results

Quality of life and level of psychological disturbances

Table 3 shows the means and standard deviations for health – related quality of life, anxiety, depression, and coping styles, as well as the proportions of participants who scored above the cut-off values for anxiety and depression, both in the overall sample and in the two subsamples. More than 25% of participants in both subsamples scored above the cut-off value for anxiety, and 10% of them above the cut-off value for depression.

Differences between Crohn's disease and ulcerative colitis

The discriminant analysis resulted in one canonical discriminant function of low discriminative power. The canonical correlation was statistically significant ($\Lambda = .87$; $p < 0.05$), and the model explained only 13% of variability between groups ($\lambda = .15$; $R^2 = .36$). A test of equality of arithmetic groups within the discriminant analysis showed significant differences between subgroups with CD and UC: in self-assessed disease activity and use of disengagement as a coping strategy: participants with CD self-evaluate the disease activity as lower than those with UC ($F = 7.77$; $p < 0.01$), and use disengagement less frequently ($F = 6.25$; $p < 0.05$). The classification results show low overall predictive accuracy of the discriminant function: in cross-validation only 60.8% of respondents were classified correctly into diagnostic groups.

Predicting the quality of life in patients with IBD

As can be seen from Table 4, the highest correlations with HRQoL were found for disease activity, anxiety, and depression, all of them negative. Age, duration of illness, and emotion-focused coping were not correlated with HRQoL, while other predictors showed low correlations with the criterion. A high correlation was also found between anxiety and depression.

In the multiple hierarchical regression analysis (Table 5) the sociodemographic variables were entered in the first step, and they explained 16% of variance of HRQoL, with higher monthly income and male gender being statistically significant predictors of a higher HRQoL.

Table 3 Health related QoL, anxiety, depression, perceived social support, and coping strategies for the whole sample of patients with inflammatory bowel diseases (*N* = 153) and for subsamples of patients with Crohn's disease (*n* = 90) and ulcerative colitis (*n* = 63)
Tablica 3. Zdravstveni QoL, anksioznost, depresija, percipirana socijalna podrška i strategije suočavanja za cijeli uzorak pacijenata s upalnim bolestima crijeva (N = 153) i za poduzorke bolesnika s Crohnovom bolešću (n = 90) i ulceroznim kolitisom (n = 63)

		Inflammatory bowel diseases *Upalne bolesti crijeva*	Crohn's disease *Crohnova bolest*	Ulcerative colitis *Ulcerozni colitis*
HRQoL	*M*	48.22	49.56	46.29
	SD	11.068	10.912	11.091
HADS-A	*M*	8.67	8.41	9.04
	SD	4.035	4.305	3.616
HADS-A (score ≥ 11)	*n*	42	26	16
	%	27.5	28.9	25.4
HADS-D	*M*	5.34	5.23	5.48
	SD	3.607	3.425	3.875
HADS-D (score ≥ 11)	*n*	16	8	8
	%	10.5	8.9	12.7
Perceived social support *Percipirana društvena podrška*	*M*	46.96	47.84	45.67
	SD	8.728	8.361	9.148
Problem-focused coping *Suočavanje usmjereno na probleme*	*M*	16.25	16.07	16.52
	SD	3.429	3.505	3.327
Emotion-focused coping *Suočavanje usmjereno na emocije*	*M*	6.46	6.26	6.74
	SD	2.524	2.520	2.523
Disengagement *Dezangažiranje*	*M*	9.10	8.51	9.94
	SD	3.538	3.325	3.688

HRQoL: Health – Related Quality of Life / *Kvaliteta života povezana sa zdravljem*
HADS-A: Hospital Anxiety and Depression Scale, anxiety subscale / *Bolnička ljestvica anksioznosti i depresije, potkategorija anksioznosti*
HADS-D: Hospital Anxiety and Depression Scale, depression subscale / *Bolnička ljestvica anksioznosti i depresije, potkategorija depresija*

Table 4 Inter-correlations of predictor socio-demographic, medical and psychological variables, and their correlations with the criterion variable of health-related quality of life in patients with inflammatory bowel disease (*N* = 153)
Tablica 4. Međusobna povezanost prediktorskih socio-demografskih, medicinskih i psiholoških varijabli i njihova povezanost s kriterijskom varijablom zdravstvenog kvaliteta života bolesnika s upalnom bolesti crijeva

