RELATIONSHIP BETWEEN HIGH SENSITIVITY-C REACTIVE PROTEIN LEVEL AND IMPAIRED COGNITIVE FUNCTION IN HIV PATIENTS

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ABSTRACT

Human Immunodeficiency Virus (HIV) infection was one of the most serious health challenges in the world. The Ministry of Health of the Republic of Indonesia reports the number of HIV cases in Indonesia as of June 2019 as many as 349,882. At present, although antiretroviral combination therapy has been found, the prevalence of neurocognitive disorders in the form of HIV-associated neurocognitive disorders (HAND) reaches 50% of HIV patients. This study aimed to determine the relationship between high sensitivity-C Reactive Protein (hs-CRP) level and cognitive impairment assessed using MoCA-INA score in HIV patients at the UPIPI Dr. Soetomo Academic Hospital Surabaya. This cross-sectional study used consecutive sampling that fulfilled inclusion and exclusion criteria. The cognitive function of the subjects was examined by MoCA-INA score and blood samples were collected for measuring hs-CRP level. Of 100 subjects, 41 had abnormal MoCA-INA score and 59 had normal score. The number of subjects with high level of hs-CRP (>= 5) who had abnormal and normal MoCA-INA score were 22 (53,7%) and 6 (10,2%) respectively. This result was significantly difference with p = 0,0001, RO = 28,072 (95% CI, 5,470-144,052). Therefore, there was a significant relationship between hs-CRP level and cognitive function, where a subject with a high hs-CRP level was more likely to have impaired cognitive function.

Keywords: HAND; HIV; hs-CRP; MoCA-INA

ABSTRAK

Infeksi Human Immunodeficiency Virus (HIV) merupakan salah satu tantangan kesehatan yang paling serius di dunia. Kementerian Kesehatan Republik Indonesia melaporkan jumlah kasus HIV di Indonesia sampai dengan Juni 2019 sebanyak 349.882. Saat ini, meskipun telah ditemukan terapi kombinasi antiretrovirus, namun prevalensi gangguan neurokognitif berupa HIV-associated neurocognitive disorders (HAND) mencapai 50% dari pasien HIV. Tujuan penelitian ini adalah mengetahui hubungan antara kadar high sensitivity-C Reactive Protein (hs-CRP) dengan gangguan fungsi kognitif yang dinilai dengan MoCA-INA pada pasien HIV di poli UPIPI RSUD Dr. Soetomo Surabaya. Penelitian cross sectional menggunakan consecutive sampling yang memenuhi kriteria inklusi dan ekslusi. Subjek penelitian dilakukan pemeriksaan kognitif menggunakan MoCA-INA kemudian dilakukan pengambilan darah untuk pemeriksaan kadar high sensitivity-C Reactive Protein (hs-CRP). Pada 100 subjek penelitian didapatkan 41 subjek dengan MoCA-INA terganggu dan 59 subjek dengan MoCA-INA normal. Hasil analisis penelitian ini didapatkan bahwa subjek penelitian yang memiliki kadar high sensitivity-C Reactive Protein (hs-CRP) ? 5 dengan MoCA-INA terganggu yaitu 22 subjek (53,7 %) lebih besar dibandingkan dengan MoCA-INA normal yaitu 6 subjek (10,2 %). Hasil tersebut dinyatakan signifikan secara statistik dengan nilai p = 0,0001, RO = 28,072 (IK 95%, 5,470-144,052). Terdapat hubungan yang signifikan antara kadar high sensitivity-C Reactive Protein (hs-CRP) dengan gangguan fungsi kognitif, di mana subjek dengan level hs-CRP tinggi lebih cenderung memiliki gangguan fungsi kognitif.

Kata kunci: HAND; HIV; hs-CRP; MoCA-INA

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INTRODUCTION

Human immunodeficiency virus (HIV) infection that causes AIDS (Acquired Immunodeficiency Syndrome) was one of the most serious health challenges in the world since the first case reported in 1981. According to data from the Joint United Nations Program on HIV/AIDS (UNAIDS), there were 37.9 million people were living with HIV at the end of 2018. AIDS-related deaths in the world in 2018 reached 770,000 cases. As

many as 61% of new cases come from Sub-Sahara Africa (Joint United Nations Programme on HIV/AIDS 2019).

