

# Increasing of Cortisol Level and Neutrophil-Lymphocyte-Ratio are Associated with Severity Level and Sleep Disturbances in Acute Ischemic Stroke

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**Background:** Acute ischemic stroke can cause sleep disturbances. These complaints involve various factors, such as disturbances of the hormone cortisol and Neutrophil-Lymphocyte-Ratio (NLR) that can cause increasing severity levels in acute ischemic stroke patients. This study aimed to determine the relationship between cortisol levels and NLR with severity levels and sleep disturbances in acute ischemic stroke patients.

**Methods:** A cross-sectional analytic observational study was conducted on acute ischemic stroke patients during August – December 2022. Examine cortisol levels using the ELISA method, NLR from blood test, asses severity levels using the National Institute of Health Stroke Scale (NIHSS), and The Pittsburgh Sleep Questionnaire Index (PSQI) is used as a measure for the initial screening of sleep disturbances—statistical analysis using Spearman correlation.

**Results:** Total study subjects were 48 patients, with the majority 62.5% women; the mean age of study subjects was above 60 years (56.3%), and the most common type of stroke was large artery atherosclerotic stroke (77.1%), the highest NIHSS score was in the moderate category (85.4%), the most common risk factor is hypertension (64.4%), and basal ganglia area is the most common ischemic stroke location (52.1%). There was a positive correlation between cortisol levels with NIHSS ( $r=0.874$ ;  $p$ -value  $<0.001$ ), NLR with sleep disturbances ( $r=0.829$ ;  $p$ -value $<0.001$ ), NLR with NIHSS ( $r=0.893$ ;  $p$ -value $<0.001$ ), and NIHSS with PSQI ( $r=0.836$ ;  $p$ -value $<0.001$ ).

**Conclusion:** There were a positive correlation between cortisol level, NLR level, and NIHSS score with sleep quality disturbances based on PSQI in acute ischemic stroke patients.

**Keywords:** acute ischemic stroke, PSQI, cortisol, NIHSS, NLR

## Introduction

Stroke is an acute condition characterized by a sudden decrease in blood flow to brain tissue, causing disruption or loss of neurological function, with symptoms lasting more than 24 hours. Ischemic stroke is one of the most common causes, accounting for 87% of all stroke cases caused by occlusion of cerebral blood vessels.<sup>1</sup> Ischemic stroke is an episode of neurological dysfunction caused by focal infarction in the brain, resulting from decreased or impaired blood circulation so that neurons do not get the substrate they need.<sup>2</sup>

The brain and stroke regulate sleep cycles can cause sleep quality disturbances because affected brain structures can play a role in sleep regulation disorders.<sup>3</sup> Approximately 21–77% of stroke patients experience sleep quality disturbances.<sup>4</sup> Research conducted by Bradley Bush in 2010 and Julia Ross in 2014 said that increased cortisol levels were the main cause of sleep quality disturbances. Research by Hanna Christensen et al in 2014 in Denmark reported that in 162 patients with acute ischemic stroke, there was an increase in cortisol levels on the first day of the stroke. Increased serum cortisol levels are associated with the mortality rate of ischemic stroke patients. However, this mechanism has not been described in detail.<sup>3,4</sup>

Inflammation of brain tissue in ischemic stroke increases in response to vascular damage. Leukocytes which are markers of systemic inflammation exacerbate ischemic brain tissue damage. Neutrophil infiltration into brain tissue begins within the first 6–12 hours of ischemic damage. Neutrophils accumulate in the cerebral vasculature within hours, disrupting microvascular perfusion by obstructing microvascular structures, and ultimately contributing to the extent of the infarction. In ischemic brain tissue, lymphocytes begin to increase after 3–6 days. This complex inflammatory response involves several different cell types in the area of brain damage and triggers brain damage and functional impairment. Higher lymphocyte and neutrophil counts have been shown to correlate with larger infarct volumes and increased stroke neurologic deficits and are associated with poor prognostic outcomes after three months.<sup>5,6</sup>

Ferre et al in Spain conducted a study using the Pittsburgh Sleep Quality Index (PSQI) and PSG questionnaire in acute ischemic stroke patients, finding that 77% experienced decreased sleep quality. The PSQI has been tested for validity and reliability (about 87%) in assessing sleep quality disturbances in patients with acute brain lesions. Researchers have widely used the PSQI to identify sleep quality disturbances in stroke patients.<sup>4</sup> PSQI has a specificity of 86.5% and a sensitivity of 89.6%.<sup>7,8</sup> It is necessary to research the relationship between cortisol, NLR levels, and NIHSS scores on sleep quality disorders in acute ischemic stroke patients. This study aimed to determine the relationship between cortisol levels and NLR with severity levels and sleep disturbances in acute ischemic stroke patients.

