

# Depression Symptoms and Inflammation in Chronic Functional Constipation Patients

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## ABSTRACT

**Background:** Inflammation in chronic functional constipation (CFC) occurs systemically and has association with depressive symptoms. Biomarkers of inflammation can be assessed by the neutrophil to lymphocyte ratio and platelet to lymphocyte ratio. These inflammation biomarkers are stable, cheap, and widely available. This study aimed to determine the profile and the correlations between depressive symptoms and inflammation in CFC patients. **Methods:** This cross-sectional study involved subjects aged 18-59 years with chronic functional constipation. We use validated Beck Depression Inventory-II (BDI-II) to assess depressive symptoms. We collected the data regarding complete peripheral blood examination, liver function, kidney function, electrolytes, and neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR). Bivariate analysis with Chi-Square test for categorical data and t-test or ANOVA test for numerical data. Multivariate analysis used logistic regression to look at risk factors for depression with  $p < 0.05$  as a statistical significant level. **Results:** A total of 73 subjects with CFC were recruited with a mean age is 40.2 years, mostly women and working as housewives. Proportion of depressive symptoms in CFC patients was 73.0%, including mild depression 16.4%, moderate depression 17.8%, and severe depression 28.8%. The mean NLR in non-depressive subjects was 1.8 (SD 0.7), while in depressive subjects was 1.94 (SD 0.1) ( $p > 0.05$ ). The mean NLR in mild depression subjects was 2.2 (SD 1.7), in moderate depression was 2.0 (SD 0.7), and in severe depression was 1.9 (SD 0.5) ( $p > 0.05$ ). The mean PLR in non-depressive subjects was 134.3 (SD 0.1), whereas in depressive subjects it was 138.9 (SD 46.0) ( $p > 0.05$ ). The mean PLR in mild depression subjects was 142.9 (SD 60.6), in moderate depression was 135.4 (SD 41.2), and in major depression was 139.0 (SD 37.1) ( $p > 0.05$ ). **Conclusion:** This study found that CFC patients were middle-aged, mostly women and working as a housewife. In general, biomarkers of inflammation were found to be higher in depressive subjects than non-depressive subjects, although not statistically significant.

**Keywords:** Chronic functional constipation, depressive symptoms, inflammation, lymphocyte to neutrophil ratio, platelet to lymphocyte ratio.

## INTRODUCTION

Chronic functional constipation (CFC) is an often-neglected digestive tract disorder. Low-grade inflammation, cell degeneration, and increased oxidative stress impair functional conditions in CFC.<sup>1,2</sup> In vivo studies demonstrated that inflammation in mice's colon occurred after transplanted with CFC patients feces, as suggested by Gobert et al.<sup>3</sup> Food containing antigen entering the digestive tract will incite the adaptive immune system.<sup>4,5</sup> Further inflammation might play a role in various disorders or diseases involving the gastrointestinal tract and psychological factors, e.g., depressive disorders.<sup>6</sup>

One probable mechanism is dysbiosis and inflammation in CFC, which interrupt serotonin regulation in the brain, and in turn, cause behavioral disorders with depression as a particular impact.<sup>7</sup> The presence of pro-inflammatory cytokines increases serotonin reuptake transporter (SERT) activity in the intestine, causing serotonin decrease as a potential cause of depression.<sup>8,9</sup> Occurring distress can impair intestinal defense, increase bacterial permeability and translocation, also activate the inflammatory system.<sup>6,10</sup> In contrast, psychological distress also activates the immune system in response to inflammation, an increase in cell movement that plays a role in immunity between blood vessels and tissues.<sup>6</sup>

The association between serotonin and serotonin transporters located in the gastrointestinal tract and inflammation has attracted the attention of researchers as to the etiology of depressive symptoms. At the same time, inflammatory markers may increase in response to depression. Simple, inexpensive, and easily reproducible inflammatory parameters may include the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), C-reactive protein (CRP) and High sensitivity C-reactive protein (hsCRP).<sup>11,12</sup> Various studies have shown that NLR and PLR are in line with CRP and hsCRP as markers of inflammation.<sup>11-18</sup> It is currently unclear whether local inflammation in CFC can cause systemic inflammation; and whether it is associated with depressive symptoms. For this reason, this study further examines inflammation marked by NLR and PLR.

## METHODS

This cross-sectional study involved 73 subjects of chronic functional constipation (CFC) subjects. Diagnosis of CFC was screened using the ROMA IV criteria and Bristol stool chart form (BSCF), validated by Blake et al.<sup>19</sup> Subjects willing to participate signed the informed consent filled out the validated, Indonesian version (in Bahasa), BDI-II questionnaire to evaluate depressive symptoms.<sup>20</sup> This study has been approved by the Ethics Committee of the Faculty of Medicine Universitas Indonesia, and all participants signed informed consent forms.

