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Original Research Article

Relationship between Sleep Quality and Low Inflammation in Medical Students of Universitas Nusa Cendana

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Abstract: Sleep is one of the basic human physiological needs that can restore the body to its physiological functions after daily activities. Lack of sleep quality can significantly impact the body, one of the effects of which is related to chronic low-level inflammation and changes in the competence of the immune system. This research aims to knowing the relationship between sleep quality levels and Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio in medical students of Universitas Nusa Cendana. It is an observational analytical study using the cross-sectional method. The number of research samples was determined using a hypothesis test formula against relative risk, with a total sample of 54 people. The population of this study is the class of 2019, 2020, and 2021 using the proportionate stratified random sampling technique, which divides populations into sub-populations in a propositional and random manner. The relationship test used is the ETA test. Based on the results of relationship testing using the ETA test, sleep quality with Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio shows that sleep quality has no significant relationship with Neutrophil Lymphocyte Ratio (p-value = 0,324); however, it has a significant relationship with the Platelet Lymphocyte Ratio (p-value = 0,042). Sleep quality does not have a significant relationship with the Neutrophil Lymphocyte Ratio but has a significant relationship with the Platelet Lymphocyte Ratio. 228 kata.

Keywords: Sleep quality, Neutrophil Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR).

INTRODUCTION

Sleep is a basic psychological human need. The human body needs sleep to restore the body to its physiological functions after daily activities (Ambarwati, 2017). A person's sleep quality describes how an individual can maintain his sleep in quality and quantity. A feature of good sleep quality is the non-occurrence of disturbances in daily life after sleep, such as the absence of excessive sleepiness, headaches, frequent yawning, swollen eyes, and frequent restlessness (Kadek Novi Ardiani & Made Subrata, 2021). Adequate sleep can restore the natural balance of neuron centers, innervation maturation, and facilitation of learning and memory processes. It can maintain metabolic balance, temperature balance, and immune competence of the body (Barrett *et al.*, 2012; Hall & Guyton, 2011). According to Guyton, the specific physiological functions of sleep for the body still need to be known, so they require further research. Sleep quality can be measured by the Pittsburg Sleep Quality Index (PSQI) instrument developed by Buysse in 1988. According to Sukmawati and Putra, PSQI is often used by clinicians in various countries and has proven levels of validation in measuring the level of sleep quality of patients (Sukmawati & Putra, 2019).

According to a study by Paceli (2022), most medical students have poor sleep quality. As many as 58% of the samples had poor sleep quality, and only

42% of the samples had good sleep quality (Paceli *et al.*, 2022).

Park (2021) states that poor sleep quality is often associated with chronic low-level inflammation. The effect of sleep on subclinical inflammation still needs to be clearly understood. However, it is believed that more significant sleep disorders have a relationship with higher levels of inflammatory markers as well (Park & Lee, 2021). According to research conducted by Dian Amalia *et al.*, (2019), sleep quality is related to increased leukocytes, lymphocytes, monocytes, and granulocytes. It is associated with the presence of interactions of melatonin with the immune system (Amalia *et al.*, 2019). Research by Almeida (2016) also states that there are changes in the body's immune composition, both innate immune system and adaptive immune system, to sleep quality in night shift workers (Almeida & Malheiro, 2016).

Inflammatory markers often used are Neutrophil Lymphocyte Ratio (NLR) and *Platelet Lymphocyte Ratio* (PLR) (Song *et al.*, 2021; Zahorec, 2021). This is because both markers are very sensitive to inflammatory reactions, easy to implement, and cheap, only with a complete blood test. However, Platelet Lymphocyte Ratio is still rarely studied and known when compared to *Neutrophil Lymphocyte Ratio* (Harun *et al.*, 2016; Martins *et al.*, 2019; Song *et al.*, 2021; Wu *et al.*, 2019; Zahorec, 2021; Zenith, 2019).

MATERIALS AND METHODS

This research is an observational analytical study using *the* cross-sectional method. The number of research samples was determined using a hypothesis test formula for relative risk, with a total sample of 54 people. The population of this study is the class of 2019, 2020, and 2021 using the *proportionate stratified random sampling* technique, which divides the population into sub-populations in a propositional and randomized manner. The relationship test used is the ETA test.

