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Relationship between Neutrophil-Lymphocyte Ratio (NLR) and Self-Esteem in Patients with Borderline Personality Disorder

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A B S T R A C T

Background: Borderline personality disorder (BPD) is a personality disorder that has low self-esteem, unstable emotions, high rejection, and is reactive to everyday interpersonal stress. The involvement of inflammatory factors in BPD has been widely reported by researchers. NLR is a specific inflammatory mediator in the adaptive immune response that can be examined through inexpensive and fast hematology tests. NLR is expected to be used as a marker of self-esteem in individuals with BPD. The study aimed to determine the relationship between NLR and self-esteem in patients with BPD. **Methods:** This is a quantitative study with a cross-sectional design. The total sample is 37 respondents who have been diagnosed with BPD from several hospitals in Semarang. Collection data use questionnaire RSES and blood sampling for NLR examination. **Results:** From 37 respondents, 27 (73.0%) subjects had low self-esteem, and 10 (27.0) subjects had high self-esteem. We found that the sensitivity of NLR was 50.00%, specificity 48.15%, positive predictive value 26.32%, negative predictive value 27.03%, and accuracy 48.65%. Area under curve (AUC) 0,537 and correlation cut off point NLR to self-esteem is no significant relationship because the p-value is 0,605 with RP 0.93(0,22-3,96) (95% CI). **Conclusion:** NLR cannot be used as a marker of high or low self-esteem in individuals with BPD.

1. Introduction

Borderline personality disorder (BPD) is a personality disorder consisting of disturbances in 4 domains, namely affective, interpersonal functioning, impulse control, and cognitive..[1] Affective domain instability is characterized by a dramatic appearance, namely a mood dysregulation characterized by impulsivity, self-destructive behavior, and unnatural anger.[2] Strong and unstable interpersonal relationships are characterized by alternating between excessive adoration and devaluation. Impulsivity is at least two areas that are potentially self-defeating, such as shopping, sex, substance use, reckless driving, and binge eating.[3] Other characteristics include low self-esteem instability, negative affect, and high feelings of rejection, and are reactive to interpersonal stress.[4]

Self-esteem is an affective response or individual attitude related to the perspective of acceptance and rejection of others towards him. High self-esteem produces positive affect, and conversely, low self-esteem is associated with negative affect. BPD individuals are sensitive to rejection which is a response to childhood rejection including neglect or abuse. These feelings are distorted into insecurity or low self-esteem.[5]

The population prevalence of BPD is estimated at around 1.6%, with a lifetime prevalence of 5.9%. About 6% are found in primary care centers, 10% among individuals visiting outpatient psychiatric clinics, 20% in psychiatric inpatients, and 30%-60% among patients with personality disorders. Women are more frequent than men and decreased in the older age

group.[6] There have been many studies examining the pathophysiology of BPD. The main etiological factor in BPD is a combination of early life traumatic events and vulnerability emotional domain.[7] BPD occurs between genetic and biological vulnerabilities that interact with an invalidating environment where the expression of a child's personal emotional experience is less accepted.[8] This condition causes individuals to experience dysregulation of stress.[9] Stress or traumatic events during childhood were found in 70% of BPD patients, including a history of physical and sexual violence, neglect, separation from caregivers, and/or loss of parents.[9] Neurobiologically, the traumatic experience causes dysfunction of serotonergic pathways and overactivity of the hypothalamic-pituitary-adrenal (HPA) axis, which is also frequently reported as pathogenesis of BPD. Several other mechanisms have also been extensively studied including neurotransmitter-related mechanisms, the endogenous opioid system, and neuroplasticity. These multiple systems are associated with neuroimaging findings that found decreased hippocampal and amygdala volumes, both of which are involved in stress response, cognition, memory, and emotion regulation, and increased β-opioid receptors in the same areas.[8]

