Impact of Shift Work and Stress Level on Nurse Brain-Derived Neurotrophic Factor (BDNF) mRNA Expression During The Covid-19 Pandemic

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Abstract

Introduction: *The project aims to investigate how the Covid-19 epidemic influenced nurses' stress levels, shift work, and BDNF mRNA expression. Hospitalized patient numbers in Indonesia were rising sharply during the outbreak. This illness has a major impact on nurses' levels of weariness and stress, which follow each other. High-stress workers have lower serum levels of brain-derived neurotrophic factor (BDNF). Workload, job conflicts, and sleep difficulties are some of the causes that lead to this stress.*
Methods: *The study was conducted at the Cempaka Putih Islamic Hospital in Central Jakarta, Indonesia, from July to September 2020. The study used an analytical observational approach and a cross-sectional design. The number of nurses who participated in this study was 89 people who were selected using This study included 89 nurses who were recruited using a purposive selection technique based on predetermined inclusion and exclusion criteria. Anthropometric measures and intravenous blood collection were used to gather data for real-time PCR analysis of the BDNF gene mRNA expression.*
Result: *The mean BDNF mRNA expression level was 8.93 ng/mL. Nurses reported work-related stress, with a significant correlation (p<0.05) between BDNF mRNA expression, work shift, and stress levels. According to the findings, those with low, moderate, and high stress levels had mean BDNF levels of 11.69, 8.65, and 7.36, respectively. Statistical testing revealed a significant difference (p<0.001) in the mean mRNA expression of the BDNF gene across subjects with low, moderate, and high stress levels.*
Conclusion: *During the Covid-19 pandemic, a statistical correlation was found between nurse stress levels, work shifts and low BDNF levels.*

Keywords: *BDNF, Shift work, Stress level, Nurse*

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Dampak Kerja Shift dan Tingkat Stres terhadap Kadar Gen Brain-Derived Neurotrophic Factor (BDNF) pada Perawat Selama Pandemi Covid-19

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Abstrak

Pendahuluan: *Penelitian ini bertujuan untuk menyelidiki bagaimana epidemi Covid-19 memengaruhi tingkat stres perawat, kerja shift, dan kadar gen BDNF. Jumlah pasien rawat inap di Indonesia meningkat tajam selama wabah. Penyakit ini berdampak besar pada tingkat kelelahan dan stres perawat, yang terjadi secara berurutan. Pekerja yang memiliki tingkat stres tinggi memiliki kadar serum brain-derived neurotrophic factor (BDNF) yang lebih rendah. Beban kerja, konflik pekerjaan, dan kesulitan tidur merupakan beberapa penyebab yang menyebabkan stres ini.*

Metode: *Penelitian ini dilakukan di Rumah Sakit Islam Cempaka Putih, Jakarta Pusat, Indonesia, dari bulan Juli sampai September 2020. Penelitian ini menggunakan pendekatan analitik observasional dan desain cross-sectional. Sebanyak 89 perawat berpartisipasi dalam penelitian ini, dipilih dengan teknik purposive sample berdasarkan kriteria inklusi dan eksklusi yang telah ditetapkan. Pengukuran antropometri dan pengambilan darah intravena digunakan untuk mengumpulkan data untuk analisis PCR real-time dari ekspresi mRNA gen BDNF.*

Hasil: *Ekspresi mRNA BDNF rata-rata 8,93 ng/mL. Perawat mengalami stres terkait pekerjaan, dengan hubungan yang signifikan (p<0,05) antara ekspresi mRNA BDNF, shift kerja, dan tingkat stres. Menurut temuan tersebut, orang dengan tingkat stres rendah, sedang, dan tinggi memiliki kadar BDNF rata-rata masing-masing 11,69, 8,65, dan 7,36. Uji statistik menunujukan perbedaan signifikan (p <0,001) dalam ekspresi mRNA rata-rata gen BDNF pada subjek dengan tingkat stres rendah, sedang, dan tinggi.*

Kesimpulan: *Selama pandemi Covid-19, ditemukan korelasi statistik antara tingkat stres perawat, shift kerja dan rendahnya kadar BDNF.*

