

# Psychological status in Iranian patients with ulcerative colitis and its relation to disease activity and quality of life

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**Background:** Psychological profile of inflammatory bowel disease patients is not well studied in Iran. We investigated the psychological status of Iranian patients with ulcerative colitis (UC) and its relationship with disease activity and quality of life (QOL). **Materials and Methods:** A cross-sectional study was conducted on adult UC patients. The Lichtiger Colitis Activity Index, Hospital Anxiety and Depression Scale, General Health Questionnaire-12, and WHOQOL-BREF, were completed by the patients. **Results:** From 120 studied patients, 35 (29.2%), 48 (40.0%), and 46 (38.3%) had significant anxiety, depression, and psychological distress, respectively. Anxiety, depression, and psychological distress were strongly correlated with disease activity ( $r = 0.357$  to  $0.439$ ,  $P < 0.01$ ). Disease activity was negatively correlated with all QOL dimensions ( $r = -0.245$  to  $-0.550$ ,  $P < 0.01$ ). Anxiety, depression, and psychological distress were also negatively correlated with all QOL domains ( $r = -0.356$  to  $-0.789$ ,  $P < 0.01$ ). In the regression models, anxiety was independently associated with active disease ( $\beta = 4.150$ ,  $P = 0.049$ ). Furthermore, disease activity was associated with the physical health ( $\beta = -0.371$ ,  $P < 0.001$ ). For almost all of the QOL domains, depression and psychological distress were independent predictors ( $\beta = -0.296$  to  $-0.453$ ,  $P < 0.001$ ). **Conclusion:** Anxiety, depression, and psychological distress are highly frequent in UC patients of our society and are strongly associated with disease activity. Depression and psychological distress are important predictors of poor QOL in these patients. Further prospective studies, as well as clinical trials, are warranted in this regard.

**Key words:** Anxiety, depression, inflammatory bowel disease, psychological, quality of life, ulcerative colitis

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## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the gastrointestinal tract. They have a chronic relapsing course and require lifelong treatment. The etiology of these inflammatory bowel diseases (IBDs) is not completely understood, but seems to be due to inappropriate inflammatory reactions in response to the intestinal flora and antigens in a genetically susceptible host. While inflammation in UC is usually limited to the mucosal layer of the

colon, CD is characterized by transmural inflammation that may involve all parts of the gastrointestinal tract.<sup>[1]</sup> The prevalence of UC and CD is reported from 7.6 to 246 and from 3.6 to 214 cases per 100,000 populations, respectively.<sup>[2]</sup> The epidemiology of IBD in Iran is not well understood, but the reported epidemiology and clinical characteristics seem to be more or less the same as in other Asian populations with the rising incidence and prevalence.<sup>[3]</sup>

Psychological disturbances and emotional responses to stress can affect gastrointestinal functions. The effects of emotion on various parts of the gastrointestinal

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tract are increasingly being investigated.<sup>[4,5]</sup> The role of psychological factors in etiology and clinical course of IBD is investigated by several studies.<sup>[6,7]</sup> These patients often suffer from psychological disorders such as anxiety and depression which impair their quality of life (QOL).<sup>[8,9]</sup> Depression and anxiety are reported in up to 40% of the patients in most studies.<sup>[10-13]</sup> The relapsing and remitting course of the disease and unpredictable flares contribute to psychological distress in these patients.<sup>[6]</sup> In addition to cross-sectional studies, prospective studies also have shown increased risk of depression and anxiety in IBD patients.<sup>[14,15]</sup> These psychological disorders are not only present in active status of the disease but also frequent in disease remission status.<sup>[16,17]</sup>

Psychological disorders and distress are among the most important factors contributing to impaired QOL in IBD patients.<sup>[18,19]</sup> Furthermore, the evidence exists that psychological factors can affect the clinical course of the disease and increase the risk of relapse,<sup>[20-22]</sup> though there have been controversial results in this regard.<sup>[23,24]</sup> Accordingly, investigators have tried to evaluate the effectiveness of psychological therapies in the management of IBD.<sup>[25]</sup> Although few studies are done in this regard, current evidence supports the benefits of such interventions.<sup>[26]</sup> These treatments must be comprehensive and include several aspects of the psychological health of the patients. Appropriate knowledge of the psychological profile of IBD patients is a prerequisite for designing comprehensive psychological interventions for these patients.<sup>[25]</sup> Although studies are conducted in this regard in other populations, unfortunately, there is a lack of data on the psychological profile of IBD patients in our society, Iran. Therefore, we aimed to investigate the psychological status of the IBD patients and its relationship with symptom severity and QOL in our society.

