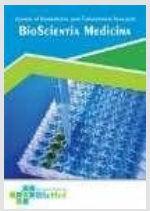
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Correlation of Neutrophil to Lymphocyte Ratio (NLR) Values to Ejection Fraction, Fraction Shortening, and E/A Ratio in Children with Rheumatic Heart Disease (RHD) at Dr. M. Djamil General Hospital, Padang, Indonesia

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ARTICLE INFO

Keywords:
Echocardiography
Ejection fraction
E/A ratio
Fraction shortening
Neutrophil to lymphocyte ratio

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v6i16.698

A B S T R A C T

Background: Monitoring the performance of the cardiac function is a must in monitoring patients with rheumatic heart disease (RHD). Echocardiography is the main diagnostic tool that plays a role in monitoring heart function, but the existence of this tool is only in tertiary health services and generally requires special expertise. This study aims to determine the correlation between the neutrophil to lymphocyte ratio (NLR) and markers of cardiac function performance on echocardiography, namely ejection fraction, fraction shortening, and E/A ratio in children with rheumatic heart disease at Dr. M. Djamil General Hospital, Padang, Indonesia. **Methods:** This was an analytical observational study with a cross-sectional approach. A total of 34 subjects were included in this study. Data analysis using SPSS was univariate and bivariate, with $p<0.05$. **Results:** There was a correlation between the NLR value and the echocardiographic ejection fraction (EF) parameter ($p>0.05$) with a very weak correlation strength, while the correlation between the NLR value and the FS echocardiography parameter ($p<0.05$), the direction of the correlation formed is positive with a strong correlation weak ($r=0.388$). As for the correlation of NLR values with echocardiographic parameters E/A ($p<0.05$), the direction of the correlation formed was positive with a weak correlation strength ($r=0.353$). **Conclusion:** There is a weak correlation between NLR values with FS and E/A echocardiographic parameters and no correlation between NLR and EF echocardiographic parameters in rheumatic heart disease patients at Dr. M. Djamil General Hospital, Padang, Indonesia.

1. Introduction

Rheumatic heart disease (RHD) is considered a manifestation of poverty and low socio-economic conditions in a country. The prevalence of silent RHD is 21.1 per 1000 children, and this is seven times higher than children who are known to have RHD based on clinical symptoms.[1,2] RHD is preceded by acute rheumatic fever caused by an autoimmune response from *Streptococcus* group A, which causes inflammation of the heart valves. Systemic inflammation usually occurs 2-4 weeks after infection with *Streptococcus* group A.[2] The role of inflammatory markers in cardiovascular disease has been studied extensively, and there is a consistent relationship between the two. Neutrophil to lymphocyte ratio (NLR) is a new additional parameter in this list of inflammatory markers. NLR is obtained from the leukocyte count with the type of leukocyte count. NLR is an inexpensive, easily available, and widely available inflammatory marker that can assist in assessing the risk level of patients with various cardiovascular diseases in addition to commonly used markers. NLR is widely used as a prognostic marker in various cardiovascular disorders, including coronary heart disease, arrhythmias, postcoronary artery bypass surgery, and heart failure.[3-7]

Monitoring of cardiac function performance is a must in the monitoring of patients with RHD. Echocardiography is the main diagnostic tool that plays a role in monitoring heart function, but the existence of this tool is only in tertiary health services and generally requires special expertise. This is a problem, and difficult to monitor RHD patients in primary and secondary health services. Exploration of new, simpler diagnostic markers has become urgent to facilitate the diagnosis and monitoring of cardiac performance in RHD patients.[8-10] This study aims to determine the correlation between NLR and markers of cardiac function performance on echocardiography, namely ejection fraction, fraction shortening, and E/A Ratio in children with rheumatic heart disease at Dr. M. Djamil General Hospital, Padang, Indonesia.