Kata Kunci: *BDNF, Kerja shift, Tingkat kerja, Perawat*

Introduction

Among the medical professionals, nurses are mostly in charge of keeping an eye on their patients and managing stressful situations. In comparison to other professions, nursing requires more work and plays a significant part in improving health condition. As a result, nurses frequently deal with a variety of circumstances and scenarios that may contribute to stress at work.[1,2] Based on the profile of Indonesia's health, 220,192 of the country's 345,508 total nursing resources were used in hospitals in 2019.[3] According to a survey conducted by Indonesian National Nurses Association, 51% of nurses suffered stress at work, were weary, were not friendly, frequently felt dizzy, a lack of rest due to a high workload and insufficient money.[4]

According to Highley in Tom Cox et al. (1996), nursing is a stressful job by nature. Nurses care for individuals with a range of health issues. A lot of the work that nurses do is disagreeable and demanding; they are frequently denigrated, feared, or even ignored. Stressors in the nursing profession are strongly associated with contact with patients and other healthcare providers.[1,5] The study found that nurses who worked in hospitals faced the following nine (9) sources of stress: dealing with death and dying; not being ready for patients' and families' emotional needs; not knowing what to expect from a treatment; having disagreements with doctors; not having support

from staff; having an excessive workload; the workplace; and discrimination.[1,2]

Nurses provide crucial treatment in hospitals, facing work-related stress owing to large workloads, asymptomatic patients, and insufficient personal protection equipment (PPE) amid the impact of COVID-19.[6] Research unequivocally shows that night shifts result in sleep disturbances for 25.6% of nurses, causing circadian rhythm disruptions, sleep deprivation, mood disorders, persistent anxiety, depression, and gastrointestinal issues.[7–9] Brain-derived neurotrophic factor (BDNF) is undeniably important in the maintenance of neurons in brain circuits and is responsible for the survival and development of these neurons in emotional and cognitive processes. The significant impact of reduced BDNF levels on stress is well-established.[10,11] BDNF, as the predominant neurotrophin in the brain, unequivocally plays a critical role in modifying the pathomechanism of stress and stress resilience.[12,13] It is imperative to note that the hippocampal tissue in the central nervous system directly produces BDNF. The extensive body of research consistently demonstrates that circumstances associated with stress and depression lead to undeniable decreases in BDNF levels.[14] The aim of this study is to confidently compare BDNF mRNA expression in nurses working shifts, unit work, and stress levels.

Method

This was a cross-sectional study and used an analytical observational method. The study was conducted from July to September 2020 at the Cempaka Putih Islamic Hospital located in Central Jakarta. The study's sample included 120 nurses who worked in the ICU, Emergency Room, inpatient ward, and operating room at the Jakarta Islamic Hospital (RSIJ). Determining the size of the research sample for descriptive research 36 using the formula developed by Isaac and Michael from a population of 120 nurses with a 5% error rate obtained a minimum sample size of 89 people as research samples, which were selected through the use of purposive sampling techniques. The inclusion criteria carried out based on screening through anamnesis of the research subjects were not consuming alcohol, not smoking, not having mental illness, not having systemic disorders, and being willing to fill out the questionnaire. Individuals with systemic disorders (vascular, neurological disease, diabetes, kidney disease, digestive and respiratory disease, thyroid, adrenal disorders), psychiatric disorders (bipolar

disorder, dementia, depression), alcoholism, smoking, or inability to complete the research series were excluded from the study. Samples were chosen, weighed, and their height was measured in order to obtain data. Using the prior research protocol, intravenous blood was obtained to assess the mRNA expression of the BDNF gene using real-time PCR.[15–17] Then the sample filled out a research questionnaire. Expanded Nursing Stress Scale (ENSS) is a research instrument to measure stress levels specifically for nurses and has been adjusted to the characteristics of nurses' work. The ENSS research instrument consists of 57 statements that must be filled in by respondents. The alternative answers to this instrument use a 5-point Likert scale (0-4). The Expanded Nursing Stress Scale (ENSS) has also been validated by Harsono (2017) and has good reliability with a Cronbach alpha value of 0.956 (very good).

The distribution of sample characteristics was seen using univariate analysis in this study, and mean difference between the two groups and their association were found using bivariate analysis using ANOVA and T-test with the IBM SPSS 26 program. The Health Research Ethics Committee has recommended ethical approval for this study of RSPTN Universitas Hasanuddin on July 9, 2020, with number 361/UN4.6.4.5.31/PP36/2020.