HIV-AIDS was first discovered in Indonesia in 1987 in the province of Bali. The Ministry of Health of the Republic of Indonesia reported the number of HIV cases in Indonesia as of June 2019 as many as 349,882. The highest number of HIV infections were reported in DKI Jakarta (62,108), followed by East Java (51,990), West Java (36,853), Papua (34,473), and Central Java (30,257). While the number of AIDS cases from 1987 to June 2019 was 117,064 people. There were 5 provinces with the highest number of AIDS; Papua (22,554), East Java (20,412), Central Java (10,858), DKI Jakarta (10,242), and Bali (8,147) (P2P Division, Indonesia Ministry of Health 2019).

At present, although antiretroviral therapy has been found, the prevalence of neurocognitive disorders in the form of HIV-associated neurocognitive disorders (HAND) remains high. Globally, it is estimated that 50% of HIV-positive people have neurocognitive disorders (Heaton et al 2010). A study by Chan et al, in 2012 reported that about 1 in 5 HIV-positive patients in South Asia was estimated to have HIV-associated neurocognitive disorders (HAND) (Chan et al 2012). HAND was a complication that has an impact on the quality of life and functional outcomes (Heaton et al 2010).

Montreal Cognitive Assessment (MoCA) was a screening tool designed to detect neurocognitive disorders and identifying HAND, even in mild form, including in mild degrees. MoCA has been widely used to filter cognitive dysfunction by assessing 8 cognitive domains, conscious only one page and takes only 10 minutes to complete the test. The validity and reliability test for the Indonesian version of the MoCA (MoCA-INA) proved to be valid according to the transcultural validation protocol (Husein et al 2010).

High sensitivity C-reactive protein (hs-CRP) was an acute-phase inflammatory molecule that has an important role in the human immune system. Recently, the relationship between hs-CRP concentration and cognitive function has been investigated by several observational studies. However, a study on the relationship between hs-CRP and HAND was still limited. A study conducted by Schouten et al in 2016 reported that inflammatory markers such as hs-CRP were one of the factors that significantly decreased cognitive function in HIV patients with p <0.05 (Schouten et al 2016). Another study by Watanabe et al (2016) showed a correlation between higher CRP concentrations and lower cognitive functions. Likewise,

Rubin et al (2018) in their study reported that high level of C-reactive protein (CRP) were the strongest predictors of cognitive impairment in HIV patients.

However, another study by Burdo et al (2013) reported that neurocognitive disorders in HIV patients receiving antiretrovirals were not associated with hs-CRP. The study of Brandon et al in 2016 showed that there was no relationship between hs-CRP and cognitive decline in HIV patients (Imp et al 2016). There are inconsistent differences in results from several studies, and the use of hs-CRP as a neurocognitive biomarker in HIV was still rare. Further studies were needed to conclude a causal correlation between hs-CRP level and cognitive function measured by MoCA-INA in HIV patients.

MATERIALS AND METHODS

This study was a cross sectional observational analytic study. The subjects were HIV patients receiving antiretroviral treatment at UPIPI Unit Dr. Soetomo Academic Hospital aged 18 years and older recruited between September and October 2019. The subjects who had GCS score lower than 15 or had depression, or had a history of brain structural lesion were excluded.

The subjects were selected from consecutive admission at the UPIPI Unit Dr. Soetomo Academic Hospital until the determined number of samples had been reached. Cognitive tests were carried out using the Moca-INA score with a cut off point less than 26 was defined as abnormal and blood sampling was performed for the patient to examine the hs-CRP level. Statistical analysis was performed with SPSS 25. Categorical data that had been collected was performed by the chi-square test.

RESULTS

This research was conducted for two months from September to October 2019 at the UPIPI Unit Dr. Soetomo Academic Hospital Surabaya. There were 100 subjects recruited in this study. Demographic characteristics included age, sex, and level of education. Based on demographic data, most of the study subjects were male (56%), age <=50 years (85%) and graduated from Senior high school (55%). The clinical characteristics of the subjects included body mass index, vascular risk factors, hs-CRP level and MoCA-INA.