2. Methods

This study was an analytic observational study with a cross-sectional approach. A total of 34 research subjects were included in this study, where the research subjects met the inclusion criteria in the form of subjects who had been diagnosed with rheumatic heart disease and had received treatment and were willing to participate in the study, and received parental consent. This study was approved by the medical and health research ethics committee at Dr. M. Djamil General Hospital, Padang, Indonesia.

The diagnosis of rheumatic heart disease is determined by a pediatric cardiology consultant pediatrician. NLR is the ratio of the percentage of the number of neutrophils divided by the number of lymphocytes obtained from the examination of the leukocyte count. Ejection fraction is the change in left ventricular volume from the end of the diastole phase to the end of the systolic phase, measured by the Teicholtz method from a long axis parasternal view, performed by a pediatric cardiologist consultant pediatrician, using Philip HD 11 XE M-Mode echocardiography with transducers pediatric 5 MHz. The normal ejection fraction value is 56-78%. Fraction shortening is the percentage change in the dimensions of the left ventricular cavity during systolic contraction and is a parameter that is often used to express systolic function, measured by echocardiography obtained from the change in dimensions from the end of diastole to the end of systole on M-mode or 2D measurements, using Philip HD 11 XE M-Mode echocardiography with transducers pediatric 5 MHz. (normal value 28-38%). E/A ratio is the ratio of E and A waves, measured by 2-dimensional transthoracic echocardiography with a pulsed wave (PW) Doppler spectrum using an apical 4 chamber view where the probe is placed at the tip of the mitral valve (mitral inflow tract) (normal value 1.5- 2,3).

Univariate analysis was used to describe each research variable. Data analysis on categorical variables is presented in the form of frequencies and percentages and numerical variables using mean values and standard deviations. The correlation between the two numerical data was tested using the Pearson correlation test if the data distribution was normal and the Spearman correlation test if the data distribution was not normal. A p-value <0.05 is considered a significant correlation. Correlation strength: 0.00-0.199 (very weak), 0.2-0.399 (weak), 0.4-0.599 (medium), 0.6-0.799 (strong), 0.80-1.00 (very strong). The test was carried out with a 95% confidence interval (CI) and $\alpha = 0.05$. The conclusion from the test results is that if the $p \leq 0.05$, then H_0 is rejected. All data analysis using the SPSS program.

3. Results

Table 1 shows the average age of the subjects, namely 12.97 ± 3.51 years. More than half of the subjects (69.6%) were male. Less than half of the subjects had normal nutritional status (39.3%), malnutrition (33.3%), and obesity (21.2%). Less than half of the subjects had mild and moderate mitral regurgitation, with 38.2% each. Less than half of the subjects had moderate aortic valve disorders (41.2%), mild tricuspid valve disorders (29.4%), and a small number of subjects had mild pulmonary valve disorders (11.8%).

Table 1. Baseline characteristics.

Characteristics	Value
Age (year), mean ± SD	12.97 ± 3.51
5 – 11	9 (27.2)
12 – 15	15 (45.5)
16 – 18	9 (27.2)
Gender, f(%)	
Male	23 (69.6)
Female	10 (30.3)
Nutritional status, f(%)	
Undernourished	11 (33.3)
Normal	13 (39.3
Overweight	2 (6.0)
Obese	7 (21.2)
Mitral regurgitation, f(%)	
Mild	11 (39.2)
Moderate	11 (39.2)
Severe	6 (21.4)
Disorders of the aortic valve, f(%)	
Mild	5 (14.7)
Moderate	14 (41.2)
Severe	1 (2,9)
Disorders of the tricuspid valve, f(%)	
Mild	10 (29,4)
Moderate	1 (2,9)
Severe	0
Disorders of the pulmonary valve, f(%)	
Mild	4 (11, 8)
Moderate	0
Severe	0
Laboratory characteristics, mean±SD	
Hb (gr/dl)	12.54 ± 1.29
Albumin (gr/dl)	4.28 ± 0.38
NLR, mean ± SD	2.47 ± 1.45
Echocardiographic parameters, mean ± SD	
EF	66.81 ± 6.30
FS	39.75 ± 9.48
E/A	2.49 ± 0.61

Table 2. Correlation of NLR values with ejection fraction, fraction shortening, and E/A ratio in rheumatic heart disease.