This research was conducted on Universitas Nusa Cendana medical students. The filling out of the PSQI questionnaire and the respondent's venous blood draw were carried out on September 10, 17, and 24, 2022 at 09.00 – 12.30 WITA in the laboratory of Universitas Nusa Cendana Medical Education Study Program, then on the same day, a blood sample of the respondent was handed over to the laboratory of the S.K Lerik Regional General Hospital for a complete blood examination.

RESULT AND DISCUSSION

Table 1: Respondents' Characteristics

Characteristic	Frequency (n) n=54	Percentage (%)
Gender		
• Man	10	18,5
• Woman	44	81,5
Total	54	100
Class		
• 2019	15	27,8
• 2020	19	35,2
• 2021	20	37
Total	54	100

Based on the data in Table 1 it is known that the most sex distribution is female (81.5%). The distribution of samples by class has been determined using the *proportionate stratified random sampling* formula.

Table 2: Sleep Quality Distribution

No.	Sleep Quality	Frequency (n)	Percentage (%)
1.	Good	15	27,8
2.	Bad	39	72,2
	Total	54	100

Table 2 data results showed that respondents' sleep quality was dominated by poor sleep quality, with 39 respondents (72.2%), while only 15 respondents (27.8%) had good sleep quality.

Table 3: Distribution of Leukocyte Count and Platelet Count

	Category	Frequency (n)	Percentage (%)
Leukocyte	Leukopenia	0	0
	Normal	54	100
	Leukocytosis	0	0
Platelets	Thrombocytopenia	0	0
	Normal	45	83,3
	Thrombocytosis	9	16,7

Table 3 shows that all respondents had leukocyte counts within normal limits. Meanwhile, nine respondents had thrombocytosis, and 45 had platelet counts within normal limits.

Table 4: Data Description

	N	Mean $\pm$ SD	*p-value*
NLR	54	1,92 $\pm$ 0,456	0,138
PLR	54	153,65 $\pm$ 35,27	0,058

Annotation: *p-value* significance if more than 0,05

Table 4 indicates that the average NLR value is 1.92. Meanwhile, the PLR value has an average of 153.65. NLR and PLR data of respondents were first tested for normality using the Shapiro-Wilk formula because the sample was less than 100. The normality test will be seen on the significance value. If the significance value is obtained: *p value* > 0.05, then the data is normally distributed. Meanwhile, if the opposite is obtained significance value of *p value* < 0.05, then the data is not normally distributed.

The significance value (p-value) in the Shapiro-wilk test for NLR is 0.138 (p-value 0.05), so the Shapiro-wilk normality test of NLR data is categorized as normal, while the significance value of PLR data with Shapiro-wilk test is 0.058 (*p value* > 0.05), so the Shapiro-wilk normality test of PLR data is also categorized as normal.

The classification of PLR data will be based on the calculation of respondents' average (mean) PLR value due to normally distributed data, where the average PLR value of respondents is 153.65. A smaller PLR value equal to 153.65 is classified as low, while a larger PLR value of 153.65 is classified as high.

Table 5: NLR and PLR Data Distribution

	Category	Frequency (n)	Percentage (%)
NLR	Normal	28	51,9
	Grey zone	24	44,4
	Mild to moderate inflammation	2	3,7
	Moderate inflammation	0	0
	Severe inflammation	0	0
PLR	Low	31	57,4
	High	23	42,6

Data table 5 shows that more than half of respondents have NLRs in the normal category, namely 28 respondents (51.9%), while 24 respondents (44.4%) have gray zone NLR value categories. Only two respondents had NLR results in the mild to moderate inflammatory category. The results of respondents' PLR measurements were dominated by the low PLR value category of 31 respondents (57.4%), while the high PLR category was only 23 respondents (42.6%).