## MATERIALS AND METHODS

### Participant and study setting

This cross-sectional study was conducted at the Psychosomatic Research Center affiliated to the Isfahan University of Medical Sciences in the Isfahan city (Iran) in January 2013. A comprehensive care program is being conducted for IBD patients in this center, and this study was done at the beginning of the program in a briefing session with all patients invited. Inclusion criteria were:

- a. Age 18 years and above,
- b. Diagnosis of UC by a gastroenterologist based on clinical symptoms, endoscopic appearance, and pathologic studies,
- c. Minimum literacy level of 5<sup>th</sup> grade and cognitive ability to complete the study questionnaires, and
- d. Willingness to participate.

The patients were referred to four gastroenterologists to attend this study. Sample size was determined where  $\alpha$  and  $\beta$  as the types I and II error rates were considered to be 5% and 20%, respectively, and the minimum predicted correlation coefficient was considered to be of 0.25. The sample size was then calculated as 116 patients considering 20% is missing data. The study was approved by the Ethics Committee of the Isfahan University of Medical Sciences (Isfahan, Iran) and informed consent was obtained from patients.

### Measurements

#### *Lichtiger Colitis Activity Index*

Symptoms of UC were assessed using the Lichtiger Colitis Activity Index (LCAI)<sup>[27]</sup> which is a frequently applied measure in clinical and observational studies on UC. It includes both objective and subjective items evaluating diarrhea (0 to 4), nocturnal diarrhea (yes/no), rectal bleeding (0 to 3), fecal incontinence (yes/no), abdominal pain/cramping (0 to 3), general well-being (0 to 5), abdominal tenderness (0 to 3), and need for anti-diarrhea medications (yes/no). The total score ranges from 0 to 21 with scores of  $\geq 4$  indicating endoscopic active disease with a sensitivity of 82% and specificity of 74%.<sup>[28]</sup>

#### *Hospital Anxiety and Depression Scale*

The Hospital Anxiety and Depression Scale (HADS) is a brief and widely used measure of psychological dysfunction in outpatient settings. It contains 14 items in two dimensions of anxiety and depression. Each item is rated on a four-point Likert scale, giving a maximum score of 21 for each of the sub-scales. At the cut-off score of 8, the HADS has a high level of accuracy in diagnosing clinically significant anxiety and depression disorder.<sup>[29]</sup>

#### *General Health Questionnaire-12*

The General Health Questionnaire-12 (GHQ-12) was used to measure psychological distress of the patients. It contains 12 items evaluating symptoms of anxiety, depression, social dysfunction, and loss of confidence with four-point response scale (0 = Less than usual to 3 = Much more than usual). The GHQ-12 gives a total score of 12 when the scoring method is bi-modal (0-0-1-1). The cut-off for the scale is 4 indicating high distress levels.<sup>[30]</sup>

#### *WHO Quality of Life-BREF*

We used the WHO Quality of Life-BREF to measure QOL as it is a general an international tool and provide the possibility for cross-cultural comparisons. This instrument evaluated QOL by 26 items in four dimensions of physical health, psychological health, social relationships, and the environment. The raw score for each dimension is transformed to a 0 to 100 scale with higher scores indicating better QOL status.<sup>[31]</sup>

For all the above-mentioned questionnaires linguistically validated and reliable Persian versions were used in this study.<sup>[32-34]</sup> An interviewer was available if the patient required description for completing the questionnaires.

**Statistical analyses**

Data were analyzed using the SPSS software version 16.0 (SPSS Inc., Chicago IL., USA). Normal distribution of quantitative data was checked with the Kolmogorov–Smirnov test. Data are reported as mean ± standard deviation or number (%) for continuous and categorical data, respectively. Comparison of patients with inactive and active disease status was done using the independent sample *t*-test or Mann–Whitney U-test for parametric and nonparametric data, respectively, and Fisher’s test for qualitative data. Correlations between the variables were checked with the Spearman’s coefficient test. Multiple regression analyses were conducted to evaluate independent predictors of disease activity, as well as QOL in various domains. A two-tailed *P* < 0.05 was considered as statistically significant in all analyses.

