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Original Article

Relationship Between Cognitive Dysfunction (MoCA-INA Score) with Disease Activity, Erythrocyte Sedimentation Rate, and C-Reactive Protein in Systemic Lupus Erythematosus Patients

Bantar Suntoko[1], Suyantohadi[2], Elfian Rachmawati[3], Suharyo Hadisaputro[4], Handono Kalim[5]

[1]Doctoral Study Program of Medical and Health Science, Faculty of Medicine, University of Diponegoro, Semarang Indonesia
[2]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, University of Diponegoro / Kariadi Hospital, Semarang Indonesia
[3]Department of Internal Medicine, Faculty of medicine, University of Diponegoro / Kariadi Hospital, Semarang Indonesia
[4]Division of Tropical infectious Diseases, Department of Internal Medicine, Faculty of Medicine, University of Diponegoro / Kariadi Hospital, Semarang Indonesia
[5]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, University of Brawijaya / Saiful Anwar Hospital, Malang Indonesia

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Author Affiliation :
Doctoral Study
Program of Medical and Health Science,
Faculty of Medicine,
University of Diponegoro, Semarang
Indonesia

Author Correspondence :
Bantar Suntoko
Dr. Sutomo Street No. 16 Semarang,
Central Java 50244, Indonesia

Email Address :
bantar28@gmail.com

Abstract

Background : Background: Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is one of the clinical manifestations affecting the brain in SLE, which the most frequent condition was cognitive dysfunction (CD). CD has a negative impact on the quality of life of SLE patients and causes impaired social function and reduced work productivity. Previous studies regarding correlation between cognitive dysfunction with disease activity, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) showed various results. The purpose of this study was to assess the correlation of CD using MoCA- INA score with disease activity (SLEDAI-2K score), ESR and CRP in SLE patients.
Methods : A cross-sectional study design was applied in this research. The subjects of this research were SLE patients measured by MoCA-INA score, SLEDAI-2K score, ESR, and CRP. Spearman rank correlation test was applied in this study to assess the relationship of the variables.
Result : The study subjects consisted of 53 women diagnosed with SLE with an average age of 34 years old. 49.1 % of the subjects had high school education background. There was a moderate significant correlation between MoCA-INA score and ESR (r= -0.408, p=0.002) and also to CRP (r= -0.314 p=0.022). There was no significant correlation of disease activity and MoCA-INA score (r = -0.086 p = 0.539).
Conclusion : The low levels of ESR and CRP were associated with CD in SLE patients.

Keywords : cognitive dysfunction, c-reactive protein, disease activity, erythrocyte sedimentation rate, systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic prototype autoimmune disease that causes inflammation and tissue damage involving almost any organ or system. It is more common in women with a ratio of 10:1.[1] SLE affects many organs such as the skin, joints, kidneys, cardiac, nervous, serous glands, and vascular systems.2 SLE has a complex pathological mechanism and a variety of clinical manifestations, ranging from mild mucocutaneous to severe multi-organ and central nervous system involvement.[1,2]

Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) is a frequent complication of SLE, characterized by various neurologic manifestations.[3] NPSLE is diagnosed with a criterion of at least one of the nineteen clinical signs and symptoms as follows: seizures, cerebrovascular disorders, movement disorders (chorea), demyelinating syndrome, myelopathy, aseptic meningitis, cephalgia, cognitive disorders, mood disorders, psychosis, acute confusion, anxiety disorders, mononeuropathy, polyneuropathy, plexopathy, autonomic nervous system disorders, and mortality. Early detection of cognitive dysfunction is important in providing appropriate treatment for patients and preventing further cognitive deterioration.[4] Cognitive dysfunction in SLE patients occurs because the ischemic process and the inflammatory process.[5]