Table 1. Demographic characteristics of subjects

Variable (N = 100)	n (%)	Average ± SB
Gender		
Man	56 (56)	
Woman	44 (44)	
Age		39,98 ± 9,618
> 50 years old	15 (15)	
≤ 50 years old	85 (85)	
Duration of Education (year)		11,65 ± 2,724
Level of education		
Elementary school	9 (9)	
Junior high school	15 (15)	
Senior high school	55 (55)	
Diploma / Bachelor Degree	21 (21)	

Table 2. Clinical characteristics of research subjects

Variable	n (%)	Average ± SB
Body mass index		22,264 ± 3,606
Thin	11 (11)	
Normal	64 (64)	
Overweight	23 (23)	
Obesity	2 (2)	
Vascular Risk Factors		
Yes	6 (6)	
No	94 (94)	
hs-CRP		5,38 ± 9,387
< 5	72 (72)	
≥ 5	28 (28)	
MoCA-INA		24,48 ± 3,761
< 26	41 (41)	
≥ 26	59 (59)	

The results of the analysis for the relationship between confounding variables such as gender, body mass index and vascular risk factors with impaired cognitive function in this study showed no statistically significant effect. Based on multivariate analysis, it was found that the age, education and hs-CRP variables had a statistically significant effect on impaired cognitive function as assessed by MoCA-INA with a p-value <0.05. Data analysis of these confounding variables can be seen in the table below with values considered significant if p <0.05.

Table 3. Relationship between age and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Age				
> 50 years old	11 (26,8)	4 (6,8)	0,013	5,042 (1,477-17,211)
≤ 50 years old	30 (73,2)	55 (93)		
Total	41 (100)	59 (100)		

Table 4. Relationship between gender and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Gender				
Woman	20 (48,8)	24 (40,7)	0,550	1,389 (0,622-3,100)
Man	21 (51,2)	35 (59,3)		
Total	41 (100)	59 (100)		

Table 5. Relationship between level of education and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Level of education				
Elementary-senior high school	39 (95,1)	40 (67,8)	0,002	0,108 (0,024-0,495)
Diploma-Bachelor Degree	2 (4,9)	19 (32,2)		
Total	41 (100)	59 (100)		

Table 6. Relationship between Body Mass Index and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Body mass index				
Overweight obesity	7 (17,1)	18 (30,5)	0,197	0,469 (0,175-1,255)
Thin – Normal	34 (82,9)	41 (69,5)		
Total	41 (100)	59 (100)		

Table 7. Relationship between vascular risk factors and MoCA-INA

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Vascular Risk Factors				
Yes	2 (4,9)	4 (6,8)	1,000	0,705 (0,123-

No	39 (95,1)	55 (93,2)	4,043)
Total	41 (100)	59 (100)

The results demonstrated statistically significant relationship between the level of hs-CRP with impaired cognitive function (p-value of 0.0001, Odd Ratio: 10,228 (95% CI, 3,601-29,048). It indicates that subjects who had the level of hs-CRP? 5 had a risk of 10,228 times greater of having impaired cognitive function than those whose level was less than 5. This result can be seen in table 8.

Table 8. Relationship between hs-CRP level with impaired cognitive function (MoCA-INA)

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Level of hsCRP				
< 5	19 (46,3)	53 (89,8)	0,0001	10,228 (3,601-29,048)
≥ 5	22 (53,7)	6 (10,2)		
Total	41 (100)	59 (100)		

The results of the analysis for the relationship between confounding variables and impaired cognitive function showed statistically significant difference for age and education variables hence we proceed to multivariate analysis. This result can be seen in table 9.

Table 9. Results of multivariate logistic regression analysis

Variable	P value	Adjusted OR	IK 95%	
			Min	Max
Age	0,004	8,297	1,957	35,174
Level of education	0,002	0,039	0,005	0,294
hs-CRP	0,0001	28,072	5,470	144,052

Based on this multivariate analysis, it was found that age, education, and hs-CRP variables had a statistically significant effect on cognitive impairment with a P <0.05. From the three variables above it can be concluded that the variables which affect cognitive function were age, education, and hs-CRP. Variables that strongly influence cognitive function were hs-CRP (P of 0.0001; OR: 28,072). This result validates that patients with hs-CRP >=5 were 28,072 times more likely to experience cognitive impairment than those whose level was less than 5.
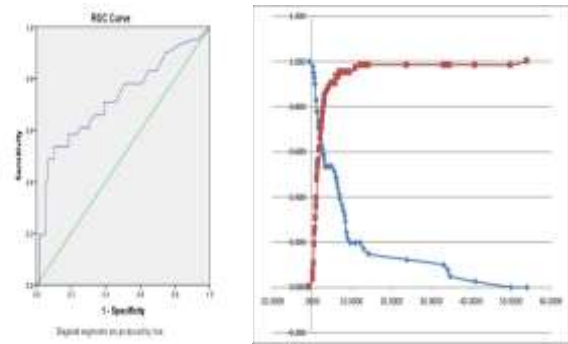