It has been studied that exposure to stress can trigger an immuno-inflammatory and oxidative response and cause an increase in inflammatory markers both in the brain and in the periphery.[10] The role of inflammation in various psychiatric disorders such as bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia is also widely found, where activation occurs IRS with markers IL-1β, IL-6, IL-8, interferon-gamma (IFN-γ), tumor necrosis factor- α (TNF- α), NLR, chemokines, etc. Increased IRS is accompanied by a compensatory immune-regulatory reflex system (CIRS) with markers including IL-4, transforming-growth factor (TGF-β), and soluble IL-2 receptor (sIL-2R). These CIRS products were released in a negative response to the IRS.[11] Proinflammatory cytokines such as IL-1, IL-6, and TNF-alpha cause irregularities in the immune response. IL-1 is secreted by immune cells such as monocytes, lymphocytes, endothelial cells, and microglia. TNF-alpha plays a role in increasing acute phase reactants and causing IL-6 neutrophilia, causing differentiation of beta cells, stimulating the growth of various beta cells, as well as activation and differentiation of T-cells. These proinflammatory cytokines will affect neurotransmitter metabolisms such as serotoninergic, glutamatergic, and dopaminergic dysfunction, HPA overactivity, and synaptic plasticity.[12] Leukocytes, neutrophils, lymphocytes, compliment, and C-reactive proteins play a role in inflammation, which occurs in response to stress caused by cytokines.[13]

NLR is the ratio between neutrophils, which is the first line of innate immune defense, while lymphocytes are specific inflammatory mediators in the adaptive immune response. The neutrophil to lymphocyte ratio (NLR) is a cheap and easy hematology test that allows the assessment of the white blood cell count in simple laboratory situations.[14] Increased NLR is found in patients with dementia, alcohol dependence, schizophrenia, bipolar affective disorder, depression, non-phobic anxiety disorder, specific personality disorder, and mild mental retardation. This condition proposes NLR as a non-specific, cross-diagnostic marker of inflammation.[15] Involvement of inflammatory factors has been widely reported by many researchers. There is a relationship between NLR and various psychiatric disorders such as depression or anxiety[16-17], but there has been no research on the relationship between NLR and self-esteem in individuals with BPD. This study aimed to find the relationship between NLR and self-esteem in BPD patients.

2. Methods

This research is a quantitative study with a cross-sectional design, which was carried out at the outpatient installation at Dr. Kariadi General Hospital Semarang and Diponegoro National Hospital Semarang in January-June 2022. The subjects of this study were patients who had been diagnosed with

BPD, had received treatment, and met the study inclusion criteria. The inclusion criteria in this study were 18-60 years of age and a minimum education of junior high school. Exclusion criteria were suffering from severe and chronic illness, suffering from psychotic disorders, and consuming immunosuppressant drugs. Sampling was done using purposive sampling. All BPD patients treated at the psychiatric outpatient polyclinic were selected based on inclusion criteria, then identification with demographic questionnaires and informed consent. Blood sampling was carried out in the hospital laboratory unit, namely as much as 3cc through a punctured vein in the cubital median, and then examined by an analyst using a Hematology Analyzer. The data taken is the value of neutrophils and lymphocytes at the time of the visit. Data analysis was carried out using the Shapiro-Wilk normality test, the sperm test using the Sperm test, and the comparison of variables with Chi-Square or Fisher's test. The test results are said to be significant if the p-value <0.05.

3. Results

This research is a quantitative study conducted at the outpatient installation of Dr. Kariadi General Hospital Semarang and Diponegoro National Hospital Semarang in January-June 2022. The total sample is 37 subjects, with the distribution of subjects based on age, gender, marital status, education, occupation, economic status, race, religion, length of diagnosis, genetic history, body mass index (BMI), consumption of drugs, and illnesses suffered are listed in Table 1.