The course of SLE is characterized by a phase of remission and flare up, so monitoring of disease activity is necessary. Comprehensive treatment includes assessing disease activity to prevent disease progression, complications and provide optimal therapy.[6] Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI -2K score) is one of the instruments that can be used in clinical practice and research has proven to be quite valid and sensitive.[7] The SLEDAI-2K scoring system has 24 variables that describe 8 organ systems. Each variable is given a weighted value that varies, depending on the severity of the clinical manifestations that occur when the organ is disturbed. Kidney disorders, neurological disorders and vasculitis have a higher value than skin disorders. The higher the SLEDAI-2K score, the heavier it is and the more organs involved.[8] Patients with increased disease activity will increase the ischemia process in the affected organs and causes inflammation, marked by the increased of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[6–8]

Several standard cognitive function measures have been developed, such as Montreal Cognitive Assessment (MoCA). MoCA has been adapted and validated in Indonesia into MoCA-INA is frequently applied as a quick screening tool to detect cognitive dysfunction in Indonesia.[9] MoCA-INA has a good sensitivity and specificity for assessing cognitive function in adults. MoCA-INA evaluates multiple cognitive functions such as attention and concentration, executive function, memory, language, visuospatial skills, conceptual thinking, and orientation. MoCA-INA was considered to have a higher sensitivity than MMSE.[9,10]

Cognitive dysfunction has a negative impact on the quality of life of SLE patients and causes forgetfulness, impaired rapid thought processes, impaired social function and reduced work productivity. Early detection of cognitive dysfunction may improve the quality of life of SLE patients.[11]

Elevated levels of CRP occur in 60% of cases of SLE that experience flare-ups (exacerbations) and are often associated with an increase in disease activity, including NPSLE.[12] ESR is a sign of an inflammatory process occurring in the patient's body. ESR will increase if there is any inflammation process occur. SLE patients experience systemic symptoms (including NPSLE) due to the systemic circulation of inflammatory mediators.[13] By knowing what factors are associated and influential with cognitive dysfunction, it is hoped that it can contribute to the management of patients with systemic lupus erythematosus. Correlation of cognitive dysfunction with disease activity and inflammatory biomarkers showed various results. [11,14,15]

The purpose of this study was to assess the correlation of cognitive dysfunction (MoCA INA score) with disease activity (SLEDAI-2K score), ESR, and CRP in SLE patients. Cognitive disorders play a role in integrated thinking. If there is cognitive impairment, it will reduce the quality of life and social function. Therefore, the diagnosis of SLE cognitive disorder must be well recognized for appropriate management.

METHODS

Observational analytical cross-sectional study was used in this study. Subjects were SLE patients at the Rheumatology Clinic of Dr. Kariadi General Hospital Semarang during July to November 2021. A total of 53 consecutive patients, who included in the 2012 SLICC (Systemic Lupus International Collaborating Clinics) classification criteria for SLE, were participated in this study. This study excluded samples with comorbid diseases and education below the elementary school.

The evaluation included disease activity evaluation using SLE Disease Activity Index-2K (SLEDAI-2K) score, and the cognitive function was assessed by using MoCA-Ina test. Cognitive dysfunction was defined as score < 26/30, adjusted for duration of formal education. The CRP and ESR data were taken in the laboratory the same day as the assessment. SPSS version 16.0 for windows was used to assess the data. Data were analyzed using bivariate comparison test and Spearman rank correlation test.

The protocol of this research was accepted by the Ethics Committee of Dr. Kariadi Hospital (No: DP

0201/1.II / 7501/2021). All included participants written informed consent prior to join in this research. All works were managed following The Code of the World Medical Association (Declaration of Helsinki).

RESULTS

The total sample of this study was 53 people. These samples were female (100%). The age distribution in this study was divided by age less than 30 years old (41.5%), followed by 31–40 years old (26.4%), 41-50 years old (26.4%), and age >50 years old (5.7%). The majority of the sample had high school education (49.1%), followed by junior high school (43.4%), and bachelor's degree (7.5%).

There was no significant difference between MoCa-INA score and disease activity (p: 0.057), while MOCa-INA score with CRP and ESR were significant (p<0.001) and ESR (p:0.001).