## Methods

### Research Subjects

The subjects in this study were all acute ischemic stroke patients treated at dr. Hasan Sadikin Bandung and RS. Muhammadiyah Bandung, with an acute ischemic stroke (confirmed by head CT scan) on day 1–3, age  $\geq 18$  years (divided into large artery atherosclerosis, small vessel, and cardioembolic), and also fully alert awareness. We excluded the patients currently taking drugs that have a sedative effect (diazepam, amitriptyline) or arousal effects (dexamethasone, morphine, heroin, amphetamines); history of depression and anxiety disorders using the Hamilton Depression Rating Scale (HDRS); patients with bronchopneumonia, Asthma, chronic obstructive pulmonary disease (COPD), Coronavirus Disease 19 infection (COVID-19); and if there are symptoms of sleep quality disturbance before the recent stroke.

### Research Methods

The research method used in this study was cross-sectional analytic observational, with the subjects of the study being acute ischemic stroke patients treated with a neurology leader at RSUP, dr. Hasan Sadikin Bandung and RS Muhammadiyah Bandung. Data on subject characteristics were obtained through interviews, physical examinations, laboratory examination, and using the PSQI questionnaire, which has been validated for sleep quality disorders. Research subject will be explained about PSQI (about 15 minutes), and they answered regarding the question in questionnaires.

### Statistical Analysis

We use IBM SPSS 22.0 (IBM Corp, Armonk, NY) for statistical analysis. This study set a confidence level of 95% ( $Z\alpha = 1.96$ , 2-way hypothesis) and test power was set at 80% ( $Z\beta = 0.84$ ). The magnitude of the  $r$  correlation coefficient between cortisol levels and RNL with sleep quality disturbances has not been found in previous studies, so the  $r$  coefficient was set at 0.4 (medium strength). From the calculation of the sample size, the minimum sample is 47 subjects. This study uses the Spearman rank test, and a  $p$ -value below 0.05 is considered significant, and the  $r$  coefficient was calculated to establish the correlation.

### Research Instruments

Head CT Scan without Contrast for confirming ischemic stroke that has been expertised by a neuroradiologist.

### Pittsburgh Sleep Questionnaire Index (PSQI)

The measurement tool widely used for the early screening of sleep disorders is the PSQI. The PSQI questionnaire was delivered using an interview-based method by the researcher. The PSQI questionnaire consists of 19 questions with four

open-ended questions and 15 with ordinal scale answers. Questions 5a–5i have a scale: never, 1 x a week, 2x a week, and  $\geq 3x$  a week, while questions 6–9 have an ordinal scale with different types of responses. The 19 question items measure seven components: namely (1) subjective sleep quality calculated based on question no 6; (2) sleep latency calculated based on the total score of questions no. 2 and 5a; (3) sleep duration as measured based on question no 4; (4) length of sufficient sleep in bed measured based on questions no. 1, 3, and 4; (5) sleep quality disturbance as measured by questions no. 5b–5j; (6) use of sleeping pills as measured by question 7; and (7) concentration disturbance during the day measured based on questions 8 and 9. All components of the PSQI questionnaire have a score on a scale of 0–3. The scores of the seven components are added together to form 1 (one) global score with a range of 0–21. There are two interpretations of the Indonesian version of the PSQI, namely, good sleep quality if the score is  $< 5$  and poor sleep quality if the score is  $> 5$ .

