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Correlation of Depression Symptoms and Interleukin-6 in Chronic Renal Disease with Regular Hemodialysis Patients

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Abstract. Depression is psychosomatic disorder are common in patients with chronic kidney disease (CKD) undergoing hemodialysis (HD). Correlated with morbidity and mortality associated with chronic inflammation in patients, that characterized by elevated levels of plasma cytokines, especially interleukin (IL)-6. Objective: To investigate the correlation of depressive symptoms with IL-6 levels in patients with CKD who underwent regular HD. Methods: One hundred and 29 CKD patients were enrolled in this cross-sectional study. All eligible patients were screened for IL-6 level. Beck Depression Inventory (BDI) II questioner were then given to determine the presence of depression. Level of IL-6 was then correlated with BDI score using Spearman test. Result: The mean BDI score was $19,32 \pm 6,18$ indicating the level of mild depression symptoms, and the mean IL-6 level ($8,697 \pm 6,947$ pg/mL) was still within normal range. There was a moderate positive correlation ($r = 0.417$) between the level of depressive symptoms and IL-6 levels. Conclusion: There was a moderate positive correlation ($r = 0.417$) between IL-6 levels and depressive symptoms in patient with HD. However, mean IL-6 levels in depressive patients are still within normal limits indicating that the cause of depression is multifactorial.

Keyword: Depression, BDI, IL-6, CKD, Hemodialysis

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1. Introduction

Depression is a condition known as mood disorder, such as feelings of sadness, despair, guilt, even lead to suicidal desires [1]. Patients with CKD who underwent HD often suffer from depression [2]. Taraz et al study showed that 20% - 40% of the population undergoing HD suffer from depression, psychosocial and environmental factors (such as loss of work, lack of social support and dialysis) make the patient vulnerable to depression [3]. Depression in HD patients is associated with morbidity and mortality. This is associated with chronic inflammation characterized by elevated plasma levels of proinflammatory cytokines, specifically interleukin (IL)-6.4 IL-6 has a strong predictive value compared with CRP in the HD patient.5,6 In several studies, there was no significant difference IL-6 levels between patient with and without depressive symptoms. But there is also several studies that suggests depression is positively correlated with IL-6 levels [3]. The underlying molecular mechanism is associated with increased activity of the HPA-axis [7]. Thus, IL-6 has a role in coordinating important biological pathways in depression [8]. This study aims to see whether there is a correlation of the level of depressive symptoms with IL-6 levels in CKD patients undergoing regular HD.

2. Methodology

This is cross-sectional analytical study with the sample size of 159 people. This study was conducted on subjects who had signed informed consent. The research was conducted in HD Unit of H Adam Malik and Pirngadi Medan Hospital with the approval of research commission of Research Faculty of USU, conducted from July 2017 - August 2017. The research begins with literature search, title consultation, proposal preparation, proposal seminar, research and data analysis preparation of reports that take up to 1 month. Research subject are male or female aged 18-69 years suffering from CKD according to K/DOQI criteria undergoing HD >3 months, in stable condition, able to speak Bahasa Indonesia and understand the contents of the questionnaire, able to communicate well, get informed and give consent to participate in voluntary and written research (informed concern). This research has received permission from Ethical clearance obtained from Medical Research Committee Faculty of Medicine Universitas Sumatera Utara.

The subjects will be excluded if the patient with malignancy, acute infection, using NSAID or glucocorticoid, refusing to be interviewed and not willing to take blood. Of the 159 subjects, 58 patients were aligible and willing to take part in the study. Blood sampling for IL-6 was performed using the Human IL-6 Immunoassay (R & D system) examination procedure. Blood sample was taken before HD procedure. Serum IL-6 was measure by Enzim-linked immunosorbent assay (ELISA). Serum IL-6 value is considered normal if the value 0-20 pg/mL. During hemodialysis procedure the patient was asked to fill out the BDI II questionnaire filled for ± 10 minutes. BDI is a self-report questionnaire, created by Beck et al. used to measure the attitudes and characteristics of depressive symptoms. The questionnaire consists of 21-item, 15 items referring to psychological-cognitive symptoms, while the remaining 6 items refer to somatic vegetative

