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SLEEP MEDICINE BOOK

Sleep Medicine:
Multidiscipline in Harmony

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Correlation between C-Reactive Protein Levels in COVID-19 Patients and Sleep Quality

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ABSTRACT

Background: Sleep disturbances are one of the most common complaints after COVID-19 infection. Sleep disturbances have an impact on the decline in the immune system and are associated with an increased inflammatory response that can increase the risk of cerebrovascular events. C-reactive protein (CRP) is a marker of acute phase inflammation and its concentration increases in the circulation during inflammation. To date, there have been no studies examining whether CRP can be used as a predictor of impaired sleep quality in the future.

Methods: This study is an analytical study with a retrospective cohort approach at Wahidin Sudirohusodo Hospital in July 2021 involving 31 samples of patients after COVID-19 infection. This study used the Pittsburgh Sleep Quality Index (PSQI) to measure sleep quality 3 months after outpatients and tested negative. CRP data obtained from medical record data when the patient was hospitalized. The correlation between CRP levels in COVID-19 patients and sleep quality was assessed by the Spearman correlation test.

Results: There was no significant correlation between CRP levels in COVID-19 patients and sleep quality ($p = 0.974$, $r = 0.006$).

Discussion: Sleep has an important role in the homeostasis and the immune system. Sleep disturbances have an impact on the decline in the immune system, increasing various kinds of pro-inflammatory cytokines, one of which is CRP. CRP has an association with cardiovascular events and stroke. In this study, CRP levels in COVID-19 patients were not significantly associated with sleep quality 3 months after COVID-19 infection. This can be due to the majority of subjects have not entered the menopause category, where sleep disturbances are more common in postmenopausal women. In addition, CRP is a marker of acute phase inflammation and its concentration decreases exponentially over 18-20 hours. CRP levels may persist after 24 hours after infection, even for several weeks to months. In this study, different results were obtained because the CRP values obtained did not coincide with the assessment of sleep quality.

Conclusion: CRP levels of COVID-19 patients cannot be used as a predictor to assess sleep quality in the future.

Keywords: COVID-19, PSQI, Sleep Quality, *C-Reactive Protein*

BACKGROUND

The definition of sleep according to the Guide to Management of Sleep Disorders by the Sleep Disorders Study Group of the Indonesian Neurologist Association (PERDOSSI) is a physiological and recurrent form of reversible decline in consciousness, usually there is a global decline in cognitive function so that the brain does not respond fully to surrounding stimuli. Sleep disturbances can occur when the quality or quantity of sleep is reduced or the circadian rhythm is disturbed. Sleep quality has several components, including: subjective sleep quality, sleep latency, sleep duration, efficiency of sleep habits, sleep disturbances, use of sleeping medications and daytime dysfunction.[1] Sleep disturbances can exacerbate systemic and lung inflammation during viral infections and can induce pro-inflammatory conditions and can be harmful during the Corona virus disease 2019 (COVID-19) pandemic.[2]

COVID-19 is an infectious disease caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), mainly affecting the respiratory system, with symptoms of interstitial pneumonia and Acute Respiratory Distress Syndrome (ARDS). Some patients experience prolonged multi-organ symptoms and complications beyond the initial period of acute infection. Long COVID-19 is persistent and/or delayed symptoms or long-term complications of COVID-19 infection after 4 weeks from symptom onset. Based on the latest literature, the definition is divided into 2 categories, namely: subacute/ongoing symptomatic COVID-19 and chronic or post-COVID-19 syndrome. Post COVID-19 syndrome includes symptoms and abnormalities that persist for more than 12 weeks from the acute onset of COVID-19.[4,5]

In a study conducted by Garrigues, et al in 2020, it showed that the majority of COVID-19 patients requiring hospitalization still experienced persistent symptoms, even up to 110 days after discharge from the hospital with a prevalence of sleep disorders of 30.8%.[6] In another study at 38 hospitals in Michigan, out of 488 patients who completed the survey, 32.6% of patients reported persistent symptoms with 18.9% reporting new or worsening symptoms. Similar findings in a European study that reported persistent symptoms in 87.4% of patients after passing the acute phase of COVID-19 infection.[7]

The pathophysiology of long COVID-19 is thought to be due to damage to the cardiorespiratory center in the brain stem. The ongoing neuro-inflammatory process can result in symptoms and neurological damage in long-COVID-19 patients. Elevated levels of pro-inflammatory markers (C-Reactive Protein (CRP), IL-6 and D-dimer) and lymphopenia have been shown to be associated with long-term COVID-19.[7]

