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Correlation Between Knee Osteoarthritis Pain and The Ability to Perform Salat

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ABSTRACT

Introduction: Osteoarthritis (OA) has affected approximately 303 million individuals worldwide, making it the second most rapidly increasing disease behind Rheumatoid Arthritis. OA is the leading cause of lower extremity disability amongst older adults with an estimated lifetime risk for knee OA being approximately 40% in men and 47% in women. Osteoarthritis affects the entire joint which has symptoms that could intense pain and discomfort, making it difficult to carry out typical routine activities. This, of course, will conflict with Muslims who are obligated to perform daily prayers or salat which is an obligatory component of the daily routine of Muslims that is performed in the same way at least five times a day.
Objective: This study aimed to analyze the correlation between knee osteoarthritis pain and the ability to perform salat.
Methods: The method used in this study is an analytic observational method with a random sampling technique which was involved by 57 respondents in total. The data obtained was collected from April to May and showed frequency and percentage. Determination of the correlation between Knee Osteoarthritis and The Ability to perform Salat is done by statistical analysis with chi-square test using the SPSS application.
Results: The asymptotic value obtained was 0.238. The obtained asymptotic value is >0.05.
Conclusions: It can be concluded that there is no significant correlation between knee osteoarthritis pain and the ability to perform salat movements.

Introduction

Osteoarthritis (OA) is a chronic joint disease that causes pain, discomfort, and loss of function globally (Hunter, D. J., & Bierma-Zeinstra 2019) Global Health Metrics estimates that 303 million individuals worldwide suffered from osteoarthritis in 2017 (James, et al 2018). The number of cases climbed by 31.4% in ten years, making it the second most rapidly

increasing disease behind Rheumatoid Arthritis (Kloppenburg, M., & Berenbaum 2020). OA is the leading cause of lower extremity disability amongst older adults with an estimated lifetime risk for knee OA being approximately 40% in men and 47% in women. The risks are higher still among individuals who are classified as obese. (Victoria et al. 2014). Obesity is still the most important risk factor for both the beginning and progression of osteoarthritis (OA). Overloading the joints due to increased weight was thought to be the primary cause of OA, leading to the loss of articular cartilage (Nedunchezhiyan et al. 2022). However, in cases of obesity, it can be overcome by intermittent fasting and physical exercise. According to research conducted by Aisyah and Salim (2022), it was concluded that intermittent fasting and exercise are both effective in losing weight.

Osteoarthritis affects the entire joint, including the cartilage covering it, the subchondral bone beneath it, the synovial membrane that lines it, the joint capsule that encloses it, the ligaments that support it, and the muscles that surround it. All joints can be affected, particularly the spine, hands, and large weight-bearing joints, mainly the knees (Mougui, et al 2023). This is because collagen and tension-reducing proteoglycans in joint cartilage change with age, and the flow of nutrients to cartilage decreases (Lozada, 2013). Ultrasound can be used to evaluate and assess osteoarthritis during a cartilage examination. Soft tissue, bone contouring in joints, cartilage, meniscus, and other pathological disorders such as osteophytes, synovial hypertrophy, and effusion, among others, may be assessed with this process. (Pane et al. 2022)

Osteoarthritis causes pain and dysfunction in patients, affecting daily activities (Aisyah et al. 2022). A study of the quality of life of osteoarthritis patients using the SF-36 indicated that patients had limited functional skills ranging from mild to severe, resulting in a decrease of 25% in their quality of life (Kawano, et al 2015). This, of course, will conflict with Muslims who are obligated to perform daily prayers or salat. According to a previous study conducted by Aisyah (2020) on sit-to-stand test osteoarthritis patients to evaluate functional motor performance, the STST score was greater than normal, indicating that osteoarthritis patients had more mobility limitations.

Salat is an obligatory component of the daily routine of Muslims that is performed in the same way at least five times a day; each consists of a repeated unit called Rak'ah, which contains a series of seven to nine different gestures and postures. Standing, arm raising and lowering,

bowing, sitting on shins, prostration, and head rotation are some examples (Aldossary, 2023).

The majority of the body's muscles and joints are normally involved in salat performance. Prayer can be considered as a form of stretching exercise. The physical activities conducted during salat are easy and mild exercises that are compatible with people of all ages and conditions. Salat combines mild muscle contraction and relaxation, resulting in muscle flexibility without over-exertion (Chamsi-Pasha M 2021). According to Rabbi (2018) previous research, seven adult subjects investigated the electrical activity of two muscles located on the dorsal surface (the erector spine and trapezius muscles) during salat and discovered that both muscles maintain a balance in terms of contraction and relaxation during bowing and prostration positions. We found in 2008, Yilmaz researched the role of this repetitive motion on knee and hip osteoarthritis and osteoporosis, concluded that prayer has no harmful effect on knee and hip osteoarthritis. There has been no recent research on the correlation between knee osteoarthritis and the capacity to conduct prayer movements in populations outside the hospital in the previous ten years.

Methods

This study was conducted from April to May 2021, among the community around Ahmad Yani Islamic Hospital in Surabaya**,** while some people were unable to visit the hospital due to the covid pandemic. Data collection was carried out through a sampling technique using a questionnaire containing several questions about patients' complaints related to knee osteoarthritis such as patients pain level using VAS score, duration of illness, other body parts complaints, activity that triggers knee pain and to reduce the pain, and pain interfere for performing salat (prayer). Especially for the knee pain, we asked the pain if the severity of pain is between the numbers 1 to 10. Where 1-4 is mild pain, 5-7 is moderate pain, and 8-10 is severe pain, on what scale did the patient feel knee pain most often.

The collected data was then presented in tables and analyzed using the Chi-Square test with the SPSS 25 application. The inclusion criteria were respondents which diagnosed with OA from the results of the questionnaire they filled out. The exclusion criteria respondents were patients who didn’t perform prayer.

Results

Fifty-seven respondents were assessed for eligibility, and 36 people (63.16%) met the inclusion criteria of knee osteoarthritis.

Their mean age was 49,30 ± 9,48. The highest frequency of patients experiencing knee OA was in patients aged 35-50 years (58.33%). The frequency distribution according to the age of respondents who had knee osteoarthritis is shown in table 1.

Table 1. Frequency distribution of knee OA based on ages

Patient's Age	Frequency (n=36)	Percentage (%)
<35	1	2.78
>65	1	2.78
35-50	21	58.33
50-65	13	36,11

Based on data from table 2, all of the respondents who met the inclusion criteria were women.

Table 2. Frequency distribution of knee OA based on genders

Patient's Gender	Frequency (n=36)	Percentage (%)
Women	36	100
Men	0	0

From table 3, The most common patient complaints of knee pain are on a scale of 1-4 or mild pain (58.33%), while the others are on moderate pain (30.56%), and severe pain (11.11%). Most patients complaint of OA 3 months until 1 year of OA (58.3%), while the less than 3 months were 19.4%, and more than 1 year were 22.2%.

Table 3. Frequency distribution of knee OA based on patient complaints

		Frequency (n=36)	Percentage (%)
Pain scale	1-4 (mild)	21	58.33
	5-7 (moderate)	11	30.56
	8-10 (severe)	4	11.11
Duration of sick	<3 month	7	19.4
	3 month – 1 year	21	58.3
	>1 year	8	22.2
Other Body Parts Complaints	Neck Pain	2	5.56
	Low Back Pain	17	47.22
	Hand/ Arm Pain	8	22.22
	None	9	25.00
Actions that trigger knee pain	Stand up from a sitting position	20	55.56
	Squat	4	11.11
	Climbing up the stairs	12	33.33
Activity to reduce the pain	Take a rest	17	47.22
	Heat patch/ Massage	2	5.56
	Take Medicine	14	38,89
	Exercise	1	2,78

	No action	2	5,56
Pain interferes with Salat	Yes	8	22.22
	Sometimes	4	11.11
	No	24	66.66

The most common complaints of pain other than knee are back pain (47.22%), the cause of knee pain when getting up from a sitting position (55.56%), and the most action that patients did to reduce the pain by taking rest (47.22%). Most patients could do salat normally (66.66%), while 22.22% could not do salat normally and 11.11% occasionally feel difficulty during salat.

The data was then processed using the IBM SPSS 25 application, with Chi-Square test. Based on the results that have been obtained, it can be concluded that there is no significant correlation between knee osteoarthritis pain and the ability to perform salat movements (p = 0,238).

Discussion

Based on the study, it was found that the highest number of knee OA patients were in the age group of 35-50 years (58.33%). These results are different from the previous research conducted by Comelia (2019), concerning the Correlation Between Age and Degree of Joint Damage in Knee Osteoarthritis Patients, in this study the results showed that the age group 60-75 has the highest incidence of knee OA, which is 74% more exactly at the age of 65 years. Meanwhile, from a study conducted by Deshpande (2016), the results showed that adults <45 years of age accounted for about 2 million cases, while those aged between 45-65 accounted for 6 million more cases.

According to table 2, the majority of patients (47.22%) experienced lower back discomfort in addition to knee pain. This conforms with Gusti's (2020) study, that the participants who had knee osteoarthritis and complained of myogenic low back pain were as high as 13 individuals, or 25%, whereas the number of study participants who did not have myogenic low back pain was as low as 12 people, or 23.1%. Low back pain in people with knee osteoarthritis is a non-specific myogenic form of pain caused by indirect muscle activity. There was an issue that LBP is likely to be caused by knee spine syndrome, a disease that produces a decreased angle in the knee. The degenerative phase of knee osteoarthritis causes lumbar lordosis (Triwahyuni et al. 2020).

Salat is a Muslim prayer that all Muslims must do five times a day. The majority of the muscles and joints are engaged during the numerous Salat postures and motions, which is akin to performing a low-intensity workout. Different Salat postures, however,

engage the biceps brachii, triceps brachii, pectoralis major, scapular musculature, rectus femoris, biceps femoris, tibialis anterior, and gastrocnemius. Salat has also been demonstrated to improve balance in both healthy and stroke patients, lessen the risk of knee osteoarthritis, and have cardiovascular and compositional advantages (Osama M, 2019).

The *p*-value obtained was 0.238 ($p > 0.05$), based on the statistical findings of the chi-square test, which shows that there is no correlation between knee osteoarthritis and the ability to pray. Therefore, it can be assumed that there is no correlation between knee osteoarthritis pain and the ability to perform prayer due to the fact that the majority of respondents only experience mild pain, which can be prevented or reduced as the prayer movement is also a movement therapy/exercise for joints that can reduce joint pain. Furthermore, because the majority of patients had less than one-year duration of OA, they might not have any limits in knee joint movement that interfered with prayer. Due to the pandemic condition, we did not take direct measurements of the knee range of motion.

Study Limitation

This study has some limitations. First, this study did not have data on the frequency and kind of drugs used by respondents, there was no control group because all of the respondents performed salat prayer. Second, the diagnosis of knee OA was only obtained by questionnaire data and did not take any further physical examination due to pandemic. Third, this study did not set up a follow-up period with participants after the assessment. Last, strongly recommend that future studies include larger samples.

Conclusion

Based on the study and statistical data testing that has been done, it can be concluded that there is no correlation between knee osteoarthritis pain and the ability to perform salat.

Ethical Consideration

This research was approved by the Research and Community Service Center of Universitas Nahdlatul Ulama Surabaya from community service activities carried out by the researcher in 2021.

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Periodontitis as a Risk Factor of Preeclampsia in Pregnancy: A Scoping Review

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ABSTRACT

Introduction: Preeclampsia (PE) is a pregnancy complication characterized by hypertension and proteinuria after 20 weeks of gestation. Although the causes of PE are still unclear, some factors play an important role in increasing the incidence of PE, namely periodontitis which has an impact on the systemic spread of pathogens and inflammatory mediators, causing adverse pregnancy outcomes. This scoping review aims to evaluate, identify, and provide a deeper understanding of the relationship and possible mechanisms between periodontitis and increased PE in pregnant women. A literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted in PubMed, ScienceDirect, Scopus, and Google Scholar until July 2023. In the end, 14 articles were included for review.
Results: All of the included studies stated that periodontitis mostly affects pregnant women with PE, and periodontitis is believed to play a role in increasing the risk of PE through the mechanism of bacteremia due to periodontal pathogens translocating from the oral cavity to the placenta and through cytokines and inflammatory mediators produced by inflamed periodontal tissue, resulting in disruption of the placenta, further increasing the risk of PE in pregnant women.
Conclusions: In conclusion, there is a significant increase in the incidence of PE in pregnant women who experience periodontitis. Future research to review the mechanisms by which periodontitis increases the risk of PE and to examine whether periodontitis treatment before and during pregnancy can prevent PE may be warranted.

Introduction

Periodontitis is a multifactorial chronic inflammation of the periodontal tissue caused by specific pathogens found in plaque biofilms, which leads to progressive destruction of the periodontal ligament and alveolar bone (Tonetti et al., 2018). Periodontitis commonly presents with several clinical signs, including gingival inflammation, clinical attachment loss (CAL), bleeding on probing (BOP), deep probing depth (PD), mobility, and pathological migration (Papapanou et al., 2018).

It is believed that almost 19% of adults globally are affected by severe periodontal disease (World Health Organization, 2023). In Indonesia, 74.1% of Indonesian people have periodontitis (Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI, 2018). This makes periodontitis a global public health problem because there has been a significant increase in the last few decades and there is some evidence to suggest that there is an association between periodontitis and systemic disease (Smyrlis et al., 2019), such as diabetes mellitus (Liccardo et al., 2019), cardiovascular disease (Rahimi & Afshari, 2021), cognitive impairment (Guo et al., 2021), renal disease (Baciu et al., 2023), rheumatoid arthritis (Krutyhołowa et al., 2022), respiratory disease (Dong et al., 2022), cancer (Tuominen & Rautava, 2021), metabolic syndrome (Pirih et al., 2021), pregnancy complications such as premature birth (Uwambaye et al., 2021), low birth weight (Bhavsar et al., 2023), and preeclampsia (PE).

PE is a complication that occurs after 20 weeks of gestation and affects around 6.7% of pregnant women (95% CI=5.8-7.6) (Macedo et al., 2020), with symptoms of blood pressure ≥140/90 mmHg followed by one or more other conditions, such as proteinuria (≥300 mg/24h), acute renal failure (creatinine ≥90 mmol/L), thrombocytopenia, liver complications, neurological complications, and uteroplacental abnormalities (Fox et al., 2019; Phipps et al., 2019; Rana et al., 2019).

The etiology of PE is multifactorial, some of these risk factors include placental oxygen imbalance, abnormal alterations in the spiral arteries, pathological placentation, fetomaternal oxidative stress, inflammation, and maternal blood circulation disturbances (Ahmadian et al., 2020). Other factors include age ≥35 years, multiple pregnancies, nullipara, chronic hypertension, obesity, pre-gestational diabetes mellitus, irregular antenatal check-ups, primigravida, family history of PE, chronic kidney disease, antiphospholipid syndrome, trisomy 13, and systemic lupus erythematosus (Rana et al., 2019; Syahfirda et al., 2023). In addition, other clinical factors significantly increase the risk of PE, including polycystic ovary syndrome (Fornes et al., 2022), sleep-related breathing disorders (Carnelio et al., 2016), periodontal disease, urinary tract infections (Yan et al., 2018), and *Helicobacter pylori* (Elkhouly et al., 2016).