4. Discussion

In this study, there were 8 male subjects and 29 female subjects with an average age of 25.49 ± 6.51. This is by previous studies which reported no significant differences in the prevalence of BPD were found between women and men in the general population. However, in the clinical setting, the female-to-male ratio has been reported as 3:1.[6] This difference in prevalence may be caused by biological differences and/or social influences between men and women. women are more likely to experience fear, guilt, and depression as well as less impulse control problems, which, if they continue to interact with impulsive aggressive attitudes, will develop into BPD.[18] BPD symptoms are associated with difficulty in decision-making and impulse control, which can result in low emotional control. From this, it can be imagined that those with BPD are more likely to be unemployed than working. In this study, 9 (24.6%) subjects had jobs, and 28 (75.7%) subjects did unemployment. Tres et al. (2018) reported that BPD symptoms are associated with decreased work performance.[19] Poor self-image makes it difficult for BPD individuals to commit to one career path, missing out on promotions or opportunities related to seniority. BPD individuals often think all or nothing so they often use a mental spitting defense mechanism, namely tending to see people and situations as all good or all bad. This makes BPD individuals fall into a feeling of failure and easily give up when receiving criticism or failure in trying a job. These changing feelings and splitting can also cause problems with relationships at work, resulting in unstable relationships and a divided workplace.[20]

Another symptom of BPD is instability in interpersonal relationships. Early separation during childhood develops excessive dependence on others, feels unable to live without the help of others and survive, but has anxiety about rejection and neglect from others. This difficulty interacting with others results in a significant increase in the likelihood of romantic conflict and marital dissolution.[21] [22] In the dominant study with unmarried subjects, although the causes were not examined, it did not show a significant difference in the subject's self-esteem. Racial/ethnic differences in BPD rates are more challenging to explain. In this study, the most common race is the Javanese. There is no explanation for this other than because the research site is located on the island of Java, so the Javanese will be dominant compared to other tribes.

Table 1. Descriptive data.

Variable	F	%	Mean ± SD	Median (min-max)
Age			25.49 ± 6.51	23 (19 – 52)
Gender				
Man	8	21,6		
Woman	29	78.4		
Marital status				
Marry	6	16,2		
Single	31	83.8		
Education				
Senior high school	14	37,8		
Associate degree	2	5,4		
Bachelor of applied science	1	2,7		
Bachelor degree	19	51,4		
Master degree	1	2,7		
Work				
Work	9	24,3		
Unemployment	28	75,7		
Economic status				
<UMR	2	5,4		
According to UMR	6	16,2		
> UMR	10	27.0		
Other	19	51,4		
Race				
Java	28	75,7		
Sunda	1	2,7		
Batak	3	8,1		
Malay	1	2,7		
Manado	1	2,7		
Chinese	3	8,1		
Religion				
Islam	23	62,2		
Christian	8	21,6		
Catholic	5	13.5		
Agnostic	1	2,7		
Length of diagnosis				
< 1 year	18	48,6		
> 1 year	19	51,4		
Genetic history				
Yes	3	8,1		
No	34	91.9		
BMI				
less BB	4	10,8		
BB normal	9	24,3		
Preobesity	14	37,8		
Obesity	10	27.0		
Drug consumption				
Antidepressants	24	64,9		
Antipsychotics	15	40.5		
mood stabilizers	7	18,9		
Illness				
Yes	13	35,1		
No	24	64,9		
NLR			2.52 ±1.13	2.21 (1.13 – 5.61)
RSES				
High self-esteem	10	27.0		
Low self-esteem	27	73.0		

Description: ǂ Mann Whitney; £ Fisher's exact.

Bivariate analysis of self-esteem with confounding variables as shown in Table 2, found that only length of diagnosis was a risk factor that could affect self-esteem (p 0.038).

Table 2. Differences in data characteristics based on RSES.