In the current COVID-19 pandemic situation, sleep is an important component of maintaining the immune system and public health. Sleep disturbances have an impact on the decline in the immune system and are

associated with an increased inflammatory response that can increase the risk of cerebrovascular events, such as hypertension and diabetes mellitus. Poor sleep quality is associated with high levels of inflammatory markers, one of which is CRP.[8] C-reactive Protein (CRP) is a marker of acute phase inflammation and its concentration increases in the circulation during inflammation. Elevated CRP levels are an independent predictor of cardiovascular disease in healthy individuals.[9] To date, there have been no studies examining whether CRP can be used as a predictor of impaired sleep quality in later life. This study aims to see the relationship between CRP levels of COVID-19 patients with quality of sleep later in life.

METHODS

This study is a retrospective cohort design, observations were carried out retrospectively on patients after COVID-19 infection who were given a questionnaire to assess sleep quality. Then the medical record data was taken when the patient was hospitalized at the Inpatient Installation of Dr. RSUP. Wahidin Sudirohusodo with a diagnosis of COVID-19. The study was conducted in July 2021 until the number of samples was met. The place of research was conducted at Dr. RSUP. Wahidin Sudirohusodo, Makassar. The population of this study were all patients who underwent hospitalization at the Inpatient Installation of Dr. RSUP. Wahidin Sudirohusodo with a diagnosis of COVID-19 and has been outpatient. The sample of this study was post-COVID-19 infection patients who met the inclusion and exclusion criteria. The inclusion criteria used were patients aged 18-65 years, both male and female after COVID-19 infection and willing to be included in this study by signing informed consent and filling out research questionnaires. While the exclusion criteria in this study were complaints after COVID-19 infection, in the form of complaints that interfere with sleep quality, consuming drugs that affect sleep quality, consuming caffeine, alcohol and/or drugs in the last 1 month and suffering from psychiatric disorders based on anamnesis and medical record data. The data analysis used in this research is correlative analytic. The correlation between CRP levels in COVID-19 patients and sleep quality using the Spearman correlation test. Statistical analysis using SPSS version 25 program.

RESULTS

This study was conducted on patients after COVID-19 infection who had been hospitalized at the Dr. Wahidin Sudirohusodo Hospital, Makassar. There were 31 samples with the characteristics mentioned in Table 1. There were a total of 31 patients who completed the sleep quality questionnaire and data on CRP values were available from medical record data when the patient was previously hospitalized. The mean age at diagnosis was 34.94 years and the majority of the sample (58.1%) were women. From the 18 female samples, 12% aged >48 years

were found. The average body mass index (BMI) of the study sample was 24.47±5.27, 48.4% had a normal BMI, only 9.7% were obese. 27 patients had elevated CRP values with 19% mild elevation, 65% moderate elevation and 3% severe elevation. Table 1 also describes the sleep quality of patients based on PSQI scores with the results that 25 patients experienced good sleep quality (80.6%) and 6 patients experienced poor sleep quality (19.4%).

In the comparative test using the Mann Whitney test, the average CRP levels in patients with good sleep quality were 11.26±18.24 and in patients with poor sleep quality 3.69±3.42. There was no significant difference in CRP levels between COVID-19 patients with good sleep quality and poor sleep quality ($p = 0.548$).

After analyzing the data using the Spearman correlation test, there was no significant relationship between CRP levels in COVID-19 patients and sleep quality ($p = 0.974$, $r = 0.006$).

DISCUSSION

Sleep is a physiological condition and has an important role in the homeostasis system, the immune system, maintaining a person's performance, restoring muscles, helping energy metabolism, improving cognitive function and neuron plasticity. Lack of sleep or irregular sleep cycles can affect health, the immune system and induce pro-inflammatory conditions.[2]

Sleep disturbances cause a decrease in physical and cognitive performance and have adverse effects on health, among others, can increase the risk of stroke, obesity, diabetes, cancer, osteoporosis and cardiovascular disease.[2] Poor sleep quality contributes to the occurrence of cerebrovascular disease through the inflammatory process. Pro-inflammatory cytokines play an important role in the formation and progression of atherosclerotic plaques on the artery walls and promote the formation of acute-phase proteins such as C-reactive protein (CRP).[10] There are many mechanisms that explain the relationship between sleep disturbances and inflammation. When the individual occasionally awakens from sleep, an inflammatory cascade occurs and when the individual wakes up from sleep more often and inconsistent sleep from day to day will exacerbate the inflammatory response. Inflammation increases during stages 1 and 2 of sleep, as well as in the Rapid Eye Movement (REM) stage, whereas inflammation during slow wave sleep is comparable to that of wakefulness. Thus, during slow wave sleep, the inflammatory response returns to a homeostatic state (inflammation goes back down). If the individual wakes up several times at different times each night, or goes to bed at different times each night, it can result in a pro-inflammatory condition characterized by an increase in CRP. The inflammatory profile is more prominent in the elderly population because in the elderly population there is an increase in the proportion of REM sleep compared to slow wave sleep and