Although the cause of PE is still unknown with certainty, some evidence has reported a significant association between infections, including periodontitis, and PE. In addition, periodontitis is an oral infection that has a negative impact on systemic health, while PE has an impact on adverse pregnancy outcomes. Therefore, the

objective of this scoping review of the published literature is to evaluate, identify, and provide a deeper understanding of the relationship and possible mechanisms between periodontitis and increased PE in pregnant women.

Methods

Review Methodology

This scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Population (P), Intervention (I), Comparison (C), and Outcome (O) questions used to answer this research were do pregnant women (P) who experience periodontitis (I) compared to pregnant women with healthy periodontal conditions (C) have an increased risk of PE (O)?

Information Sources

A comprehensive literature search was conducted until July 2023 on the following databases: PubMed, ScienceDirect, Scopus, and Google Scholar.

Search Strategy

In the search, several keywords were used such as [(periodontitis) OR (periodontal disease) OR (maternal periodontitis)] AND [(preeclampsia) OR (pre-eclampsia) OR (pregnancy outcomes)]. Search results were limited to articles written in English, published within the last 10 years, and studies conducted on humans.

Selection Process

All search results that matched the keywords used were then grouped and duplicates, if any, were removed. Studies were then screened according to the predetermined inclusion criteria, if they did not match, they were excluded. In the final stage of the study selection process, all fully accessible articles were extracted. The article documentation process was carried out in Microsoft Excel for Windows. The entire study selection process was conducted by independent researchers: FMR, AOA, NNP, EPL, and BPNA.

Results

A total of 5,867 articles were identified from initial searches through databases. After the removal of duplicates, 4,871 articles were filtered based on inclusion criteria, resulting in 482 remaining articles. The findings were then screened based on the title and abstract and irrelevant articles were excluded, leaving 58 full-text articles which were then assessed for eligibility. In this final stage, 14 articles were included for review, including 10 case-control studies, 3 prospective cohort studies, and 1 cross-sectional study. The entire study selection process is presented in **Figure 1**.

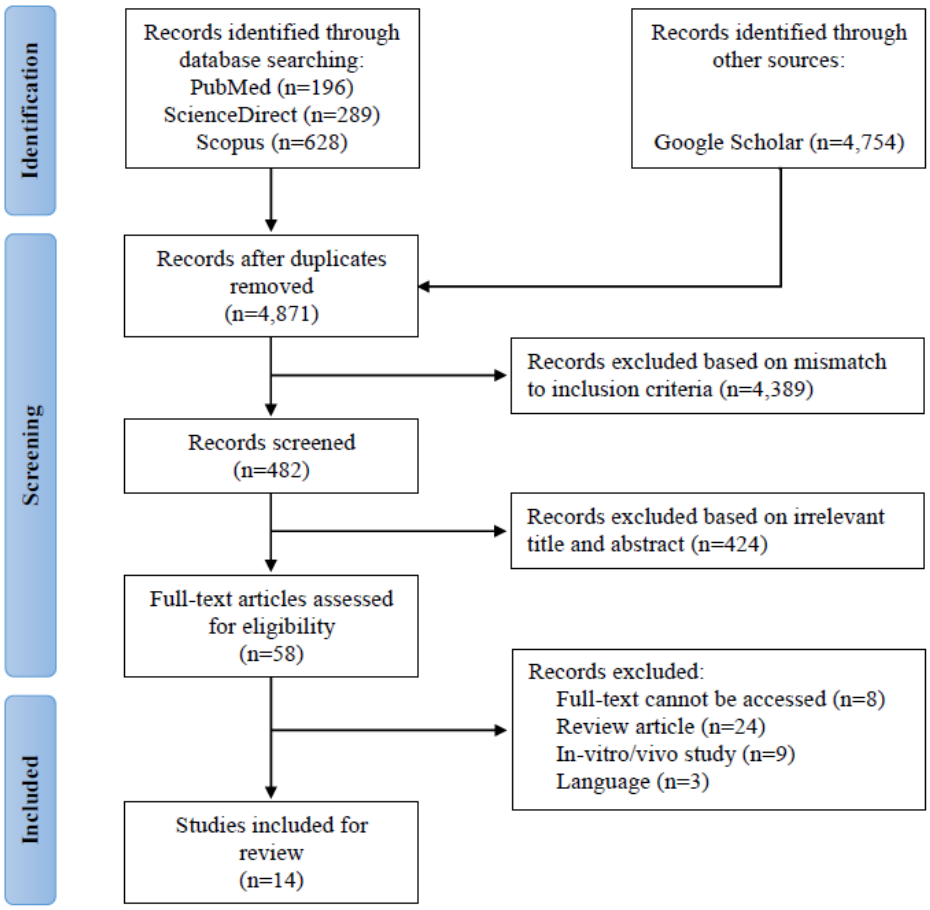

Figure 1. PRISMA flowchart.

Table 1. Summary of the included studies.

References	Country	Design	Participant	Result
Afshari et al. (2013)	Iran	Case-control study	180 cases, 180 controls	Pregnant women who have poor periodontal conditions have a higher risk of PE. The results of the study concluded that the progression and severity of periodontitis increased the risk of PE and adverse pregnancy outcomes.
Chaparro et al. (2013)	Chile	Case-control study	11 cases, 43 controls	There was a relationship between PE and plasma CRP levels. PE was correlated with IL-6 levels elevation in GCF samples in early pregnancy, resulting in increasing the risk of PE.
Pralhad et al. (2013)	India	Case-control study	100 cases, 100 controls	The study results showed that the prevalence of periodontal disease was

				65.5% and was significantly higher in women with hypertension (p<0.0001).
Ha et al. (2014)	Korea	Prospective cohort study	283 pregnant women	Periodontitis enhanced the risk of PE among pregnant women who had never smoked. Periodontitis has been linked to a higher risk of developing PE.
Jahromi et al. (2014)	Iran	Case-control study	100 cases, 100 controls	A significant relationship existed between PE and periodontal disease. Gingivitis occurred more frequently in mild PE cases (56.8%) compared to severe PE cases (31.6%). Periodontitis occurred more often in cases with severe PE.
Aly et al. (2015)	Egypt	Case-control study	40 cases, 40 controls	The PE group had a greater number of anaerobes in both blood and placental samples in comparison to the control group. A notable difference was observed between the two groups in terms of TNF-α levels as measured by the ELISA assay in serum.
Desai et al. (2015)	India	Case-control study	120 cases, 1120 controls	Maternal periodontitis was associated with PE. After primiparity matching, maternal periodontitis was still associated with the incidence of PE.
Lee et al. (2016)	Korea	Prospective cohort study	328 pregnant women	Periodontitis had a 5.56-fold increased risk of experience preterm birth with PE in pregnant women, in comparison to pregnant women without periodontitis.
Mahendra et al. (2016)	India	Case-control study	25 cases, 25 controls	Pregnant women with PE showed significantly higher BOP and CAL in comparison to normotensive pregnant women. The PPAR-γ expression was decreased and NF-κB was significantly increased in pregnant women with PE in comparison to normotensive pregnant women.
Soucy-Giguère et al. (2016)	Canada	Prospective cohort study	258 pregnant women	Periodontal disease diagnosed early in pregnancy was correlated with a significantly increased risk of developing PE.

Khalighinejad et al. (2017)	USA	Case-control study	50 cases, 50 controls	Apical periodontitis was significantly more common in the case group. Maternal apical periodontitis can significantly predict the incidence of PE.
Jaiman et al., (2018)	India	Case-control study	15 cases, 15 controls	The periodontal condition of pregnant women with PE was statistically worse in comparison to those who were normotensive.
Sumathy et al., (2018)	India	Case-control study	100 cases; 100 controls	46% of all patients suffer from periodontitis. Of the 46% of patients, 67 patients experienced PE.
Chitra et al., (2019)	India	Cross sectional study	60 preeclamptic pregnant women	88.3% of PE patients were found to have mild periodontal disease and 11.7% had moderate periodontal disease. A correlation existed between elevated CRP levels caused by periodontal disease and a higher incidence of PE.

Discussion

Based on its prevalence, periodontitis is often found in pregnant women who experience PE, proven by several studies which report that the prevalence of the periodontal disease is quite high in pregnant women who experience PE, ranging from 72.8% to 93.3% (Afshari et al., 2013; Chaparro et al., 2013; Jaiman et al., 2018; Pralhad et al., 2013; Sumathy et al., 2018). Pregnant women with periodontitis are at increased risk of developing PE, as reported by the results of studies conducted by Pralhad et al. (OR=5.5; 95% CI=2.7-11.4), Desai et al. (OR=19.8; 95% CI=7.8-48.94), Ha et al. (OR=4.51; 95% CI=1.13-17.96), Lee et al. (OR=5.56; 95% CI=1.22-25.39), Soucy-Giguère et al. (RR=5.79; 95% CI=1.23-27.36), Khalighinejad et al. (OR=2.23; 95% CI=1.92-6.88), and Sumathy et al. (OR=6.03; 95% CI=3.28-11.31). Therefore, it can be concluded that there exists a significant correlation between periodontitis and the occurrence of PE.

Although there was a positive association between periodontitis and PE in these studies, there were differences in odds ratio (OR) values between studies, which may be due to ethnic factors in the study population, study sample size, control variables, and, most importantly, the definition of periodontitis used. We found several clinical indices used varied between studies to define periodontitis, such as PD ≥4 mm and BOP (Afshari et al., 2013;

Soucy-Giguère et al., 2016), PD ≥4 mm, CAL ≥3 mm, presence of inflammation and BOP (Aly et al., 2015; Chaparro et al., 2013; Desai et al., 2015; Mahendra et al., 2016; Sumathy et al., 2018), gingival index (GI) >1, oral hygiene index (OHI) >3, PD >4 mm, or CAL >3 mm (Pralhad et al., 2013), and several studies defined periodontitis using only one indicator, namely PD ≥4 mm (Chitra et al., 2019) and CAL ≥4 mm (Ha et al., 2014; Lee et al., 2016). This is believed to be one of the factors that causes significant differences in OR values between studies, however, periodontitis remains a risk factor for increasing the incidence of PE in pregnant women.

Several possible mechanisms link periodontitis with the increased incidence of PE in pregnant women, namely bacteremia from periodontitis and cytokines and mediators (Smyrlis et al., 2019). First, periodontitis causes the translocation of oral bacteria through bacteremia into the fetomaternal blood circulation (Jaiman et al., 2018), and then spreads the bacteria to the fetoplacental unit, leading to ectopic infection and/or triggering inflammatory reactions and increasing levels of cytokines and inflammatory mediators (Madianos et al., 2013). Second, cytokines and mediators produced by inflamed periodontal tissue cause the accumulation of mediators in large amounts or in the liver, causing an inflammatory response with the production of C-reactive protein (CRP) and fibrinogen (Chandy et al., 2017).

A large amount of several periodontal pathogens, such as *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Treponema denticola*, *Tannerella forsythia*, *Micromonas micros*, and *Eikenella corrodens*, are found in the placenta, chorionic trophoblastic, and several types of cells, such as amniotic epithelium, decidua, blood vessels, and amniotic fluid, and are associated with PE and gestational hypertension (Konopka & Zakrzewska, 2020; Le et al., 2022; Zi et al., 2015). Based on the results of several studies, there are significant similarities between the microorganisms found in the placenta and in the oral cavity of periodontitis patients (Curtis et al., 2020; Salminen et al., 2015).

Additionally, *P. gingivalis*, *Bergeyella sp.*, *T. forsythia*, *Capnocytophaga spp.*, *E. corrodens*, *Parvimonas micra*, and *T. denticola* are reported to be detected in women with preterm birth (Bobetsis et al., 2020; Mesa et al., 2013; Wang et al., 2013). Among these pathogens, *F. nucleatum* is known to cause adverse effects on pregnancy (Chitra et al., 2019), including PE, preterm birth, low birth weight with or without intrauterine infection, early neonatal sepsis, and stillbirth (Bobetsis et al., 2020). Another study added that *A.*

actinomycetemcomitans and *Prevotella intermedia* were also detected in placental samples from pregnant women with PE, where these bacteria would colonize in placenta through bacteremia (Fischer et al., 2019), which would impact adverse pregnancy outcomes, including PE.

Periodontitis during pregnancy has been linked to adverse pregnancy outcomes, including preterm birth, early miscarriage, low birth weight, and PE which is believed to be caused by an increased systemic inflammatory response (Jaiman et al., 2018). There was an increase in interleukin (IL)-6 in the gingival crevicular fluid (GCF) and an increase in CRP in early pregnancy that was 65% higher than in pregnant women without periodontitis (Chaparro et al., 2013; Jahromi et al., 2014), and an increase in matrix metalloproteinase (MMP)-9 (Desai et al., 2015). Furthermore, periodontitis induces an inflammatory response through increasing pro-inflammatory mediators such as IL-1β, prostaglandin (PG) E2, IL-6, tumor necrosis factor (TNF)-α (Mata et al., 2021), CRP, 8-isoprostane, soluble intercellular adhesion molecule (sICAM)-1, fibronectin, and α-fetoprotein in serum, umbilical cord blood, and amniotic fluid (Starzyńska et al., 2022).

Increased IL-6 and TNF-α impact endothelial cell function by increasing vascular permeability and inducing trophoblast cell apoptosis. Both cytokines stimulate and damage endothelial cells, causing complex inflammatory reactions in pregnant women, and contributing to the pathophysiology of PE (Aggarwal et al., 2019). This is corroborated by research conducted by Aly et al. (2015) and Chaparro et al. (2013) which confirmed that there were significant differences seen between the control group and the pregnant women in the PE group, regarding IL-6 and TNF-α in serum.

CRP functions as an indicator of inflammation and the level of damage to endothelial cells, which are factors that contribute to the development of PE (Renu et al., 2022). Elevated CRP levels in the blood are observed in cases of acute infections, cancer, and inflammatory disorders. CRP has the ability to attach to chromatin, which is liberated from necrotic or apoptotic cells, and small ribonucleoprotein nuclear particles. It suggests that CRP may contribute to the initiation of the inflammatory response that is characteristic of PE (Nasruddin et al., 2018). CRP is primarily formed in hepatocytes, although it is also produced by smooth muscle cells, endothelial cells, lymphocytes, macrophages, and adipocytes, under the influence of IL-6 and TNF-α (Sproston & Ashworth, 2018).

The aforementioned statement is in line with research conducted by Chitra et al. (2019) which stated that the mean of CRP

levels in individuals with mild and moderate periodontal disease were 1.155±1.8 mg/dL and 9.26±9.4 mg/dL, respectively, with a *p*-value of 0.001. This shows that the mean of CRP level in pregnant women with periodontitis is increased, possibly caused by periodontal pathogens, which not only trigger local inflammation but are also involved in increasing systemic inflammatory and immune responses.

The study carried out by Mahendra et al. (2016) concluded that there was a decrease in peroxisome proliferator-activated receptor gamma (PPAR-γ) expression ($p<0.05$) and an increase in nuclear factor kappa B (NF-κB) expression ($p<0.05$) significantly in pregnant women with PE in comparison to normotensive pregnant women. The results of the study are corroborated by evidence showing that the concentration of PPAR-γ activator in the bloodstream of pregnant women with PE is significantly reduced (Hu et al., 2022) while the NF-κB expression is increased, resulting in excessive inflammatory reactions, abnormal placentation, and consequently uteroplacental dysfunction, release of pro-inflammatory cytokines into the bloodstream, endothelial stress, and development of PE in pregnant women (Socha et al., 2021). This strengthens the evidence that pregnant women with periodontitis can increase NF-κB expression and decrease PPAR-γ expression which will increase the occurrence of PE.

