ORIGINAL ARTICLE

The Effect of Sleep Patterns to Incident of Hypertension: A Case-Control Study of Fishermen on the Puger Coast, Jember District

Pengaruh Pola Tidur terhadap Kejadian Hipertensi: Studi Kasus-Kontrol pada Nelayan di Pesisir Puger Kabupaten Jember

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ABSTRACT

Background
Hypertension prevalence in coastal areas is higher (53.3%) than in mountainous areas (6.8%). The high prevalence of hypertension in coastal areas is caused by lifestyle, one of which is poor sleep patterns. The research purpose was to determine the effect of sleep patterns on hypertension incidence in Puger fishermen.

Methods
This research used a Case-Control design. This research was conducted in February-March 2023. The research sample was calculated using a formula Lemeshow and there were 31 respondents in each group for a total of 62 respondents. The sampling technique used simple random sampling and the data taken included the variables hypertension and sleep patterns which consist of quality, duration, latency, efficiency, sleep disturbances, use of sleeping pills, and concentration problems during the day. Analysis data used frequency distribution for univariate analysis and tests Chi-Square and Fisher for bivariate analysis.

Results
The results showed that both groups had short sleep duration, it’s <7 or 8 hours. The results showed that 93.5% of fishermen in the case group experienced poor sleep patterns (score>5), while as many as 45.2% of fishermen in the control group experienced poor sleep patterns. Obtained (p-value <0.001; OR 17.6; CI 95%: 3.6-87.0), which means that the influence between sleep patterns and hypertension is the incidence in Puger fishermen and the OR value is 17.6 indicates that fishermen who have a poor sleep pattern have a 17.6 times risk attacked of hypertension than fishermen who have a good sleep pattern.

Conclusions
Sleep pattern is a risk factor for hypertension in Puger fishermen, so it’s recommended that respondents implement sleep patterns by optimizing sleeping hours as well and for The Puger Community Health Center to encourage respondents to utilize the facilities so they can monitor symptoms of hypertension.

Keywords: Case-Control Study; Fishermen; Hypertension; Risk Factors; Sleep Patterns.
ABSTRAK

Latar Belakang
Prevalensi Hipertensi di wilayah pesisir lebih besar (53.3%) daripada wilayah pegunungan (6.8%). Tingginya prevalensi hipertensi di pesisir diakibatkan oleh gaya hidup, salah satunya yaitu pola tidur yang buruk. Tujuan penelitian ini adalah untuk mengetahui pengaruh pola tidur terhadap kejadian hipertensi pada nelayan di pesisir Puger Jember.

Metode

Hasil
Hasil penelitian didapatkan pada kedua kelompok memiliki durasi tidur yang pendek, yaitu < 7 atau 8 jam. Pada hasil didapatkan sebanyak 93.5% nelayan pada kelompok kasus mengalami pola tidur buruk (skor total >5), sedangkan sebanyak 45.2% nelayan pada kelompok kontrol yang mengalami pola tidur buruk. Didapatkan nilai p-value sebesar <0,001 dan OR 17.6 (CI 95%: 3.6-87.0) yang artinya terdapat pengaruh antara pola tidur dengan kejadian hipertensi pada nelayan di pesisir Puger Jember dan nilai OR sebesar 17,6 menyatakan bahwa nelayan yang memiliki pola tidur buruk memiliki risiko 17.6 kali terkena hipertensi daripada nelayan yang memiliki pola tidur baik.

Kesimpulan
Pola tidur merupakan faktor risiko hipertensi pada nelayan di pesisir Puger Jember, sehingga disarankan kepada responden untuk menerapkan pola tidur dengan mengoptimalisasikan jam tidur serta kepada pihak Puskesmas Puger untuk lebih mengajak responden memanfaatkan fasilitas kesehatan terkait agar dapat memonitoring gejala hipertensi.

Kata Kunci: Studi Kasus-Kontrol; Nelayan; Hipertensi, Faktor risiko; Pola Tidur.

