Relationship between Anxiety Score and Erythrocyte Sedimentation Rate (ESR) in Hemodialysis Patient

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ABSTRACT

Background: Anxiety in hemodialysis patients often impaired quality of life. Complex interaction between Chronic Kidney Disease (CKD) and anxiety are dynamic and multifactorial, including socio-economic, lifestyle and biological factors. Biological factors are closely related to anxiety in CKD including the immune system, inflammatory pathways of disorders of Hypothalamic-Pituitary-Adrenal Axis (HPA). Erythrocyte sedimentation rate (ESR) is one of the non-specific inflammatory marker that show the degree of inflammatory reaction, Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) also found as an easy and inexpensive measureable marker to show the degree of inflammation. This study aimed to examine relationship between anxiety and hematology inflammation markers in hemodialysis patient.

Subjects and Method: This was an observational study with a cross-sectional design. The study was conducted at Dr. Moewardi general hospital, Surakarta, Central Java. A sample of 30 hemodialysis patients was selected for this study. The dependent variables were ESR, NLR, and PLR. The independent variable was anxiety. Anxiety was measured by Taylor Manifest Anxiety Scale (TMAS).

Data on ESR, NLR, and PLR, were measured using an assessment from RAND Corporation. The data were analyzed by a multiple linear regression.

Results: Anxiety increased NLR and it was marginally significant (b= 0.37; 95% CI= -0.01 to 0.22; p= 0.080). Anxiety decreased ESR and it was statistically significant (b= -0.57; 95% CI= -0.02 to 0.01; p<0.001). Anxiety decreased PLR (b= -0.16; 95% CI= -0.02 to 0.01; p= 0.440) and duration of hemodialysis (b= -0.27; 95% CI= -0.03 to 0.01; p= 0.167), but they were statistically non-significant.

Conclusion: Anxiety increases NLR. Anxiety decreases ESR, PLR, and duration of hemodialysis.

Keywords: chronic kidney disease, hemodialysis, hematology markers, inflammation

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BACKGROUND

Chronic kidney disease (CKD) is damage in renal structure or function which has now become a serious public health problem (Iwagami et al., 2017) and has an effect on almost 10% of the global population (Bautovich et al., 2014). Patients with end-stage kidney disease will face complications in all

organ systems and common psychiatric complications are depression, anxiety, dementia, delirium, coping difficulties and marital or family problems (Valsaraj et al., 2016).

Anxiety in patients with chronic kidney disease often occurs together with depression and even worsens symptoms of depression and impaired quality of life. Both depression and anxiety are predictors of morbidity and mortality in patients undergoing hemodialysis, and are responsible for medication adherence and decreasing their immunity and nutritional status. From a cross sectional study of 200 stage III CKD patients to V-D in Haryana state, India, found 71% prevalence of anxiety (Aggarwal et al., 2017).

Previous studies have examined several markers that can be used to assess inflammation in patients suffering from CKD, including Interleukin (IL), Tumor Necrosis Factor-α (TNF-α), C-Reactive Protein (CRP), Sedimentation Rate (ESR), neutronphil-lymphocyte ratio (NLR) and thrombocyte-lymphocyte ratio (PLR) with meaningful results (Turkmen et al., 2017, Lopresti et al., 2014, Zahed et al., 2017). However, no studies have examined the relationship between hematologic inflammatory markers, namely ESR, NLR, and PLR in CKD patients who experience anxiety and undergo hemodialysis therapy. The aim of this study was to find differences and the relationship between changes in anxiety scores and hematologic inflammatory markers in CKD patients undergoing hemodialysis therapy.

SUBJECTS AND METHOD

1. Study design
This was a cross sectional study conducted at the Hemodialysis Unit of Dr. Moewardi Hospital, Surakarta, Central Java, in October 2018

2. Population and Sample
A total of 30 hemodialysis patients in the Hemodialysis Unit Dr. Moewardi hospital, Surakarta, were selected by purposive sampling.

Patients whose body temperature was above 37.4° C or below 36°C, history of severe (psychotic) mental disorders, substance and alcohol abuse and those who have been diagnosed and underwent therapy for depression and anxiety, taking anti-inflammatory drugs or steroids (<72 hours since last taking the medicine), and cancer patient and have blood disorder were excluded.