Based on the results of the review conducted, there are limitations in the research reviewed, namely the population coverage of all the research studied, such as the absence of research from European and several Asian regions populations, thus it cannot reflect the results of the research from various populations and races. In addition, there are differences in the use of clinical indicators to define periodontitis which has an impact on varying OR values. However, the results of this scoping review can conclude that there is a relationship between periodontitis experienced by pregnant women and an increased incidence of PE as proven in studies with case-control study, prospective cohort study, and cross-sectional study designs which provide an overview for conducting research in the future regarding the mechanisms and prevention of PE through periodontitis treatment by dentists.

Conclusion

We concluded that there was a significant increase in the incidence of PE in pregnant women with periodontitis as indicated by the high prevalence of pregnant women with periodontitis who experience PE, in comparison to normotensive pregnant women. The

elevated prevalence of PE in pregnant women with periodontitis is caused by the translocation of periodontal pathogens to the fetoplacental unit through bacteremia and the activity of cytokines and inflammatory mediators that cause excessive inflammatory reactions in the placenta.

The results of our review require future research to investigate the mechanism of periodontitis in increasing the development of PE in pregnant women, as well as whether dental intervention aimed at preventing and treating periodontitis before or during pregnancy can have a positive impact on pregnancy outcomes, including reducing the occurrence of PE.

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The Correlation Between Medication Adherence and Role of Medication Supervisor with Prevalence of Pulmonary TB Recurrence in Serang City, Banten

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ABSTRACT

Introduction: Pulmonary tuberculosis (TB) is one of the deadliest diseases and is still a major health problem in the world. The standard treatment for pulmonary TB is within 6 months. Failure of pulmonary TB sufferers to seek treatment and good adherence to medication consumption plays an important role in the recurrence of pulmonary TB. Treatment supervision (PMO) in pulmonary TB patients contributes to patient compliance in taking medication, so it can be concluded that PMO is also important in the recurrence of pulmonary TB.
Objective: This study aims to determine the relationship between medication adherence and the role of medication supervisors with the prevalence of pulmonary TB recurrence in the city of Serang, Banten, so that it can be developed as an effort to prevent an increase in TB prevalence in the future.
Methods: This research was conducted at the Unyur, Banten Girang, and Singandaru Health Centers in January-May 2023 with a total sample of 41 people. The research design used was a case-control design and used a total sampling technique. The analysis used was univariate and bivariate analysis using the Chi-square test and if cells did not meet the Chi-square test requirements, the alternative test was Fisher's exact
Results: The results of this study concluded that there was no significant relationship between adherence to taking medication and monitoring taking medication with recurrence of pulmonary TB, namely obtaining p value = 0.906 and in the role of supervisor taking medication obtained p value = 0,719.
Conclusions: Based on the results, the conclusion of this research is that there is no significant relationship between the level of treatment compliance and lung disease. recurrence of TB. Apart from that, there was no significant relationship between the role of monitoring medication taking and recurrence of pulmonary TB.

Introduction

Pulmonary tuberculosis (TB), an infectious disease caused by the bacterium Mycobacterium tuberculosis which attacks the respiratory tract, is one of the top deadly diseases and is still a major health problem in the world. The World Health Organization (WHO) in its 2021 Global TB Report reported that Indonesia was ranked second in the burden of pulmonary TB disease which accounts for more than two-thirds of the total incidence of pulmonary TB in the world (WHO, 2022; MacNeil, et al., 2020). According to the results of the 2018 Basic Health Research (RISKESDAS), Banten has a pulmonary TB prevalence of 0.76% with the second highest prevalence percentage after Papua (0.77%). Meanwhile, Serang City is ranked third in terms of the highest prevalence of pulmonary TB cases (0.71) after Tangerang (0.90) and South Tangerang City (0.72) (Kemenkes, 2022).

The high number of pulmonary TB cases is influenced by many factors. Among them are social factors, environment, behaviour and nutritional status (Shukla, Pandey, Singh, & Sharma, 2019). The behavior of people who live in densely populated environments and poor nutritional status contribute to the transmission process and play a major role in increasing the number of TB cases. If an individual experiences pulmonary TB, they must be treated immediately with standard pulmonary TB treatment, namely treatment within 6 months. (Loscalzo, 2016) If pulmonary TB patients neglect to take medication, the pulmonary TB disease agent becomes more resistant, developing and increases in number and has the potential to attack other organs. (Sudoyo, 2014; Lestari, 2019)

The proportion of pulmonary TB sufferers who do not regularly take medication in Indonesia based on RISKESDAS 2018 is 30.8% with the following most common reasons: (1) feel healthy (37.51%), (2) do not routinely seek treatment (28.42%), (3) cannot tolerate side effects (15.66). Meanwhile, the proportion of pulmonary TB sufferers who do not regularly take medication in Banten Province is 41.7% for various reasons such as: (1) do not routinely seek treatment (57.98%), (2) feel healthy (39.8%), (3) cannot tolerate side effects (36.75%) (Indonesian Ministry of Health, 2022). This data shows a high percentage of patients who do not seek treatment regularly and indicates low compliance with pulmonary TB treatment procedures in taking medication regularly to recover from their pulmonary TB disease and break the chain of transmission of pulmonary TB in Banten province. Even in conditions of this high number, the public's sense of concern and vigilance regarding compliance with taking medication in pulmonary TB patients is

low, thereby increasing the difficulty in handling cases of recurrence. (Nurhaini et al, 2022)

The failure of pulmonary TB patients to receive treatment and adhere to proper and correct medication consumption plays an important role in the recurrence of pulmonary TB and the risk of developing RR/MDR TB. The absence of medication-taking supervisors (PMO), whether from family, cadres, community leaders or Puskesmas officers who should ensure patient compliance in taking medication according to the dosage and schedule, also influences non-compliance with taking medication in pulmonary TB patients (Ministry of Health of the Republic of Indonesia, 2019). Meanwhile, the recurrence rate for pulmonary TB patients in Indonesia was recorded at 5,082 cases with Rifampicin Resistant/Multi-Drug TB (RR/MDR TB) confirmed at 8,268 cases (TBC Indonesia, 2022).

Unyur Community Health Center, Walantaka Community Health Center, and Banten Girang Community Health Center, Serang City, Banten have the situation, area coverage, and geographical location of these Community Health Centers in Serang as the capital of Banten Province, being community health centers with strategic working areas chosen as the location for this research which aims to determine the relationship Compliance with taking medication and the role of supervisors taking medication with the prevalence of pulmonary TB recurrence so that this research can be developed as an effort to prevent pulmonary TB recurrence in the future. (Dinkes Banten, 2022)

This study aims to analyze the relationship between the level of medication adherence and the role of medication-taking supervisors with the prevalence of pulmonary TB recurrence in Serang City in 2022. To achieve this goal, it is necessary to know the distribution of the level of medication-taking compliance and patient recurrence, the distribution of the level of the role of medication-taking supervisors and recurrence. patients, prevalence of patient recurrence, analysis of the relationship between the level of adherence to taking medication and the relationship between the role of the supervisor taking medication with the prevalence of recurrence in pulmonary TB patients in Serang City in 2022.

Methods

This research uses a descriptive-analytic correlation research method with a case-control aims to reveal the correlative relationship between 2 variables (independent and dependent) retrospectively. The research was carried out on pulmonary TB patients who experienced a recurrence for the case group

and pulmonary TB patients who did not experience a recurrence for the control group at the Unyur, Banten Girang, and Singandaru Community Health Centers in January-May 2023. The sampling technique in this study was total sampling with a large The research sample was 41 respondents.

The sample selection criteria in this study included selection of case and control samples. The case samples in this study were pulmonary TB patients who had been declared cured but had experienced a relapse and were seeking treatment at the Unyur Community Health Center, Banten Girang during the 2022 period. Meanwhile, the control sample was patients who had been declared cured and had not experienced a recurrence who were seeking treatment at the Unyur Community Health Center, Banten Girang, and Singandaru over a period of time similar to the case population when declared cured. Both groups must meet the inclusion and exclusion criteria.

Inclusion criteria are pulmonary TB sufferers who are able to communicate well, are cooperative and willing to be respondents. Exclusion criteria include: If the sufferer's family does not agree with the sufferer being a research respondent, pulmonary TB sufferers with comorbidities, namely HIV/AIDS, those who have moved address and received treatment outside the working area of the Unyur, Banten Girang and Singandaru Community Health Centers, also pulmonary TB sufferers who have died.

Material

The instrument used in this research was the MMAS (Morisky Medication Adherence Scale) questionnaire.

Statistical analysis

The analysis used was univariate and bivariate analysis using the Chi-square test and if cells did not meet the Chi-square test requirements, the alternative test was Fisher's exact. A value of $P< 0.05$ was considered significant.

Result

The research was carried out on April 1-30th 2023 on relapsed and recovered pulmonary TB patients who underwent treatment at the Unyur, Banten Girang and Singandaru Community Health Centers with a research sample of 46 respondents who were included in the inclusion criteria, namely 41 respondents. There were 5 respondents who were included in the exclusion criteria on the grounds that 1 respondent had died, 2 respondents had addresses not found, and 2 respondents had moved house out of town. Of the 41 respondents, there were 21 case group respondents and 20 control group respondents. Data collected included the level of adherence to taking medication and the role of supervisor of medication taking

(independent variable) with recurrence of pulmonary TB (dependent variable). The research results are explained as follows.

Table 1. Frequency distribution of respondents' characteristics in Puskesmas Unyur, Banten Girang, and Singandaru

Respondent characteristic	Control		Cases	
	n	%	n	%
Gender				
Male	12	60%	19	90,5%
Female	8	40%	2	9,5%
Age				
Elderly (>60 years old)	7	35%	8	38,1%
Adult (<60 years old)	13	65%	13	61,9%
Education				
No school	2	10%	1	4,8%
Elementary	11	55%	6	28,6%
Primary high school	5	25%	13	61,9%
Secondary high school	2	10%	1	4,8%
Public Health Center				
Puskesmas Unyur	0	0%	4	9,7%
Puskesmas Banten Girang	15	36,5%	5	12,1%
Puskesmas Singandaru	0	0%	20	48,7%

Based on table 1, it could be seen that from the 41 respondents, 12 (60%) respondents from the control group and 19 (90.5%) respondents from the case group were male. A total of 13 respondents from the control group (65%) and the case group (61.9%) were in the adult category. In the control group, 11 (55%) respondents had education up to primary education, while in the case group 13 (61.9%) respondents had education up to secondary education.

Table 2. The frequency distribution of respondents was based on medication adherence and the role of drug taking supervisors with pulmonary TB recurrence at Unyur, Banten Girang, and Singandaru Health Centers

Variable	Control		Cases	
	n	%	n	%
Obedience				
Bad	8	40%	7	33,3%
Good	12	60%	14	66,7%
Medicine Supervisor (PMO)				
Bad	5	25%	4	19%
Good	15	75%	17	81%
Total	20	100%	21	100%

Based on table 2, 12 (60%) respondents in the control group and 14 (66.7%) respondents in the case group adhered to taking medication. There were 15 (75%) respondents from the control group and 17 (81%) respondents from the case group who had good medication monitoring.

Table 3. The relationship between respondents' medication adherence and lung TB recurrence at Unyur, Banten Girang, and Singandaru Health Centers

Obedience	Pulmonary TB Relapse				Total		OR 95% CI value
	Control (Not relapse)		Cases Relapse				
	n	%	n	%	n	%	
Bad	8	53,3%	7	46,7%	15	100%	0,13
Good	2	46,1%	14	53,9%	16	100%	(0,37)

Based on table 3, it can be found that 8 (53.3%) respondents who did not comply with taking medication did not experience a relapse. There were 14 respondents who adhered to taking medication and experienced a recurrence of pulmonary TB. The results of the chi-square statistical test in the table above where the cell has an expected value of less than 5, a maximum of 20% shows a p value = 0.906 p⩾0.05, so H0 is accepted, meaning there is no significant relationship between compliance and recurrence of pulmonary TB.

Table 4. The relationship between the role of supervisors taking respondents' medication with lung TB recurrence at Unyur Health Center, Banten Girang, Singandaru

Obedience	Pulmonary TB Relapse				Total		OR 95% CI value
	Control (Not relapse)		Cases Relapse				
	n	%	n	%	n	%	
Bad	5	55,5%	4	44,5%	9	100%	0,17
Good	5	46,8%	17	53,2%	22	100%	(0,32)

Based on table 4, it was found that 5 respondents (55.5%) who had poor supervision of taking medication did not experience a relapse. Meanwhile, 17 respondents (53.2%) who had good medication monitoring experienced a recurrence of pulmonary TB. The results of the Fisher's Exact statistical test because the Chi-square test requirements were not met, the table above showed a p value = 0.719 or p⩾0.05, so H0 was accepted, meaning there was no significant relationship between the role of supervisory medication taking and recurrence of pulmonary TB.

Discussion

Based on the research results, the characteristics of the respondents obtained were gender, age, education, and work area of the health center. Regarding gender, the respondents were mainly male. The high incidence of recurrence in men is due to fact that most men have activity patterns outside the home and smoking habits are related to the incidence of pulmonary tuberculosis, while high activity outside the home can cause higher transmission of germs. The age characteristics of the respondents are dominated by adults rather than the elderly. This can happen because in the adult age group, which is the productive age, each individu will tend to have high activity, so that the transmission of germs is greater. In addition, andogenic reactivity (bacilli that are already in the body become active again) tends to occur during productive age.