Figure 1. Cut off hs-CRP against cognitive impairment

Based on this study, the cut-off of hs-CRP level for cognitive impairment was 2.2 (p 0,003, OR : 3,761 (95% IK, 1,622-8,720)). It means that subjects whose hs-CRP level were >=2.2 had a risk of 3,761 times greater of having abnormal MoCA-INA score compared to those whose level was <2.2. This result can be seen in Table 10.

Table 10. Relationship between hs-CRP level using 2.2 cut-off with impaired cognitive function (MoCA-INA)

	MoCA-INA		p	OR (95%IK)
	Abnormal (%)	Normal (%)		
Level of hsCRP				
< 2,2	14 (34,1)	39 (66,1)	0,003	3,761 (1,622-8,720)
≥ 2,2	27 (65,9)	20 (33,9)		
Total	41 (100)	59 (100)		

DISCUSSION

This study was an observational analytic study with a cross-sectional design to determine the relationship between hs-CRP level and impaired cognitive function which was assessed using MoCA-INA score in HIV patients in The UPIPI Dr. Soetomo Academic Hospital, Surabaya.

This study found that subjects who were older than 50 years old tend to have abnormal MoCA-INA scores (P 0.004). A study by Jade et al in 2017 in South Africa found that age > 50 years was associated with the risk of developing HAND (P = 0.003) (Mogambery et al 2017). A Study by McCombe et al. in 2012 in Canada also obtained results that age was a predictor of HAND in HIV/AIDS patients even though they have received a combination of antiretroviral (P <0.05) (Mccombe et al 2013). Another cross-sectional study in 2010 in Botswana showed an increase in the prevalence of cognitive impairment in HIV patients with increasing age (Lawler et al 2010). According to Kamkwalala and Newhouse (2017), many factors influence brain aging in the HIV-positive population. Infiltration of HIV at an

early age could trigger an inflammatory and neurodegenerative process that would eventually cause HAND. Hence, older HIV-positive patients were more likely to have impaired cognitive function than younger ones.

This study also shows the relationship between sex and cognitive impairment assessed using the MoCA-INA score was not statistically significant with P = 0.550. This was consistent with research by Garrido et al in 2013 that reported no significant differences were found between sex and cognitive impairment in the HIV patient population (Garrido et al 2013). The same results were obtained in a study by McCutchan et al (2012) that reported there were no statistically significant differences between the sexes and impaired cognitive function with p 0.92.

In this study, the results of the analysis of the relationship between education and cognitive function disorders found statistically significant differences with p 0,002. Individuals who were highly educated reportedly showed a slower decline in cognitive function compared to those with poorly educated. This was because education has a protective effect on cognitive function (Catroppa & Anderson 2010). A study by Kathy et al in 2010 found that education level significantly affected cognitive functions in HIV patients (Lawler et al 2010). A study by Kabuba et al (2018) found that higher education was protective against the occurrence of HIV-associated neurocognitive disorder (HAND).

Overweight and obesity were associated with chronic systemic inflammation. In this study, the results of the analysis of the relationship between body mass index with impaired cognitive function did not demonstrate a statistically significant difference with P = 0.197. These results were consistent with a study by Okafor et al in 2017 who reported that body mass index ie overweight and obesity were not statistically related to cognitive function (Okafor et al 2017). The same results were obtained in Ku et al's study in 2014 which concluded that body mass index was not statistically significant with HAND (P = 0.105) (Ku et al 2014).

Vascular risk factors associated with poorer cognitive function include hypertension and diabetes. Mechanically, these factors cause inflammation and oxidative stress in blood vessels and cause cerebral hypoxia-ischemia and endothelial dysfunction of blood vessels (Tedaldi et al 2015). In this study, the results of the analysis of the relationship between vascular risk factors and cognitive impairment assessed using MoCA-INA did not have a statistically significant relationship with P = 1,000. These results were following previous

studies conducted by McCutchan, et al. in 2012 who reported that vascular risk factors were not statistically significant with impaired cognitive function with P = 0.07 (McCutchan et al 2012).