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13
SIBDQ (k)	.20**	.02	.17*	.35**	-.15*	-.65**	.03	-.61**	-.59**	.22**	.17*	-.02	-.27**
Gender (p1) *Spol*		.01	-.06	.09	-.08	-.13	-.07	-.16*	-.06	-.11	-.06	-.28**	.08
Age (p2) *Dob*			-.01	-.00	-.02	-.05	.47**	-.04	-.03	-.10	.15*	-.02	-.03
Education (p3) *Obrazovanje*				.31**	.14*	-.21**	-.04	-.01	-.03	-.08	.05	.15*	-.04

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13
Income (p4) *Prihod*					-.03	-.28**	.00	-.22**	-.34**	-.01	.06	.02	-.21**
Diagnosis (p5) *Dijagnoza*						.22**	-.02	.08	.03	-.12	.06	.09	.20**
Disease activity (p6) *Aktivnost bolesti*							-.02	.25**	.32**	-.15*	-.11	.00	.09
Illness duration (p7) *Trajanje bolesti*								-.06	-.07	.03	.18*	-.07	-.01
HADS-A (p8)									.70**	-.23**	-.24**	.00	.32**
HADS-D (p9)										-.36**	-.25**	-.06	.23**
Social support (p10) *Društvena podrška*											.21**	.08	-.01
Coping – problem (p11) *Nošenje s problemom*												.06	-.02
Coping – emotions (p12) *Nošenje s emocijama*													-.12
Disengagement (p13) *Dezangažiranje*													

* *p* < 0 .05 (unidirectional) ** *p* < 0.01 (unidirectional)
SIBDQ: The Short Inflammatory Bowel Disease Questionnaire / *Kratak upitnik bolesti upale crijeva*
HADS-A: Hospital Anxiety and Depression Scale, anxiety subscale / *Bolnička ljestvica anksioznosti i depresije, potkategorija anksioznosti*
HADS-D: Hospital Anxiety and Depression Scale, depression subscale / *Bolnička ljestvica anksioznosti i depresije, potkategorija depresija*

Table 5 Results of multiple hierarchical regression analysis with socio-demographic, medical and psychological variables as predictors and quality of life as criterion in patients with inflammatory bowel diseases (*N* = 153)
Tablica 5. Rezultati višestruke hijerarhijske regresijske analize sa sociodemografskim, medicinskim i psihološkim varijablama kao prediktorima i kvalitetom života kao kriterij u bolesnika s upalnim bolestima crijeva

Step Korak	Predictors Prediktori	β	R^2	ΔR^2
1	Gender / *Spol*	.17*		
	Age / *Dob*	.01		
	Level of education / *Razina obrazovanja*	.08	.16**	
	Average monthly income per household member *Prosječan mjesečni dohodak po članu obitelji*	.31**		
		$F_{(4.148)} = 6.91$**		
2	Gender / *Spol*	.11		
	Age / *Dob*	-.03		
	Level of education / *Razina obrazovanja*	.01		
	Average monthly income per household member *Prosječan mjesečni dohodak po članu obitelji*	.17*	.46**	.30**
	Diagnosis / *Dijagnoza*	-.00		
	Self-evaluated disease activity *Samoprocjena aktivnosti bolesti*	-.58**		
	Illness duration / *Trajanje bolesti*	.05		
		$F_{(7.145)} = 17.78$**		

3	Gender / *Spol*	.07		
	Age / *Dob*	-.03		
	Level of education / *Razina obrazovanja*	.05		
	Average monthly income per household member *Prosječan mjesečni dohodak po članu obitelji*	.06	.66**	.20**
	Diagnosis / *Dijagnoza*	-.01		
	Self-evaluated disease activity *Samoprocjena aktivnosti bolesti*	-.47**		
	Illness duration / *Trajanje bolesti*	.01		
	Anxiety (HADS–A) /*Anksioznost*	-.35**		
	Depression (HADS–D) / *Depresija*	-.17*		
	F (9.143) = 31.12**			
4	Gender / *Spol*	.08		
	Age / *Dob*	-.03		
	Level of education / *Razina obrazovanja*	.06		
	Average monthly income per household member *Prosječan mjesečni dohodak po članu obitelji*	.05	.67**	.01
	Diagnosis / *Dijagnoza*	.01		
	Self-evaluated disease activity *Samoprocjena aktivnosti bolesti*	-.47**		
	Illness duration / *Trajanje bolesti*	.01		
	Anxiety (HADS–A) /*Anksioznost*	-.32**		
	Depression (HADS–D) / *Depresija*	-.17*		
	Perceived social support *Percipirana socijalna podrška*	.03		
	Problem-focused coping *Suočavanje usmjereno na probleme*	-.01		
	Emotion-focused coping *Suočavanje usmjereno na emocije*	-.03		
	Disengagement *Dezangažiranje*	-.08		
	F (13.139) = 21.51**			

* $p < 0.05$ ** $p < 0.01$

Medical variables entered in the second step explained additional 30% of variance of HRQoL, with disease activity being the only significant predictor from this group - the higher the activity of IBD, the lower the quality of life. As expected on the basis of the discriminant analysis results, diagnosis (CD vs. UC) was not predictive for HRQoL. After introducing medical factors into the model, the contribution of average monthly income per household member remained statistically significant, while gender lost its predictive significance.