In terms of education, there were 13 respondents who had secondary education. Education plays a role in sufferers' ability to receive information about disease, especially pulmonary TB. A low level of education will result in a low level of knowledge in terms of maintaining personal and environmental hygiene (Trasia et al, 2014)

The working areas of the community health centers in this study include the Unyur, Banten Girang, and Singandaru Community Health Centers. Unyur Community Health Center was chosen as the research location because it had the highest rate of smear positive pulmonary

TB in Serang District, Serang City in 2021. Meanwhile, the Banten Girang and Singandaru Community Health Centers were selected as research locations to meet the minimum sample for this study because they had patients with the required respondent criteria. The frequency distribution of respondents based on the variables they want to study, namely medication adherence and medication monitoring, is presented in univariate analysis.(Afriani, 2021)

In the analysis of medication adherence, there were 14 respondents who adhered to taking medication but experienced a relapse. Patients with a high level of compliance but still experiencing relapses can occur because the patient has a wrong perception about the rules for taking medication, where the sufferer considers himself to be obedient to taking medication by taking medication according to the medication schedule but not according to the time or hours that have been determined. Patients who were non-compliant and did not experience recurrence were 8 respondents (53.3%) with research observations that this could be influenced by the patient's nutritional status and the patient's immunity. Observation results show that 50% of respondents who were non-compliant were caused by several things, namely the respondents' low knowledge of the importance of compliance with taking medication, boredom with the duration of treatment, and the patient's lack of awareness in remembering when to take medication so that treatment had to be repeated. (Asriani, 2018)

The results of this research are in line with research conducted by Yohana et al (2019) regarding the factors causing recurrence of tuberculosis cases in the Palangka Raya City Health Center with 30 respondents. Cross-sectional data obtained from statistical tests using chi-square, namely a p value of 0.283 p⩾0 .05 so there is no relationship between history of taking medication and recurrence of pulmonary TB in Palangkaraya City. Palangkaraya City in Central Kalimantan Province has a complete treatment rate for tuberculosis at 63.8%, whereas Banten Province is at 74.1%. This condition allows for similar research results. (Azizah, 2020)

This research proves that patients who are compliant and patients who are not compliant with taking OAT both have the same chance of experiencing a relapse of pulmonary TB. Patients who are not adherent to taking medication have the opportunity to experience a relapse because non-compliance in taking medication creates problems with the organism's resistance to the drug and can then experience reactivation into cases of pulmonary TB relapse. In patients who adhere to taking OAT, the patient still has a

chance of experiencing a recurrence of pulmonary TB which is caused by several things such as reinfection (recurrent infection) due to a weakened overall immune system due to poor nutritional status or decreased respiratory tract immunity due to exposure to cigarette smoke or the presence of comorbidities that increase the risk of reinfection with *Mycobacterium tuberculosis* bacteria. (Bagaskoro, 2016)

In the analysis of the role of medication-taking supervisors, there were 17 respondents who had good medication-taking supervisors and experienced relapse. Respondents with PMO who did not play a good role but did not experience a recurrence were 5 respondents (55.5%), the results of observations obtained in the study showed that the patient's motivation and hope to recover was so great, so that the patient continued to carry out treatment well even without assistance. by PMO. Meanwhile, respondents with a good PMO role but still experiencing relapse may occur because of the boredom experienced by the patient because of the many and long treatments so they neglect treatment without the PMO's knowledge, but the patient still takes treatment at the health center because motivated by supervisors to take their medication. (Goldie, 2018)

Research conducted by Atikah et al (2020) on the relationship between adherence to taking medication and the incidence of relapse of tuberculosis in children at Al-Ihsan Regional Hospital, Bandung, where data obtained from statistical tests using Exact Fisher obtained p value=1,000 ($p \geqslant 0.05$) which This means that there is no relationship between supervision of taking medication and TB recurrence because most respondents have quite good supervision of taking medication. This research was carried out using a case-control method with a retrospective approach in accordance with this research. Apart from that, Bandung in West Java Province has quite high availability of PMO, namely at 69.9% with a pulmonary TB prevalence of 0.63% while Banten is at 54.1% with a pulmonary TB prevalence of 0.76%. This assumes that the high availability of PMO is not related to the incidence of pulmonary TB relapse cases.(Gordon et al, 2018)

The results of this research are in line with research conducted by Marini et al (2021) regarding the relationship between knowledge, attitude and behavior of PMOs on the incidence of recurrent tuberculosis in Muara Enim Regency, where statistical test data were obtained using the Chi-square test with a p value of 0.574 ($p \leq 0.05$) then there is no relationship between knowledge, attitudes and behavior of supervisors taking medication and recurrence of pulmonary TB. This research by Marini also used a

case-control design and a retrospective approach similar to the research carried out here. Muara Enim District in South Sumatra Province also has a high availability of PMO at 77.7%, however with 138 research samples that have been studied, knowledge, attitude and behavior of PMO are not significantly related to pulmonary TB recurrence. (Keliat et al, 2018)

The limitation of this study is that it has not involved smoking status, nutritional status, including weight of respondents and their level of some vitamins as vitamins D. Prescription of the immunomodulators next to drugs might help in prevention the relapse. In addition to education history also working status should be considerred. Respondents who have good medication-taking supervisors experience a relapse and vice versa are still unknown, but lead to alleged antibiotic resistance. The level of knowledge to transmission, symptoms, risk factors and preventive behavior needs to be explored more in further studies.

Conclusion

Based on the results of the research and discussion regarding the relationship between adherence to taking medication and the role of supervisors taking medication with the prevalence of recurrence of pulmonary TB in Serang City, Banten, it can be concluded that the distribution of levels of adherence to taking medication and recurrence of pulmonary TB patients is 7 respondents who are non-compliant and 14 respondents who are compliant with taking medication suffers from relapse. It is known that the distribution of the level of the role of medication taking supervisor (PMO) and recurrence of pulmonary TB is that 4 respondents with a poor PMO role and 17 respondents with a good PMO role experienced a recurrence. The incidence of relapsed and cured pulmonary TB was 41 patients with 21 relapses and 20 cured patients. There is no significant relationship between the level of adherence to taking medication and recurrence of pulmonary TB in Serang City, Banten. There is no significant relationship between the role of medication taking supervisor and recurrence of pulmonary TB in Serang City, Banten.

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Vasospastic Angina and its Contemporary Review of Pathophysiology, Diagnosis and Management

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ABSTRACT

Introduction: Patients presenting with angina who have an unobstructed coronary artery is almost 50% incidence. Patients with chest pain in the absence of obstructive coronary artery disease (CAD) remain a challenge. These patients undergoing invasive coronary angiography do not have epicardial coronary disease obstructive enough to explain these symptoms. This needs to be considered as it can lead to very serious arrhythmias leading to a fatal heart attack. The exact pathophysiological mechanisms behind this phenomenon remain partially unclear, leading to restricted treatment options for affected patients. This review offers an in-depth overview of the pathophysiological mechanisms of vasospastic angina and explores the treatment choice. Additionally, this review evaluate the existing diagnostic methods for patients presumed of having vasospastic angina.

Result:
Coronary microvascular tone and subsequently, its blood flow is regulated through various vasodilating and vasoconstricting mechanisms. Coronary endothelial dysfunction and vascular smooth muscle hyperreactivity are proposed mechanism causing coronary artery spams. This may cause transient ST-Elevations, malignant arrhythmias and significant heart blocks. Various non-invasive and invasive exams may identify and differentiate these variant anginas.

Conclusions:
Vasospastic angina can be precisely diagnosed in a catheter laboratory, with pharmacological treatment being the primary management approach.

Introduction

Vasospastic angina (VSA) involves sudden coronary flow reduction due to spasms in either the epicardial or microvascular vessels, resulting in myocardial ischemia and angina (Prinzmetal et al., 1959a). A large proportion of patients perform provocative tests and undergo invasive coronary angiography, but have no epicardial coronary disease to explain their symptoms (Jespersen et al., 2012; Knuuti et al., 2020a). This condition is categorized as angina with non-obstructive coronary arteries (ANOCA) and ischemia with non-obstructive coronary arteries (INOCA) when there is evidence of myocardial ischemia (Kunadian et al., 2020). INOCA

encompasses the endotypes of epicardial coronary vasospasm and coronary microvascular dysfunction (CMD) (Beltrame et al., 2015a; Ong et al., 2018). microvascular angina is the result of myocardial ischaemia caused by CMD. CMD has been researched for a long time and is well known for its worse prognosis. (Sara et al., 2015; Shimokawa et al., 2021). Additionally, CMD significantly affects quality of life due to the difficulty in managing symptoms, leading to higher rates of emergency room visits, hospital admissions, and invasive procedures (Jespersen et al., 2013). This literature review aims to ensure comprehensive insights into the latest updates of VSA, covering its pathophysiology, diagnostic methods, and latest treatments. A brief overview of vasospastic angina and its management is presented in Figure 1.

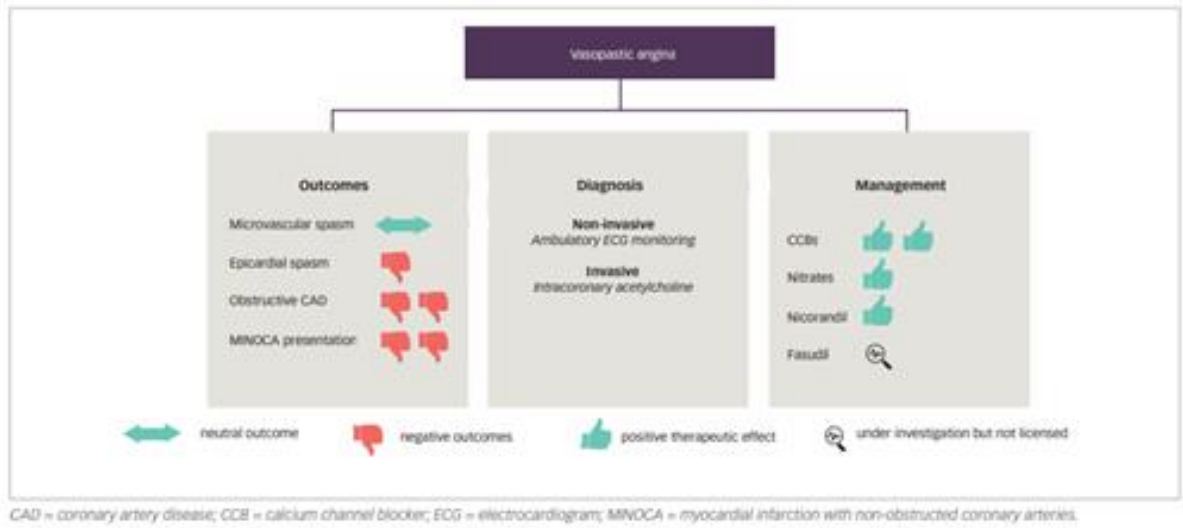


Figure 1. Summary of vasospastic angina and its management

Vasospastic angina refers to a type of angina caused by a spasm in the coronary artery, characterized by sudden, severe vasoconstriction of an epicardial artery segment, leading to a significant decrease in blood flow (J. C. Kaski et al., 1989). This condition was described as a unique pathology causing chest tightness at rest, notable ST-segment elevation, also higher incidence of ventricular arrhythmias compared to classic effort angina. (Prinzmetal et al., 1959b).

In its classic form, vasospastic angina (Prinzmetal's variant angina) typically occurs at rest, but in some patients, it can also be triggered by physical exertion or stress. The spasm can happen at the site both significant and non-significant coronary stenosis. Moreover, spasm can also occur in the epicardial arteries which are normal in

the angiographical analysis and may sometimes affect multiple coronary segments (multifocal spasm).

This condition most commonly appears in adults aged 50 to 60 years and has a male-to-female prevalence ratio of 5:1. Notably, more than half of women with stable chest pain who undergo coronary angiography (CAG) have no obstructive coronary artery disease (CAD), compared to only one-third of men. (Jespersen et al., 2012; Prinzmetal et al., 1959a).

Vasospastic angina has been recognized for many years, yet it remains under-diagnosed and insufficiently investigated. Vasospastic angina, despite this, has the dangerous potential to cause severe arrhythmias leading to VF and death. The incidences of this condition are prevalent in Asia, possibly because provocative tests are performed oftentimes. In contrast, such tests are less frequently performed in France, possibly because they often yield negative results.

Pathophysiology

Prinzmetal and colleagues suggested that variant angina pectoris results from the temporary occlusion of a large, diseased coronary artery with a narrow lumen due to increased vessel wall tone (Prinzmetal et al., 1959a). Later studies confirmed that coronary artery spasm causes myocardial ischemia in patients with variant angina, occurs in apparently functional coronary arteries and at areas of organic stenosis (Curry et al., 1979; Higgins et al., 1976). Yasue et al. found that in 70% of Japanese patients with coronary artery spasm, coronary arteriograms appear normal or nearly normal (Yasue & Kugiyama, 1997). Figure 4 presents representative coronary arteriograms showing coronary artery spasm in a patient with variant angina (JCS, 2014; Kishida et al., 1985; Yasue et al., 2008). Diagnostic provocation methods using acetylcholine and ergonovine have been developed to identify coronary artery spasm. However, this test should only be performed by a doctor who has the competence and is carried out in health services that have adequate infrastructure in the angiography laboratory. This is due to the fact that this procedure can cause serious complications (Yasue et al., 2008). Although the exact cause of coronary artery spasm is still unclear, endothelial dysfunction and increased vascular smooth muscle contractility have been suggested to be the two main mechanisms. (Shimokawa, 2000; Yasue et al., 2008).

The coronary vasculature is composed of epicardial arteries (>400 μm), prearteriolar vessels (400–100 μm), arterioles (<100 μm), and capillaries (<10 μm) (J.-C. Kaski et al., 2018). The balance between epicardial coronary vessels and the microcirculation is essential for proper

myocardial perfusion. The prearteriolar vessels are responsible for sustaining pressure at the downstream arteriolar source in a limited range. This occurs regardless of fluctuations in the pressure or flow of coronary perfusion. Distal segments are responsive to pressure changes, whereas proximal segments are responsive to flow changes. These vasomotor actions are primarily driven by myogenic mechanisms rather than the direct action of myocardial metabolites (Sinha et al., 2020). The microvascular compartment, including arterioles and capillaries, regulates coronary blood flow (CBF) over a wide range of perfusion pressures by adjusting vessel diameter through myogenic and metabolic mechanisms (Recio-Mayoral et al., 2013). In this process, nitric oxide (NO) and other vasodilator substances produced by the endothelium play a critical role in modulating vascular tone and, consequently, myocardial blood flow (Tonet et al., 2021). Figure 2 illustrates the macro/microcirculation angina endotypes.

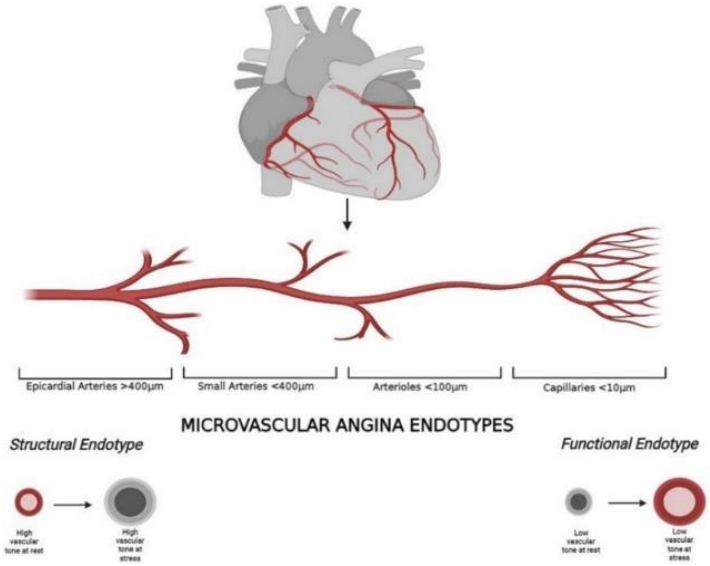


Figure 2. Coronary macro- and microcirculation and microvascular angina

Coronary Endothelial Dysfunction

Endothelial-dependent dysfunction results from the pathological constriction of a vessel or vascular bed. Diffuse distal epicardial and microvascular constriction leads to ST depression and can manifest as either rest or stress angina (Ong et al., 2012). Diffuse epicardial constriction is likely due to the same processes as microvascular endothelial dysfunction and carries similar risks (Halcox et al., 2002). Without coronary vasomotion studies, clinically distinguishing between epicardial endothelial dysfunction and microvascular

angina is difficult. Diffuse epicardial constriction suggesting that microvascular constriction may initiate the process and propagate proximally (Ong et al., 2013). Endothelial dysfunction significantly contributes to chest pain without obstructive coronary disease, which will be discussed further in this review.

The vascular endothelium regulates local vascular tone by inducing smooth muscle relaxation and vasodilation through the release of nitric oxide (NO), prostacyclin (PGI2), and endothelium-derived hyperpolarizing factor (EDHF), or by causing vasoconstriction through the release of thromboxane A2, endothelin-1, or free radicals.(Epstein et al., 1990). Imbalances favoring microvascular constriction among these factors may lead to endovascular dysfunction. NO is the most studied of these factors, as it is the primary mediator of vascular tone in conduit vessels.