INTRODUCTION

Indonesia is an archipelagic country with three-quarters of its territory consisting of the sea, so it has quite extensive coastal areas.¹ In addition, Indonesia has the most islands in the world and 60% of its population lives in coastal areas.² East Java Province is one of the provinces. on the island of Java which has a fairly extensive coastal area. It is known that the coastal area in East Java is 3,498.12 km.³ Coastal areas, which are inhabited by many people, also have various kinds of problems to be researched, especially health problems, one of which is hypertension.

Hypertension is a disease characterized by an increase in blood pressure exceeding 140/90 mmHg and is a type of Non-Communicable Disease (NCD) that is currently still a global problem that has not been resolved properly.⁴ Hypertension is a disease that is nicknamed the "silent killer", where hypertension attacks suddenly and without warning, causing many deaths in the world.⁵ As many as 1.28 billion adults in the world aged 30-79 years suffer from hypertension, and the majority, namely two-thirds, live in low-income countries. and middle.⁶ The prevalence of people suffering from hypertension in Indonesia reached 34.11%, with details of the prevalence of hypertension in women (36.85%) being higher than in men (31.34%).⁷ The prevalence of hypertension in Jember Regency was 31.7% of the total elderly population. This figure is higher than in other areas, namely
The prevalence of hypertension is estimated to increase by 42% in 2025 if it is not treated properly.³ Hypertension sufferers are more likely to live in coastal areas than mountainous areas.⁴ It is known that the prevalence of hypertension in the Natuna Islands (coastal) is 53.3%, greater than in the Jayawijaya mountains, namely 6.8%.⁵ The prevalence of hypertension in fishermen is 50.9%. This prevalence was obtained from respondents aged 25-60 years and the majority were male.⁶ The prevalence of hypertension on the coast, where the majority of people are fishermen, was 62%, with a vulnerable age group of 45-64 years.⁷ Based on data from a preliminary study conducted by researchers in January at the Puger Community Health Center, data on the incidence of hypertension was obtained from as many as 5,461 cases (20%) with ages >45 years old. This data is accumulated data from one year, namely 2022.

The high prevalence of hypertension in coastal areas, especially in fishermen, is caused by many factors, both internal and external. An example of an external factor, namely a bad lifestyle, one of which is sleep patterns. Bad sleep patterns are also a factor causing hypertension (OR=9.022).⁸ Sleep patterns, both in terms of quality and quantity, can affect a person's blood pressure.⁹ Poor sleep patterns can change the stress hormone cortisol and the sympathetic nervous system, resulting in increased blood pressure.¹⁰ Specifically, continuously disturbed sleep quality causes physiological changes in the body, where the balance of sympathetic and parasympathetic nerves is disturbed. Disturbed sleep quality will increase the sympathetic nervous system which triggers increased blood pressure, while the parasympathetic nervous system decreases. Apart from sleep quality, sleep duration indirectly influences the occurrence of hypertension. Shorter sleep duration will increase the hemodynamic load over 24 hours which gradually increases the sympathetic nervous system. If a person has a shorter sleep duration continuously it will cause adaptations of the structure of the cardiovascular system, such as left ventricular hypertrophy and arterial constriction which can gradually increase the balance of blood pressure.¹¹

Fishing is a tough and dangerous job with a high risk of work-related and endemic diseases globally,¹² where fishermen go to sea from early morning until late afternoon or from late afternoon until early morning so fishermen rarely pay attention to their sleep time.¹³ Based on this lifestyle, the incidence rate of Hypertension on the coast, especially among fishermen, is quite high. Therefore, researchers want to know more about the factors that cause hypertension in fishermen, especially in terms of sleep patterns, including a description of sleep patterns and the relationship and influence of sleep patterns with hypertension in fishermen on the Puger coast of Jember by dividing into two groups, namely cases, and controls. It is hoped that this research can be a source of information regarding hypertension among fishermen so that prevention can be carried out to reduce and control hypertension rates so that complications do not occur in the future.