3. Study variables
The dependent variables were ESR, NLR, and PLR. The independent variable was anxiety.

4. Operational definition of variables
Anxiety score examined using The Taylor Manifest Anxiety Scale (TMAS), was a validated measure of anxiety, with a score limit defined by 2 anxiety scales based on T-MAS, measurement results:

Score <21: without anxiety

Score ≥ 21: with anxiety

Erythrocyte sedimentation rate was a measurement of plasma viscosity by assessing the tendency of red blood cells to aggregate and settle in varying plasma viscosity over a period of 1 hour (in mm / hour).

5. Clinical measurement
The instrument used to examine anxiety scores is TMAS (Taylor Manifest Anxiety Score). The scale was created by James Taylor and is one form of psychological inventory test used to determine the level of anxiety. The TMAS scale has been translated into Indonesian, and is often used in study to determine the subject's anxiety level as a general reaction to his inability to overcome problems or reactions to the absence of security,

The validity and reliability test results for anxiety instruments (TMAS) shows the value of instrument reliability/ Cronbach's Alpha of 0.846 (Arismawati, 2016) And for the inflammatory biomarker were examined at Prodia Laboratory, for a complete blood counts, a quantitative blood check tool and a leukocyte difference count method that works automatically for clinical diagnostic in the form of blood analyzer with impedance method and for ESR is westergren modification method is used with the infrared barrier. The inspection parameters have been accredited SNI ISO 15189 by KAN with certificate no. LM-033-IDN.

6. Statistical analysis
Sample characteristics were described in univariate analysis. Multivariate analysis was conducted by a multiple linear regression.

7. Research ethics
The study was conducted after passing the ethical review and received permission from the Head of Psychiatry Section of the Faculty of Medicine, Universitas Sebelas Maret/ Dr. Moewardi hospital, Surakarta, obtained the Ethical Clearance from Ethics Research Committee of Dr. Moewardi hospital, Surakarta. Before conducting the study, patients were given an explanation of the objectives and activities of this study. Study subjects gave written informed consent.

The study was conducted with reference to the basic principles of bioethics. In accordance with the principle of respect for autonomy, the authors ask prospective subjects to sign a study permit after they get sufficient explanation and are given the opportunity to ask questions that are still unclear. There is no compulsion to follow the study. Subjects can also stop participating in study if they feel negative things that arise during the study. The principle of justice is fulfilled because it does not distinguish individuals, for example gender, ethnicity, and religion. Thus, the principle of non-maleficence has also been fulfilled, that is no negative impacts were found on participants arising from this study.

RESULTS

1. Sample characteristics
Table 1 described demographic sample data.

Table 1. Demographic Sample Data

Variables		N	%
Gender	Male	14	1.05
	Female	16	
Age	Adolescent	1	1.75
	Young adult	10	
	Old adult	17	
	Elderly	2	
Duration of hemodialysis	< 3 Months	8	1.07
	≥ 3 Months	22	
Education	Not Educated	1	0.97
	Elementary	5	
	Junior High School	7	
	Senior High School	10	
	Bachelor Degree	6	
	Post Graduate	1	
Income	< 5 Million	26	
	≥ 5 Million	4	0.49

In this study, male patients were 14 samples (46.67%) while women were 16 samples (53.33%). The most age group of patients was 41-60 years (56.67%). Most of patients had highest education in senior high school (33.33%). Patients had an average income of less than 5 million rupiahs (Table 1).

Table 2. Biomarker differences in blood inflammation in patients with anxiety and not anxiety

Independent Variables	Mean Difference	95% CI		p
		Upper limit	Lower limit	
ESR	30.14	49.63	10.44	0.004
NLR	-1.01	-0.34	-2.35	0.134
PLR	-4.28	-7.84	-16.39	0.463

From Table 2, we found a significant difference in ESR biomarkers between patients who experienced anxiety and those who did not but not for the neutrophil lymphocyte ratio and platelet lymphocyte ratio biomarkers.

Table 3. The results of multiple linear regression on the relationship between anxiety score and erythrocyte sedimentation rate (ESR) in hemodialysis patient

Independent Variables	b	95% CI		p
		Lower limit	Upper limit	
ESR	-0.57	-0.02	-0.01	<0.001
NLR	0.37	-0.01	0.22	0.080
PLR	-0.16	-0.02	0.01	0.440
Age	0.05	-0.01	0.01	0.290
Duration of HD	-0.27	-0.03	0.01	0.167

2. Association between anxiety score and ESR

From Table 3, there was an association between anxiety scores and ESR compared with NLR and PLR, age of sample, and duration of the HD patient.