Under normal conditions, shear stress activates mechanoreceptors on endothelial cells, prompting endothelial NO synthase (eNOS) to convert L-arginine into NO with the aid of its cofactor tetrahydrobiopterin (Förstermann & Münzel, 2006). However, conditions like systemic inflammation can hinder eNOS's ability to produce NO, a phenomenon referred to as 'eNOS uncoupling' (Förstermann & Münzel, 2006). Previous studies have shown decreased nitric oxide action in with coronary artery spasm conditions (Kugiyama et al., 1996).

Additionally, research suggests that coronary endothelial dysfunction contributes to the development of coronary artery disease. Animal models with eNOS gene mutations are particularly prone to coronary artery spasm (Nakayama et al., 1999). Acetylcholine (ACh) is often used in catheter labs to evaluate coronary endothelial integrity due to its dual action on muscarinic receptors in both endothelial and vascular smooth muscle cells.

Dysfunctional endothelial cells release endothelin-1 (ET-1), a powerful vasoconstrictor. There was an elevated levels of ET-1 in the coronary sinus plasma of patients who exhibit coronary artery spasm during provocation tests (Toyo-oka et al., 1991). Rho kinase, activated downstream of endothelin-1, significantly contributes to vascular smooth muscle constriction and is implicated in the vasospastic response in patients with endothelial dysfunction and microvascular angina (Mohri et al., 2003).

Ford et al. (2018) demonstrated reduced vasorelaxation in response to ACh and increased vasoconstriction to ET-1 in gluteal biopsy samples, suggesting systemic endothelial dysfunction in these patients. Additionally, Reriani et al. (2010) reported improved coronary endothelial function in

patients with non-obstructive coronary artery disease in response to treatment with an endothelin A receptor antagonist. Yet, although coronary endothelial dysfunction is involved in coronary artery spasm, we should note that an underlying endothelial dysfunction is not present in all vessels predisposed to spasm. (Yamamoto et al., 1992).

This indicates that there could be another factor contributing to coronary artery spasm, even when coronary endothelial dysfunction is not present. The potential role of vascular smooth muscle hyperreactivity as this additional mechanism will be further explored in the following sections.

Vascular Smooth Muscle Hyperreactivity

Porcine models of coronary spasm have shown that the calcium handling mechanism of contractile proteins and the expression of vasoconstrictor-promoting cellular receptors remain unchanged (Miyata et al., 2000; Satoh et al., 1990). Additionally, animal studies have implicated the protein kinase C-mediated pathway in the development of coronary artery spasm (Kadokami et al., 1996). These findings suggest that the initial trigger of coronary artery spasm is calcium (Ca2+) influx through L-type Ca2+ channels in vascular smooth muscle (VSM) cells, potentially enhanced through a protein kinase C-dependent mechanism. Indeed, functional upregulation of L-type Ca2+ channels at spastic sites has been demonstrated in porcine models of coronary spasm (Kuga et al., 2000).

Animal research has also shown upregulation of rho kinase at spastic sites, which plays a critical role in inducing VSM hypercontraction by inhibiting myosin light chain phosphatase (Kandabashi et al., 2000). The rho kinase inhibitor fasudil has been found to significantly reduce acetylcholine - induced coronary vasoconstriction in patients with coronary artery spasm (Masumoto et al., 2002). It has been proposed that while coronary endothelial dysfunction may predominantly contribute to diffuse multi-vessel spasm, vascular smooth muscle hyperreactivity likely plays a greater role in focal spasm.

There are interaction of two components that result in coronary spasm. First, the local hyperreactivity to vasoconstrictor stimuli in coronary segments. Second, ongoing vasoconstrictor stimuli triggering spasm in hyperreactive segments (J.C. Kaski et al., 1986). This hyperreactivity in vascular smooth muscle is likely due to abnormal regulation of myofibril contraction post-receptorally, as indicated by the ability to induce spasm with several stimuli acting on different cellular receptors and limited effectiveness of specific receptor antagonists (i.e alpha-blockers, serotonin

antagonists) in preventing angina attacks in these patients (Lanza, 2003; Lanza et al., 1996).

Several studies have suggested that increased membrane Na+-H+ activity, a key regulator of intracellular pH, leads to abnormal vasoreactivity. (Myerburg et al., 1992).In a further study, rho kinase activity and impaired K+-ATP-dependent channel function may be among the cellular pathways involved in coronary spasm (Masumoto et al., 2002).

Clinical Findings and Outcome

Prinzmetal et al. noted that patients experiencing chest pain without obstructive coronary artery disease (CAD) present a clinical challenge. They observed distinct differences in the clinical manifestation of variant angina compared to classic effort angina. Variant angina typically manifests as pain occurring at rest or during normal activities, rather than being triggered by exercise. Electrocardiograms during these episodes show ST segment elevations with reciprocal depressions (Prinzmetal et al., 1959a).

Ambulatory electrocardiographic monitoring has revealed a circadian pattern in ischemic episodes among patients with variant angina, with transient ST-segment elevations often occurring from midnight to early morning, peaking around 5 o'clock in the morning (Kishida et al., 1985; Yasue & Kugiyama, 1997).

While Prinzmetal et al. reported that variant angina pain occurs primarily at rest or during ordinary activities (Prinzmetal et al., 1959a), Yasue et al. found that anginal attacks can also occur during mild exercise in the morning, but it is possible that they can occur in the evening during intense exercise, although this is rare. (Yasue et al., 2008; Yasue & Kugiyama, 1997). This circadian variation in exercise capacity is common among most patients with variant angina (Yasue et al., 2008; Yasue & Kugiyama, 1997).

Based on previous studies, in variant angina showed that 82% of ischaemic episodes were asymptomatic thus becoming an important point. As well as syncopal episodes, syncope occurred in 12.5% of patients with variant angina. (KISHIDA et al., 1996)

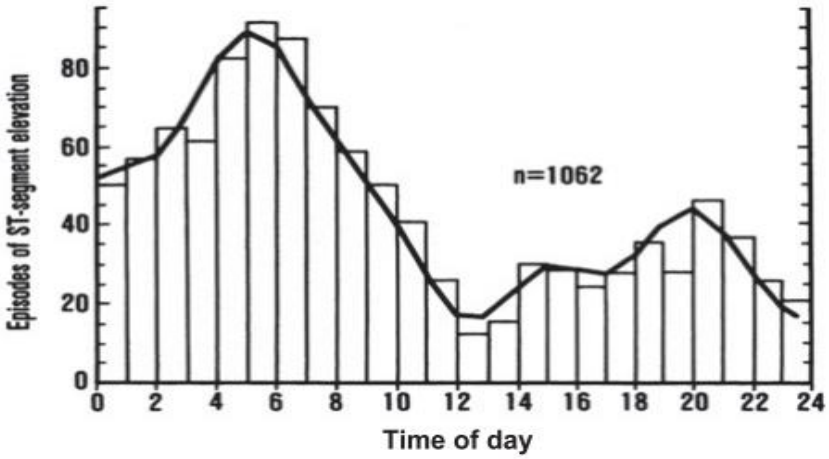


Figure 4. Circadian in ST segment elevation episodes in patients with variant angina
Source: Kusama et al, (2011)

Transient ST-segment elevations accompanied by reciprocal depressions, indicating transmural myocardial ischemia, are typical electrocardiographic findings in variant angina. These ST-segment elevations typically correspond to the distribution of the affected major coronary artery. During attacks, additional electrocardiographic changes may include a taller and broader R wave, disappearance of the S wave, and an elevated T wave (Prinzmetal et al., 1959a). Negative U waves may also appear intermittently during attacks, often in the same leads displaying ST-segment elevation. These U waves typically emerge as the ST-segment elevation begins to subside, gradually becoming more prominent before eventually disappearing (Kishida et al., 1985).

Severe arrhythmias, such as ventricular tachycardia (Figure 5), high-degree atrioventricular block (Figure 6), and bradyarrhythmia leading to syncope, can occasionally occur during a variant angina attack (Kishida et al., 1996). Therefore, to detect dynamic electrocardiographic changes in patients with variant angina, continuous outpatient electrocardiographic monitoring has been shown to be beneficial.

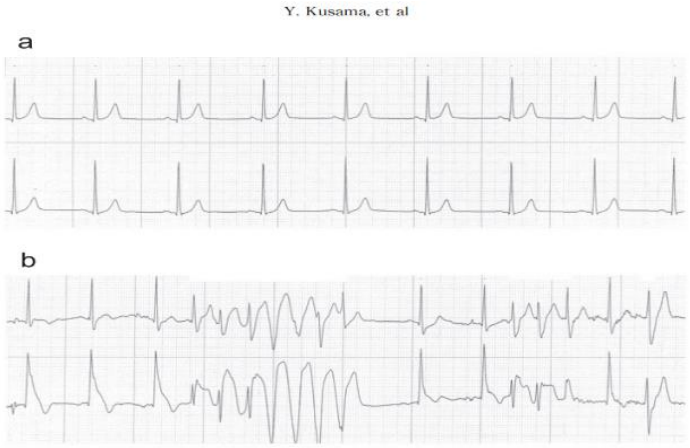


Figure 5. Ambulatory electrocardiographic recordings in a patient with variant angina. a: control recordings. b: recordings during an attack showing ST segment elevation and ventricular tachycardia.
Source: Kusama et al (2011)

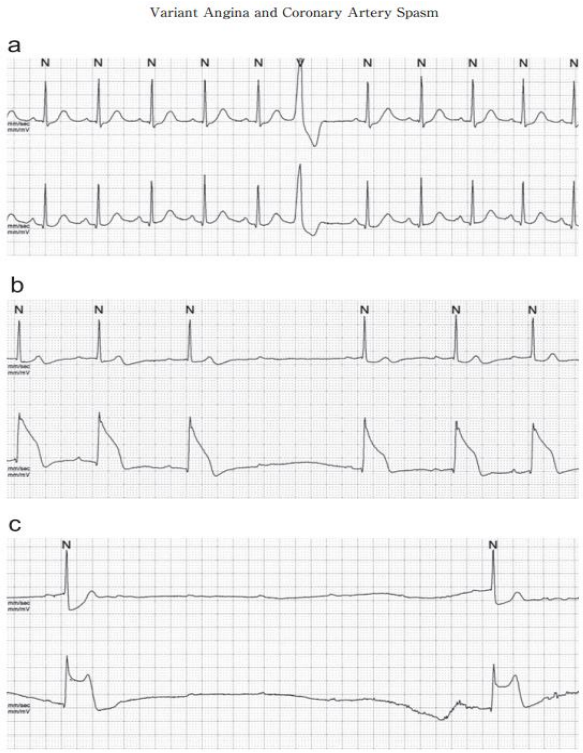


Figure 6. a: control recordings b and c: recordings during an attack in a patient with variant angina, showing ST-segment elevation and second-degree atrioventricular (AV) block (panel b) and advanced AV block (panel c).
Source: Kusama et al (2011)

Yasue et al. proposed that vasospastic angina can be diagnosed even without coronary angiography if nitroglycerin quickly relieves anginal attacks and if any of the following criteria are met: 1) attacks occur at rest, especially during the night and early morning hours; 2) significant diurnal variation in exercise tolerance is observed,

particularly with reduced exercise capacity in the early morning; 3) attacks are accompanied by ST-segment elevation on electrocardiogram; 4) attacks are triggered by hyperventilation; or 5) attacks are alleviated by calcium channel blockers but not by beta-blockers (Yasue et al., 2008). Recently, the diagnostic criteria and diagnostic flowchart in the guidelines for the diagnosis and treatment of patients with vasospastic angina have been updated (JCS 2008; Knuuti et al., 2020b).

Diagnosis

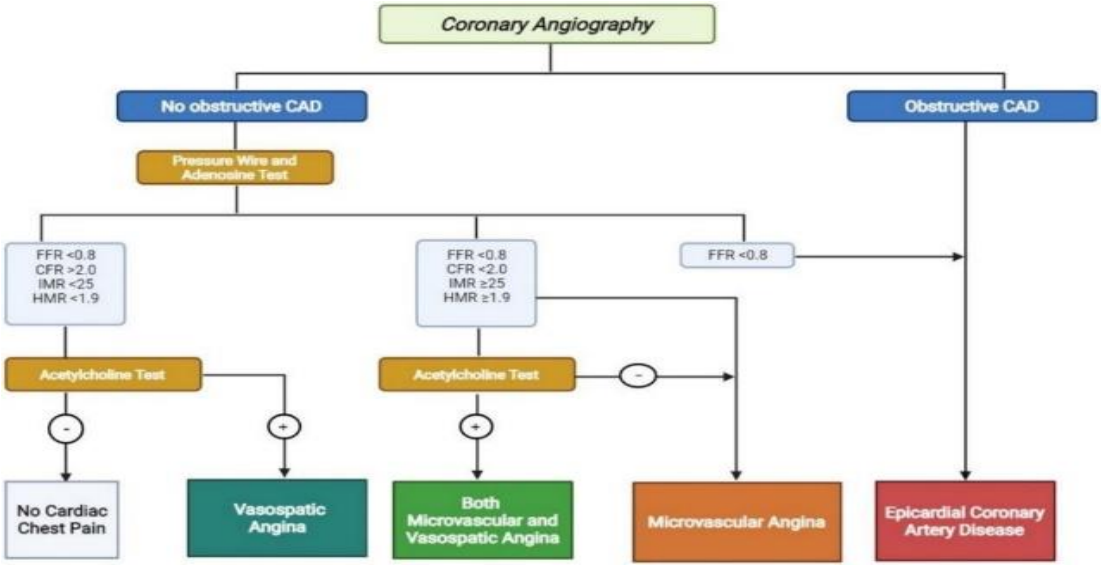
In 2015, the Coronary Vasomotion Disorders International Study (COVADIS) group introduced standardized diagnostic criteria for vasospastic angina (VSA) to promote consistency in clinical and research practices. These criteria allow for a diagnosis of 'definitive VSA' through either coronary angiography with pharmacological stimulation or ambulatory electrocardiogram (ECG) monitoring. Both approaches are endorsed by the European Society of Cardiology and the Japanese Circulation Society for evaluating patients suspected of having VSA (Beltrame et al., 2015b).

According to COVADIS, vasospastic angina is characterized by near-total (≥90%) occlusion of an epicardial coronary artery, leading to nitrate-responsive angina and ischemic changes on electrocardiogram. This occlusion can occur spontaneously or in response to a provocative stimulus (Beltrame et al., 2015b). The COVADIS group delineated specific diagnostic criteria for vasospastic angina, as depicted in Figure 7 of their guidelines.

Non-invasive Assessement of Coronary Vasospasm

According to the COVADIS criteria, if an episode of spontaneous rest angina is accompanied by transient ischemic changes on the ECG and no other cause for these changes is identified, coronary artery spasm is presumed to be the underlying cause. In such cases, a definitive diagnosis of vasospastic angina may be made even bypassing formal documentation of coronary artery spasm. Yet, the documentation of ischaemic ECG alterations during spontaneous episodes of rest angina is often impractical. Additionally, coronary artery spasm frequently coexists with epicardial coronary artery disease (CAD) and/or endothelium-independent coronary dysfunction. Therefore, comprehensive assessment of coronary vascular function, such as through coronary angiography with invasive physiology evaluation (including fractional flow reserve, coronary flow reserve [CFR], acetylcholine [ACh] flow reserve [AChFR], and spasm assessment), is now considered

the preferred diagnostic approach for this patient group (Perera et al., 2023a).



CAD : coronary artery disease;
FFR : fractional flow reserve;
CFR : coronary flow reserve;
IMR : index of microvascular resistance;
HMR : hyperemic microvascular resistance.
Positive Acetylcholine Test: >90% reduction in epicardial coronary artery with angina and ECG modifications.