**METHODS**

This research is a type of observational analytical research, namely research that observes and analyzes the influence of sleep pattern variables on hypertension variables in fishermen. This study used a case control design with a retrospective approach, namely collecting data related to hypertension first and then looking for the causes. This research was carried out in February-March
2023 on the Puger Coast of Jember. The population in this study were all fishermen who lived on the Puger coast of Jember. The sample in this study was divided into two groups, namely the case group and the control group. The sample was calculated using the Lemeshow formula with a significance level of 5% and a test power of 90% and a sample of 31 people was obtained in each group with a ratio of 1:1, so the total number of samples was 62 samples. The sampling technique used simple random sampling by paying attention to the following inclusion criteria, for the sample in the case group were fishermen who had hypertension either grade 1 or 2, aged >18 years, and lived on the Puger Coast. The inclusion criteria for the control group sample were that fishermen had normal blood pressure, were >18 years old, and lived on the Puger Coast. Meanwhile, the exclusion criteria for the two groups were fishermen in the Puger coast of Jember who had a family history of hypertension. This research does not use matching on specific samples, thereby allowing selection bias to occur. The way to minimize the impact of bias is by using a sample reserve of 10% of the sample for each group.

This study examines sleep pattern variables and their relationship to hypertension in fishermen on the Puger coast of Jember. The sleep pattern data collection technique was carried out using structured door-to-door interviews in the villages of Puger Kulon and Puger Wetan using the Pittsburgh Sleep Quality Index (PSQI) questionnaire instrument. The questionnaire has been validated as an instrument and obtained a validity value of one hundred percent and reliability α=0.766. The instrument contains 19 questions that measure 7 assessment components, namely sleep duration, subjective sleep quality, sleep disturbance, effective sleep duration in bed (habitual sleep efficiency), sleep latency, use of sleeping medication (sleep medication), and impaired concentration during the day (daytime dysfunction). The way to measure sleep patterns is by assessing the PSQI questionnaire by paying attention to the following, namely to assess the components of sleep duration by subtracting question 1 from 3 and obtaining a score of 0 for >7 hours, score 1 for 6-7 hours, score 2 for 5-6, and a score of 3 for <5 hours. Questions regarding sleep efficiency are assessed by dividing item number 4 by 2 and multiplying by 100%, then given a score of 0 for >85%, score 1 for 75-84%, score 2 for 65-74%, and score of 3 for <65%. Sleep latency assessment is carried out by adding items number 2 and 5a, then a score of 0 is obtained for 0, a score of 1 is for 1-2, a score of 2 is for 3-4, and a score of 3 is for 5-6. Sleep disorders are assessed by adding items number 5b to 5j, then a score of 0 is obtained for 0, a score of 1 is for 1-9, a score of 2 is for 10-18, and a score is 3 for 19-27. Assessment of concentration disorders during the day is carried out by adding up the points for items number 7 and 9, then obtaining a score of 0 for 0, score 1 for 1-2, score 2 for 3-4, and score 3 for 5-6. Question items number 3, 4, 6, 7, 8, and 9 have 4 answer choices, 0 (answer that has a mild risk) to 3 (answer that has a severe risk). Based on these 9 questions, the final score is then added up, and if the score is ≤5 then it means you have a good sleep pattern, if >5 then you have a bad sleep pattern. The raw data was analyzed using two analyses, namely univariate using a frequency distribution to determine the frequency of fishermen's sleep duration, and bivariate analysis using the Chi-square test and Fisher's test with a significance level of 95% and an error rate of α=5% (0.05). This research has received permission (ethical clearance) from the Ethics Commission of the Faculty of Public Health with ethical number 318/KEPK/FKM-UNEJ/II/2023. This research has obtained permission from the local Community Organization and all research participants have agreed to everything stated in the informed consent form.
RESULTS