Variable	RSES		p.s
	High self-esteem (n = 10)	Low self-esteem (n = 27)	
Age	23.5 (19 – 37)	23 (19 – 52)	0.732 ǂ
Gender			
Man	1 (10%)	7 (25.9%)	0.288 £
Woman	9 (90%)	20 (74.1%)	
Marital status			
Marry	1 (10%)	5 (18.5%)	0.475 £
Single	9 (90%)	22 (81.5%)	
Education			
Senior high school	4 (40%)	10 (37%)	0.580 £
Associate degree	0 (0%)	2 (7.4%)	
Bachelor of applied science	0 (0%)	1 (3.7%)	
Bachelor degree	6 (60%)	13 (48.1%)	
Master degree	0 (0%)	1 (3.7%)	
Work			
Work	4 (40%)	5 (18.5%)	0.177 £
Unemployment	6 (60%)	22 (81.5%)	
Economic status			
<UMR	1 (10%)	0 (0%)	0.220 £
According to UMR	1 (10%)	5 (18.5%)	
> UMR	3 (30%)	3 (11.1%)	
Other	5 (50%)	19 (70.4%)	
Race			
Java	9 (90%)	19 (70.4%)	0.216 £
Sunda	0 (0%)	1 (3.7%)	
Batak	0 (0%)	3 (11.1%)	
Malay	0 (0%)	1 (3.7%)	
Manado	0 (0%)	1 (3.7%)	
Chinese	1 (10%)	2 (7.4%)	
Religion			
Islam	5 (50%)	18 (66.7%)	0.290 £
Christian	3 (30%)	5 (18.5%)	
Catholic	2 (20%)	3 (11.1%)	
Agnostic	0 (0%)	1 (3.7%)	
Length of diagnosis			
< 1 year	2 (20%)	16 (59.3%)	0.038 £ *
> 1 year	8 (80%)	11 (40.7%)	
Genetic history			
Yes	1 (10%)	2 (7.4%)	0.624 £
No	9 (90%)	25 (92.8%)	
BMI			
less BB	2 (20%)	2 (7.4%)	0.220 £
BB normal	3 (30%)	6 (22.2%)	
Preobesity	2 (20%)	12 (44.4%)	
Obesity	3 (30%)	7 (25.9%)	
Drug consumption			
Antidepressants	5 (50%)	19 (70.4%)	0.220 £
Antipsychotics	2 (20%)	13 (48.1%)	0.120 £
mood stabilizers	2 (20%)	5 (18.5%)	0.626 £
Illness			
Yes	2 (20%)	11 (40.7%)	0.219 £
No	8 (80%)	16 (59.3%)	

Analysis of the relationship between the NLR variable and self-esteem using the Sperman's correlation test found a non-significant relationship where the regression coefficient (r) -0.0 57 was obtained with a p-value of 0.738 as shown in Table 3.

Table 3. Results of Spearman correlation test NLR to RSES.

RSES	NLR	p.s	r
High self-esteem	2.32 (1.51 – 4.68)	0.738	-0.057
Low self-esteem	2.21 (1.13 – 5.61)		

Diagnostic test analysis of NLR values for self-esteem obtained a cut-off point (COP) NLR value of 2.21, with an area under the curve (AUC) of 0.537, %, a sensitivity of 50%, and a specificity of 48.15%, a positive predictive value of 26.32%, a value predict negative 26.32% with 48.65% accuracy as shown in Figure 1 and Table 4 and Table 5.

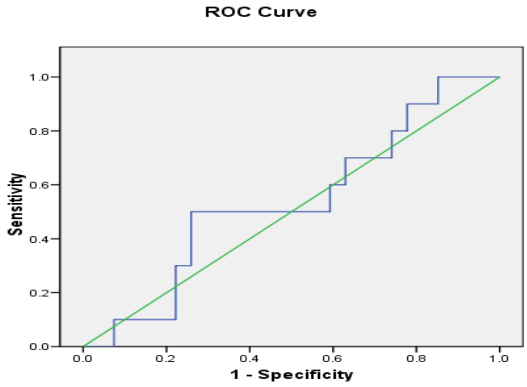

Figure 1: Receiver operating curve.

Table 4. The area under curve NLR on self-esteem.

Variable	AUC	Asymp. Sig	CI 95%		Cut off point
			Lower	Upper	
NLR	0.537	0.732	0.330	0.744	2,21

Table 5. NLR diagnostic test for RSES.