Figure 7. Diagnostic algorithm for no obstructive and obstructive coronary artery disease.

Invasive Coronary Physiology Assessement in the Catheter Laboratory

Assessment of coronary vasomotion using ACh stimulation is both feasible and safe for patients suspected of having VSA (Ong et al., 2014). It is advised that patients with angina and non-obstructive coronary artery disease (ANOCA) undergo coronary physiology assessment to identify any underlying coronary vascular dysfunction that could lead to myocardial ischemia. The Coronary Flow Reserve is the main standard used to differentiate between normal and abnormal coronary vascular function. CFR measures the ability of the coronary vessels to increase blood flow in response to increased demand. A reduced CFR (<2,0) indicates impaired coronary vascular function and suggests potential myocardial ischemia. Epicardial artery spasm is diagnosed when an ACh bolus causes ≥90% coronary vasoconstriction, along with ischemic ECG changes and chest pain. This diagnostic approach has shown high sensitivity and specificity for detecting coronary spasm in patients with VSA symptoms. (Beltrame et al., 2015b; Okumura et al., 1988). Microvascular spasm, on the other hand, is diagnosed when an ACh bolus induces ischemic ECG changes and chest pain without ≥90% coronary vasoconstriction. An AChFR <1.0

with ACh bolus, indicating flow attenuation in the absence of significant epicardial spasm, also suggests microvascular spasm (Beltrame et al., 2015b). An illustrative example of significant epicardial spasm in response to an ACh bolus is depicted in Figure 8.

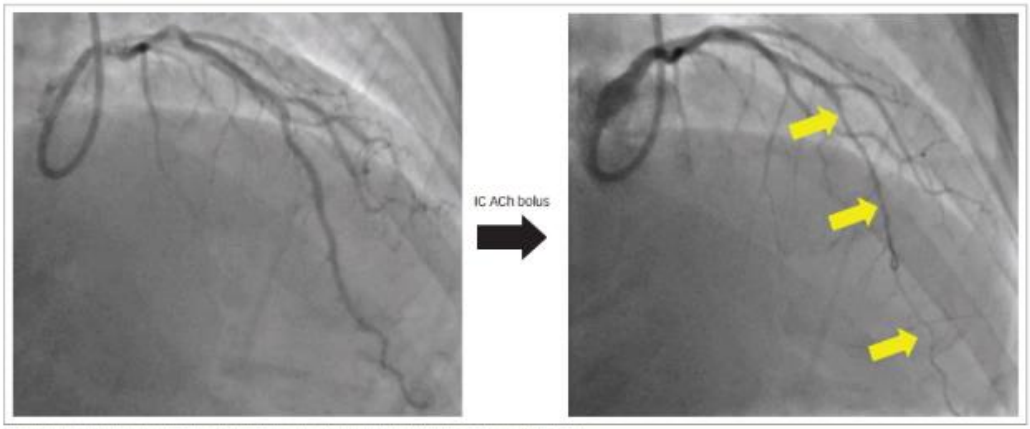


Figure 8. Coronary angiography images of the left coronary artery at baseline (left) and following an acetylcholine bolus (right) in a patient experiencing epicardial coronary artery vasospasm

The precise dose and infusion rate of ACh that matches physiological levels of coronary spasm remains unclear, as ACh can induce spasm in anyone above a certain threshold (Konst et al., 2021). This effect was demonstrated in a study examining various ACh concentrations in patients with normal epicardial arteries (Newman et al., 1990). Researchers observed an increase in epicardial vessel diameter and coronary blood flow with ACh concentrations up to 10^-4 mol/L; however, concentrations of 10^-3 mol/L caused significant vasoconstriction and chest pain (Newman et al., 1990). This variability led the authors to propose that the local ACh concentration and the specific coronary vascular segment studied may greatly affect the response to ACh (Newman et al., 1990).

Furthermore, there is variability among centers regarding the diagnostic threshold for defining the degree of epicardial vasoconstriction in response to ACh. While most centers use a 90% vasoconstriction threshold, some employ different arbitrary thresholds, such as 75% vasoconstriction (Ong et al., 2014; Perera et al., 2023b). These differing thresholds can affect the sensitivity and specificity of the diagnostic process.

Indications

Provocative spasm testing carries considerable risk, so experienced personnel are required. In addition, the risks and benefits to patients must be carefully evaluated. Recommended indications for provocative spasm testing are shown in Table 1. Based on the relative risks and benefits of the investigation these indications are classified into conventional Class I-III groups,.

Table 1. Indications for Provocative Coronary Artery Spasm Testing

Class I (strong indications)
• History suspicious of VSA without documented episode, especially if:
  • Nitrate-responsive rest angina, and/or
  • Marked diurnal variation in symptom onset/exercise tolerance, and/or
  • Rest angina without obstructive coronary artery disease
  • Unresponsive to empiric therapy
• Acute coronary syndrome presentation in the absence of a culprit lesion
• Unexplained resuscitated cardiac arrest
• Unexplained syncope with antecedent chest pain
• Recurrent rest angina following angiographically successful PCI

Class IIa (good indications) • Invasive testing for non-invasive diagnosed patients unresponsive to drug therapy • Documented spontaneous episode of VSA to determine the ‘site and mode’ of spasm
Class IIb (controversial indications). • Invasive testing for non-invasive diagnosed patients responsive to drug therapy
Class III (contra-indications) • Emergent acute coronary syndrome • Severe fixed multi-vessel coronary artery disease including left main stenosis • Severe myocardial dysfunction (Class IIb if symptoms suggestive of vasospasm) Patients without any symptoms suggestive of VSA

Management

Management of vasospastic angina (VSA) primarily involves pharmacological interventions, lifestyle modifications such as smoking cessation, and avoiding triggers known to provoke coronary spasm, such as beta blockers and triptans. Various anti-ischemic medications are commonly prescribed for these patients.

In most cases, attacks of variant angina can be effectively controlled with antianginal drugs. However, some patients do not achieve adequate control of coronary artery spasm even with combination therapy (Yasue et al., 2008). A Japanese study defined incurable vasospastic angina as persistent angina. Even post-treatment with two different coronary vasodilators. The study found that out of 2,251 patients with angina pectoris, 921 (40.9%) had vasospastic angina, and 126 (13.7%) of these experienced intractable symptoms. Patients with incurable vasospastic angina were generally younger at diagnosis, greater risk of smoke-related behaviour, and often had normal blood pressure compared to those with treatable vasospastic angina. (JCS Joint Working Group, 2014). Figure 9 illustrates invasive diagnostic methods and management strategies for angina in patients with non-obstructed coronary arteries.

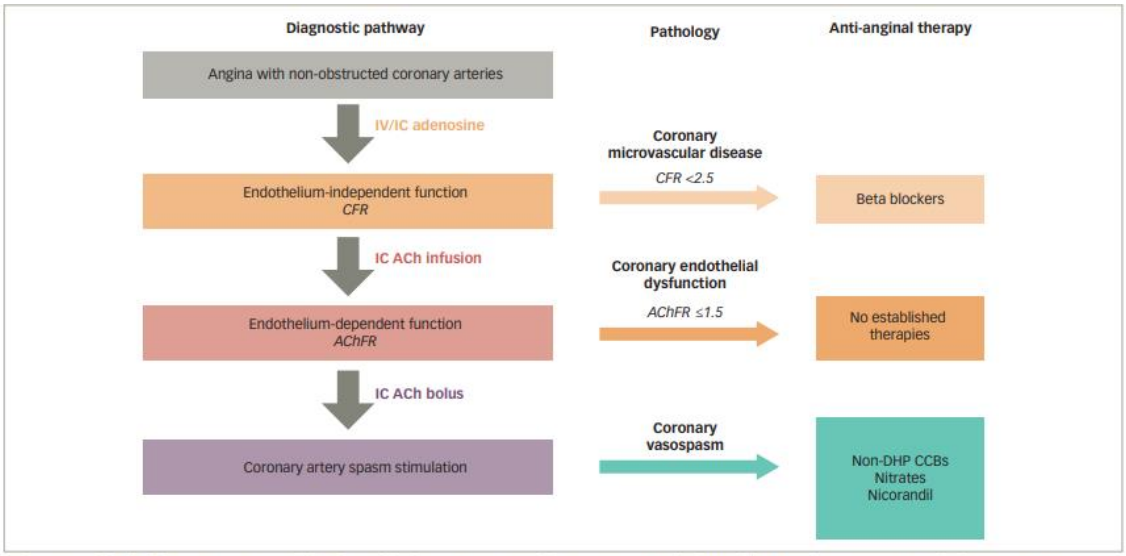


Figure 9. Examples of contemporary invasive diagnostic pathways, and management strategies, in patients with angina with non-obstructed coronary arteries

Calcium Channel Blocker CCB

Multiple therapeutic methods are used to manage vasospastic angina (VSA). Calcium channel blockers (CCBs) prevent the activation of voltage-dependent L-type Ca2+ channels, which reduces the activation of calcium-induced myosin light chain kinase and suppresses inducible coronary spasm. This leads to fewer angina episodes and a better prognosis. (Goldberg et al., 1979; Ong et al., 2014).

Long-acting Nitrates

Nitrates function as nitric oxide (NO) donors, causing vasodilation, and combining CCBs with nitrates targets separate pathways involved in coronary spasm (Nishigaki et al., 2010)

Nicorandil

Nicorandil stimulates soluble guanylate cyclase, increasing cyclic guanosine monophosphate levels, and opens adenosine triphosphate-sensitive potassium channels, resulting in hyperpolarization and subsequent closure of calcium channels, thereby reducing anginal burden in VSA patients (Ginsburg et al., 1982). The Japanese Cardiology Society recommends nicorandil as Class IIa for VSA treatment, although it is second-line in European guidelines (JCS Joint Working Group, 2014).

Rho Kinase Inhibitors

Fasudil, a rho kinase inhibitor, has proven effective in reducing ACh-induced coronary artery spasm by inhibiting myosin-binding substrate and inducing vasodilation (Masumoto et al., 2002; Mohri et al., 2003). These treatments focus on essential cellular pathways in regulating coronary vasomotor function: CCBs target L-type calcium channels, nitrates release NO, nicorandil boosts cyclic guanosine monophosphate production, and endothelin receptor antagonists and rho kinase inhibitors reduce endothelin and rho kinase-dependent vasoconstrictive mechanisms.

Pleitropic Agents

Clinical studies, including a randomized trial comparing fluvastatin and CCB combination therapy versus CCB alone, have demonstrated superior outcomes in preventing ACh-induced spasm with combination therapy (Konst et al., 2021). Registry-based studies also indicate lower rates of recurrent angina, major adverse cardiac events, and mortality at five years in VSA patients using angiotensin-converting enzyme inhibitors (Beltrame et al., 2015b). A survey on drug treatment in Japan highlighted high efficacy rates of calcium channel blockers like nifedipine, diltiazem, verapamil, and their combinations in managing variant angina, with newer agents such as benidipine and amlodipine also proving highly effective (Konst et al., 2021; Lablanche et al., 1993).

Conclusion

Vasospastic angina (VSA) can be precisely diagnosed in the catheter laboratory, ensuring accuracy and safety. Management primarily relies on pharmacotherapy, with calcium channel blockers (CCBs) and long-acting nitrates recommended as initial treatments, while nicorandil serves as a secondary option. Emerging therapies targeting specific mechanistic pathways

have demonstrated encouraging results in clinical trials. Further dialogue and investigation could aid clinicians in enhancing both diagnosis and treatment strategies for vasospastic angina.

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The Relationship between The Characteristics of Type-2 DM Patients and The CKD Stage during The COVID-19 at RSI Jemursari

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ABSTRACT

Introduction: The prevalence of diabetes mellitus has risen globally, posing a substantial health challenge, with a marked increase reported in both developed and developing nations. Diabetes is a primary contributor to the global prevalence of Chronic Kidney Disease (CKD). During the pandemic, there is a considerable challenge, especially for CKD patients, including a loss in health services, vulnerability to COVID-19 infection, stressful events during social distancing, and a decrease in therapy adherence. Hence, the COVID-19 pandemic may give rise to various characteristics in individuals with chronic kidney disease.
Objective: To investigate the correlation between the characteristic of patients with type 2 diabetes mellitus and the chronic kidney disease (CKD) stage at RSI Jemursari Surabaya during the COVID-19 pandemic.
Methods: An observational analytical cross-sectional study was conducted on individuals with chronic kidney disease (CKD) previously diagnosed with diabetes mellitus (DM) during the COVID-19 pandemic from 2020 to 2022. A total of 169 samples were obtained using a simple random sampling method. The variables considered include age, gender, HbA1c, blood pressure, cardiovascular comorbidities, Pulmonary comorbidities, and history of COVID-19.
Results: The study demonstrated a significant correlation between blood pressure and kidney function tests, including blood creatine level, BUN, and eGFR, with CKD stage ($P<0.05$). Randomised blood glucose also has a significant correlation to the CKD stage. No notable correlation was observed among age, gender, HbA1c levels, cardiovascular comorbidities, pulmonary comorbidities, and history of COVID-19.
Conclusions: The presence of hypertension and abnormal kidney function test results correlate with the stage of chronic kidney disease (CKD) during a pandemic.

Introduction

In 2021, there were 537 million persons worldwide living with diabetes mellitus (DM). According to the International Diabetes Federation (IDF), diabetes affects approximately one-tenth of the global population. The predicted estimate for this amount is expected to rise to approximately 643 million by 2030 and 738 million by 2045. Diabetes is responsible for 6.7 million deaths, with one death occurring every 5 seconds by 2021 (IDF, 2021).

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia. This may result from impaired insulin secretion, resistance to peripheral insulin action, or a combination of both 9carillo, et al 2019). Chronic hyperglycemia, in synergy with other metabolic abnormalities in diabetic patients, can lead to damage in various organ systems, culminating in the development of debilitating and life-threatening health complications. The most prominent among these are microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications that significantly increase the risk of cardiovascular diseases two to four times (Regina, et al 2022)

Approximately 50% of type 2 diabetes and a third of type 1 diabetes patients develop Chronic Kidney Disease (CKD), marked by kidney function impairment or increased urinary albumin excretion. The specific percentage of CKD attributed solely to diabetes remains unclear. Other contributors to kidney dysfunction include hypertension, dyslipidemia, obesity, vascular diseases, acute kidney injury, glomerular atherosclerosis, renal ischemia, and age-related nephron loss. Precisely defining 'Diabetic Kidney Disease' (DKD) in epidemiology or clinical practice, especially in type 2 diabetes, is challenging. Therefore, it is more accurate to identify patients with both diabetes and CKD and implement comprehensive renoprotective strategies (Thomas, et al 2015).

A previous study by Farah et al. (2021) found that diabetic kidney disease patients with an average age of 59 years exhibited correlations between older age, high triglycerides, low HDL, and increased severity of the disease. Metformin and ACEi-ARB usage showed a negative correlation with albuminuria incidence and the risk of severe CKD. The World Health Organization (WHO) notes that elderly individuals and those with pre-existing conditions like diabetes mellitus, chronic kidney disease, and heart disease are more susceptible to severe outcomes when exposed to COVID-19, with higher mortality rates (farah et al, 2021). However, the application of proven ACEi-ARB treatment for diabetic kidney disease in COVID-19 remains controversial due to

concerns about potential virus entry pathways (Abdulaziz et al, 2022). Type 2 diabetes patients experiencing diabetic kidney disease may exhibit different characteristics, especially during the COVID-19 pandemic. [MOU1] This study aims to investigate the correlation between the characteristics of patients with type 2 diabetes mellitus and the chronic kidney disease (CKD) stage at RSI Jemursari Surabaya during the COVID-19 pandemic. So that based on these data, researchers are motivated to conduct research for future purposes.