Table 1. Characteristics of Fisher Respondents on the Puger Coast

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case (n=31)</th>
<th></th>
<th>Control (n=31)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19 - 40 y.o</td>
<td>7</td>
<td>22.6</td>
<td>18</td>
<td>58.1</td>
</tr>
<tr>
<td>41 - 60 y.o</td>
<td>24</td>
<td>77.4</td>
<td>13</td>
<td>41.9</td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>23</td>
<td>74.2</td>
<td>16</td>
<td>51.6</td>
</tr>
<tr>
<td>Secondary school</td>
<td>6</td>
<td>19.4</td>
<td>12</td>
<td>38.7</td>
</tr>
<tr>
<td>High school</td>
<td>2</td>
<td>6.4</td>
<td>3</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Based on Table 1, it was found that the age of the case group was most vulnerable at 41-60 years, while respondents in the control group were most vulnerable at 19-40 years. As people get older, they are more susceptible to hypertension due to changes in the elasticity and flexibility of blood vessels. In Table 1 it is also found that the highest education level of respondents in the case group is elementary school, while respondents in the control group mostly have elementary school education.

Table 2. Fishermen's Sleep Duration

<table>
<thead>
<tr>
<th>Sleep duration</th>
<th>Case (n=31)</th>
<th></th>
<th>Control (n=31)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age 19-40 years old:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 hours (good)</td>
<td>1</td>
<td>3.3</td>
<td>4</td>
<td>12.9</td>
</tr>
<tr>
<td>&lt;8 hours (bad)</td>
<td>6</td>
<td>19.4</td>
<td>15</td>
<td>48.4</td>
</tr>
<tr>
<td>Age 41-60 years old:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 hours (good)</td>
<td>1</td>
<td>3.3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;7 hours (bad)</td>
<td>23</td>
<td>74.2</td>
<td>12</td>
<td>38.7</td>
</tr>
</tbody>
</table>

Source: Primary Data

Based on Table 2, it was found that the case group had mostly poor sleep duration, both from all age categories, namely 6 people aged 19-40 years and 22 people aged 41-60 years. This also happened in the control group who had mostly poor sleep duration, namely 15 people aged 19-40 years and 12 people aged 41-60 years. Respondents' sleep duration is influenced by working hours as fishermen, where fishermen have time to sleep in the early morning and will wake up at noon or vice versa. 4 Fishermen's sleep duration will be different again if it is during the harvest season, some respondents even admitted that they do not get time to sleep during the harvest season.

Table 3. Relationship between sleep patterns and the incidence of hypertension in fishermen

<table>
<thead>
<tr>
<th>Sleep Pattern</th>
<th>Hypertension Incident</th>
<th></th>
<th></th>
<th>p-value</th>
<th>OR (Confidence Interval 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case (n=31)</td>
<td>Control (n=31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Good (&lt;5 from total score)</td>
<td>2</td>
<td>6.5</td>
<td>17</td>
<td>54.8</td>
<td>&lt;0.001* 17.6 (3.6-87.0)</td>
</tr>
<tr>
<td>Bad (&gt;5 from total score)</td>
<td>29</td>
<td>93.5</td>
<td>14</td>
<td>45.2</td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test
a,b = scores follow the PSQI Questionnaire in general, ref: reference

Based on Table 3, it was found that the majority of the case group had poor sleep patterns, namely 29 people (93.5%), while in the control group, the majority had good sleep patterns, namely 17 people (54.8%). Table 3 also shows the results of bivariate analysis to determine the influence...
between sleep patterns and the incidence of hypertension in fishermen on the Puger Coast. Obtaining a p-value of 0.001 with an OR value of 17.6 (CI 95%: 3.6-87.0) means there is an influence between sleep patterns and the incidence of hypertension in fishermen on the Puger Coast. The OR value of 17.6 states that fishermen who have poor sleep patterns have a 17.6 times higher risk of developing hypertension than fishermen who have good sleep patterns.

**DISCUSSION**

**Characteristics of Respondents**

Most of the fishermen on the Puger Coast of Jember are aged between 41-60 years. Several studies stated that the majority of fishermen who were respondents were aged 35-40 years (<60 years). In other studies, it was also stated that the majority of fishermen were aged 30-70 years, this age is the productive period of a fisherman. Productive age is the age that can work optimally and earn maximum income.

Ages 41-60 years are still considered productive age. However, this vulnerable age is also a vulnerable age, whereas age increases, especially age >40 years, the risk of developing hypertension increases. In addition, based on Table 2, it is found that the majority of fishermen who are at this vulnerable age have a long sleep duration. Short sleep duration allows the risk of developing hypertension to be greater.