Relative risk was measured using bivariate analysis concluded that increasing CRP in SLE patient had 1.6-fold greater incidence of cognitive dysfunction. Whereas, increasing ESR in SLE patient had 2.4-fold greater incidence of cognitive dysfunction (Table 3).

In this study, SLEDAI-2K scores range from 0 to 16, with a median value of 6. Approximately 79.2% of the subjects in this study had moderate disease activity. Based on the Rank–Spearman correlation test, there was a weak relationship (figure 1).

A significant negative correlation between the erythrocyte sedimentation rate and the MoCA-INA score (r = -0.48) (p = 0.002) and between CRP levels and MoCA-INA score (r = -0.314) (p= 0.022). These data indicated higher CRP value resulted in a lower MoCA-INA score which described the occurrence of cognitive dysfunction (figure 2 and figure 3).

DISCUSSION

Data collected by researchers from July to September 2021

TABLE 1
Data on the charateristic of research subjects

Characteristic		n
Age (years), mean ± SD		34.5 ± 9.53
	≤ 30	22 (41.5)
	31 – 40	14 (26.4)
	41 – 50	14 (26.4)
	> 50	3 (5.7)
Level of education, n (%)	Junior High school	23 (43.4)
	Senior High School	26 (49.1)
	Bachelor	4 (7.5)
Disease activity (SLEDAI-2K Score), mean ± SD	Mild	10 ± 5.64
	Moderate	42 ± 8.0
	Severe	1
CRP, mean ± SD	Normal	15 ± 3.68
	Elevated	38 ± 9.6
ESR, mean ± SD	Normal	14 ± 52.9
	Elevated	39 ± 72.5
MoCA-INA score, mean ± SD	Normal (≥ 26)	10 ± 23.1
	Cognitive disfunction (< 26)	43 ± 19.5
MoCA-INA domain dysfunction, n (%)	Executive Dysfunction	14 (32.5)
	Visuospatial	8 (18.6)
	Memory and Language	21 (48.9)

Note: SD = Standard Deviation, n = frequency, % = percentage, CRP = C-Reactive Protein, ESR: erythrocyte sedimentation rate, SLEDAI-2K = Systemic Lupus Diseases Activity Index-2K, MoCA-INA = Montreal Cognitive Assessment-Indonesia

TABLE 2
The bivariate comparison test of cognitive dysfunction (MoCa-INA) based on disease activity (SLEDAI-2K score), CRP, and ESR

Variable		MoCA-INA score		p-value
		Normal n = 10	Cognitive disfunction n = 43	
Disease activity (SLEDAI-2K Score)	Mild	4 (40%)	6 (60%)	0.057‡
	Moderate	6 (14.3%)	36 (85.7%)	
	Severe	0 (0%)	1 (100%)	
CRP (C-reactive protein)	Normal	9 (60%)	6 (40%)	<0.001£*
	Elevated	1 (2.6%)	37 (97.4%)	
Erythrocyte Sedimentation Rate	Normal	9 (39.1%)	14 (60.9%)	0.001£*
	Elevated	1 (3.3%)	29 (96.7%)	

Note: * Significant; ‡ Mann Whitney test; £ Fisher's Exact Test
Notes: Bivariate comparison analysis, significant if p<0.05

TABLE 3
Bivariate analysis CRP and ESR with relative risk of cognitive dysfunction

Variable	Range	Mo-CA Score		95% CI		RR
		Cognitive Dysfunction	Normal	Lower	Upper	
ESR	High (>35 mm/hr)	29 (96.7%)	1 (3.3%)	1.137	2.219	1.588
	Normal (≤ 35 mm/hr)	14 (60.9%)	9 (39.1%)			
CRP	High (>0.3 mg/dL)	37 (97.4%)	1 (2.6%)	1.307	4.534	2.434
	Normal (≤ 0.3 mg/dL)	6 (40.0%)	9 (18.9%)			

at the Rheumatology Clinic, Dr. Kariadi General Hospital, obtained 53 subjects who were female. These results support the previous study of Fan Y et al. (2020) that stated the incidence of SLE was more common in women with a ratio of 10:1.[1]