## Examination of Cortisol Levels

Sampling was done by consecutive selection. Blood and saliva samples were taken in the morning at 07.00–09.00; laboratory tests were carried out at Hasan Sadikin Hospital, Bandung. Serum and salivary cortisol levels were examined using a cortisol kit with a competitive ELISA method. The normal level of salivary cortisol is 4.5–7.0 ng/mL.<sup>9</sup>

## Ethical Clearance

Dr. Hasan Sadikin General Hospital Bandung Human Research Ethics Committee (LB.04.01/A05/EC/222/VI/2022) approved this study. This study complied with all relevant ethical regulations (including The Declaration of Helsinki). All patients were informed about the purpose of the research and obtained written consent.

A study flow diagram listed in [Figure 1](#).

## Results

### Characteristics of Research Subjects

Subjects who met the inclusion and exclusion criteria were 48 people ([Supplementary Material](#)). The characteristics of the study subjects can be seen in [Table 1](#), where the majority were female (62.5%), the average age of the study subjects was above 60 years (56.3%), the most common type of stroke was large artery atherosclerosis stroke (77.1%), the highest NIHSS score in the study subjects was in the moderate category (85.4%), the highest risk factor was hypertension (64.4%), the second is dyslipidemia (47.9%), and the third is diabetes mellitus (33.3%), the location of the most stroke lesions is in the basal ganglia area (52.1%), then cortical (25.0%), pons (22.9%), thalamus (8.3%) and others (4.2%).

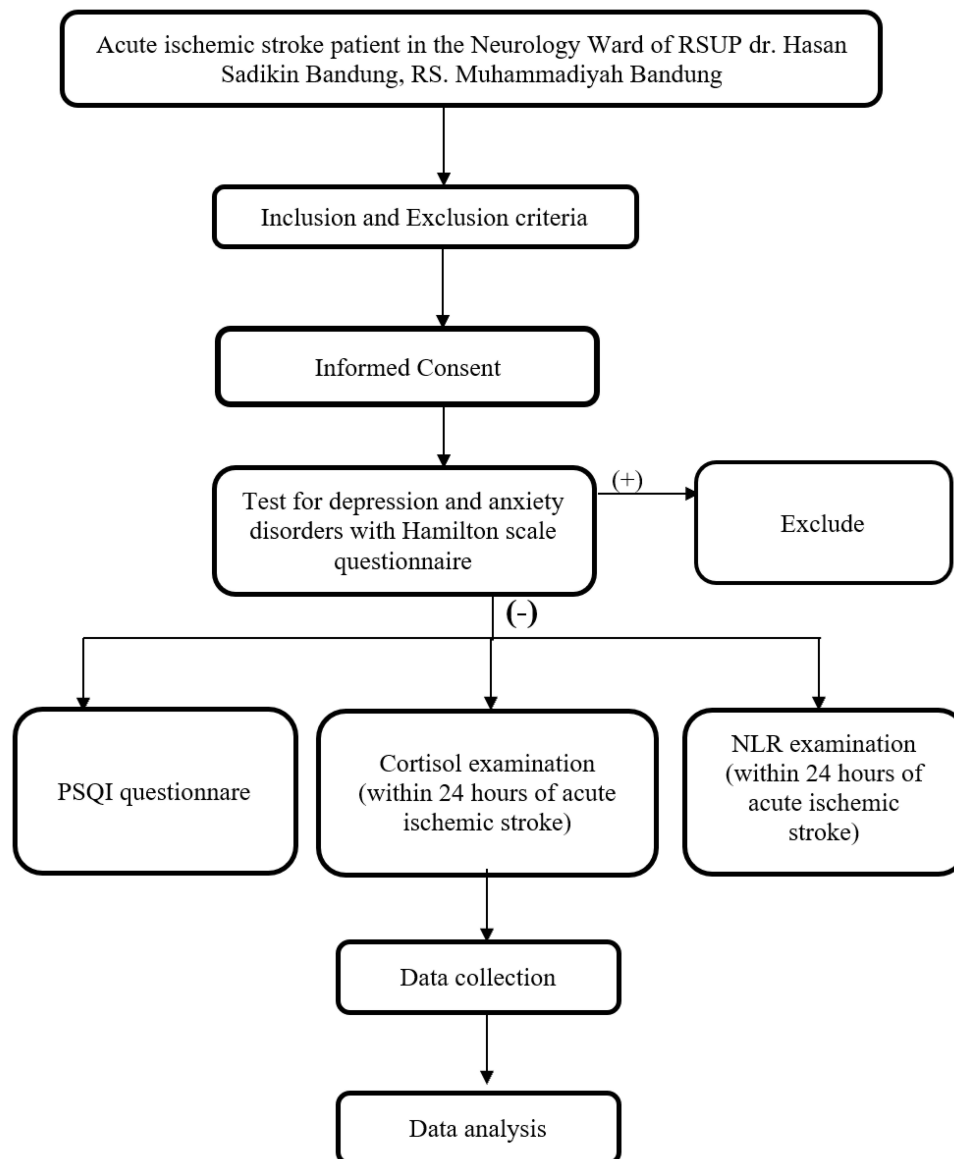
Description of cortisol levels based on characteristics in patients aged  $>60$  years had an average of  $10.38 \pm 9.030$  while those aged  $\leq 60$  years had an average of  $12.06 \pm 8.397$ , male patients had an average of  $11.97 \pm 9.127$ . In contrast, in patients women have an average of  $10.73 \pm 7.996$ . Patients in the mild NIHSS category had an average of  $3.51 \pm 1.378$ , while patients in the moderate NIHSS category had an average of  $12.78 \pm 8.570$ .