Methods

An analytical observational cross-sectional study using data from medical records was conducted on individuals with Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD) between 2020 and 2022. The data collection process was conducted at RSI Jemursari Surabaya using random sampling from August to October 2023.

The study's population comprises medical data from patients with DM and CKD who went to RSI Jemursari Surabaya from 2020 to 2022. A total of 150 samples was calculated using the cross-sectional minimal sample size formula with a known population. The study variables include the patient's characteristics, namely age, gender, HbA1c levels, blood pressure level, presence of heart disease, history of COVID-19, D-dimer values, and history of prior lung diseases. The data will undergo editing and will be provided in the form of frequency and distribution tables.

The study employed inclusion and exclusion criteria: 1. Inclusion Criteria: Patients with a confirmed diagnosis of diabetic renal illness and type 2 diabetes, aged 18 years or older, and possessing comprehensive medical record information. Exclusion Criteria: The patient needs comprehensive medical record information.

This research has been approved by the Research Ethics Committee of RSI Jemursari Surabaya Hospital No. 084/KEPK-RSISJS/V/2023. This study analyzed dependent variables using two data formats. The Pearson Chi-Square test tests demographic data if it meets the minimum test requirements. However, Kendall's test was used on categorical variables beyond 2 degrees. Age, Creatinine, urea levels, eGFR, LOS in hospital, HbA1c and RBG levels were evaluated using the ANOVA test. If data were not normally distributed, Kruskal Wallis was used.

Results

Table 1. The characteristic variable of Chronic Kidney Disease Patients in early, late and regular hemodialysis

Variable	Early stage (n=40)	Late stage (n=42)	Regular HD (n=68)	P-value
Age (year)	58,59 ± 11,07	61,13 ± 11,11	58,84 ± 11,41	0,506*
Gender (Male) – n (%)	23 (57,7)	23 (54,8)	31 (45,6)	0,813**
Blood pressure (%) Hypotension Normal Hypertension grd 1 Hypertension grd 2 Crisis hypertension	 3 (7,5) 18 (45) 12 (30) 6 (15) 8 (2,5)	 6 (14,3) 16 (38,1) 11 (26,2) 8 (19) 1 (2,4)	 7 (43,8) 15 (22,1) 17 (25) 18 (26,5) 11 (16,2)	0,004***
COVID-19 status Positive result	 14 (35)	 12 (28,6)	 16 (23,5)	 0,438**
Serum Creatinin	1,53 ± 0,36	3,74 ± 1,61[a,c]	9,14 ± 5,74[a,b]	<0,001****
BUN	29,12 ± 12,7	60,05 ± 27,34[a,c]	80,02 ± 37,3[a,b]	<0,001****
eGFR	52,9 ± 16,51	19,96 ± 4,85[a,c]	8,66 ± 3,19[a,b]	<0,001****
Cardiovascular disease history	24 (60)	25 (59,5)	42 (61,8)	0,968**
Pulmonary disease history	22 (55)	25 (59,5)	34 (50)	0,616**
LOS in hospital (days)	6,05 ± 4,92	5,40 ± 3,7	5,16 ± 4,5	0,530****
Outcome (Death event)	5 (12,5)	14 (33,3)	15 (22,1)	0,078**

* One-Way ANOVA test
** Pearson Chi-Square test
*** Kendall's tau b test
**** Kruskal-Wallis test
Mann-Whitney test: [a] sig P<0,05 (vs Early stage), [b] sig P<0,05 (vs Late stage), [c] sig P<0,05 (vs Reguler HD).

Based on Table 1, the research findings demonstrated no significant correlation between characteristic age and gender in this study (P>0,05). COVID-19 status also has a non-significant correlation compared to the CKD stage, even during the pandemic. Also, there is no significant association between cardiovascular and pulmonary comorbidities and the stage of chronic kidney disease (CKD). Furthermore, there is no association between the length of stay and death's worst consequence. However, the study found a significant correlation between Blood pressure and kidney function tests (P<0,05).

Table 2. Characteristic of HbA1c level and Random Blood Glucose variable of Chronic Kidney Disease Patient stage

Variable	Early stage (n=29)	Late stage (n=20)	Regular HD (n=12)	P-value
HbA1c - n (%)				
<7	8 (27,9)	7 (35,0)	4 (33,3)	0,540*
7-9	12 (41,4)	5 (25)	2 (16,7)	
>9	9 (31,0)	8 (40)	6 (50)	
RBG	210 ± 91	276 ± 126	159 ± 86[a]	0,041**

* Kendall's tau-b test
** Kruskall-Wallis test
Mann-Whitney: [a] sig P<0,05 (vs Late stage)

Based on Tabel. 2, the research findings demonstrated no significant correlation between characteristic HbA1c and CKD stage in this study. However, the study found a significant correlation between random blood glucose levels and CKD stage during admission.

Discussion

The COVID-19 pandemic has caused significant effects, particularly on individuals with chronic kidney disease (CKD). Prior studies have demonstrated that the COVID-19 pandemic has both direct and indirect impacts on the quality of life of individuals with chronic kidney disease (CKD). Chronic Kidney Disease has been identified as a separate risk factor for the illness and death caused by COVID-19. Multiple investigations have consistently linked kidney comorbidities with disastrous outcomes of COVID-19 (Sidorenkov et al, 2014).

The study demonstrates that individuals with hypertension are associated with advanced CKD stages. The serum creatinine and blood urea nitrogen (BUN) levels have experienced a notable rise, especially in Regular HD patients and in the late stage compared to the early stage. The study also shows a significant relationship between BUN and serum Creatinine in the CKD stage, according to this study. However, there is no significant relationship between other variables,e.g. age, gender, COVID-19 status, and Cardiovascular and pulmonary disease history. Our study also found no correlation between length of stay (LOS) in hospital and worst outcome between CKD stage groups. This finding proves that CKD stage characteristics may differ greatly if compared between stages, except for Blood pressure variables and kidney function test abnormalities, e.g. BUN, Serum Creatinine and eGFR.

Previous study data (Diamantidis et al, 2023, Mohamed et al, 2021) between the pandemic periods showed a different result: age and gender characteristics show a relationship with the CKD state but not the CKD stage. In contrast to our work, many studies have attempted to compare the CKD and Non-CKD groups, but not specifically

the different stages of CKD. According to COVID-19 status in CKD patients, a previous study (Diamantidis et al, 2023) also showed that COVID-19 infection worsened the stage of CKD and rapid kidney function decline. Unlike our study, no relation occurred between the CKD stage groups.

The difference in results between the two studies could be attributed to the disparity between the populations and methodologies employed in the research.

Furthermore, our investigation revealed a potential correlation between blood pressure levels and chronic kidney disease (CKD) stage during the pandemic. Hypertension is recognized as associated with CKD and is responsible for developing interstitial fibrosis and tubular atrophy (Mathew et al, 2023). Advanced chronic kidney disease (with an estimated glomerular filtration rate of 30 mL/min/1.73 m2) is marked by impaired endothelium functioning, and these endothelial layer changes are closely associated with hypertension (Haruhara et al, 2015). However, chronic kidney disease (CKD) also contributes to an elevated rate of arterial stiffness, which in turn leads to hypertension. The most detrimental outcome occurs when hypertension leads to an increase in oxidative metabolism, which is related to renal hypoxia and contributes to raised blood pressure and the advancement of chronic kidney disease (CKD) (13). COVID-19 also has a role in a decrease in patient hypertension therapy adherence (Dhaun et al, 2006) and medical care for and self-management of chronic hypertension (Fine et al, 2008), resulting in uncontrolled blood pressure.

Cardiovascular and pulmonary comorbidities are strongly associated with the severity and mortality of COVID-19 (Rahman et al, 2021). However, its correlation with the CKD stage remains unclear, especially during the pandemic. According to Li et al. (2014), patients with cardiovascular comorbidity do not correlate with the stages of CKD except in the dialysis group. The result may differ from our study because of the number of patients and the different conditions between the pandemic and the non-pandemic state. As previously mentioned, the pandemic plays a role in increasing cardiovascular comorbidity in every stage of CKD and contributing to cardiovascular events during the pandemic (Gotanda et al, 2022). Two common pulmonary comorbidities are COPD (Lie at al, 2014) and Asthma (Honardoos et al, 2021). A previous study by (Lie at al, 2014) demonstrated that COPD decreases renal filtration function based on blood creatinine results but not Urea levels. However, COPD alone does not significantly decrease GFR unless it is accompanied by concomitant hypertension.

However, it is difficult to assume that pulmonary history can cause reduced kidney function unless accompanied by additional variables such as sepsis and others.

The study also found that CKD stages did not increase the length of stay in the hospital and the worse outcome. However, during a pandemic, mostly CKD is accompanied by primary diseases that worsen kidney function, such as COVID-19. Our closed analysis showed that COVID-19 infection with CKD has a longer length of stay and worse outcomes when compared to CKD without COVID-19 infection. Previous studies (Gok et all, 2021, Boiko et all, 2022) have shown a linear result. The study also showed significant mortality and more hospitalization duration in comparison between early CKD and late CKD with COVID-19. In conclusion, our study only compared the CKD stage during the pandemic without COVID-19 status, so our comparison of early and late CKD stages and regulator HD patients was non-significant.

Our study also examined the correlation between HbA1c and random blood glucose levels to explain the fluctuation level during the pandemic according to the CKD stage. The study demonstrated no significant correlation between HbA1c and RBG levels according to the CKD stage. A previous study (Kuo et al, 2016), but not in pandemic situations, demonstrated that the only positive correlation between HbA1c and eGFR exists in stage 5 CKD. However, The prognostic role of HbA1c in patients with stage 5 CKD was unclear because of impaired glucose metabolism in advanced CKD, and the HbA1c level may be altered by anemia or erythropoiesis-stimulating agent use (Mak, 2000). According to a study, there was a decrease in HD patients during the pandemic, a primary reason for fears of COVID-19 (Sultan et al, 2022). Therefore, it is challenging to generalize non-significant results in HbA1c and RGB levels during the pandemic due to a limited number of patients.

Conclusion

There is a correlation between the presence of hypertension and abnormal kidney function tests with the stage of chronic kidney disease (CKD) during a pandemic. The study also notes if there is a correlation between random blood glucose levels according to CKD stage. It is recommended that type 2 DM patients with CKD continue to be carefully monitored and managed during this pandemic. Strict preventive measures and interdisciplinary collaboration must be improved to reduce the risk of more severe complications in these patients. Emphasis on patient education regarding holistic disease

management is also essential to minimize possible adverse effects.

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Forensic Examination in Infanticide Case

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ABSTRACT

Introduction: Infanticide is a crime in which a mother kills her baby during or shortly after birth. In 2020, infanticide cases in Indonesia reached 16.85%. Infanticide is mainly carried out through mechanical asphyxia in the form of smothering and strangulation.
Case: The body of an unidentified female newborn baby was found in the Sandubaya area, Mataram City, on Monday, July 10th 2023. The observation was carried out through external and internal examination of the body.
Discussion: There were bruises and peeling skin all over the body. The autopsy showed a haemorrhage all over the lower part of the scalp, severe injury to the neck, and blood seepage on the right chest.
Conclusions: The cause of death was due to severe neck injury resulting in asphyxia.

Introduction

Infanticide is the killing of one's child by the biological mother to her baby at birth or shortly after birth. The motive for the act is usually triggered by the mother not wanting the baby's birth to be known by others (Atmoko & Niufti, 2023). Data from the Indonesian Central Bureau of Statistics in 2023 states that the three provinces with the highest percentage of homicides are DKI Jakarta (4.12%), Bangka Belitung Islands (2.29%), and West Nusa Tenggara (2.00%). In this study, the author focuses on infanticide cases. In 2020, infanticide cases in Indonesia reached 16.85%, and one of the provinces with the highest infanticide cases was West Nusa Tenggara Province. In 2020, the infant mortality rate in West Nusa Tenggara (NTB) reached 24.64%, especially in the Mataram city area, reaching 14.46%. In Indonesia, the act of infanticide is regulated in the Indonesian Criminal Code (KUHP) articles 341-342. Some of the factors that encourage infanticide are overwhelming anger due to psychological factors, economic factors, and fear and shame due to the birth of a child from an extramarital relationship.

A baby is born alive if the baby is separated from the mother after birth and

there are signs of life, such as breathing, a beating heart, active movement and crying. There are indicators to say that the baby already has life or is alive, namely, breathing, blood circulation and heartbeat, changes in oxygen levels in the blood, the contents of the digestive tract, the condition of the umbilical cord, and the presence of crying. If at least one of these six characteristics is not present, the baby can be declared lifeless (Amelinda, Hoediyanto, & Kalanjati, 2018). In infanticide cases, death can be unnatural. The mechanism of death in infanticide is physiological mechanisms such as bleeding, asphyxia, or organ damage, and the cause of death could be violence and can have several causes. First, negligence is due to a lack of attention to what should be done for the newborn to survive. Second, due to violence such as birth trauma, blunt force and sharp force. Meanwhile, the cause of death can be due to asphyxia, haemorrhage, hypothermia and dehydration and can not be determined if the body has experienced advanced decomposition (Atmoko & Niufti, 2023). This study aims to describe infant deaths based on external and internal examinations of the Forensic and Medicolegal Installation of Bhayangkara Hospital in Mataram, NTB.

Case

This study was conducted on Wednesday, July 13th 2023, in Bhayangkara Hospital, Mataram City. This study was an observational descriptive with a case series approach. The observation was carried out through external and internal examination. This study describes an infanticide case of an unidentified female newborn baby that was found in the Sandubaya area of Mataram City on Monday, July 10th, 2023.

Result

The baby girl's body was covered with a brown cardboard box marked "Alia Digital Printex", wrapped in a red plastic bag, a green, black, and yellow floral prayer mat and another red plastic bag, and the body was wrapped in a grey and dark blue sweater, (see Figure 1).

Figure 1. Objects found within the body

An external examination was conducted on Wednesday, July 13th, 2023. The body of a baby girl aged 9 months gestation with a body length of 47 cm and a body weight of 2.05 kg, corpse bruises and skin are peeling all over the body, see Figure 2. Straight black hair with an average length of 3 cm, head circumference 32. 5 cm, chest circumference 34 cm, upper arm circumference 11 cm, both eyes are reddish, there is an umbilical cord with a length of 78.5 cm still attached to the placenta

weighing 0.2 kg, the skin of the placenta is decomposed, there are 17 cotyledons, there is body fat (*cervix caseosa*) in the thigh folds.

Figure 2. Bruises and skin peeling all over the body

External examination also shows other signs of asphyxia, such as dilation of the eye's blood vessels and blueness of the mucosa of the lips, as in Figure 3. Other external examination results found evidence of suspected strangulation in the neck, as in Figure 4.

Figure 3. Blueness of the mucosa of the lips and dilation of the eye's blood vessels.

Figure 4. Neck Injuries

Internal examination results are dilation of blood vessels in the brain and a severe head injury that led to bleeding all over the scalp. There was a severe neck injury causing airway obstruction. There was blood infiltration in the right chest Costa 4, 5 and 6 levels, measuring 3.5 cm x 2.5 cm, and dilated veins.