Result

According to Table 1, out of the 89 respondents who fulfilled the research criteria, 76.4% were female, 83.1% had a diploma, 82.0% were married, the majority of respondents—61,8%—worked in inpatient units, 51.7% worked night shifts, and 42.7% of respondents classified their stress level as moderate. The age of individuals varies with a range of 23 - 55 years. On average, respondents were 38.75 years old. They had an average of 15.88 years of employment, ranging from one to 34 years. The average BDNF mRNA expression among participants was 8.93 ng/ml, with a range from highest to lowest of 13.43 ng/ml and 5.34 ng/ml as determined by blood testing.

According to Table 2, there was a substantial correlation (p-value <0.05) between the BDNF mRNA expression, work shift and respondent's stress level. Work unit factors, however, had no correlation with the levels of the BDNF with p-value > 0.05.

According to this study, there are more women than men working as nurses, most of them have diplomas in their fields, most of

Tabel 1. Demographic and Clinical Characteristics

Characteristics	N	%
Sex		
Women	68	76.4
Men	21	23.6
Education level		
Diploma	74	83.1
Degree	15	16.9
Marital status		
Single	16	18.0
Married	73	82.0
Unit work		
Emergency Room	11	12.4
Inpatient	55	61.8
Surgery room	7	7.9
Intensive Care Unit (ICU)	16	18
Length of Shift Work		
Morning shift (8 am – 3 pm)	37	41.6
Afternoon shift (3 pm – 9 pm)	6	6.7
Night shift	46	51.7
Stress level		
Low	21	23.6
Medium	38	42.7
High	30	33.7
Age	Mean (SD) 38.75 (9.550) Range 23 years -55 years	
Length of work	Mean (SD) 15.88 (9.408) Median : 17 years Min-Max: 1 year -34 years	
BDNF gene mRNA expression	Mean (SD) 8.93 ng/ml (1.89 ng/ml) Median : 8.63 ng/ml Min-Max: 5.34-13.43	

Table 2. Correlation Between BDNF Levels, Unit, Shifts, and Stress Level

Variables	Mean	SD	95% CI		p-value
			Lower	Upper	
Unit work					
The emergency room	8.99809	1.355873	8.0872	9.90898	0.102
Inpatient room	8.60964	1.817556	8.11828	9.10099	
Surgery room	10.28600	2.505303	7.96898	12.60302	
Intensive care unit	9.39856	1.972006	8.34775	10.44937	
Length of Shift Works					
Shift 1–morning (8 am - 3 pm)	8.94623	1.645348	-0.77318	0.83087	0.007*
Shift 2-Night (9 pm – 8 am)	8.91739	2.114105	-0.76686	0.82454	
Stress level					
Low	11.68752	1.018085	11.2241	12.15095	0.000*
Medium	8.65197	0.810925	8.38543	8.91852	
High	7.35583	1.063881	6.95857	7.75309	

them are married, and the majority of them are in the inpatient ward. To maintain a nursing staff, schedules or shifts are distributed essentially in the same way during the day. Nurses' stress levels were somewhat higher in the medium range. Nurses experience stress due to pressures and obligations at work. The unit work was not associated with BDNF mRNA expression, according to the findings. This demonstrates that all unit works have the same amount of stress, meaning that the average BDNF level is the same for all unit works. BDNF gene with low stress level subjects is 11.69 FC with a standard deviation of 1.02 subjects with moderate stress level the average mRNA expression of BDNF gene is 8.65 FC with a standard deviation of 0.81 and subjects with high stress level the average mRNA expression of BDNF gene is 7.36 FC with a standard deviation of 1.06. The results of the statistical test obtained p-value <0.001, meaning there is a significant difference in the average mRNA expression of BDNF gene between subjects with low, moderate and high stress levels.
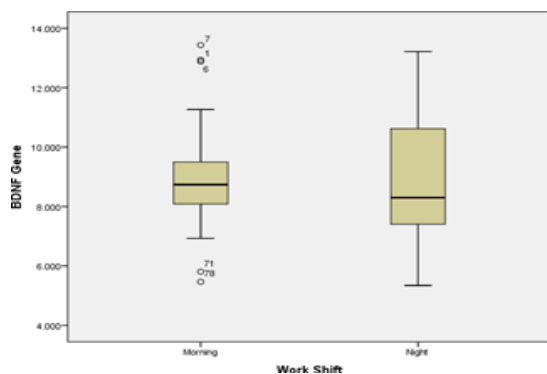