Anxiety increased NLR and it was marginally significant (b= 0.37; 95% CI= -0.01 to 0.22; p= 0.080).

Anxiety decreased ESR and it was statistically significant (b= -0.57; 95% CI= -0.02 to 0.01; p<0.001).

Anxiety decreased PLR (b= -0.16; 95% CI= -0.02 to 0.01; p= 0.440) and duration of hemodialysis (b= -0.27; 95% CI= -0.03 to 0.01; p= 0.167), but they were statistically non-significant.

DISCUSSION

Inflammation is a biological process that has been increasingly researched in chronic mental and physical diseases over the past decade, because it has a clear role in its pathophysiology. Although stress exposure can directly lead to increased inflammation in the absence of pathogens, activation of the HPA axis and the autonomic nervous system also modulates the inflammatory process due to stress reciprocally (Michopoulos et al., 2016). Prolonged exposure to stressful stimuli that cause fear and anxiety will activate both central and peripheral immune cells and induce an inflammatory response to NLRP3, a multiprotein complex that processes activation of inflammatory cytokines, and leads to the release of IL-1β (Alcoce et al., 2017). In glial cells, IL-1β induces NF-B transcripttional activity which results in increased circulating concentration of IL-6 (Michopoulos et al., 2016; Alcocer et al., 2017) and Tumour Necrosis Factor (TNF)-α (Miller and Raison, 2016). The release of these pro-inflammatory cytokines will activate CRH in the

hypothalamus which then stimulates the secretion of adrenocorticotropic hormone (ACTH) and starts HPA-axis activity by releasing glucocorticoids (cortisol) into the circulation (Melmed and Jameson, 2015).

The condition of uremia also affects the immune response of the patient which causes a failure of the immune response caused by:

- Decreased phagocytic function of granulocytes and monocytes / macrophages.
- Defects in the antigen presenting cells function.
- Decreased number and antibodies that produce B lymphocytes
- Increased T-cell reshuffle and apoptosis which leads to a decrease in CD 4+ and CD 8+ T-lymphocytes.
- Failure of cellular immunity.

The mechanism of the exact cause of this disorder is not entirely clear because there are many factors that contribute to this abnormality (Vaziri, 2012).

ESR is a marker of acute phase reactions. When inflammation occurs, the ESR change due to an increase in the concentration of fibrinogen and alpha globulin. This test mainly measures plasma viscosity by assessing the tendency of red blood cells to aggregate and settle in plasma viscosity that varies over a period of time (usually 1 hour) in millimeters (mm)/hour (Bray et al., 2016, Harrison, 2016).

The high ESR is found in depressed patients compared to healthy people (Lopresti et al., 2014; Nicolau, 2017). This is supported by the statement that chronic inflammation plays an important role in the pathophysiology of depression (Zahed et al., 2017). Due to the study it provides that chronic inflammation in several diseases can lead to anxiety and depression applies reciprocally for a worsening of the diseases / disorders.

In HD patient there was a lot of stress stimulus such as in internal and external stimulus such as thought for the diseases, how the patient feels about the diseases, etc. All of the stressor stimulus can lead to anxiety, depression or both. PLR and NLR is negative maybe because of the inflammation was not acute, as mention in previous study that lymphocyte tend to high in an acute inflammation process but not in chronic.

In several studies that have been carried out, ESR is a sign of increased inflammation in patients with CKD other than CRP, interleukin, and ferritin, which leads to worsening depression followed by malnutrition, atherosclerosis, cardiovascular disease and death in patients with late stage kidney disease (Zahed et al., 2017). Furthermore, in patients undergoing HD therapy, the ESR value also increased significantly (Bilen et al., 2014).

There was a difference between the ESR biomarker results among subjects who experienced anxiety and those who did not and found an association between ESR and anxiety scores, but for NLR and PLR there was no association with anxiety in hemodialysis therapy. Many things can affect the biomarkers of hematological inflammation.

AUTHOR CONTRIBUTION

manuscript. All authors contributed to and have approved the final manuscript.

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