	Echocardiographic parameters	r	p-value
NLR value	EF	0.098	0.582
	FS	0.388	0.023*
	E/A	0.353	0.041*

*p<0.05 significant; Spearman correlation.

Table 2 shows that there is a correlation between NLR values and EF echocardiography parameters (p>0.05) with a very weak correlation strength, while the correlation between NLR values and FS echocardiography parameters (p<0.05), the direction of the correlation formed is positive with a strong, weak correlation (r=0.388). As for the correlation of NLR values with echocardiographic parameters E/A (p<0.05), the direction of the correlation formed was positive with a weak correlation strength (r=0.353).

4. Discussion

In this study, there is a correlation between NLR and EF with a weak correlation strength (NLR vs. EF: r = 0.128, p = 0.07) and still significant between NLR and FS (NLR vs. FS: r = 0.228, p = 0.001). The

correlation of NLR values with weak correlation strength with EF is possibly caused by differences in the NLR cut-off point values. In other studies, it was stated that NLR values > 6.5 were independently associated with a decrease in EF values.[11,12] The direction of the NLR correlation to the FS formed is positive with a weak correlation strength (r=0.399). In addition, there is a correlation between NLR values and E/A echocardiographic parameters ($p<0.05$), with the direction of the correlation, formed being positive with weak correlation strength (r=0.340). Another study stated that high NLR was strongly associated with the degree of myocardial damage and negatively related to cardiac contractility (EF and FS).[13,14] Inflammation and anti-inflammatory cytokines increase significantly when the NLR is greater than 4. It is possible that a higher NLR over a longer period of time (greater systemic inflammation) and greater myocardial damage trigger remodeling and recovery processes, which obscures adverse effects on myocardial function. NLR is a biomarker for systemic inflammation. The correlation between NLR and myocardial contraction (EF or FS) suggests that the degree of inflammation is associated with contractile dysfunction of cardiac function. In addition, high NLR values are also associated with left ventricular diastolic function in chronic kidney disease. This is related to physiological stress by the heart wall, which causes an increase in cortisol secretion, which makes the heart work harder.[15-17]

Another study reported that the NLR value in RHF patients with carditis involvement was higher than in healthy patients, which was an average of 1.81 vs. 3.0. This suggests a more severe inflammatory process in RHF patients with valve disorders.[18,19] Another study reported that NLR elevation could be used as an independent predictor of spontaneous echocardiographic contrast in patients with rheumatic mitral stenosis. Another study also reported that the severity of mitral valve stenosis in RHD increased along with an increase in NLR, and when the cut-off value is taken at 2.56, it has the strength to predict the severity of RHD mitral valve stenosis with a sensitivity of 75% and a specificity of 74%. Other studies reported that NLR values of 3.0 could predict heart failure with a sensitivity of 86.3% and a specificity of 77.5%. In addition, an increase in NLR is mainly found in a state of infection or after a bacterial infection, one of which is *Streptococcus* infection.[20,21]

5. Conclusion

There is a weak correlation between NLR values with FS and E/A echocardiographic parameters and no correlation between NLR and EF echocardiographic parameters in rheumatic heart disease patients at Dr. M. Djamil General Hospital, Padang, Indonesia.