NLR	Self-esteem		Sens. (%)	Spe. (%)	NDP (%)	NDN (%)	Acc. (%)
	High	Low					
≥ 2.21	5	14	50.00	48.15	26,32	27.03	48.65
< 2.21	5	13					

In previous research reports, it is also difficult to explain specific racial/ethnic differences in individuals with BPD. It is important to note that no previous epidemiological studies of BPD have allowed prevalence estimates in the White, Black, Native American, Asian American, and Hispanic populations of the United States. They only noted that BPD was more common among Native Americans and African Americans, whereas rates of BPD in Asian Americans were significantly lower than in white Americans.[23]

Related to religion, two studies are reporting a negative correlation regarding Religiosity and religious presence being negatively correlated with borderline personality traits, especially with anger, mood instability, feelings of emptiness, and self-defeating behavior. The terms "religion" and "spirituality" are sometimes used interchangeably in literature. Unlike religion, which can be defined as well-established and organized beliefs and behaviors regarding the sacred, spirituality lacks a precise and well-established definition, especially in the study of mental health. Studies assessing the relationship between religious presence and borderline personality traits using structured psychiatric interviews are lacking.[24] In this study, it was found that the religion most widely adhered to was Islam, but there was no significant difference in self-esteem on the subject. Specific features of BPD emerge during childhood and adolescence. Recognizing these predictors of precociousness may have significant clinical implications. Early onset of this complex and serious personality disorder is associated with a high risk of negative outcomes and poor long-term psychosocial functioning. Early identification of BPD symptoms and

accurate investigation of protective and risk factors are fundamental to promoting prompt and adequate intervention programs and enhancing the natural course of the disorder.[25] In this study, the diagnosis time was set for more than 1 year or less than 1 year to determine the effect on self-esteem and obtain significant results in influencing self-esteem.

BPD history in the family and heritability is estimated at 46%, this should be the focus of the clinic to be aware of the increased risk in individual relatives of BPD. The remaining percentage is explained by environmental factors that will differ from one individual to another.[26] In this study, only 8.1% of subjects who had a family genetic history of having mental disorders did not specifically explain the form of the disorder, while the rest said they did not have a family with mental disorders. Both do not provide a significant difference in self-esteem. The DSM-IV-TR describes BPD as a "pervasive pattern of instability" characterized by impulsiveness that affects approximately two percent of the general population. Previous research has reported a link between eating disorders and personality disorders. Van Hanswijck et al reported that one in 15 patients (6.6%) with binge eating disorder had BPD.[27] Given this, there is an assumption that BPD is related to obesity which is the result of impulsive eating disorders. However, BPD is found in a minority group of obese individuals.[28] In this study, 27% of patients were obese and 37.8% were pre-obese, but there was no significant difference in self-esteem.

Regarding comorbidities, BPD is rarely self-diagnosed and BPD shows the strongest associations with lifelong mood episodes (especially major depressive episodes and mania) and with lifelong anxiety disorders (especially panic disorder with agoraphobia, generalized anxiety disorder, and PTSD). BPD is significantly associated with various other personality disorders, especially schizotypal, narcissistic, and dependent. These co-morbidities will be related to the disorder and dysfunction and will be the reason for the individual seeking professional help. [23]. In this study, most of the BPD subjects sought outpatient mental health care. The lifetime therapy/consultation acceptance rate among individuals with BPD was 74.9%, which is similar to the 73% 10-year therapy utilization rate reported by Hörz, Zanarini, Frankenburg, Riech, and Fitzmaurice. In the report, Zanarini et al reported on the results of a 6-year follow-up of BPD individuals and prediction of remission over time that more than 70% underwent individual therapy at least weekly and took at least one drug. Polypharmacy is still very common, with more than 50% of respondents taking two or more drugs, more than 35% taking three or more, about 20% taking four or more, and more than 10% taking five or more. In terms of specific treatment, 67% of BPD took antidepressants, 28% took anxiolytics, 27% took antipsychotics, and 22% took moods. [29] In this study, the results were almost the same as the research report above where the subjects were outpatient and received medication for disorders on axis 1, the use of antidepressants was 64.9%, indicating that axis 1 was mostly depression, antipsychotics 40.5%, and mood stabilizers 18.9%.