symptoms. Based on the depression scores are classified into; score 0-13 without symptoms of depression, score 14-19 showed symptoms of mild depression, score 20-28 symptoms of moderate depression, score 29-63 symptoms of major depression [11]. subjects who did not suffer depression were excluded. Demographic data were obtained from questionnaires. Clinical data were obtained from the medical record. Analysis of the basic characteristics of population data used tabulation to show descriptive description. To see the data normality test used Shapiro-Wilk test. The correlation of depressive symptom level with IL-6 level were analyzed using Spearman correlation test. Data were analyzed using SPSS statistics program for Windows, version 18.0 (SPSS Inc., Chicago, Illinois, USA); with p value <0.05 considered statistically significant.
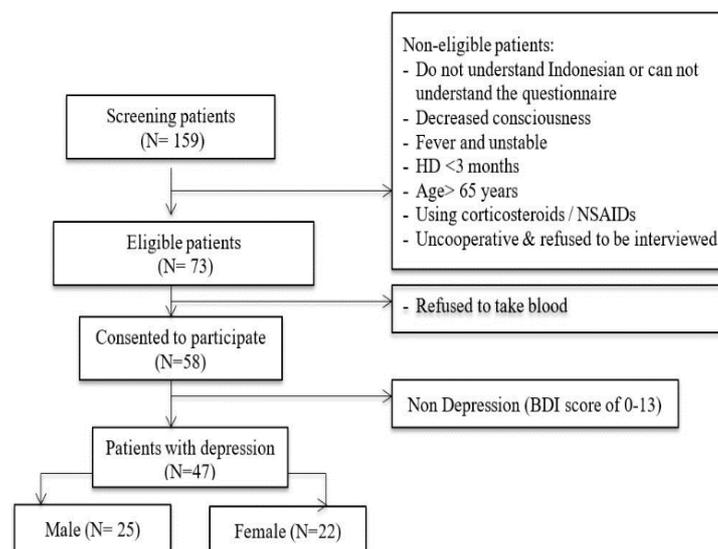

Figure 1. Flowchart of Patients In The Study

3.   Result

Of the 159 participants, 47 patients included in the study consist of 25 men and 22 women (**Figure 1**). Characteristics based on age, CKD sufferers are generally> 40 years old (80.9%), with more male (53.2%), high school education (59.6%), and junior high (4,3%), most of employment is self-employed / private employee as much as 46,8%, followed by housewife (31,9%) and lowest pensioner 8,5% and marital status almost 97,9% married. Based on the etiology of CKD with the most hypertensive nephropathy (HN) (59,6%) followed by diabetic nephropathy (DN) (19,1%) and lowest with Chronic Glomerulonephritis (8,5%) and the highest level of depression symptoms were mild depression (61,7%), moderate depression as many as 23.4% and the lowest severe depression (14.9%) (**Table 1**).

Table 1. Characteristics of Subjects of Patients with Ckd with Depression

Characteristics Patients	Frequency	Percentage %
Age (years)		
≤40	9	19,1
>40	38	80,9
Sex		
Male	25	53,2
Female	22	46,8
Education		
Primary School	5	10,6
Junior High School	2	4,3
Senior High School	28	59,6
College	12	25,5
Occupation		
Government employees	6	12,8
Employees entrepneur	22	46,8
Pensionary	4	8,5
Housewife	15	31,9
Marriage		
Married	46	97,9
Single	1	2,1
Etiology CKD		
HN	28	59,6
DN	9	19,1
Obstructive Kidney Disease	6	12,8
Chronic Glomerulonephritis	4	8,5
Level of depression		
Mild	29	61,7
Moderate	11	23,4
Total	47	100%

CKD patients with depression had mean IL-6 levels 8,697 ± 6.947 pg / mL, indicating that they were still within normal limits. Based on the assessment of depressive symptom level using BDI scores, the mean value of BDI score was 19.319 ± 6.182 indicating the level of mild depression symptoms (**Table 2**).