Cortisol levels in patients with the large artery atherosclerosis stroke category had an average of  $13.15 \pm 4.254$ ; in cardioembolism, it had an average of  $22.93 \pm 8.572$ ; lacunar had an average of  $2.20 \pm 0.707$ . Cortisol levels in the single risk factor group averaged  $5.09 \pm 1.824$ , and the multiple risk factor group averaged  $14.31 \pm 8.910$ .

Cortisol levels with basal ganglia lesions had an average of  $9.95 \pm 7.331$ ; cortical lesions had an average of  $21.03 \pm 9.206$ , thalamus lesions had an average of  $14.65 \pm 5.979$ , medulla oblongata lesions had an average of  $7.95 \pm 1.061$  while patients with other locations mean of  $8.12 \pm 7.161$ .

### Distribution of Cortisol Levels, NIHSS and PSQI

Of the 48 acute ischemic stroke subjects examined, cortisol levels were correlated with NIHSS and PSQI scores. In [Table 2](#), the median cortisol level is 8.0 ng/mL (IQR: 5.9–14.6) with a minimum range of 1.7 ng/mL and a maximum of 34.6 ng/mL, the median NLR is 5.9 (IQR: 3.2–8.1) with a minimum range of 2.0 and maximum 20.0, then a median NIHSS of 9.3 (IQR: 6.6–15.7) with a minimum coverage of 3.0 and a maximum of 20.0, a median PSQI of 9 (IQR: 6–10) with a minimum range of 2 and a maximum of 20, and 87.5% experienced poor sleep quality disturbances.



**Figure 1** A study flow diagram.

### Correlations of Cortisol Levels, NIHSS, and PSQI

From [Table 3](#), the results of the statistical analysis of Spearman correlation test between cortisol levels with poor sleep quality and NIHSS with poor sleep quality there was a significant relationship between cortisol levels with sleep quality disturbances ( $p$ -value  $<0.001$ ) and NIHSS with poor sleep quality ( $p$ -value  $<0.001$ ). This shows a significant correlation in the direction of correlation between cortisol levels and impaired sleep quality and NIHSS with poor sleep quality.

### Correlations of Cortisol Levels, NLR Level, and NIHSS

Statistical analysis of the Spearman correlation test between the variables cortisol levels and NIHSS showed a significant positive correlation between cortisol levels with NIHSS ( $r=0.874$ ;  $p$ -value  $<0.001$ ), NLR with sleep disturbances ( $r=0.829$ ;  $p$ -value  $<0.001$ ), and also a significant positive correlation between NIHSS and PSQI ( $r=0.836$ ;  $p$ -value  $<0.001$ ). This was shown that the higher the cortisol level and the higher the NIHSS will impair sleep quality using PSQI tools ([Table 4](#)).