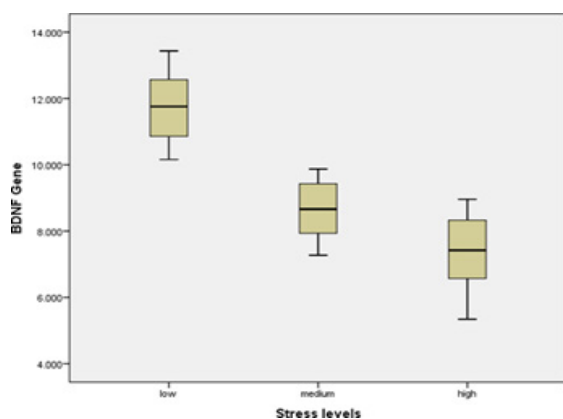**Figure 1. Box Diagram Showing Serum BDNF Concentrations at Different Stress Levels in Nurses Based on Work Shifts**

Figure 2. Box Diagram Showing Blood BDNF Concentrations at Different Stress Levels in Nurses

Discussion

BDNF is a neurotrophin found throughout the central nervous system (CNS), primarily in the prefrontal cortex and limbic areas, with the highest amounts observed in the hippocampus. In animal studies, after exposure to stress, BDNF transcript expression increases in the amygdala. Different stressors may regulate different levels of BDNF transcripts in specific areas. BDNF, including some of its transcripts, has been shown to be regulated by DNA methylation in numerous studies. Stress may also affect the expression of certain BDNF isoforms through DNA methylation in other brain regions. Stress has been shown to have sex-specific effects. Previous preclinical and clinical studies have supported the finding that females with abnormal phenotypes and BDNF levels in certain brain areas are more susceptible to stress than males.[18] Stress and the biological systems involved in the stress response are thought to play a role in BDNF alterations. Indeed, animal models have demonstrated that chronic stress reduces hippocampal BDNF mRNA expression and inhibits neuronal branching and neurogenesis.[15] High levels of glucocorticoid hormones and pro-inflammatory cytokines, two essential components in the stress response, have been associated with lower BDNF levels. This study showed that nurses working on night shifts from 8 p.m. to 8 a.m. had a mean score of 8.91739 ng/ml for the BDNF gene, which was lower than that of nurses working on morning and afternoon shift which showed mean score of 8.94623 ng/ml. A significant association was seen between shift work and nurses' levels of the BDNF gene. Because nights are usually spent sleeping, nurses who work night shifts—9 pm to 8 am—have lower blood levels of the BDNF gene. Night shifts will affect nurses' sleep patterns, according to research. Brain-derived neurotrophic factor (BDNF), which is linked to this condition, may play a part in sleep regulation. This amazing outcome validates a recent study conducted at a general hospital in Beijing on 244 healthcare professionals, which found a substantial correlation between serum BDNF levels and sleep disorders which showed by statistical analysis (p<0.05). Individuals with short sleep duration insomnia exhibited considerably lower serum BDNF levels than those without.

The study shows that health workers who sleep for less than 6 hours have lower serum BDNF levels compared to those who

sleep for 6 hours or more. The interesting to note that health workers with regular sleeping habits, whether or not they experienced insomnia, had the same serum BDNF levels. However, the levels of serum BDNF in health workers with insomnia were far lower than those of healthcare professionals who did not suffer from sleeplessness.[18] Another study discovered that nurses on the night shift had far higher serum levels of BDNF following an hour of rest.[19] A prior investigation revealed a correlation between BDNF and sleep deprivation and insomnia.[11] The relationship between stressful events and sleep perceptions influences the level of BDNF.[10] The BDNF levels of nurses who worked at night decreased because they slept less than nurses who worked throughout the day.