also in individuals with depression. Sleep and circadian processes are involved in the regulation of inflammatory cytokines. Recent evidence suggests that inconsistent sleep can increase the risk of metabolic disease. Therefore, it can be said that inflammation plays a role in the pathogenesis of metabolic diseases.[8]

In an epidemiological study, it was found that short sleep duration in adolescents and adults is associated with excessive body fat and an increased risk of developing type II diabetes mellitus. Poor sleep quality and quantity are also associated with poor glycemic control in patients with type II diabetes mellitus. Inflammatory factors are thought to be a potential mechanism linking poor sleep quality with diabetes. The results of this study are consistent with other studies evaluating the relationship between sleep disturbances and CRP, IL-6 and TNFα which state that sleep disturbances are associated with elevated CRP and IL-6.[11]

In the current COVID-19 pandemic situation, many sleep disorders are found after COVID-19 infection. Garrigues, et al in 2020 said that the prevalence of sleep disturbances in patients after COVID-19 infection reached 30.8%.[6] Another study by Nalbandian et al in 2021 reported that patients after COVID-19 infection experienced non restorative sleep and sleep difficulties in 25% of patients at 6 months of follow-up. The mechanisms that cause neuropathology in COVID-19 may overlap between direct viral infection, severe systemic inflammation, neuroinflammation, microvascular thrombosis and neurodegeneration.[5]

Other sleep disorders, such as Obstructive Sleep Apnea (OSA) can hypothetically exacerbate systemic inflammation and lung inflammation that occurs during viral infections, including in COVID-19 patients. OSA is a sleep disorder characterized by complete or partial obstruction of the upper airway during sleep. OSA is associated with comorbidities that are considered risk factors for COVID-19 patients, such as hypertension, diabetes, cardiovascular disorders and obesity. OSA can be associated with immunological and inflammatory factors that result in morbidity and mortality so it needs to be a concern in patients with COVID-19.[2]

OSA causes chronic intermittent imbalance between excessive sympathetic activation and decreased parasympathetic activity, and hypoxia, all of which have the potential to increase levels of IL-6, TNF- and IL1-β. Exacerbation of the inflammatory response resulting in airway damage is the most common manifestation of infection with SARS-CoV-2. This can aggravate COVID-19 patients and cause Acute Respiratory Distress Syndrome (ARDS). Acute and massive release of pro-inflammatory cytokines in response to viral infection and/or secondary to bacterial infection increases the occurrence of cytokine storms. Uncontrolled inflammation can lead to multiple organ failure.[2] Sleep fragmentation due to OSA was also significantly associated with high CRP levels.10 Pro-inflammatory conditions in individuals with OSA may be

associated with poor outcomes in COVID-19 patients. In contrast, the cardiovascular and respiratory consequences of COVID-19 can be even worse, even leading to OSA due to inflammation of the upper airway and persistent hypoxia from infection.[2]

Although viral particles have been reported in the brain in other coronavirus infections, there is no evidence that SARS-CoV-2 can infect neurons. However, at autopsy it was found that SARS-CoV-2 can cause changes in brain parenchyma and blood vessels, possibly through effects on the blood-brain/blood-cerebrospinal fluid barrier, resulting in inflammation of neurons and their supporting cells and brain vasculature.[5]

Sleep disturbances have an impact on the decline in the immune system, increasing various kinds of pro-inflammatory cytokines, one of which is CRP.[12] CRP is an acute inflammatory protein that increases in infectious and inflammatory conditions and has long been used as a marker of infection and predictor of cardiovascular events. There is evidence that CRP is not only a marker of inflammation but also plays an active role in the inflammatory process. CRP is present at sites of inflammation and tissue damage, binds to damaged cell membranes and contributes to the inflammatory response.[9]

The majority of studies that have been conducted state that CRP has a relationship with the incidence of cardiovascular disease and stroke.[9] However, to date there have been no studies examining whether CRP can be used as a predictor of impaired sleep quality in later life. Therefore, in this study, an assessment of the relationship between CRP levels in COVID-19 patients and quality of sleep in later life was carried out.