**Table 1** Characteristics of Research Subjects

Variable	N=48	Cortisol Level (ng/mL) Mean±Std
>60 year	27(56.3%)	10.38±9.030
≤60 year	21(43.8%)	12.06±8.397
Gender		
Male	18(37.5%)	11.97±9.127
Female	30(62.5%)	10.73±7.996
NIHSS		
Mild	7(14.6%)	3.51±1.378
Moderate	41(85.4%)	12.78±8.570
Severe	0(0%)	
Stroke type		
Large Artery Atherosclerosis	37(77.1%)	13.15±4.254
Cardioembolic	9(18.8%)	22.93±8.572
Small vessel	2(4.2%)	2.20±0.707
Risk factors		
Diabetes Mellitus	16(33.3%)	
Hypertension	31(64.6%)	
Cardiac problem	7(14.6%)	
Dyslipidemia	23(47.9%)	
Others	6(12.5%)	
Single risk factors	15(31.25%)	5.09±1.824
Multiple risk factors	33(68.75%)	14.31±8.910
Stroke location		
Basal ganglia	25(52.1%)	9.95±7.331
Cortical	12(25.0%)	21.03±9.206
Pons	11(22.9%)	14.65±5.979
Thalamus	4(8.3%)	7.95±1.061
Others	2(4.2%)	8.12±7.161

**Abbreviation:** SD, Standard Deviation.

**Table 2** Distribution of Cortisol Level, NLR, NIHSS, and PSQI

Variable	n=48
Cortisol level (ng/mL)	
Median (IQR)	8.0 (5.9–14.6)
Min–Max	1.7–34.6
NLR	
Median (IQR)	5.9 (3.2–8.1)
Min–max	2.0–20.0
NIHSS	
Median (IQR)	9.3 (6.6–15.7)
Min–Max	3.0–20.0
PSQI	
Median (IQR)	9.0 (6.0–10.0)
Min–Max	2.0–20.0
Sleep quality, n (%)	
Good	6 (12.5)
Poor	42 (87.5)

**Abbreviation:** IQR, Inter Quartile Range.

**Table 3** Correlation Between Cortisol Level, NIHSS, and PSQI

Variable	PSQI		P-value	R
	Good N=6	Pair N=42		
Cortisol level			0.001	0.861
Mean±Std	3.37±1.206	12.58±8.568		
Median	3.25	8.60		
Range (min-max)	1.70–4.90	2.80–34.60		
NLR			0.001	0.871
Mean±Std	2.52±0.444	8.58±5.945		
Median	2.50	6.45		
Range (min-max)	2.00–3.00	2.00–20.00		
NIHSS			0.001	0.821
Mean±Std	2.52±0.444	9.58±5.945		
Median	2.50	9.45		
Range (min-max)	2.00–3.00	3.00–20.00		

**Table 4** Correlation Between Cortisol Level, NLR, and NIHSS

Variable	Correlation	R	p-value
Cortisol level and NIHSS	<i>Spearman</i>	0.874	0.0001
NLR level and NIHSS	<i>Spearman</i>	0.893	0.0001
NIHSS and PSQI	<i>Spearman</i>	0.836	0.0001

## Discussion

This study found a strong correlation between cortisol, NIHSS, and PSQI in acute ischemic stroke patients. The higher the cortisol level, the higher the NIHSS and the higher the disturbance of sleep quality in acute ischemic stroke patients. In acute ischemic stroke patients, there is an association between cortisol hormone plasma levels and clinical neurological conditions, cognitive function, and emotional status.<sup>10</sup>

This study found that most acute ischemic stroke patients were of productive age with an average age of over 60 years, and the majority were female, as many as 59 people (58.5%). This is consistent with the epidemiology of stroke, which states that stroke most often occurs at the age of over 60 years.<sup>11</sup> Based on the research of Min Jung Kim et al that the higher the age, the higher the quality of sleep disturbance, especially in women.<sup>12</sup>

The subjects of this study showed that there were 62.5% more women than men. According to research by Sheryl Martin Schild et al, in America, the average incidence of stroke is more in women, around 60%, than in men.<sup>5</sup> This is due to the higher life expectancy in women. Age is an important risk factor for stroke. Epidemiological studies conducted by Koh et al in America reported that 40% more women have insomnia than men because hormonal factors influence it.<sup>6</sup>