Table 2. Mean Levels of Il-6 and Depression Scores

Results	IL-6	BDI
n	47	47
Mean	8,697	19,319
Std. Deviation	6,947	6,182
Minimum	1,481	14
Maximum	28,881	38

From this study showed that the correlation of IL-6 level with depressive symptom level had correlation coefficient value 0.417 and p value <0.05. This explains that there is a significant positive correlation of IL-6 levels with depression levels with moderate correlation strength (**Figure 2**).
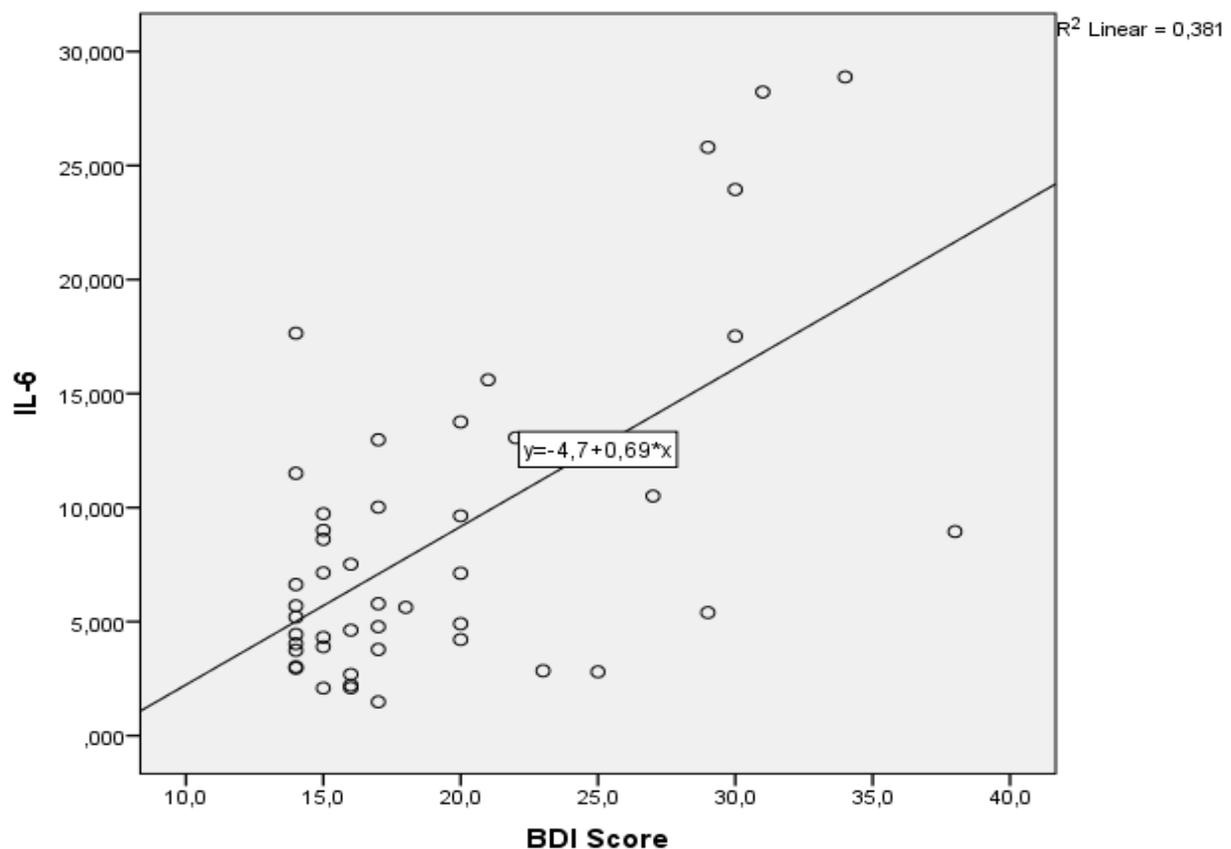

Figure 2. Correlation of Depression Symptoms with Il-6 Levels

4. Discussion

Depression is one of the most common psychosomatic problems in patients with CKD. The prevalence of depression in CKD patients varies widely in different studies, in different populations using different assessment tools [9,10]. The results of this study found the highest rates of depressive symptoms were mild depression symptoms (61.7%) and the lowest is severe depression (14.9%). In contrast to research conducted by Thomas et al using the Zung Self-rating

Depression Scale (ZSDS) method to assess the level of depressive symptoms in patients with CKD with the highest prevalence was moderate depression (76.47%) [10].