Blood sample was taken to analyze peripheral blood cell count and inflammation of the neutrophile-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). Demographic characteristics are age, gender, ethnic group, occupation, the socioeconomic level, the education level, and clinical characteristics, including CFC signs and symptoms. This study considered high socioeconomic status as those with monthly income higher than the minimum wage in Jakarta. Based on the educational attainment, this study grouped those attained at least a highschool diploma as highly educated.

We provided depression symptom data according to BDI-II in the form of proportion, mean, and or median. We performed bivariate analysis with Chi Square test for categorical data and t test or ANOVA test for numerical data. Multivariate analysis relied logistic regression to find out risk factors for depression with  $p < 0.05$  as a significant level. Pearson's or Spearman's rho method independently assessed the correlation between NLR and PLR to depressive symptoms. Pearson's or *Spearman's rho* method independently assessed the correlation between NLR and PLR to depressive symptoms.

## RESULTS

The mean age of the subjects in this study was 40.2 (SD 11.25) years, and almost all CFC patients were women (90.4%). A larger proportion of subjects were of Betawi ethnic group (64.3%), working as house wife (78.1%), having low socioeconomic status (95.8%) and high education levels (64.5%). The three most commonly reported

constipation-related complaints were straining, defecate <3 times every seven days and hard stool consistency. Laboratory examinations of complete peripheral blood, liver function, kidney function and electrolytes were within normal range. The proportion of depressive symptoms (73.0%) was high in CFC patients, further classified into mild depression (16.4%), moderate depression (17.8%), and severe depression (28.8%). A

complete description of the subject profile, see **Table 1**. In **Table 2** and **3** were the results of bivariate and multivariate analysis of factors related to depressive symptoms, respectively. The results of significant level of peripheral blood cell count, NLR and PLR of CFC based on depression and without depression symptoms (**Table 4**) and the severity level of depressive symptoms (**Table 5**).

**Table 1.** Characteristics of the study participants.

Profiles	All (n=73)
<b>Age (Mean) years</b>	<b>40.2 (11.25)</b>
<b>Gender, n (%)</b>	
Female	66 (90.4)
Male	7 (9.6)
<b>Race, n (%)</b>	
Betawi	47 (64.3)
Sunda	3 (4.1)
Jawa	11 (15.1)
Sumatra	7 (9.7)
Nusa Tenggara	2 (2.7)
N/A	3 (4.1)
<b>Work, n (%)</b>	
Housewife.	57 (78.1)
Entrepreneur	7 (9.6)
Employees/Labourers	5 (6.8)
Jobless	4 (5.5)
<b>Socioeconomic status, n (%)</b>	
Low	70 (95.8)
High	3 (4.2)
<b>Level of Education, n (%)</b>	
Low	28 (38.4)
High	45 (61.6)
<b>Sign and Symptoms CFC, n (%)</b>	
Straining	67 (89.3)
Hard stool	60 (80.0)
Perceived incomplete evacuation of bowel movements	48 (64.0)
A blocked or full sensation in the lower intestine or anus	38 (50.7)
Doing movements to make defecation easier (requiring tools)	20 (26.7)
Less than 3 bowel movements per week	64 (85.3)
<b>Laboratory Result (Mean (SD))</b>	
Haemoglobin. (Hb) g/dL	12.97 (1.55)
Haematocrit (Ht) %	38.71 (3.81)
Leucocyte 10 <sup>3</sup> /μl	7.67 (2.07)
Absolute Neutrophil count 10 <sup>3</sup> /μl	4.42 (1.60)
Absolute Lymphocyte count 10 <sup>3</sup> /μl	2.49 (0.94)
Platelet 10 <sup>3</sup> /μl	318.31 (78.41)
NLR	1,90 (0.88)
PLR	137.17 (47.74)
AST (U/L),	20.84 (9.99)
ALT (U/L)	20.99 (18.02)
Bilirubin (mg/dL)	0.50 (0.18)
Creatinine (mg/dL)	0.71 (0.16)
Urea (mg/dL)	20.68 (5.46)
Blood Glucose(mg/dL)	98.11 (51.49)
Potassium (K)	4.18 (0.53)
Sodium (Na)	139.00 (2.17)
Chloride (Cl)	104.66 (2.25)

<b>Depression symptoms</b>		
No symptoms of depression		27 (37.0)
With depression		46 (73.0)
<b>Depression symptoms level</b>		
No symptoms of depression		27 (37.0)
Mild		12 (16.4)
Moderate		13 (17.8)
Severe		21 (28.8)

Note: ALT: Alanine transaminase; AST: Aspartate aminotransferase NLR = Neutrophil lymphocyte ratio; PLR = Platelet lymphocyte ratio.