Anxiety and depression, entered in the third step, explained the additional 20% of variance of HRQoL: the higher the level of anxiety and depression, the lower the quality of life. After introducing the factors of psychological disturbances into the model, the contribution of average monthly income per household member ceased to be a significant predictor, probably due to its shared variance with anxiety and depression.

Perceived social support and coping strategies were entered in the fourth step and did not further increase the percentage of explained variance of HRQoL. The final model explained 67% of variance of HRQoL, with self-evaluated disease activity, anxiety and depression as significant predictors.

Discussion

Quality of life and level of psychological disturbances

Numerous studies established a reduced overall quality of life[11] and HRQoL[11,22,26,52,61-63] in IBD patients in comparison to healthy individuals. In our overall sample of participants with IBD (Table 3) the

HRQoL was slightly below the rates of good HRQoL (defined by the SBDQ score > 50),[64] suggesting moderately impaired quality of life. HRQoL in the CD group corresponded to the one determined by Irvine et al.,[55] while in the UC group was somewhat lower. A high variability in HRQoL both in CD (Min = 14, Max = 69) and UC group (Min = 17, Max = 68), which almost encompassed the overall theoretical span of results in the questionnaire, suggests high interpersonal differences in clinical manifestation and consequences of IBD.

Depression scores in our total sample were similar to those found in a recent study,[52] while anxiety scores were higher, indicating normal levels of depression and borderline abnormal anxiety levels. On the other hand, anxiety scores in both CD and UC samples corresponded to those determined by Goodhand et al.,[65] while the depression scores in both diagnostic groups were slightly higher. It should be noted that in both studies[52,65] these anxiety and depression scores in patients with IBD were found to be higher than in healthy controls. In the light of our findings on correlation between psychological disturbances and a reduced HRQoL in patients with IBD, also established in previous studies,[11,12,22-23] especially alarming is the fact that 27.5% of participants in our study had a clinically relevant score (≥ 11) on the anxiety subscale, and 10.5% a clinically relevant score (≥ 11) on depression subscale (*Table 3*). This is in accordance with Guthrie et al.'s[12] finding that 25.9% of subjects with IBD score ≥ 11 on the anxiety or depression subscale, as well as with the overall conclusion from the recent study that mental health disorders often accompany chronic somatic disease with an estimated prevalence between 24% and 58%.[66] However, when interpreting our results, it should be taken into consideration that in this study only 2.2% of subjects with CD and 3.2% with UC evaluated their disease as being in a severe, active phase. Therefore, in more representative samples we could expect to find even higher proportions of clinically relevant anxiety and depression scores, given the findings that frequency of anxiety and depression in subjects with IBD during relapse reaches up to 80% for anxiety and 60% for depression.[67] Overall, both our findings and those from previous studies warn on a high prevalence of psychological disturbances in subjects with IBD, higher than in healthy controls even in the absence of active inflammation,[9,52,65,68-69] and their correlation with a reduced HRQoL.[11,12,22-23]

In fact, the overall findings suggest the reciprocal relation between the symptoms of IBD and psychological disturbances through interconnections among the psycho-neuro-endocrine-immune systems, indicating a self-perpetuating cycle of IBD: the incurable and unpredictable course of IBD, their severity, and their overall negative impact on QoL lead to depression and anxiety, and, in return, psychological disturbances lead to worsening of IBD. The significant correlations between disease activity and higher level of anxiety and depression, also established in previous studies,[52,65,67,70-73] together with the findings that proinflammatory cytokines have the ability to access the brain through humoral, neural and cellular pathways[74] and precipitate depression,[75] that intestinal microbes might be involved centrally in modulating behavior and brain biochemistry,[76] that risk of clinical depression or anxiety in the year following an IBD diagnosis[9,77] and after surgery or hospitalization[78] becomes higher, imply that active disease and more severe disease course may predispose to psychological morbidity. The other way around, the correlations between disease activity and psychological disturbances, together with the findings that psychological disturbances contribute to a higher risk for further disease activity,[34,70,79-80] poorer adherence to treatment[81-82] and higher risk for surgery;[83] predictive value of anxiety and depression for the presence of symptoms such as irritable bowel syndrome (IBS) in patients with IBD;[3,19-20] the findings that mood disorders can stimulate production of proinflammatory cytokines and thereby adversely affect the course of IBD;[79] that environmental influences such as stress can affect the microbial balance in the gut;[76] findings from animal studies of the brain-gut axis that depression increased susceptibility to experimental colitis[84] and worsened colitis severity regardless of whether it was induced prior to inducing the colitis or following the colitis onset;[85-86] all point to anxiety and depression as not only the consequences, but also as perpetuating factors in IBD.