In terms of education, the majority of fishermen on the Puger Coast of Jember have elementary school education. In general, the average education level of fishermen is elementary school and some have not even completed elementary school. The low level of education of fishermen is caused by several things, one of which is cultural and economic factors. Fisherman is a job that is very dependent on the sea. Many fishermen in Indonesia work because they have been hereditary from previous families. Young people are already working as fishermen, this is the reason why many fishermen have low education. Apart from that, economic factors also encourage fishermen to decide to work rather than continue their education.

This low education is related to an individual's knowledge regarding something. Insufficient knowledge can impact individual awareness of the causes and prevention of hypertension. Lack of knowledge due to low education makes it difficult for individuals to receive information (counseling) provided by local health workers, thus having an impact on a healthy lifestyle.

**Sleep Patterns of Fishermen on the Puger Coast of Jember**

Fishing is a hard job with high risks. Fishermen have three disturbances when going to sea, namely weather, lack of sleep, and boat damage. It was stated that 91 out of 550 fishermen admitted that they had a short time, namely only 4 hours to eat and sleep. They choose to sleep rather than eat, but 4 hours of sleep is not enough to overcome sleepiness. In research on the sleep patterns of Puger coastal fishermen, it was found that fishermen who had health problems were those who had poor sleep patterns. Poor sleep patterns are caused by many fishermen who have a habit of sleeping after 10 pm or even early in the morning because fishermen are busy working in the morning. The optimal time to sleep is 10 pm. Apart from that, fishermen's sleep duration is also relatively short, in the study, fishermen only started sleeping at 11 or midnight and woke up at 4 in the morning. If calculated, the fishermen's sleep duration was less than 7 hours,
even though most of the fishermen in the study were aged 41-60 years old, at that age the need for sleep was 7 hours. Apart from that, lack of sleep triggers physical fatigue in fishermen which causes the fishermen's sleep quality to be poor. It was stated that the majority of fishermen experienced insomnia due to the thought of shaking while on the ship, and the majority said they often felt sleepy during the day due to lack of sleep activity. Fisherman respondents also complained of dizziness and aches which disrupted the quality of their sleep. This is supported by research which states that high activity will trigger physical fatigue. This physical fatigue is one of the factors in increasing blood pressure.

**Influence of Sleep Patterns on the Incident of Hypertension in Fishermen**

Sleep is a physiological process in humans. Sleep is needed to regularly improve the body's biological processes. During sleep, low waves in the body will release growth hormones to repair cells such as epithelial cells and brain cells. Sleep is very important in cognitive recovery of the brain because sleep is associated with changes in blood flow to the brain, increased oxygen output, increased cortical activity, and release of epinephrine.

Usually, the sleep process of a normal adult begins in the pre-sleep period and gradually progresses to a period of sound sleep for 10-20 minutes, then deep sleep, and finally the deepest sleep, at this stage a person finds it difficult to wake up from. This is different for someone who experiences difficulty sleeping, those who have difficulty falling asleep can take up to an hour in the second stage, and it will affect other sleep processes. When the sleep process is disturbed, it will cause a person's sleep quality to become poor. Poor sleep quality will affect the hormone cortisol and glucose metabolism. Where, when a person sleeps, the brain will use less glucose because the nervous system is less active, and the hormone cortisol will decrease. The hormone cortisol is a hormone produced by the adrenal glands that plays a role in stress management and helps maintain blood pressure.

Stress and sleep patterns have a reciprocal relationship where if you don't get enough sleep or poor sleep quality it will increase stress hormones and these stress hormones also trigger bad sleep patterns because they inhibit sleep. A person who has a poor sleep pattern, both in terms of quality and quantity, will be affected by psychological and physical stress. Psychological stresses in question include depression, anxiety, and decreased concentration. Meanwhile, physiological include easy fatigue, weakness, decreased daily activities, decreased body endurance, and unstable vital signs. Disturbances in sleep patterns can increase the stress hormone cortisol and the sympathetic nervous system and stimulate the renin-angiotensin-aldosterone system, namely hormonal mechanisms that regulate the balance between fluids and blood pressure. In addition, catecholamine hormones will increase the release of the hormones epinephrine and norepinephrine to overcome physical and emotional stress by increasing heart rate and blood pressure.