The average age in this study was 34.5 ± 9.53 years, the majority of patients being high school graduates (49,1%) and junior high school graduates (43.4%). Assessment of cognitive function through the MoCA-INA score of 53 SLE patients studied obtained 43 people around 81.1% of research subjects experienced cognitive dysfunction (Score <26), the most domain were memory and language 48.9%, executive dysfunction 32.5% and visual spatial 18.6%. This study was similar reported by Ajalia S et al. (2017) that 50% of SLE patients had cognitive dysfunction, most of which (86.67%) had impaired memory domains.[16] The characteristics of education in this study were high school (49.1 %), junior high school (43.4%), and bachelor degree (7.5%). This data was almost the same as reported by Saepudin A et al. (2019) at Hasan Sadikin Hospital Bandung that the majority samples were high school graduates (60,5%).[9]

Several scoring systems have been developed to monitor SLE disease degree of activity. The most widely used scoring system is SLEDAI-2K. In this scoring system, there are 24 variables describing eight organ systems.[17,18] This score records disease manifestations within ten days before the measurement; higher scores indicate more severe disease activity. In this study, SLEDAI scores range from 0 to 16, with a median value of 6. Approximately 79.2% of the subjects in this study had moderate disease activity. This SLEDAI-2K score also didn't differ much from a study conducted by Saepudin A et al. (2019) that had the same median value with a score range of 0 to 23.[9] Correlation between disease activity (SLEDAI-2K score) and MoCA-INA in this study was in line with research conducted by Saepudin A et al. on 38 patients at Hasan Sadikin Hospital Bandung in 2019 which stated that the SLEDAI score had no significant relationship with cognitive dysfunction as

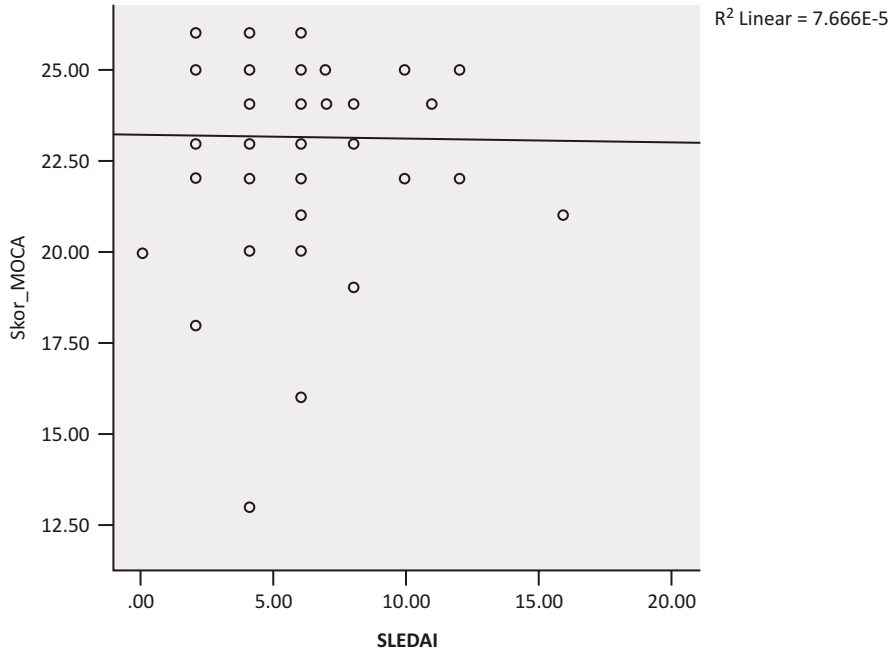

Figure 1. Scattered Plot Graph of correlation between disease activity (SLEDAI score) and MoCA-INA score (r = -0.086) (p = 0.539).
Notes: Correlation analysis using Spearman Rank test, significant if p<0.05