**RESULTS**

**Participant characteristics**

From a total of 500 patients who were invited to attend the meeting, 200 patients participated and 144 patients

completed the study questionnaires (response rate of 72%); 10 patients with CD, 120 patients with UC, and 14 patients with indeterminate colitis. Only data of 120 UC patients were included in the analyses. Demographic data and disease characteristics are summarized in Table 1. In total, 35 (29.2%) and 48 (40.0%) patients had significant anxiety and depression (score of ≥8). Furthermore, 46 (38.3%) patients had psychological distress (GHQ-12 score ≥4). In overall, 61 (50.8%) patients had at least one significant psychological disturbance. Comparisons between patients with inactive disease and those with active disease status are presented in Table 2. There was no difference between inactive and active disease status regarding demographic data (*P* > 0.05). Patients with active disease had higher scores of anxiety (*P* < 0.001), depression (*P* < 0.001), and psychological distress (*P* = 0.002), and lower QOL scores in all dimensions (all *P* < 0.05) [Table 2].

**Table 1: Demographic data and disease characteristics of the patients, (n = 120)**

Variables	Data
Age, year	40.8±12.4
Female/male	50 (41.7)/70 (58.3)
Education level, year	12.2±3.9
Marital status	
Single	13 (11.9)
Married	92 (84.4)
Divorced	2 (1.8)
Widow	2 (1.8)
Unknown	11
Job status	
Homemaker	24 (32)
Salary employed	19 (25.3)
Retired	6 (8)
Self-employed	26 (34.7)
Unknown	45
Smoking	
Never smoked	75 (80.6)
Current smoking	10 (10.8)
Former smoker	8 (8.6)
Unknown	27
Age of disease onset, year	33.2±12.6
Disease duration, year	8.0±6.3
LCAI	4.98±3.42
LCAI ≥4	70 (58.3)

Data are presented as mean ± SD or number (valid percent). LCAI = Lichtiger colitis activity index; SD = Standard deviation

**Table 2: Comparison of psychological status and QOL between patients with inactive and active disease**

Variables	Inactive disease (n = 50)	Active disease (n = 70)	<i>P</i>
Demographic and disease variables			
Age, year	41.2±12.1	40.6±12.8	0.796*
Gender, female/male	19 (38)/31 (62)	31 (44.2)/39 (55.7)	0.309†
Education level, year	12.7 (0.5)	11.9 (0.4)	0.209††
BMI, kg/m <sup>2</sup>	24.8±3.5	24.4±3.8	0.558*
Current smoker <sup>a</sup>	4 of 39 (10.2)	6 of 54 (11.1)	>0.999†
Disease duration	9.1 (0.9)	7.3 (0.8)	0.141††
Marital status <sup>a</sup> , married/single	39 (92.8)/3 (7.1)	53 (84.1)/10 (15.8)	0.235†
Job status <sup>a</sup> , employed/unemployed	20 (62.5)/12 (37.5)	25 (58.1)/18 (41.8)	0.444†
Psychological variables			
Anxiety score	3.8±2.7	6.6±3.8	<0.001*
Anxiety score ≥8	6 (12)	29 (41.4)	<0.001†
Depression score	5.8±3.2	8.1±3.8	<0.001*
Depression score ≥8	13 (26)	35 (50)	0.008†
GHQ-12 score	2.1 (0.3)	3.8 (0.4)	0.002††
GHQ-12 score ≥4	11 (22)	35 (50)	0.002†
QOL dimensions' scores			
Physical health	63.8±16.8	48.0±16.5	<0.001*
Psychological health	57.7±18.2	46.5±19.0	0.001*
Social relationships	55.2±15.1	48.2±14.5	0.011*
Environment	55.2±15.1	48.2±14.5	0.011*

Data are presented as mean ± SD, number (valid percent), or mean (SE). <sup>a</sup>Valid percents are reported in the case of missing data; \*Independent sample *t*-test; †Chi-square test; ††Mann–Whitney U-test. SD = Standard deviation; SE = Standard error; GHQ-12 = General health questionnaire-12; QOL = Quality of life; BMI = Body mass index