Shen et al reported in their study that 12 categories of physical comorbidities were more common in BPD patients than in controls.[30] These results are consistent with previous studies in the United States. showed that BPD was significantly associated with arteriosclerosis or hypertension, liver disease, cardiovascular disease, digestive system disease, arthritis, and venereal disease. Gender differences in physical comorbidities also differ between BPD men and women. Comorbidities from the respiratory system, digestive system, genitourinary system, endocrine, metabolism, and immune system, and neoplasms are more common in female patients than in male patients.[31] In this study, the NLR of BPD subjects was obtained with an average of 2.52 ± 1.13 and a mean value of 2.21 (1.13-5.61). There has been no previous study that reported on the appearance of NLR in BPD so these results can be used as a reference for future research. Most of the studies that measure BPD individual self-esteem use self-report questionnaires such as the Rosenberg self-esteem

scale (RSES). This measurement approach is based on explicit self-esteem constructs. Individuals with BPD reported significantly lower explicit self-esteem than controls, or compared with major depression and social phobia.[32] Philip et al. reported that self-esteem instability is a specific symptom that forms a pathology unique to BPD. Zeiggler and Abraham (2006) also reported that BPD individuals are characterized by unstable low self-esteem, unstable negative affect, and feelings of rejection, which are very reactive to everyday interpersonal stress.[33]

To the authors' knowledge, no studies have directly investigated the correlation between NLR and self-esteem in BPD patients. Here, the authors report an investigation of the relationship between NLR and self-esteem in BPD individuals. In this study, it was found that 73.0% of the subjects had low self-esteem, and 27.0% had high self-esteem and had a significant relationship with the duration of BPD diagnosis. A negative correlation was found between self-esteem and NLR values with an r-value of -0.057 and a p-value of 0.738 so it was concluded that there was no significant relationship between self-esteem and NLR. According to a recent systematic review and meta-analysis of Major Depressive Disorder (MDD) in patient groups in China, NLR, PLR, and MLR were all elevated in patients with depression compared to healthy controls. Likewise with ADHD, Obsessive Compulsive Disorder both in adults and children. Depressed adolescents have higher NLRs, which are positively correlated with depression severity. This marker has also been reported to be associated with suicidal susceptibility in MDD and bipolar disorder. Previous studies in adolescents with NSSI have shown that MLR and PLR are superior to NLR, and the levels of MLR and NLR are positively correlated with suicide severity.[34]

Based on previous findings, we hypothesize that NLR has a relationship with BPD individual self-esteem, and NLR can be used as an effective marker to assess self-esteem in BPD. The results of this study are inconsistent with the author's hypothesis, which found no significant relationship between NLR and self-esteem. The NLR ROC curve on self-esteem is displayed with a blue line with an AUC of 0.537 %, a sensitivity of 50% and a specificity of 48.15%, a positive predictive value of 26.32%, a negative predictive value of 26.32% and an accuracy of 48.65%. The reason for the non-significant finding of NLR in this study is unclear. The shape of the curve is quite stable in the direction of a straight line, so the AUC obtained is low for NLR (0.537). This value is quite large, and it can be interpreted that the level of accuracy of the model is quite sensitive in classifying NLR to self-esteem but is less specific in assessing self-esteem. With ROC analysis, it can be concluded that NLR cannot be used as a self-esteem classification tool.

5. Conclusion

In line with previous studies, in this study, the characteristics of BPD patients were found to be an average age of 25.49 ± 6.51, more women than men, single, with most undergraduate education, not working, Javanese ethnicity, Islam, duration of diagnosis of more than 1 year, no genetic history, pre-obesity, taking antidepressants and no comorbid physical disease. The self-esteem of BPD patients is low but cannot be related to the NLR value, so the NLR value cannot be used as a marker of self-esteem in BPD patients.

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