Estradiol and progesterone in women can influence sleep by modulating the circadian pattern of sleep activity. Estrogen receptors are located in the suprachiasmatic nucleus (SCN), the site of the main circadian clock. SCN neurons respond to estradiol with an increased light-induced expression of transcription factors, shifts in clock-related rhythms of gene expression, and increased firing of some of the changes in sleep-wake diurnal patterning observed after estradiol and progesterone treatment may be due to differences in circadian timing mechanisms in the SCN.<sup>13</sup>

This study found that subjects with the most types of stroke were acute ischemic stroke. This study showed that large artery atherosclerosis stroke was the most common type of acute ischemic stroke (77.1%), the most common stroke risk factor was hypertension (64.4%), both dyslipidemia, (47.9%), the third was diabetes mellitus (33.3%). These factors have a major role in the atherothrombotic process.<sup>11,12</sup>

Previous studies showed that decreased Nitric Oxide (NO) availability causes endothelial dysfunction in hypertension. Another opinion states that hypertension is associated with changes in endothelial function and morphology, causing an increase in cell volume so that the endothelium bulges into the lumen. The interaction between the endothelium, platelets, and monocytes in hypertensive vessels increases. Another opinion about the mechanism of NO damage is the production of oxidative stress. Oxidative stress is a condition where there is an imbalance between reactive oxygen species (ROS) that exceeds the capacity of the antioxidant defense system. Excess reactive oxygen species suppressed antioxidant capacity, or a combination of both can cause oxidative stress. Persistent oxidative stress can deplete antioxidant molecules, deactivate antioxidant enzymes, and thereby damage the antioxidant defense system, causing inflammation characterized by increased C-reactive protein (CRP), interleukin-6 (IL-6), leukocyte elastase, lipoprotein, intracellular adhesion molecule-1 (ICAM-1), and E-selectin in ischemic stroke patients. Elevated IL-6 and CRP may also lead to poorer ischemic stroke outcomes.<sup>6,14,15</sup>

This study found that the NIHSS of acute ischemic stroke patients who experienced sleep quality disturbances were in the moderate NIHSS with values in the range of 5–20, and most locations were found in the basal ganglia area. Physiologically, striatal GABAergic neurons in the basal ganglia project to the globus pallidus internal (GPi) and substantia nigra reticulata (SNr) in the direct pathway and polysynaptically to GPi/SNr via the globus pallidus external (GPe) and subthalamic nucleus (STN) in an indirect way.<sup>16,17</sup> Because the main output of the basal ganglia is inhibition from GPi/Snr to the thalamus, the direct pathway inhibits GPi/SNr. It discharges thalamic and cortical neurons, while the indirect path increases GPi/SNr and inhibits thalamic and cortical neurons.<sup>18</sup> This is also supported by the findings of previous studies that bilateral lesions of the striatum and nucleus accumbens lead to a significant decrease in waking conditions. Therefore, these findings prove that the striatum has a role in maintaining wakefulness. Lesions to the external globus pallidus also cause insomnia in rats, with a 45% increase in the duration of the awake state.<sup>18,19</sup> This is by a cross-sectional study in 2020, which found 20 acute stroke patients, based on PSQI results showing that ten patients had a poor sleep. Among the ten sleep-deprived individuals, the most common lesion was the basal ganglia.<sup>19</sup>

In addition, there is a positive correlation between NIHSS scores and sleep quality disturbances seen based on the PSQI questionnaire. That the higher the NIHSS, the higher the sleep quality disturbance in acute ischemic stroke patients.<sup>20</sup>

## Correlation Between Cortisol Level, NIHSS, and PSQI in Acute Ischemic Stroke Patients

This study found a strong correlation between cortisol, NIHSS, and PSQI in acute ischemic stroke patients. The higher the cortisol level, the higher the NIHSS and the higher the disturbance of sleep quality in acute ischemic stroke patients. In acute ischemic stroke patients, there is an association between cortisol hormone plasma levels and clinical neurological conditions, cognitive function, and emotional status. In addition, the level of cortisol hormone secretion can be used as a predictor of clinical outcomes in ischemic stroke cases. Plasma cortisol levels in the morning are associated with the severity of the patient's hemiparesis. Increased serum cortisol levels are associated with the mortality rate of ischemic stroke patients. However, this mechanism has yet to be described in detail. In addition to acute ischemic stroke, activation of the HPA axis is thought to occur within hours of ischemic onset. Based on research using experimental rat models that were induced to experience ischemia in the brain, increasing production of pro-inflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, caused cortisol levels in these conditions. These conditions will increase levels of the hormone cortisol in the blood.<sup>10</sup>