The results of the study conducted by filling out the PSQI questionnaire to 54 respondents found that as many as 15 respondents (27.8%) had good sleep quality and 39 respondents (72.2%) had poor sleep quality, where it was concluded that the majority of Universitas Nusa Cendana medical students had poor sleep quality. According to Bianca *et al.,* (2021) at the Faculty of Medicine, Udayana University, it was found that 43 respondents (41.7%) had good sleep quality, and 60 respondents (58.3%) had poor sleep quality.(Bianca *et al.*, 2021) According to Ibrahim *et al.*, (2017) in medical students at *King Abdulaziz University* showed a significant difference in numbers, namely 70.4% of respondents out of a total of 576 respondents had poor sleep quality (Ibrahim *et al.*, 2017).

According to Ibrahim *et al.*, (2017), anxiety is the main factor in medical students' decline in sleep quality. Students with major depression will have a worse sleep quality than normal students. This study stated that students with good study scores have significantly worse sleep quality than other students. The use of social media at night is known to have no

strong association with poor sleep quality (Ibrahim *et al.*, 2017).

According to Bardosono (2022), poor sleep quality is related to poor food consumption quality. A decrease influences a person's mood, which will affect a person's dietary behavior. According to Kefi (2022), an irregular diet significantly correlates with the dyspeptic syndrome. Irregular eating habits will make it difficult for the stomach to adapt, where the production of stomach acid will increase so that it can irritate the stomach, which triggers an inflammatory reaction (Bardosono *et al.*, 2022; Giovani *et al.*, 2022).

A person's sleep quality can affect the body's immune quality. According to Savard *et al.*, (2003), an individual with good sleep quality will have a much higher amount of TCD3$^+$, TCD4$^+$, and TCD8$^+$ than insomniacs (Savard *et al.*, 2003). Poor sleep quality is known to increase the risk of viral infections in the respiratory tract. This increase may be due to a decrease in the number of NK cells and a decrease in the response of the Th1 effector, which plays a vital role in the activation process of TCD4$^+$ lymphocytes. Circulation of immune cells, including T cells and B cells, occurs at the beginning of the evening and will decrease during the nocturnal time, then exit the circulation to lymphoid organs and virus-infected cells. Sleep disturbances will lead to decreased regulation of IL-2 production by T cells and sleep deprivation associated with decreased *in vitro* proliferation ability of T cells (*Prather et al.*, 2015).

An increase in the total number of leukocytes, especially the number of neutrophils, can be found in individuals with poor sleep quality. Boudjeltia *et al.*, (2008) stated a significant increase in the number of leukocytes and neutrophils in individuals with sleep restrictions on the third night. Limiting sleep to 4 hours for three days in a row can provoke an increase in the number of leukocytes, especially the number of neutrophils, in healthy young individuals (Zouaoui Boudjeltia *et al.*, 2008).

The results of statistical tests using the ETA test can conclude that there is no relationship between sleep quality and NLR. These results are in accordance with a study conducted by Zhang *et al.*, (2020) in China which stated that there was no significant difference between the group of Covid-19 patients with good sleep quality and the group of Covid-19 patients with poor sleep quality in the increased in NLR in the first seven days of treatment. However, in the second week, low sleep quality in patients showed a significant association with slowing healing from lymphopenia and an increase in NLR. On the 14th and 21st days of hospitalization, patients with low sleep quality had a slower healing process and increased NLR levels. This evidence suggests the need for a period for an individual with poor sleep quality to have an increased

NLR (Zhang *et al.*, 2020). According to Nie *et al.*, (2022), patients with chronic insomnia will have a higher NLR than normal patients. This event can occur due to an increase in the number of neutrophils and a decrease in the number of lymphocytes that will increase the number of NLR (Nie *et al.*, 2022). Neutrophil Lymphocyte Ratio is commonly used as a biomarker of systemic inflammatory processes in diabetes mellitus, acute coronary syndrome, and other inflammatory diseases (E. L. S. Setianingrum & Widyastiti, 2019). According to Setianingrum (2019), a low lymphocyte count is related to the patient's poor cardiovascular condition. Lymphocytopenia is a marker of chronic inflammatory events due to increased apoptosis of lymphocytes (E. Setianingrum & Ap, 2019).