With regards to the associations of the study variables with psychological status, disease severity, and QOL dimensions analyses showed better psychological health in males compared with females (54.118.3 vs. 46.8.19.1,  $P = 0.028$ ). Marital status was not significantly associated with any of the outcome variables ( $P > 0.05$ ). Correlations among the study variables are summarized in Table 3. Lower age was associated with higher anxiety ( $r = -0.194$ ), and higher education level was associated with lower depression ( $r = -0.230$ ). The significant and strong correlation was present between anxiety and depression ( $r = 0.726$ ). Anxiety and depression were also strongly correlated with the GHQ-12 score ( $r = 0.773$  and  $0.742$ , respectively). Factors associated with higher disease severity scores were lower education level ( $r = -0.211$ ), shorter disease duration ( $r = -0.294$ ), and strongly anxiety, depression, and the GHQ-12 scores ( $r = 0.357$  to  $0.451$ ). Regarding the QOL dimensions, higher education level was associated with better QOL in environment domain ( $r = 0.215$ ). Longer disease duration was associated with better physical health ( $r = 0.241$ ). Those who were employed had better physical health compared with unemployed ones ( $57.9 \pm 16.4$  vs.  $49.9 \pm 19.2$ , Mann-Whitney U-test:  $P = 0.025$ ). Higher LCAI score was negatively associated with all QOL domains ( $r = -0.289$  to  $-0.550$ ). Anxiety, depression, and the GHQ-12 score were also negatively associated with all QOL domains ( $r = -0.356$  to  $-0.789$ ).

Possible predictors of disease activity and QOL dimensions were included into the regression models, Tables 4 and 5, respectively. We included anxiety, depression, and distress as dichotomous variables into the models to prevent multicollinearity. Regarding disease activity, anxiety (odds ratio [OR] [95% confidence interval (95% CI)] = 4.150 [1.004 to 17.150],  $P = 0.049$ ), and nonsignificantly psychological distress (OR [95% CI] = 3.209 [0.945 to 10.879],  $P = 0.062$ ) were associated with active disease status. Regarding QOL dimensions, LCAI score was significantly associated with the physical health score ( $\beta = -0.371$ ,  $P < 0.001$ ). For all of the QOL domains, depression was a significant

predictor ( $\beta = -0.296$  to  $-0.453$ , all  $P < 0.01$ ). Distress was also a significant predictor of almost all the QOL domains ( $\beta = -0.322$  to  $-0.409$ , all  $P < 0.05$ ) except the environment domain ( $\beta = -0.211$ ,  $P = 0.104$ ).

## DISCUSSION

The aim of the present study was to investigate the psychological status of IBD patients in our society and the relationship of psychological factors with disease activity and QOL in these patients. We found a high frequency of significant anxiety and depression and psychological distress in general. Half of the patients in our study had at least one psychological disturbance. The severity of psychological disturbances was strongly associated with disease activity and anxiety was independently associated with active disease status. As expected, disease activity was associated with impaired QOL in all dimensions. Psychological status was also associated with QOL in all dimensions and depression and psychological distress were independent predictors of almost all QOL dimensions' scores. These results, in overall, highlight the importance of considering psychological health in the management of IBD patients in our society.

The frequency of significant anxiety, depression, and psychological distress in IBD patients of our study (29.2%, 40%, and 38.3% respectively) was considerably higher than that of general population in our society (14%, 28%, and 23.9% respectively).<sup>[35,36]</sup> The frequency of anxiety and depression in our study was comparable to previous few reports from our society, as well as reports from other populations. For example, Zhang *et al.* studied 105 patients with either CD or UC. Using the Beck's Depression Inventory, they found depression in 25% of the patients. Similar to our results, depression was the most significant predictor to poor QOL in this study.<sup>[12]</sup> In another study, Nahon *et al.* evaluated psychological and socioeconomic factors and adherence to treatment in a large sample of IBD patients ( $n = 1663$ ). Similar to our study, these investigators