The results of research related to the influence of sleep patterns on the incidence of hypertension in fishermen on the Puger Coast, Jember Regency, showed a p-value of 0.001 and an OR value = 17.6 with a CI value of 95% (3.6-87.0). This proves that there is an influence between sleep patterns and the incidence of hypertension in fishermen on the Puger Coast, Jember Regency. This OR value means that fishermen who have poor sleep patterns are 17.6 times more likely to develop hypertension than fishermen who have good sleep quality. This is supported by
research in the Tanah Kali Kedinding Kenjeran Surabaya Health Center Area which states that sleep patterns are related to the occurrence of hypertension with a p-value of 0.000 <α (0.05) and has an OR value of 9.02 with a CI of 95% (2.86-29.65). This shows that respondents who have poor sleep patterns are 9 times more likely to develop hypertension than those who have good sleep patterns. Other research also states that sleep disorders are associated with the incidence of hypertension with a value of (p=0.03; OR: 6.7; 95% CI=1.22-36.64). This states that respondents who experience sleep disturbances are 6.7 times at risk of developing hypertension. However, this research contradicts research which states that there is no relationship between sleep duration and the incidence of hypertension in fishermen. This may be due to the lack of specific research on sleep patterns because it only examines sleep duration and not other aspects of sleep patterns which include sleep disturbances, sleep quality, and sleep latency.

**Study Limitations**

This research, which was conducted on fishermen on the Puger Coast, has limitations, including that this research has a limited sample and the possibility of biases such as selection bias or biases that are not paid enough attention by researchers which become confounding variables such as consumption of stimulants, alcohol consumption, smoking habits, body composition, other metabolic disorders, and stress. This research only explores information regarding the influence of sleep disorders and quality which refers to sleep patterns on the incidence of hypertension in fishermen on the Puger Coast of Jember. The research results obtained have a high OR value, an OR value that is too high is likely to occur because not enough samples were used. Sample limitations are due to using Lemeshow calculations without considering the entire population, but by considering the proportion of cases in previous research. However, the research design used, by comparing the case group and the control group, was able to interpret the relationship between the two variables even though the sample size was small. However, the case-control research design with a retrospective approach has limitations for researchers in selecting case groups.

**Clinical Implications**

It is hoped that this research can become a reference for increasing the importance of optimizing sleep hours to produce good sleep patterns so that it can reduce the occurrence of hypertension in fishermen. Apart from that, the local health center is expected to be able to regularly monitor blood pressure in fishermen.

**CONCLUSION**

The average age of respondents is 41-60 years old and has an elementary school education. The average sleep duration of respondents is low according to their age group category. Most respondents' sleep patterns were poor in the case group (93.5%) and good in the control group (54.8%). The research results showed that there was a significant relationship between sleep patterns and the incidence of hypertension in fishermen on the Puger Coast of Jember. Based on this research, it was found that the sleeping patterns of fishermen on the Puger coast of Jember are classified as poor. This research has limitations, namely, there is selection bias and confounding bias. However, it is hoped that this research can become a policy recommendation to local cadres and the Puger Community Health Center to increase knowledge among coastal communities, especially fishermen, regarding poor sleep patterns which can be a cause of hypertension, and
encourage people to use related health facilities to monitor the symptoms of hypertension. It is also hoped that future researchers can carry out further research related to risk factors for hypertension in fishermen at a larger sample level, place, and different research design with more attention to possible biases.

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AUTHORS CONTRIBUTION

NWM; Article writing, research concept, and design, data collection, data analysis. NFWA; Writing the contents of the article, reviewing, and approving the final manuscript, correspondence.

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CONFLICT OF INTEREST

There are no conflicts of interest between the authors.

REFERENCES


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