The mechanism of sleep quality disturbance in acute ischemic stroke patients involves many factors, including hormonal factors. Cortisol is the primary hormone product of the Hypothalamus Pituitary Adrenal (HPA) axis. Activation of the hypothalamus will release Corticotropin Releasing Hormone (CRH) and vasopressin, which affect Adrenocorticotropic Hormone (ACTH). This hormone stimulates the adrenal glands to secrete glucocorticoids (cortisol). Cortisol is the primary hormone product of the hypothalamus-pituitary-adrenal (HPA) axis. Activation of the hypothalamus will release CRH and vasopressin, which affect the anterior pituitary gland in secreting ACTH. This hormone stimulates the adrenal glands to secrete cortisol. Glucocorticoids and cytokines affect the brain by acting directly on receptors and indirectly through various mechanisms such as neurotransmission, intracellular signaling, and subsequent gene expression. Cortisol receptors are



expressed in the hippocampus, amygdala, and prefrontal cortex. Cortisol circulating in the periphery can penetrate the blood-brain barrier and then binds to glucocorticoid receptors.<sup>21–23</sup>

Research conducted by Bradley Bush in 2010 and Julia Ross in 2014 said that increased cortisol levels were the main cause of sleep quality disturbances. A study by Hanna Christensen et al in 2014 in Denmark reported an increase in cortisol levels in 162 patients with acute ischemic stroke on the first day of the stroke.<sup>12</sup> The negative feedback mechanism for cortisol is by inhibiting the pituitary and raphe nuclei from producing ACTH and serotonin and interfering with melatonin resulting in impaired sleep quality in acute ischemic stroke patients.<sup>4</sup>

In an ischemic stroke, an excess of glutamate will cause damage to neuron cells through protease, nuclease, and caspase enzymes. Excessive glutamate release also occurs due to cell wall damage and necrosis, as well as apoptosis which causes the influx of calcium ions into cells. The accumulation of neurotransmitters in the extracellular causes the excitotoxicity of glutamate. This process will cause the release of calcium ions (Ca) into the intracellular, then increased calcium influx which causes cell death. In addition, another effect of increased glutamate is an increase in cortisol through the hormones CRH and ACTH, causing dysfunction of the HPA axis where increased cortisol causes a decrease in serotonin and melatonin and disrupts sleep quality in acute ischemic stroke patients. Impaired peak melatonin secretion can produce disturbances of day-night perception in the early days of stroke. Research using rats induced by ischemic stroke showed that the presence of ischemia causes a narrowing of the duration of melatonin secretion and a delay in peak melatonin levels in the blood after treatment. The mechanism that causes disturbances in sleep quality and melatonin levels after ischemic stroke in humans still needs to be studied further.<sup>24–26</sup>

In acute-onset illness, the hypothalamic-pituitary-adrenal (HPA) axis is activated. HPA axis activation will cause an increase in cortisol levels. This condition can be caused by an inflammatory process that occurs or due to loss of inhibition of the HPA axis, especially in stroke lesions that arise in the frontal or medial temporal lobes. Elevated cortisol levels can occur up to 7 days after stroke onset. A stroke will disrupt the diurnal variation of cortisol secretion until 7–14 days after onset. Cortisol levels have a positive relationship with stroke severity, longer duration of hospitalization, and mortality rate of stroke patients. In patients with acute ischemic stroke, there is a negative association between plasma levels of the hormone cortisol and clinical neurological conditions, cognitive function, and emotional status. In addition, the level of cortisol hormone secretion can be used as a predictor of clinical outcomes in ischemic stroke cases.<sup>27</sup> Plasma cortisol levels at 7 am and 7 pm positively associated with the severity of hemiparesis in patients. Increased serum cortisol levels are associated with the mortality rate of ischemic stroke patients. However, this mechanism has not been explained in detail.<sup>28</sup>