The results showing that depression increased susceptibility to stressful events through the amplification of subjective perception of stress and emotional and physiological response to stressful events[87-89] and that anxiety might induce visceral oversensitivity, i.e. heightened sensations and pain during abdominal distension, associated with the presence of IBS symptoms and disease-related distress,[90-94] suggest that psychological disturbances contribute to the exacerbation of IBD through the mediating role of psychological stress and its adverse impact on GI functioning. Although research findings on the role of stress in IBD have been confusing and controversial because of the contradictory results and methodological shortcomings,[95-96] there is a growing amount of evidence supporting the relationship between stress and IBD, showing that stress is a

triggering[47-50,97] and exacerbating[38,42-45,98] factor in relation to the course and symptoms of IBD, as well as one of the determinants of disease relapse,[33-35] thus providing support for the beliefs of more than 90% of patients with IBD that stress influences their disease activity.[99] Furthermore, the suggested relationship between psychological stress and IBD could explain the functional bowel symptom exacerbation[99] and symptom reporting[46] in the absence of acute inflammation.

Overall, these findings on adverse impact of psychological disturbances on symptoms of IBD and HRQoL suggest that additional attention in IBD management should be given to prevalent worries and concerns that affect the subjects' personal perceptions of disease impact on their social, leisure and working life – worry of lack of energy, the sense of lack of control, disrupted body image, isolation and fear, feeling of beeing a burden to others, feeling dirty, etc.[100] Furthermore, findings on the brain-gut axis and the bidirectional interconnections between psychological and GI functioning give new opportunities for IBD management suggesting that treating one component of the mood-disease interrelationship may help to address the other component.[101]

Differences between subjects with Crohn's disease and ulcerative colitis

The comparability of subsamples with CD and UC regarding age, gender and illness duration is in accordance with the findings of epidemiological studies.[51,77] A low discriminativeness between two diagnostic groups ($\Lambda = 0.87$; $p < .05$) is parallel to the findings of similar levels of anxiety and depression in the two groups[12,19,22] and similarly disrupted overall and specific quality of life within patients with IBD,[12,13,15,22] although some previous studies established a poorer quality of life,[14,51,53] and higher level of depression[3,51] and anxiety[3,26,51-52] in patients with CD compared to those with UC. It should be emphasized that our finding on similar HRQoL scores in patients with CD and UC contradicts the one from the most recent meta-analyses of QoL in IBD showing significantly lower QoL scores for those with CD versus UC,[14] most probably because our participants with CD self-evaluated the disease activity as lower than participants with UC. However, our finding of lower self-evaluated disease activity in patients with CD needs to be taken with reservations because of the non-representativeness of the samples considering disease activity, and statistically dubious role of disease activity in discriminatory analysis (because of its statistically significant aberration from normal distribution).

A finding of less frequent use of disengagement as a coping strategy in participants with CD contradict those of higher frequency of depressive coping with stress (self-blame, strategies of avoidance) in patients with CD compared to patients with UC.[25] Considering the possible differences between our subsamples in the disease activity, the low reliability of the disengagement subscale ($\alpha = 0.49$) and inconsistent findings, a possible discriminatory value of coping strategies in IBD is yet to be determined in further studies.

In conclusion, the low discriminativeness between two diagnostic groups implies that within both the research and therapeutic approach the focus should be shifted from diagnostic subgroups to heterogeneity of clinical manifestations of IBD, because of the high interindividual and intraindividual variability in the intensity of symptoms, course of the disease and its psychosocial consequences, as shown in the high variability of HRQol measured in both our subsamples.