This study involved 31 subjects who met the inclusion criteria. The inclusion criteria used included: post-COVID-19 infection patients aged 18-65 years and willing to participate in this study. Subjects with a history of taking drugs with sedating effects such as alprazolam, diazepam, lorazepam, clobazam or amitriptyline, consumption of alcohol, caffeine and/or drugs (narcotics, psychotropics and other addictive substances) during the last 1 month were excluded from the study because of these factors can affect sleep quality. In addition, psychiatric disorders such as depression, schizophrenia, anxiety are also excluded because sleep disorders are estimated to occur in 30-80% of these patients.[13] Patients' sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) score. The PSQI is a valid and reliable questionnaire in many populations and is suitable for assessing qualitative aspects of sleep in addition to sleep duration and other symptoms of insomnia.[10]

In addition to factors that can affect sleep quality, there are also factors that also affect CRP levels. The baseline value of CRP can be influenced by age, sex, smoking history, weight, lipid levels and blood pressure. Elevated CRP levels are usually affected by disease, but liver failure is one condition that can interfere with CRP production. Very few drugs can lower CRP levels. Decreased CRP levels may occur with treatment of the underlying disease.[9]

As described above, sleep disturbances can lead to increased levels of CRP which have a negative effect on the cerebrovascular system. However, high CRP levels when infected with COVID-19 do not necessarily cause sleep disturbances later in life. This is evidenced in this study, where after data analysis, there was no significant correlation between CRP levels in COVID-19 patients and sleep quality later in life ($p = 0.974$, $r = 0.006$).

Of the 31 subjects involved in this study, the majority were female (58.1%), of which 88% had not yet entered menopause. Based on the Survey of Women's Health Across the Nation, sleep disturbances occur 1.6-3.4 times more often in postmenopausal women. In addition to gender and age, other factors that can confound the relationship between sleep quality and inflammation , namely BMI and visceral obesity.[10] In Table 1 it can be seen that the mean BMI of the subjects involved in this study was 24.47 kg/m2 (normal BMI based on WHO).15 A higher BMI is associated with low-grade chronic inflammation.[11]

CRP is a marker of acute phase inflammation and its concentration increases in the circulation during inflammation. However, after the stimulation is gone, CRP levels decrease exponentially for 18-20 hours.[9] In contrast to the results of the study conducted by Ewett et al, it is said that CRP levels are quite stable for 24 hours after infection, even persisting for several hours. weeks to months after the inflammatory process ends.[10] In this study, CRP levels were obtained when the patient was infected with COVID-19 and evaluation of sleep quality was carried out approximately 3 months after being negative. The study conducted by Dzierzewski et al said that higher CRP levels were associated with poorer sleep quality.[8] In this study, different results were obtained because the CRP values obtained were not in conjunction with sleep quality assessments. Peripheral inflammatory markers are present only at certain points in time.[9]

Based on the description above, CRP levels when infected with COVID-19 cannot be used as a predictor of sleep disturbances in the future. However, CRP levels when infected with COVID-19 can be used as a parameter that needs to be considered in patients with cardiovascular comorbidities (hypertension, diabetes, obesity, smoking, and stroke) because sleep disturbances can worsen the inflammatory response that has an impact on disease progression.

CONCLUSION

CRP levels of COVID-19 patients are not significantly related to the quality of sleep of patients after COVID-19 infection, so they cannot be used as predictors to assess sleep quality in the future.

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TABLES

Table 1. Frequency Distribution

Characteristic		n	%	Mean	SD
Gender	Male	13	41,9		
	Female	18	58,1		
Age 22-48 years old	Male	12	92%		
	Female	16	88%		
Age >48 years old	Male	1	8%	34,94	11,06
	Female	2	12%		
BMI (kg/m^2)	Underweight	2	6,5%		
	Normal	15	48,4%		
	Overweight	11	35,5%	24,47	5,27
	Obese	3	9,7%		
C-reactive protein	Normal	4	13%		
	Mild Elevation	6	19%		
	Moderate Elevation	20	65%	9,78	16,82
	Severe Elevation	1	3%		
PSQI	Good	25	80,6		
	Poor	6	19,4		
Total		31	100,0		

Table 2. Spearman Correlation Test Analysis Result

	PSQI
CRP	r = 0.006 p = 0.974 n = 31

Spearman Correlation Test

Table 3. Mann Whitney Test

PSQI	CRP		p value
	Mean	SD	
Good	11,26	18,42	0,548
Poor	3,60	3,42	
Total	9,78	16,82	