The results of statistical tests using the ETA test can conclude that there is a relationship between sleep quality and PLR. The ETA value of the relationship between sleep quality and PLR is 0.278, so according to the relationship degree guidelines, sleep quality and PLR have a weak correlation. *Platelet Lymphocyte Ratio* can increase if there is an increase in platelet count and a decrease in lymphocyte count. This weak correlation is due to the rapid increase in platelet count when inflammation occurs, but it takes a chronic time for the lymphocyte count to decrease. These results are in accordance with research conducted by Krummenacher *et al.*, (2009), one of which examines the relationship between poor sleep quality and platelet count. The study found that high platelet counts were associated with poor sleep quality. Platelet count is relatively higher in patients with problems initiating sleep, frequent awakenings at night and frequently wakes up not feeling refreshed in the morning (Krummenacher *et al.*, 2009). An increase in platelet count can result from an inflammatory process. According to Stokes and Granger (2012), Inflammatory mediators such as Interferon-gamma (IFN-γ), *Interleukin-2* (IL-2), and C-C *Chemokine Ligand* 22 (CCL22) motifs can activate platelets. Oxidative stress that produces inflammatory mediators through the activation of phospholipase A2 and the formation of *platelet-activating factor* (PAF) can also activate platelets (Stokes & Granger, 2012). According to Irwin MR *et al.*, (2016), the greater a person's sleep disorder, the greater the number of inflammatory markers circulating in the blood. The sympathetic nervous system and insulin resistance are the main effector systems in explaining the relationship of sleep quality to inflammatory markers. The sympathetic nervous system will become more inactive when sleeping but will increase if a person has a sleep disorder. Insomnia patients are described as having increased sympathetic nervous system activity, resulting in increased levels of adrenaline and noradrenaline in the circulation. This event is related to the increase in inflammatory markers in a person with a sleep disorder which will then increase the number of platelets (Park & Lee, 2021).

This study shows that poor sleep quality can affect the body's immune system and trigger chronic low inflammation. An increase in neutrophils and platelets can occur in individuals with poor sleep quality. Excessive amounts of neutrophils and other leukocytes can increase the risk of coroner heart disease through the ability to cause proteolytic and oxidative damage to the coroner's arteries. Stimulated neutrophils can secrete proteolytic proteases that can trigger the release of endothelial cells from the walls of blood vessels and the attachment of platelets in subendothelial collagen and fibronectin (Zouaoui Boudjeltia *et al.*, 2008). Platelet increase can be a sign of a low-level inflammatory process and is one of the risk factors for venous thromboembolism (Krummenacher *et al.*, 2009). Decreased sleep quality can also decrease the number and function of lymphocyte cells. The decrease in the number and function of lymphocyte cells will affect the body's ability to respond to the viral infection process, so the incidence of illness will increase (Prather *et al.*, 2015). Therefore, lifestyle changes with enough sleep to improve sleep quality are very important.

Education about lifestyle changes for adequate sleep is essential to improve the health status of the public, especially medical students. According to Bi'i (2021), one suitable information dissemination medium is video because it attracts more attention and motivation from the audience (Bi'i *et al.*, 2021).

CONCLUSION

1. There is no relationship between the level of sleep quality and the Neutrophil Lymphocyte Ratio in medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, and there is a relationship between the level of sleep quality and the *Platelet Lymphocyte Ratio* in medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana.
2. Measuring the sleep quality of medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, shows that most students have poor sleep quality.
3. Measurement of leukocyte count for medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana shows that all students have a leukocyte count within normal limits.
4. Measurement of the platelet count of medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana showed that the majority of students had platelet counts within normal limits and only a few respondents had thrombocytosis.
5. Analysis of the *Neutrophil Lymphocyte Ratio* (NLR) in medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, shows that most students own a low NLR level.
6. Analysis of *Platelet Lymphocyte Ratio* (PLR) in medical students, Faculty of Medicine and Veterinary Medicine, Universitas Nusa Cendana, shows that most students have low PLR levels.

RECOMMENDATIONS
1. **For Future Researchers**
    It is hoped that this study can be perfected by controlling other factors in assessing respondents' sleep quality, such as physical environmental conditions, psychological stress, and chemical substances, and can be expanded by examining other factors that can affect NLR and PLR as new indicators in assessing risk factors for diseases and inflammatory processes.

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