**Table 3: Correlations of study variables with symptom severity and psychological status**

Demographic and disease variables	Psychological variables			LCAI score	QOL dimensions' score			
	Anxiety score	Depression score	GHQ-12 score		Physical health	Psychological health	Social relationships	Environment
Age	-0.194*	-0.058	-0.172	-0.098	0.062	0.063	0.044	0.081
Education level	-0.141	-0.230*	-0.109	-0.211*	0.144	0.117	0.043	0.215*
Disease duration	-0.135	-0.112	-0.076	-0.294*	0.241*	0.185	0.113	0.035
LCAI score					-0.550**	-0.409**	-0.245**	-0.289**
Psychological variables								
Anxiety score		0.726**	0.773**	0.439**	-0.533*	-0.684**	-0.356**	-0.438**
Depression score			0.742**	0.451**	-0.642**	-0.789**	-0.543**	-0.502**
GHQ-12 score				0.357**	-0.656**	-0.737**	-0.496**	-0.496**

\* $P < 0.05$ , \*\*  $P < 0.01$ . Data are presented as Spearman's correlation coefficients. LCAI = Lichtiger colitis activity index; GHQ-12 = General health questionnaire-12; QOL = Quality of life

used the HADS to evaluate anxiety and depression, but in contrast to our results, they found higher frequency of anxiety (41%) and lower frequency of depression (11%). This study also found age, disease severity, being nonadherent to treatment, disabled or unemployed status, and socioeconomic deprivation as factors associated with anxiety and depression.<sup>[13]</sup> In contrast, we found no significant association of employment status with anxiety or depression which might be related to the definition of job status in our study. In the study by Cohen *et al.*, a sample of newly diagnosed IBD patients were studied with regards to fatigue, QOL, overall disability, work impairment, and depression. Authors reported the strong association of fatigue with poor QOL, disability, and depression while controlling for disease activity.<sup>[37]</sup> Fatigue is a common and important but not well-studied complaint in IBD patients which needs to be further evaluated in future studies.<sup>[38]</sup>

With regards to the studies performed in our society we found only two similar reports. In the study of Besharat *et al.*, 50 recently diagnosed IBD patients were evaluated with the Beck Depression Inventory. The author reported depression in 32% of the patients. In contrast to our results, this study found no significant association between depression and disease activity which might be related to the study small sample size or the studied population (recent diagnosis of IBD).<sup>[39]</sup> In another study, Fakheri *et al.* studied 108 UC patients with regards to anxiety, depression, and personality

traits. Authors reported the unexpectedly high frequency of anxiety in 81.5%, depression in 43.5%, and introvert personality in 75% of the subjects. About 70% of the patients in this study have had active disease status compared to 59% of our patients. Furthermore, applying different disease activity measures might contribute to differences in frequency of psychological disturbances between the studies.<sup>[40]</sup> However, it must be noted that anxiety and depression are not only frequent inactive disease status but also reported in 24% to 39% of the patients in the remission phase.<sup>[16,17]</sup>

Psychological disorders and distress are important contributors to impaired QOL in IBD patients.<sup>[6]</sup> We found a strong correlation between psychological status and all dimensions of QOL in the studied IBD patients which was even greater than the disease activity. These findings are similar to the results of previous studies.<sup>[17-19]</sup> The association of psychological health and disease activity in IBD patients is bidirectional.<sup>[6]</sup> A number of studies have reported effects of psychological disturbance on the clinical course of the disease. For example, Ghia *et al.* induced depression in a mouse model of IBD and found reactivated inflammation in the mice after a quiescent phase.<sup>[21]</sup> In a clinical prospective study, Mittermaier *et al.* followed 60 patients with clinically inactive IBD for 18 months and found a significant correlation between baseline depression and anxiety severity with the total number of relapses during follow-up.<sup>[22]</sup> However, some other studies found no association between depression and clinical course of IBD.<sup>[23,24]</sup> On the other hand, cohorts have found increased incidence of psychological disturbance in IBD patients compared with non-IBD subjects. For example, the prospective cohort study by Loftus *et al.* found higher risk of developing anxiety and depression (hazard ratio of 2.28 and 1.74, respectively), as well as persistent anxiety and depression (hazard ratio of 4.35 and 2.75, respectively), in CD patients compared with controls.<sup>[14]</sup> A retrospective cohort study by Panara *et al.* also found female gender, aggressive disease, and active disease as independent predictors for development of depression.<sup>[15]</sup> In addition