Acute ischemic stroke can cause several complications, including sleep quality disturbances. Research conducted by Ferre et al in Spain in 2010 reported that 20–77% of stroke patients experienced sleep quality disturbances.<sup>29</sup> Ancoli and Ruth, 30% studied 100 acute ischemic stroke patients from various countries showing one or more symptoms of sleep quality disturbance.<sup>30</sup> Research conducted by Leppavuori in Finland in 2010 for three months reported that of 277 stroke patients, 56.7% complained of sleep quality disturbances. Whereas in Indonesia, it was reported that around 25–50% of acute ischemic stroke patients experienced sleep quality disturbances obtained from the Pittsburg Sleep Quality Index (PSQI) > 5.<sup>31</sup>

In ischemic conditions, the brain will produce an inflammatory reaction that begins within hours or days and can last several months. NLR describes the inflammatory condition in patients, by comparing the number of neutrophils and lymphocytes in peripheral blood. The NLR value was associated with stroke severity, worse functional outcome, and recurrent ischemic stroke in patients. A retrospective cohort study involving 899 ischemic stroke patients found that NLR levels were associated with greater stroke severity, as measured by The National Institutes of Health Stroke Scale (NIHSS). The median NLR value was significantly higher ( $p < 0.001$ ) in stroke patients with moderate severity (NIHSS > 8), with a median of 3.53 (interquartile range (IQR) 2.43–5.25) compared to mild (NIHSS ≤ 8) with a median NLR of 2.63 (IQR 1.93–3.64). This mechanism is thought to be caused by the emergence of an increase in the hormone cortisol in the acute condition of ischemic stroke, which will increase neutrophil production and trigger a decrease in the number of lymphocytes through the mechanism of apoptosis. Interleukins, a subclass of functional cytokines, mediate the inflammatory response. The effect of releasing proinflammatory IL-1, IL-6, and TNF- $\alpha$  causes disruption of cell dysfunction in the form of increased glutamate. Excess glutamate release will activate the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) and N-methyl-D-aspartate receptor NMDA receptors so that calcium ions (Ca) enter the cell. The calcium ion that enters the intracellular cause cell death and influences neurological deficits in acute ischemic stroke patients. In addition, increased glutamate can cause dysregulation of the HPA axis by



stimulating the release of CRH in the hypothalamus. CRH acts to secrete ACTH into systemic circulation. ACTH acts on the fasciculate zone in the adrenal cortex to initiate cortisol synthesis. Increased cortisol causes negative feedback on the bioavailability of tryptophan in brain tissue, causing a decrease in serotonin and melatonin levels resulting in sleep quality disturbances. Besides that, the effects of decreased serotonin are anxiety disorders, depression, and gastrointestinal disorders, which can also cause sleep quality disturbances.<sup>9,32–36</sup>

Cortisol hormone secretion is also thought to be influenced by the SCN. Under normal conditions, cortisol levels experience a nadir or lowest level around midnight, increasing 2–3 hours after sleep onset and continuing to increase until waking time. The existence of higher cortisol levels in nadir conditions can cause disturbances in the sleep cycle. This condition is found in ischemic stroke patients, especially in the early days after stroke onset. Cortisol can be seen as an independent short-term prognostic marker of functional outcome and mortality in Chinese patients with acute ischemic stroke, even after correcting for confounding factors. The combined model can add significant predictive information to the NIHSS clinical score. This mechanism is thought to cause impaired sleep quality in post-ischemic stroke patients.<sup>37,38</sup>

## Research Limitations

1. Researchers did not assess sleep quality disturbances before the onset of acute ischemic stroke and after passing the acute phase of stroke.
2. Impaired sleep quality due to serotonin-depleting effects such as pain, depression, gastrointestinal disturbances, and anxiety disorders was not reassessed by the researchers.
3. Small sample size since only 48 volunteers can be considered low statistical power and have biases in the interpretation of the results.

## Conclusion

A strong correlation exists between cortisol levels, NLR levels, NIHSS, and sleep quality disturbances in acute ischemic stroke patients. Further research is needed regarding sleep quality disturbances in acute ischemic stroke patients seen before the onset and after the acute stroke phase has passed by neurotransmitter levels that influence the impairment of sleep quality with bigger sample size.

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## Disclosure

The authors report no competing interest in this work.

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