A multicentered cross-sectional research of 4,275 nurses from 14 hospitals in Shandong, China discovered that 48.5% of nurses suffered shift work sleep issues during the COVID-19 epidemic.[20] In the area not designated for COVID-19 patients, a study using the Spearman's test revealed a significant correlation between workload and stress levels, with a p-value of 0.001.[21] Prolonged physical exhaustion, mental strain, working night shifts consistently for more than six months in a year, performing demanding night shifts frequently, working more than 40 hours a week, working more than four night shifts per month, sleeping more than the recommended eight hours before the night shift, using sleep aids, eating irregularly, and engaging in fairly intense physical activity have all been correlated with an elevated likelihood of experiencing shift work sleep disorder.[20] During the COVID-19 pandemic, nurses successfully managed a severe workload by prioritizing infection prevention and control procedures for their own and the community's safety. This resulted in severe stress for the nurses, who normally have a service term of 6-10 years, according to the study.[22] Various factors influence workload, including age, gender, education, weight, height, nutrition, physical health, motivation, trust, job satisfaction, and aspirations. Additionally, external factors such as work structure, activities, tasks, and environmental variations also play a significant role. It's worth noting that health workers with high workloads are nearly 10 times more likely to experience work fatigue.[23]

Another study discovered a link between the length of work and nurses' ability to adopt coping mechanisms when delivering nursing care during the COVID-19 outbreak.

This is because the term of work is tied to work experience, and numerous events experienced by someone while working can be used to improve the quality of work.[22] With a doctor-to-nurse ratio of 0.4 and a nurse-to-health worker ratio of 2.1, Indonesia's response to the COVID-19 pandemic was not optimal, according to the data. This was in stark contrast to industrialized nations where the ratio was more than 2.5 doctors to 5.5 nurses. Then, infrastructural considerations and the distribution of medical material equipment affect the readiness of health staff to provide medical services during a pandemic calamity.[24]

Work stress affects nursing performance at Panembahan Senopati Hospital in Bantul. Based on statistical analytic on Spearman rank which have p-value of 0.001 (p<0.05).[25] Stress affects nurses' daily lives and work output. It is important to begin to understand how work-related stress can affect nurses and what components of the workplace frequently cause severe stress.[26] Job stress has negative impacts directly and indirectly on the quality of life and health of nurses. Job stress can also hamper the level of care performance which can immediately become a variable that affects the outcome of care to patients.[27] Hospitals should efficiently manage nurses' workload during the COVID-19 epidemic and offer particular therapies for nurses facing occupational stress. Nurses must use effective stress management strategies such as relaxation techniques, time management, and problem resolution.[28]

Exercise training (ET) is widely known as a non-pharmacological method for treating clinical depression. One of the biological factors that positively reacts to ET is brain-derived neurotrophic factor (BDNF), which increases its expression and production.[29] Individuals suffering from depression who engage in physical exercise were found to have higher levels of BDNF.[30] Additionally, a separate study indicated that aerobic exercise has the potential to elevate BDNF levels, reduce hippocampal atrophy, enhance memory performance, and alleviate symptoms of depression.[31]

The study findings suggest a notable link between the stress levels of nurses and the expression of the BDNF gene. This indicates that higher stress levels are associated with reduced BDNF gene expression. The observed decrease in BDNF levels appears to have a significantly affect by stress.[10,11] Giese et al.'s (2013) study revealed a connection between BDNF and stress in those who did not have in-

somnia. A previous study using a case-control study over four years showed that moderate to major depressive disorder was associated with lower blood BDNF levels.[32–34] Additionally, serum BDNF levels decreased in individuals with schizophrenia.[32–34] The results of this study can be a support for improving nurse welfare based on stress levels that can be measured objectively based on BDNF gene expression. In this study, there are several limitations, firstly is the absence of selection bias because the stress level is assumed to be only due to work environment factors without estimating other stressor factors. Second, there are confound brain-derived neurotrophic factor (BDNF) levels, including age, gender, psychological disorders and food consumption before the examination which may affect BDNF gene expression levels.

Conclusion

The study's findings suggest that nurses' work schedules and stress levels are linked to lower BDNF levels. These findings allow us to do further investigation in the connection between genetic background, environment, and demography with lower BDNF mRNA expression.

Conflicts of Interest

The authors declare no conflict of interest.

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