Characteristics of the subjects of this study were CKD sufferers who underwent regular hemodialysis with frequency depression most prevalent in men (53.2%) aged> 40 years (80.9%). This is in accordance with the results of a study reported by Amira in Nigeria using a cross-sectional study that assessed the prevalence of depressed symptoms in patients with CKD with the highest frequency was men 73 people (61.9%) with an average age of 40, 3 ± 12.1 years [9]. However, the frequency of males in depressed patients is inconsistent with the theory according to WHO [11] and research conducted by Deshpande et al. in India which states that depression is more common in women. According to research Deshpande et al women are more susceptible to stress, especially in the family, prolonged stress causes women to be more sensitive to problems relationships at home or workplace [12]. This may be due to the higher progression of CKD in men than in women [12,13].

In this study the mean IL-6 levels (8.697 ± 6.947 pg / mL) were still within normal limits with depressive symptoms using BDI scores with a mean score of 19.319 ± 6.182 indicating mild depressive symptoms may be due to depression in patients with hemodialysis CKD multifactorial. Not only is it caused by IL-6 alone but it can also be caused due to extrinsic factors such as psychosocial stressors, environmental and dialysis and intrinsic factors such as uremia that often occur in patients with CKD2. However, in this study the mean IL-6 levels increased significantly as the rate of depressive symptoms increased and these findings were consistent with meta-analysis studies conducted by Dowlati et al which showed IL-6 was significantly higher in the depressed group than in the control group [14].

From the results of this study found that based on Spearman correlation test showed a significant positive correlation between the level of depressive symptoms with IL-6 levels in CKD patients undergoing regular hemodialysis, with moderate correlation strength (r = 0.417). This suggests that in CKD patients undergoing regular hemodialysis, increased rates of depressive symptoms will be followed by elevated levels of IL-6 by moderate degree. This is in line with research conducted by Hung et al with a cross-sectional study of 146 CKD patients who underwent regular hemodialysis every three times a week for 3 months. In a study by Hung et al. which assessed the correlation of depressive symptoms using a BDI questionnaire with IL-6 levels with the results found a significant positive correlation between BDI and IL-6 levels in CKD patients undergoing regular hemodialysis, with moderate correlation strength (r = 0.47) [15]. Similar results were also conducted by Bob et al that assessed the correlation of BDI II with IL-6 concentration with IL-6 result significantly positive correlation with BDI II (r = 0.47, p <0.01) [16].

In contrast to the research conducted by Uglešić et al.17 who assessed the correlation of depressive symptoms with IL-6 levels in patients with CKD with hemodialysis every 3 times a

week, compared with patients with continuous ambulatory peritonel dialysis (CAPD). Depression symptoms were assessed using a BDI score with the results of a correlation of depressive symptoms with IL-6 levels in CKD patients with CAPD with strong correlation strength (r = 0.58), and no correlation between depressive symptoms and IL-6 levels in patients with hemodialysis. The low correlation between BDI score and IL-6 levels in the study was suspected because in many hemodialysis patients were exposed to several inducing factors such as contact with the dialysis membrane, endotoxin contamination and non-endotoxin-inducing factors that could interfere with the correlation [17].

The limitations of this study are cross-sectional research designs which are only possible to determine the relationship between variables and not causal relationships. Some important aspects for depression assessment such as family history, social life background are not evaluated. Symptoms of anxiety and measures of quality of life are also not assessed because it is not the main focus of this study.

In conclusion, there was a positive correlation with moderate strength (r = 0.417) between the level of depressive symptoms and IL-6 levels in CKD patients with regular hemodialysis. However, mean IL-6 levels in depressive patients are still within normal limits indicating that the cause of depression is multifactorial.

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