**Table 2.** Bivariate analysis of factors related depression symptoms in CFC patients.

Profiles	No depression n (%)	Depression n (%)	P-value
<b>Gender</b>			
Female	23 (34.8%)	43 (65.2%)	p 0.014
Male	6 (85.7%)	1 (14.3%)	
<b>Ethnic group</b>			
Betawi	18 (38.3%)	29 (61.7%)	p 0.775
Non-Betawi	8 (34.8%)	15 (65.2%)	
<b>Work</b>			
Unemployed or housewife	23 (37.7%)	38 (62.3%)	p 0.426
Employee, labourer, or entrepreneur	6 (50.0%)	6 (50.0%)	
<b>Socioeconomic status</b>			
Low	27 (38.0%)	44 (62.0%)	p 0.154
High	2 (100.0%)	0 (0.0%)	
<b>Level of Education</b>			
Low	6 (21.4%)	22 (78.6%)	p 0.012
High	29 (39.7%)	44 (60.3%)	
<b>Smoking</b>			
yes	6 (85.7%)	1 (14.3%)	p 0.014
no	23 (34.8%)	43 (65.2%)	

**Table 3.** Multivariate analysis of factors related depression symptoms in CFC patients

Profiles	No depression	Depression	p
Level of Education	Low	6 (21.4%)	0.032
	High	29 (39.7%)	
Smoking	yes	6 (85.7%)	0.06
	No	23 (34.8%)	

**Table 4.** Peripheral blood cell count, NLR, and PLR of CFC based on depression and without depression symptoms.

Profiles	No depression (n =27)	Depression (n=46)
Leukocytes, mean (SD) 10 <sup>3</sup> /μl	7.3 (2.1)	7.9 (2.0)
Absolute neutrophil count, mean (SD) 10 <sup>3</sup> /μl	4.1 (1.4)	4.6 (1.6)
Absolute lymphocyte count, mean (SD) 10 <sup>3</sup> /μl	2.45 (0.7)	2.6 (1.1)
Platelets, mean (SD), 10 <sup>3</sup> /μl	304.6 (68.2)	326.35 (83.5)
NLR, mean (SD)	1.8 (0.7)	1.94 (0.1)
PLR, mean (SD)	134.3 (43.9)	138.9 (46.0)

Note: NLR = Neutrophil lymphocyte ratio; PLR = Platelet lymphocyte ratio; SD = Standard Deviation. \* t-Test p>0.05/ not statistically significant

**Table 5.** Peripheral blood cell count, NLR and PLR of CFC based on the level of depression symptoms.

Profiles	No Depression (n=27)	Mild Depression (n=11)	Moderate Depression (n=14)	Severe Depression (n=21)
Leukocytes, mean (SD), 103/ $\mu$ l.	7.3 (2.1)	8.1 (2.1)	7.9 (2.4)	7.7 (1.9)
Absolute Neutrophils, mean (SD), 103/ $\mu$ l	4.1 (1.4)	4.9 (2.1)	4.5 (1.8)	4.50 (1.4)
Absolute Lymphocytes, mean (SD), 103/ $\mu$ l	2.4 (0.7)	2.5 (0.6)	2.7 (1.7)	2.6 (0.8)
Platelets, mean (SD), 103/ $\mu$ l	304.6 (68.2)	339.2 (97.6)	311.2 (83.8)	329.7 (78.6)
NLR, mean (SD)	1.8 (0.7)	2.2 (1.7)	2.0 (0.7)	1.9 (0.5)
PLR, mean (SD)	134.3 (43.9)	142.9 (60.6)	135.4 (41.2)	139.0 (37.1)

Note: NLR = Neutrophil lymphocyte ratio; PLR = Platelet lymphocyte ratio; SD = Standard Deviation.

## DISCUSSION

Complete laboratory examination of peripheral blood, liver function, kidney function and electrolytes were within normal limits which indicated that all subjects of this study were functional disorders, thus strengthening the diagnosis of functional constipation in Rome IV criteria.<sup>21</sup> This study found that 73 subjects of CFC were middle-aged, primarily women, mostly the ethnic is betawi, working as house wife, with low socioeconomic status, and high education levels. The demographic profile in our study was similar with study conducted by Mokhtar et al.<sup>22</sup> that 240 subjects of CFC highest among female, 72.3%, non-smokers 93.6% and had lower income 89.4%.