Predicting the quality of life in patients with IBD

Our results are in accordance with previous findings of a negative correlation between IBDs' activity and the participants' QoL,[11-16] predictive value of psychological disturbances for a lower QoL,[22-23] and independent contribution of disease activity and psychological disturbances in explaining the variance of HRQoL.[12] A somewhat lower predictive value of depression is probably the consequence of the well-known effect of overlapping of clinical elements and high correlation between anxiety and depression.

Although male gender and income were predictive for HRQoL in the first model, when analyzing the contribution of socio-demographic factors only, their predictive value was not significant in the final model, probably due to negative correlations between male gender and anxiety, and between income and disease activity, anxiety and depression. This suggests that psychological disturbances and disease activity could be mediators in explaining the correlations of gender and income with HRQoL. A well-documented lower prevalence of anxiety in men beneficially influences the HRQoL in male subjects. As for the income, apart from a simple explanation that IBDs' activity and accompanying psychological disturbances may represent significant limitations in earning, it is possible that subjects with higher income experience fewer existential problems which can be a prominent trigger of psychological stress, which in turn lowers the HRQoL. It is also possible that subjects with a higher income have better financial opportunities for managing the IBDs' activity and accompanying psychological disturbances, as well as adopting a more

suitable lifestyle. Age was not predictive for HRQoL, consistent with Hauser's[22] findings. Although a low positive correlation of illness duration with problem-focused coping ($r = 0.18$; $p < 0.05$) could mean that with time subjects learn to cope with clinical manifestations of the disease in a more active and better way, the fact that there was no correlation between illness duration and QoL suggests that the frequency of relapses and the intensity of the disease, as well as possible adaptations of one's lifestyle to the limitations of the disease, have far more influence on quality of life than the illness duration itself.

Although the perceived social support and problem-focused coping with stress were positively, and disengagement negatively correlated with QoL, they did not significantly contribute to further increase in explained variance of HRQoL. This could be due to coping as a possible mediator of the impact of mood on QoL in IBD. As perceived social support and problem-focused coping were negatively and disengagement positively correlated with anxiety and depression, participants with lower levels of anxiety and depression could perceive the social support they receive as higher and use constructive strategies of coping with the disease more frequently, thus increasing their QoL. Both our findings and those from a previous study[102] that coping strategies did not independently predict QoL in patients with IBD after illness perceptions were controlled for, support this explanation of the relationship between psychological distress, coping and QoL in IBD, with mood as the primary determinant of QoL and coping as a mediator. Alternatively, the perceived social support and problem-focused coping could lead to the reduction of anxiety and depression, while disengagement could enhance them, thus indirectly influencing the QoL. In line with this notion, there is evidence of the effectiveness of self-management interventions in IBD in improving psychological well-being and healthcare resource use and reducing symptom reporting.[103-104] Moreover, when interpreting the role of coping strategies, we must take into consideration the low reliability of the questionnaire used so that this study does not allow any firm conclusions about the role of coping strategies in the QoL.

The findings of independent contribution of psychological disturbances in predicting the quality of life, positive correlation of anxiety and depression with disease activity, a high percentage of clinically relevant anxiety and depression among subjects suffering from IBD with both active and inactive disease, and overall findings on bidirectional relation between the symptoms of IBD and psychological disturbances have important clinical implications.

Taken together, they suggest the need for a routine screening for anxiety and depression in IBD patients with both active and inactive disease and specific psychological support directed towards anxiety and depression management for subjects with IBD.

List of abbreviations
CDAI: Crohn's Disease Activity Index
CNS: central nervous system
COPE: Coping Orientation to Problems Experienced questionnaire
ENS: enteric nervous system
GI: gastrointestinal
HADS: Hospital Anxiety and Depression Scale
HADS-A: Hospital Anxiety and Depression Scale, anxiety subscale
HADS-D: Hospital Anxiety and Depression Scale, depression subscale
HBI: Harvey-Bradshaw Index of Crohn's Disease Activity
HRQoL: Health – Related Quality of Life
HUCUK: Croatian Crohn's and Ulcerative Colitis Association
IBD: Inflammatory Bowel Diseases
IBD-IBS: Inflammatory Bowel Diseases with presence of symptoms such as irritable bowel syndrome during remission
IBS: Irritable bowel syndrome
K-S: Kolmogorov-Smirnov test for normality of the distribution
QoL: Quality of Life
SCCAI: Simple Clinical Colitis Activity Index
SIBDQ: The Short Inflammatory Bowel Disease Questionnaire
SPSS: Statistical Package for the Social Sciences
SS-A: Social Support Appraisals Scale

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