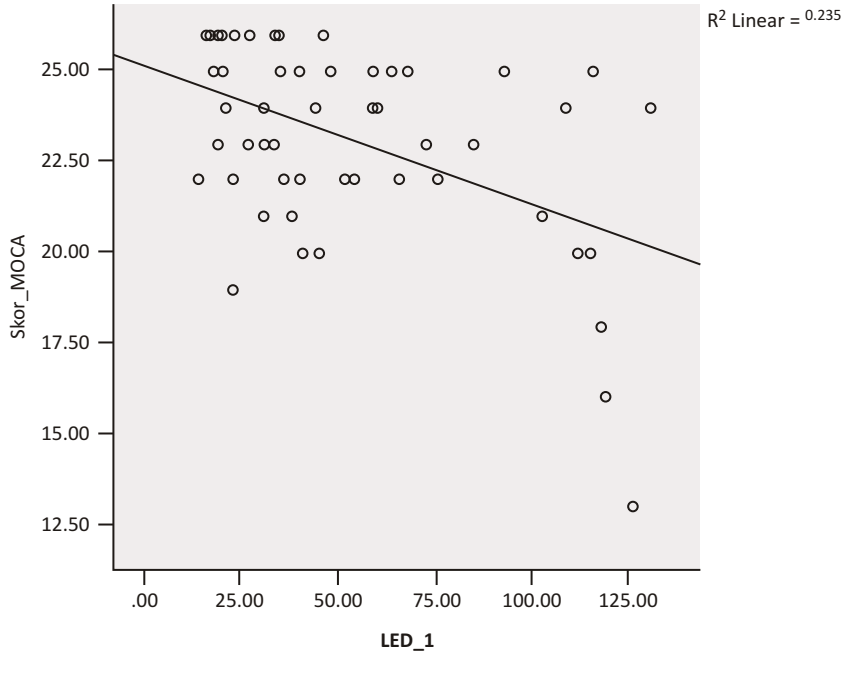

Figure 2. Scattered Plot Graph of Correlation between Erythrocyte Sedimentation Rate and MoCA-INA Score (r = -0.408) (p = 0.002)
Notes: Correlation analysis using Spearman Rank test, significant if p<0.05

measured by the MoCA-INA score 9, as well as research by El-Shafey AM et al. (2012) on 50 SLE patients in Egypt and Allan C et al. (2016) on 62 patients in the Philippines that SLEDAI scores did not have a significant relationship with cognitive dysfunction.[19,20] Maneeton B et al (2010) reported a correlation between cognitive dysfunction and disease activity in SLE patients, but Maneeton B et al. using Mini mental state examination (MMSE), Clock Drawing Test (CDT) and 5-item version of Instrumental Activities of Daily Living Modified Lawton's Scale (5-IADL), while disease activity using Mexican Systemic Lupus Erythematosus Disease Activity (MEX SLEDAI).