**Table 4: Logistic regression model: Predictors of disease activity, LCAI  $\geq$  4**

Variables	OR (95% CI)	P
Age	1.018 (0.979-1.057)	0.371
Gender, male versus female	0.792 (0.315-1.990)	0.619
Education level	1.016 (0.904-1.142)	0.787
Disease duration	0.951 (0.884-1.024)	0.184
Distress	3.209 (0.945-10.879)	0.062
Anxiety	4.150 (1.004-17.150)	0.049
Depression	0.738 (0.205-2.660)	0.642
Nagelkerke $R^2$	0.239	

LCAI = Lichtiger colitis activity index; OR = Odds ratio; CI = Confidence interval

**Table 5: Linear regression model: Predictors of QOL with regard to each domain**

Variables	Physical health		Psychological health		Social relationships		Environment	
	Beta	P	Beta	P	Beta	P	Beta	P
Age	-0.085	0.289	-0.021	0.760	0.016	0.875	0.045	0.656
Gender, female versus male	0.036	0.630	0.045	0.493	-0.026	0.777	-0.117	0.217
Education	-0.015	0.848	-0.091	0.174	-0.160	0.095	0.125	0.196
Disease duration	0.139	0.074	0.037	0.591	0.041	0.675	-0.044	0.654
LCAI score	-0.371	<0.001	-0.069	0.358	-0.046	0.665	-0.005	0.961
Distress	-0.335	0.001	-0.409	<0.001	-0.322	0.013	-0.211	0.104
Anxiety	0.140	0.156	-0.012	0.894	0.128	0.302	-0.050	0.688
Depression	-0.296	0.004	-0.453	<0.001	-0.361	0.005	-0.310	0.018
$R^2$ (adjusted)	0.569 (0.528)		0.664 (0.633)		0.319 (0.254)		0.302 (0.237)	

LCAI = Lichtiger colitis activity index; QOL = Quality of life

to these observational studies, clinical trials have shown beneficial effects of anti-depressants on clinical course and symptoms in IBD patients.<sup>[41,42]</sup> Likewise, psychological interventions are demonstrated to have efficacy for the management of IBD.<sup>[43-45]</sup> However, controlled trials are limited, results have been controversial, and a clear conclusion could not be made in this regard.<sup>[25,46]</sup>

A finding in our study was an association between education level and disease activity. It is expected that patients with higher education level have better knowledge about the disease, and therefore, more adherence to the treatments.<sup>[47,48]</sup> In this regard, Rezailashkajani *et al.* have evaluated disease knowledge in Iranian patients with IBD and found a positive but weak correlation between the level of education and disease knowledge.<sup>[49]</sup> However, a number of studies showed no association between education level and treatment adherence.<sup>[50,51]</sup> Even highly educated patients may not be adherent to the treatments due to lack of disease specific knowledge or due to their beliefs about medications' efficacy.<sup>[48]</sup> This necessitates the need for including disease specific education in the comprehensive care program for IBD patients. The association between education level and disease activity may also be mediated by psychological factors. In our study, lower education level was associated with higher depression level, similar to other reports in IBD patients<sup>[52]</sup> and in the general population.<sup>[35,36]</sup> Accordingly, the psychological interventions of the IBD patients should be individualized according to such associated factors.

Our study has some limitations. The results of this cross-sectional study cannot be considered as causal relationships. We studied a very selective sample of UC patients and the results of our study may not be completely generalizable to the general IBD populations. The study has no real control group for comparisons with the general population. Further, we measured anxiety and depression symptoms by self-reported scales, while a psychiatric interview could provide more valid data in this regard.

## CONCLUSION

Anxiety, depression, and psychological distress are highly frequent in UC patients of our population and are strongly associated with disease activity in these patients. Likewise, these psychological disturbances are related to poor QOL in various dimensions with an association stronger than that of disease activity. Comprehensive care of the IBD patients will require especial attention to the psychological health of these patients. Further prospective studies, as well as clinical trials, are warranted in this regard.

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## Conflicts of interest

There are no conflicts of interest.

## AUTHOR'S CONTRIBUTIONS

MT contributed in the conception of the work, conducting the study, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HA contributed in the conception and design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HRR contributed in the conception and design of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. HD contributed in the conception and design of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AF contributed in the conception of the work, analysis and interpretation of data for the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MRS contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MT contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. FN contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. PA contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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