6. References

1. Zachariah JP, Samnaliev M. Echo-based screening of rheumatic heart disease in children: a cost-effectiveness Markov model. J Med Econ. 2015; 18: 410–9.
2. Rothenbühler M, O'Sullivan CJ, Stortecky S, Stefanini GG, Spitzer E, et al. Active surveillance for rheumatic heart disease in endemic regions: a systematic review and meta-analysis of prevalence among children and adolescents. Lancet Glob Heal. 2014; 2: e717–26.
3. Bhat T, Teli S, Rijal J, Bhat H, Raza M, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013; 11: 55–9.
4. Oh J, Kang SM, Hong N, Choi JW, Lee SH, et al. Relation between red cell distribution width with echocardiographic parameters in patients with acute heart failure. J Card Fail. 2009; 15: 517–22.
5. Doğdu O, Akpek M, Yarlıoğlueş M, Kalay N, Ardıç İ, et al. Relationship between hematologic parameters and left ventricular systolic dysfunction in stable patients with multi-vessel coronary artery disease. Turk Kardiyol Dern Ars. 2012; 40: 706–13.
6. Elemary M, Elmeligy N, Tabl M, Abd Elhaleem AE. Usefulness of novel hematologic

inflammatory parameters: neutrophil to lymphocyte ratio in patients with rheumatic valve diseases. Am J Res Commun. 2016; 4: 43–62.

7. Akboğa MK, Akyel A, Şahinarslan A, Yayla Ç, Alsancak Y, et al. Neutrophil-to-lymphocyte ratio is increased in patients with rheumatic mitral valve stenosis? Anatol J Cardiol. 2015; 15: 380.
8. Walker MJ, Barnett TC, McArthur JD, Cole JN, Gillen CM, et al. Disease manifestations and pathogenic mechanisms of group A *Streptococcus*. Clin Microbiol Rev. 2014; 27: 264–301.
9. Guilherme L, Kalil J, Cunningham M. Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease. Autoimmunity. 2006; 39: 31–9.
10. Zühlke LJ, Beaton A, Engel ME, Hugo-Hamman CT, Karthikeyan G, et al. Group A *Streptococcus*, acute rheumatic fever and rheumatic heart disease: epidemiology and clinical considerations. Curr Treat Options Cardiovasc Med. 2017; 19: 15.
11. Remenyi B, ElGuindy A, Smith Jr SC, Yacoub M, Holmes Jr DR. Valvular aspects of rheumatic heart disease. Lancet. 2016; 387: 1335–46.
12. Reményi B, Wilson N, Steer A, Ferreira B, Kado J, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. Nat Rev Cardiol. 2012; 9: 297–309.
13. Leal MTBC, Passos LSA, Guarçoni FV, Aguiar JM de S, Silva RBR da, et al. Rheumatic heart disease in the modern era: recent developments and current challenges. Rev Soc Bras Med Trop. 2019; 52.
14. Bhaya M, Panwar S, Beniwal R, Panwar RB. High prevalence of rheumatic heart disease detected by echocardiography in school children. Echocardiography. 2010; 27: 448–53.
15. Kane A, Mirabel M, Touré K, Périer MC, Fazaa S, et al. Echocardiographic screening for rheumatic heart disease: age matters. Int J Cardiol. 2013; 168: 888–91.
16. Khoiriah F, Anggraini DI. Congestive heart failure NYHA IV et causa rheumatic heart disease with grade II hypertension and malnutrition. J Major. 2017; 6: 102–8.
17. Roberts KV, Brown ADH, Maguire GP, Atkinson DN, Carapetis JR. Utility of auscultatory screening for detecting rheumatic heart disease in high-risk children in Australia's Northern Territory. Med J Aust. 2013; 199: 196–9.
18. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015; 131: 1806–18.
19. Nugroho A, Nawawi AM. Relationship between neutrophil-lymphocyte ratio and score of sequential organ failure assessment in patients treated in the intensive care unit. J Anestesi Perioper. 2013; 1: 189–96.
20. de Jager CPC, van Wijk PTL, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, et al. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. Crit Care. 2010; 14: 1–8.
21. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, et al. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in the Asian population. Int Arch Med. 2012; 5: 1–6.