Meanwhile, the total number of subjects experiencing depressive symptoms was 73.0%; with 34 % having moderate and severe depressive symptoms and only 12% having mild depressive symptoms. This result was higher than studies that have been done by Mokhtar et al.<sup>22</sup> which found 67.1% had no depressive symptoms, 32.1% experienced mild/borderline depressive symptoms and only two (0.83%) had probable a moderate-severe depressive symptoms. However Mokhtar et al.<sup>22</sup>, use Rome III criteria for functional constipation and the Center for Epidemiologic Studies Depression Scale Revised (CESD-R) to asses depression which can make the difference.

There was a bidirectional relationship between depressive symptoms and gastrointestinal disorders. Psychological disorders such as depression will contribute negatively to a person's life and his/her family.

Poor understanding of psychological health results in bias, namely that respondents fill out a depression symptom screening questionnaire that does not match the actual situation, but this study shows that screening can find depressive symptoms faster. Psychological disorders such as depression are still a stigma in society, so many do not realize they are experiencing depressive symptoms. This argument is per a qualitative study conducted by Subu et al.<sup>24</sup> in 2017, which suggested that the stigma against patients with psychological disorders in Indonesia is quite apparent, preventing patients from seeking professional help. Subu et al.<sup>24</sup> also found that a person who has a psychological disorder will continue to worsen and find it difficult to access mental health services because of the ongoing stigma. A qualitative study by Holis et al.<sup>25</sup> shows that the wrong coping mechanism occurs due to the stigma against psychological disorders. According to the qualitative study of Meng et al.<sup>26</sup>, it was found that dealing with distress depends on one's psychodynamic and adaptive abilities.

Until now, there were no studies that measures inflammatory conditions in CFC systemically. Our findings suggested no systemic involvement due to local gastrointestinal inflammation. Peripheral Blood Cell Count, NLR and PLR of CFC were higher in depression than in normal conditions, but not statistically significant. The finding of this study is similar to that of study conducted by Mazza MG et. al.<sup>27</sup> who found that NLR and PLR were higher in patients with mood disorders compared to healthy controls and were also not statistically significant, which means that

the inflammatory condition that occurs is only local gastrointestinal tract which has no impact systemically. This study also found that NLR and PLR ratio in CFC is higher than in the normal population, especially in CFC with depression.<sup>12</sup>

According to a study by Singh et al.,<sup>28</sup> there were mastocytes and eosinophil cells in the descending colon associated with irritable bowel syndrome. Leukocytes, absolute neutrophils, NRL, and PLR were higher in subjects with depressive symptoms than those without depression. Meanwhile, the lymphocyte levels were almost equal between the two subject conditions. This finding is consistent with the study of Ucar et al.<sup>29</sup> which showed that depressed patients experienced a decreased lymphocyte response to mitogen stimulation and impaired neutrophil activity. This study also follows the study of Ozturk et al.<sup>30</sup> which showed statistically insignificant but apparent trend in inflammatory biomarker levels.

Although NLR and PLR were not significantly correlated with depressive symptoms, there was a higher NLR and PLR in depressed CFC patients compared to patients without depressive symptoms. Further research should be done. This study of inflammation in depressive symptoms was confirmed by Sunbul et al.,<sup>11</sup> who explained that NRL was significantly increased in both major and very severe depressive symptoms. Although subjects with major depression were not large enough in this study, the correlation test may have had less statistical power to assess significance.

This study has a fairly good internal validity, so that bias in the selection can be minimized. Due to the strict inclusion criteria, the number of samples obtained was not large, but still sufficient to represent the research sample to be generalized. The study location may represent urban areas in one research group to be generalized to other urban areas in Indonesia. The significant factors for the incidence of depression in CFC from this study were only low education and not smoking. Therefore, it is necessary to do future studies from the aetiological side of the diagnosis of depressive symptoms. Other contributing factors to depressive symptoms that require further investigation are stresses in

daily life, lack of social support, and a history of eating disorders.<sup>31</sup> In depression, serotonin levels decrease because the serotonin transporter mRNA and its regulatory proteins are increased. Inflammatory conditions associated with free serotonin depletion are changes in inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$ .<sup>29</sup>

## CONCLUSION

This study found that CFC patients were in middle age, mostly women and working as housewives with depressive symptoms. Eventhough not statistically significant, it tends that biomarker of inflammation is higher in depressive symptoms subjects than in non-depressive symptoms subjects, represented by mean of NLR and PLR. Increasing of NLR and PLR values might indicate depression. In the future, researchers are advised to reproduce similar study with a larger sample population, to analyze serum serotonin levels, other inflammatory factors, and to analyze other factors associated with depressive symptoms.

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