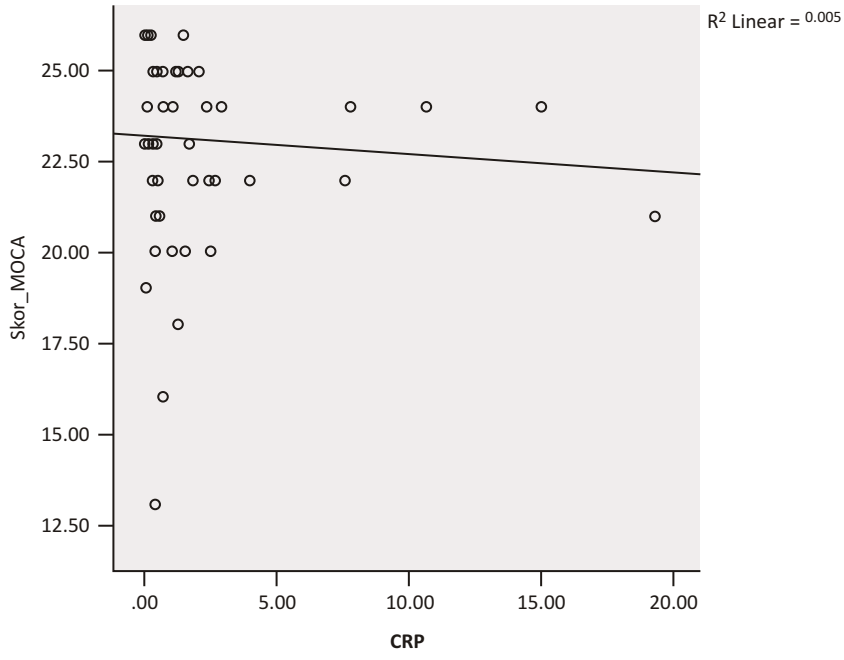

Figure 3. Scattered Plot Graph of Correlation between CRP and MoCA-INA Score (r = -0.314) (p = 0.022)
Notes: Correlation analysis using Spearman Rank test, significant if p<0.05

21 Different methods and instruments used can produce different research results.

There are several screening instruments used to evaluate cognitive dysfunction in SLE patients. MoCA and MMSE are the two most frequently used screening instruments in examining cognitive function, both in clinical practice and research studies. MoCA-INA was chosen for this study because it has been validated and could be a quick screening tool to detect cognitive dysfunction in Indonesia. MoCA-INA also has a higher sensitivity than MMSE, which can detect milder cognitive impairment better than MMSE.[22]

In contrast to the SLEDAI-2K score examination, the examination of inflammatory biomarkers turned out to have a statistically significant relationship with cognitive dysfunction as measured using the MoCA-INA instrument. The data showed that a higher ESR value led to a lower MoCA-INA score.

ESR is used conventionally as an indicator of a common disease. ESR reflects plasma levels of acute-phase proteins (mainly fibrinogen and globulins), causing an increase in the sedimentation rate in the reaction tube. According to Keenan RT et al. (2008), decreased cognitive function correlated with increased inflammatory biomarkers levels such as CRP and ESR in middle-aged and elderly individuals. Chronic inflammatory processes are associated with cerebrovascular disease. Therefore, cerebrovascular changes may contribute to cognitive impairment.[23]

SLE is associated with higher CRP levels, a likelihood of developing cerebrovascular disorders, and patterns of subcortical cognitive deficits (such as the appearance of disturbances in psychomotor speed and poor working memory). It shows that changes in the microvasculature can affect cognitive function in SLE.[23,24]

Correlation CRP with MoCA-INA score in this data were indicated that the higher CRP value led to a lower MoCA-INA score which described cognitive dysfunction. The results were supported by the previous study conducted by Barraclough M et al. (2019) in the UK with 336 SLE patients. The results show a significant correlation between quantitative CRP levels and the incidence of cognitive dysfunction using CANTAB (Cambridge Neuropsychological Test Automated Battery) (p=0,013).[13] A study conducted by Shucard JL et al. (2007), SLE patients with elevated CRP levels had worse PASAT (The Paced Auditory Serial Addition Test) scores. PASAT itself is an instrument used to assess psychomotor speed and memory.[24]

The results also support another study conducted by Watanabe Y et al. (2016) in Japan with a sample of 454 elderly patients with an average age of 70.5 years. The study concluded a significant relationship between increasing CRP scores and the incidence of cognitive decline as measured by the MMSE (Mini-Mental State Examination) score with p = 0.018. The higher the CRP value, the lower the MMSE score.[25]

It is necessary to conduct further multicenter research by including duration of illness, use of drugs or medication adherence and comorbidities for the further research. The number of samples needs to be expanded with prospective cohort studies in order to evaluate the

effect of treatment on the incidence of cognitive dysfunction in SLE patients.

CONCLUSION

There was a significant negative correlation between ESR and CRP levels with cognitive dysfunction (MoCA-INA score) in patients with SLE. There was no significant correlation between disease activity and MoCA-INA score.

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