The results of the analysis of the relationship between hs-CRP level with impaired cognitive function assessed using MoCA-INA showed statistically significant results with P = 0.0001 and an Odds Ratio value of 28,072 (95% CI, 5,470-144,052). It means that the subjects who had level of hs-CRP >=5 had a 28,072 times greater risk of experiencing MoCA-INA disturbed than patients who had hs-CRP level <5. The results of this study were consistent with the study by Rubin et al. who reported that a high levels of hs-CRP were the strongest predictors of impaired cognitive function in HIV patients (Rubin et al 2018). A study conducted by Schouten et al in 2016 reported that inflammatory markers such as hs-CRP were one of the factors that significantly influenced cognitive decline in HIV patients with a p-value < 0.05 (Schouten et al 2016). The results of the analysis of the relationship between hs-CRP level with impaired cognitive function assessed using MoCA-INA showed statistically significant results, but these results could also be influenced by other conditions in the form of opportunistic infections, such as lung, brain, eye, nose and ear infections mouth and acute skin infections were mostly found in HIV patients. To reduce the bias due to these conditions, researchers sought to take the sample of the study in the Internal disease unit in The UPIPI on patients who came to control anti-retroviral therapy. This study did not take samples from other units at UPIPI such as pulmonology, ophthalmology, dermatology, ENT (ear nose and throat), or neurology unit.

In this study, a cut off level of hs-CRP was 2.2 for cognitive impairment. The results found that subjects who had hs-CRP level >=2.2 with impaired and normal MoCA-INA were 27 subjects (65,9%) and 20 subjects (33,9%) respectively. Whereas subjects whose hs-CRP level <2.2 with abnormal and normal MoCA-INA scores were 14 (34,1%) and 39 (66,1%) respectively. The above results were statistically significant (p-value of 0,003, OR: 3,761 (95% IK, 1,622-8,720)). It suggested that subjects who had hs-CRP level ? 2,2 had a risk of 3,761 times greater of having abnormal MoCA-INA compared to those whose level was less than 2,2.

The limitation of this study was that this study did not classify any affected cognitive domains of the subjects. The value of this study was that this study was the first study conducted at Dr. Soetomo Academic Hospital concerning the relationship between high C-Reactive Protein (hs-CRP) level and impaired cognitive function

assessed using MoCA-INA in HIV Patients in UPIPI Unit Dr. Soetomo Academic Hospital Surabaya.

Neurodegeneration in HIV-associated neurocognitive disorders (HAND) was associated with neuroglia activity. Damage to the nervous system in HIV infection occurs through 2 mechanisms: 1.) Toxicity occurs directly (direct) from HIV itself or through the release of viral proteins, such as Tat and gp120). Indirect toxicity was mediated by monocyte/macrophage cells (Hong & Banks 2016). The HIV-infected monocyte pathway was activated across the blood-brain barrier, infecting microglia and macrophages. Activation of macrophages and microglia would release proinflammatory products, such as IL-6 (Hong & Banks 2016). These proinflammatory cytokines could induce hepatocyte cells to synthesize CRP. CRP would cause the accumulation of reactive oxygen species (ROS) and vice versa. Reactive Oxygen Species (ROS) would cause an inflammatory process. Inflammasome regulated the activation of caspase-1. Caspase-1 functions to break down IL-1 cytokines into active forms namely IL-1? and IL-18 and cause pyroptosis and inflammation which ultimately resulted in HIV-related complications, such as HIV-associated neurocognitive disorders (HAND) (Galloway et al 2015).

Various neurotoxin and increased free radicals in the form of Reactive Oxygen Species (ROS) that caused inflammation processes had an important role in the incidence of HIV-associated neurocognitive disorders (HAND). Antiretrovirals were only able to reduce the density of the virus in the patient's body but were unable to overcome the influence of Reactive Oxygen Species (ROS) which were formed in many HIV patients (Nasronudin 2014). Even with a combination of suppressive antiretroviral, HIV-induced neuroinflammation continues (Rubin et al 2018).

CONCLUSION

There was a significant relationship between hs-CRP level and cognitive function, where subject with high hs-CRP level was more likely to have impaired cognitive function.

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