While supporting examination results, the lungs are mosaic. The right lung measures 7 cm x 4 cm x 1.5 cm, and the left measures 5.5 cm x 5 cm x 2 cm. The lung buoyancy test shows both lungs are buoyant; see Figure 5. The heart measures 3.5 cm x 3.5 cm x 1 cm. There are no other tests that are used to find out that the baby was born alive, such as Wreden's test and Bresslau's test, because internal organs such as the intestines, stomach, and others have experienced advanced decay.

Figure 5. Lung buoyancy test

Discussion

According to the Indonesian Criminal Code (KUHP), murder consists of several types, namely ordinary murder, premeditated murder, murder to commit another crime and infanticide. In the Indonesian Criminal Code (KUHP) infanticide is a murder committed by a mother for fear of being caught giving birth to a baby at the time of birth or shortly after birth, intentionally or unintentionally taking the life of her child listed in the chapter of

crimes against the life of the person articles 341, 342 and 343 (Radja, Saragih, & Henok, 2023; Tantimin, Febriyani, & Putra, 2023). In infanticide cases, several things must be known, namely, evidence that the baby was born alive and there are signs of violence that caused the death (Khoiriah & Pratiwi, 2019; Langer, 1974; Susanti, 2012). There are several indicators that a baby is considered newborn and alive, namely full term or not, gestational age, postnatal age, baby's first nutritional intake, crying, moving limbs, and breathing. One of the early infant deaths is characterized by no visible signs of the mother's initial care for the baby (Atmoko & Niufti, 2023; Shkrum, 2007).

In terms of proving infanticide cases, it can be seen from whether the baby was born alive or dead (Atmoko & Niufti, 2023; Langer, 1974). Based on the results of the examination, there is a mosaic picture in the lungs, and the results of the lung buoyancy test show a positive result, which means that the baby was breathing, so it can be said that in this case, the baby was born alive (Shkrum, 2007). In some cases, it has been shown that if the lungs have a mosaic pattern, the lung buoyancy test is particular to be positive, and it can be concluded that the baby was breathing and was born alive (Afandi, Hertian, Atmadja, & Widjaja, 2008; Atmoko & Niufti, 2023). Mechanical asphyxia accounts for 90-95% of the 30-40 deaths per year (Afandi et al., 2008; Pradhika, 2011).

Mechanical asphyxia is suffocation and strangulation, which can be seen based on the results of external and internal examinations. Suffocation or strangulation is the easiest way for the perpetrator to commit infanticide; asphyxia is done to prevent the baby from crying so that her actions are not known by others (Afandi et al., 2008; Atmoko & Niufti, 2023; Langer, 1974; Oberman, 2001; Tantimin et al., 2023). There were no bruises and abrasions in this case, but the skin was peeling all over. There were corpse bruises all over, the body, the eyes were red.

The infant had severe neck injuries, as in Figure 4, suggesting that the infant's neck had been twisted or kicked. The external examination results in Figure 3 there are findings that support signs of asphyxia, such as the blood vessels of the eyes and the blueness of the mucosa of the lips. In addition, there were severe head injuries characterized by haemorrhaging over the entire lower area of the scalp. There were no injuries caused by violence with sharp objects, and no open wounds were found. However, blood was found on the right side of the chest at the level of the fourth, fifth and sixth ribs, indicating signs of blunt force trauma.

Based on external examination, it was determined that the body was a newborn

baby who had not been cared for because there were no signs of care. This conclusion is supported by the fact that the umbilical cord is still attached to the placenta weighing 0.2 kg with a cord length of 78.5 cm, and the cervix caseosa can be seen around the thigh folds. The gestational age was approximately 37-42 weeks or 9-10 months, which results from calculating the Haase formula, where the baby's body length is 47 cm divided by 5. In cases of infanticide, the best estimate of gestational age can be seen by measuring the head circumference (Afandi et al., 2008; Atmoko & Niufti, 2023). The examination of the baby showed that the baby had a head circumference of 32.5 cm, which means that the baby was full term (37-42 weeks).

Babies are said to be able to live outside the womb when their gestational age is more than 28 weeks, birthweight equal to or less than 2,5 kg (Kaminski, Goujard, & Rumeau-Rouquette, 1973), body length > 45,4-55,6 cm, head circumference > 32,7-35,8 cm (WHO, 2024). In this case, it can be concluded that the corpse can live, it weighs 2.05 kg, its chest circumference is 34 cm, its upper arm circumference is 11 cm, its body length is 47 cm, its head circumference is 32.5 cm. There are no visible organ abnormalities or birth defects that cause death in this corpse (Ningsih & Arafat, 2022).

In this case, it can be concluded that this case is a case of infanticide (Atmoko & Niufti, 2023; Langer, 1974; Tantimin et al., 2023). Some literature says that mechanical asphyxia is the easiest to perform compared to blunt force and sharp force of all infanticides (Afandi et al., 2008; Overpeck, Benner, Trumble, Trifletti, & Berendes, 1998; Väli, Lang, Soonets, Talumäe, & Grjibovski, 2007). Some other indicators that this was an infanticide case were that the body was found on the riverbank. In infanticide cases, 95% of the babies are born outside the hospital, and 71% are born in the perpetrator's home (Afandi et al., 2008; Atmoko & Niufti, 2023; Overpeck et al., 1998). According to Abraham Maslow (Ashari, Wahyuni, & Kusmiadi, 2023; Nurwatie, Fauzia, & Akbar, 2016), a person can kill due to low self-confidence, feelings of not being able to fulfil their needs, weak, helpless and worthless, so some supporting indicators of suspects can commit infanticide are people with low education, unmarried and under 19 years of age (Afandi et al., 2008; Atmoko & Niufti, 2023; Sulmustakim, 2021; Susilaningsih, 2004). Several other studies explain that the perpetrators of infanticide are women with low social, occupational, and economic status, or the perpetrators are involved in infidelity (Lonza, 2002; Sulmustakim, 2021; Susilaningsih, 2004). Other predictors include the suspect never had a

pregnancy examination (Afandi et al., 2008; Friedman, Horwitz, Ph, & Resnick, 2005) and mothers with psychiatric disorders (Dekawati & Marbun, 2022; Sulmustakim, 2021; Susilaningsih, 2004).

Conclusion

On external examination, it was found that the corpse's skin was peeling all over the body, and finding support signs of asphyxia such as the blood vessels of the eyes and blueness of the mucosa of the lips. In contrast, internal examination results are dilation of blood vessels in the brain and a severe head injury that led to bleeding all over the scalp. The infant had severe neck injuries. While supporting examination results, the lungs are mosaic, and both lungs are buoyant. There are no other tests that are used to find out that the baby was born alive, such as Wreden's test and Bresslau's test, because internal organs such as the intestines, stomach, and others have experienced advanced decay. It can be concluded that the death is unnatural because of suffocation. In comparison, the mechanism of death is due to asphyxia or airway obstruction because of severe neck injury. The estimated time of death was more than one day before the examination.

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Monitoring Pediculosis Capitis in Students At Al-Muhajirin Islamic Boarding School, Cikarang Pusat, West Java, Indonesia

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ABSTRACT

Introduction : Pediculosis capitis is a scalp hair disorder caused by an infestation of the lice of *Pediculus humanus capitis*. The spread of this disease is dominant in Islamic boarding school students. This disease besides causing itching and lesions on the scalp also causes loss of concentration and enjoyment of learning in children. The objective of this study was to determine the percentage of female students infested with *P. humanus capitis*.
Methods : The design of this research is cross-sectional. The sample for this study was 41 female students of grade 7 at AL-Muhajirin Islamic Boarding School, Central Cikarang, West Java. Examination of *P. humanus capitis* on all female students was carried out using the serit method. The *P. humanus capitis* lice found were then collected and preserved preparations were made for microscopic morphological identification.
Results : The results of this study showed that from 41 samples, 36 (87.8%) students were found to be positive for *P. humanus capitis*.
Conclusions : The conclusion from this study is that the percentage of pediculosis capitis in female students is high, so it is necessary to take countermeasures in the form of head lice medication and education about personal hygiene for class 7 female students at Al-Muhajirin Islamic Boarding School, Central Cikarang, West Java

Introduction

Pediculosis capitis is a scalp disorder caused by an infestation of the lice (lice) of *Pediculus humanus capitis* commonly called head lice. This disease generally attacks school children in poor countries and develops by spreading (transmission) through hair, clothes, combs, hats, towels, and personal items from one person to another. Meanwhile, in Indonesia, pediculosis capitis is still classified as a neglected disease with the highest prevalence rate in girls living in Islamic boarding schools. Therefore, the prevalence of pediculosis capitis in Indonesia is still dominant in Islamic boarding schools (Octavia *et al*., 2020).

According to Massie *et al*. (2020) the prevalence rate of pediculosis capitis is generally influenced by climate, geographical environment, health conditions, income, and family density. Some data on the percentage prevalence of pediculosis capitis mentions that the Asian continent is 15.1% ± 12.8%, Europe is 13.3% ± 17.0%, South America is 44.1% ± 28.0%. At the country level, the prevalence of pediculosis capitis in Turkey is 9.4%, Iran is 4%, Saudi Arabia is 12%, Jordan is 13.4%, Egypt is 21.6%, Philistines is 32.4%, Malaysia is 35%, Pakistan is 87%, Bangkok 23.32%, and Argentina 42.7%. Meanwhile, based on the literature review Octavia *et al*. (2020) the prevalence rate of pediculosis capitis in Indonesia at Islamic boarding schools is above 50% with more female than male sufferers.

The high prevalence rate of pediculosis capitis creates a public health problem, especially in children aged 5-11 years. This is because *P.humanus capitis* will enter its saliva and feces when it sucks blood on the human head.

According to Adham *et al*. (2020) *Pediculus humanus capitis* bites can cause pruritus (itching on the head) causing skin disorders in the form of erythema, macules and papules. If when scratched it produces a wound (abrasions) then it has the potential to cause a secondary infection in the form of impetigo and furunculosis. Considering that the activity of *P. humanus capitis* bites increase at night, it will trigger itching and head-scratching responses, causing children to experience sleep disturbances at night. In cases of chronic infestation of pediculosis capitis can cause anemia, lethargy, drowsiness thereby affecting learning performance, children's cognitive function.

Sulistyani and Khikmah (2019) *Pediculus humanus capitis* bites can cause pruritus (itching on the head) causing skin disorders in the form of erythema, macules and papules. If when it is scratched it produces a wound (abrasion) then it has the potential to cause a secondary infection in the form of impetigo and furunculosis. Considering that the activity of *P. humanus capitis* bites increas at night, it will trigger itching and head-scratching responses, causing children to experience sleep disturbances at night. In cases of chronic infestation of pediculosis capitis can cause anemia, lethargy, drowsiness which affects learning performance, children's cognitive function.

Kartashova *et al*. (2019) adding that pediculosis capitis also causes psychological impacts, namely children feel embarrassed and ostracized from the social environment because other children are worried about being infected by children who are infested with pediculosis capitis.

Referring to the problems and impacts caused by pediculosis capitis, it is necessary to carry out surveys and research on pediculosis capitis in Indonesia, especially in Islamic boarding schools in the Bekasi area. As for several previous studies regarding pediculosis capitis in Islamic boarding schools in several cities in the Greater Jakarta area (Jakarta, Bogor, Depok, Tangerang, Bekasi) have been carried out by Gumsah and Apriani (2021) reported the percentage of pediculosis capitis in children aged 3-12 years in the Babakan Asem, Teluknaga, Tangerang area of 68%. Khamaruddin *et al*. (2020) stated that the percentage of pediculosis in students of Al Hamid Islamic Boarding School, East Jakarta was 69%. Nurdiani (2020) added that the percentage of children aged 6-12 years at the Sirojan Mustaqim Islamic Boarding School and the residents of RW 03 Pondok Ranggon Village, Cipayung District, East Jakarta was each 71 (64.54%) with the distribution as follows: 41 (57.7%)) in dormitories and 30 (42.3%) in residential areas.

The results of other studies reported by Sisirawaty & Siahaan (2016) found the egg stage of on conventional motorcycle taxi helmets in Bekasi City at 16.7%. Research Suhesti & Pramitaningrum (2020) revealed that the percentage of pediculosis capitis in children aged 3-12 years in one of the Cibitung housing areas, Bekasi Regency was 73%. Based on the results of previous studies, not much data has been published regarding the percentage of pediculosis in Islamic boarding schools in Bekasi City. In fact, information regarding the incidence of pediculosis capitis in Bekasi City is needed for the Health Service which is integrated.

Methods

Research design

This type of research is descriptive quantitative with cross sectional design. The research location is the Al-Muhajirin Islamic Boarding School, Central Cikarang, Bekasi Regency, West Java. Research tools and materials include serit combs, plastic clips. chambers, object glass, cover glass, pipettes, microscopes, 10%, 15% Potassium Hydroxide (KOH), aquadest, 30%, 50%, 96% alcohol, absolute alcohol, and xylol. The sample of this research were 41 female students of class 7 at Al-Muhajirin Islamic Boarding School

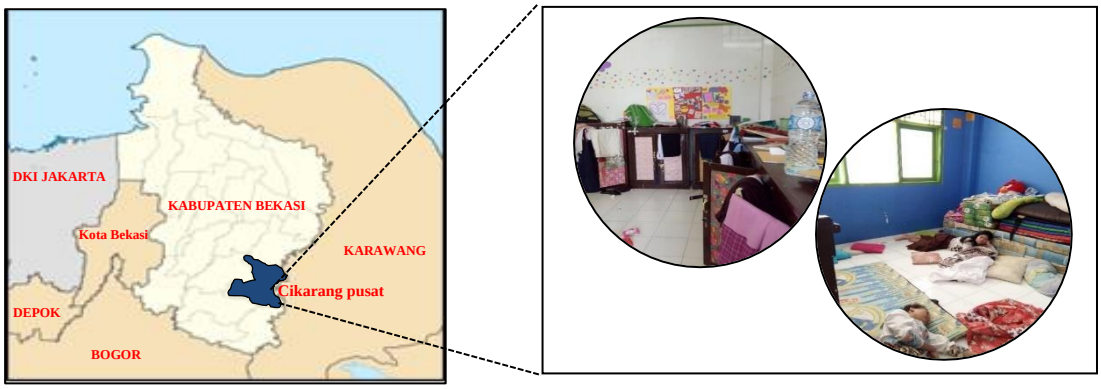

Figure 1. Map of the location and condition of the Al-Muhajirin boarding school's rooms

Examination of P. humanus capitis

Examination of *P. humanus capitis* was carried out by combing female students' hair using a fine-toothed/serit comb. The female students' hair is wetted first, then a piece of plain paper is placed under the head. Hair is combed from top to bottom, left side and right side of the head. The presence of *P. humanus capitis* that fell on the paper was then observed, recorded, and preserved preparations were made for morphological examination of *P. humanus capitis* microscopically.

Figure 2. Examination of *P. humanus capitis* using serit comb

Sequentially the preparation of preserved preparations was carried out by soaking *P.humanus capitis* in 10% KOH, 15% (24 hours), distilled water (rinsing), 30% alcohol (15 minutes with 3x change of solution). The body of *P. humanus capitis* was then pressed with 2 glass objects to remove the fluid from the body. The samples were then immersed in 50%, 96%, and absolute alcohol (15 minutes). Then the

samples were immersed in Xylol 2x each with a duration of 5 minutes, 15 minutes, 25 minutes and 60 minutes. The sample is then placed on a glass object, given an entelan, covered with a cover glass, and observed under a microscope to examine the morphological identification of *P. humanus capitis.* The morphological identification of *P. humanus capitis* refers to the book ATLAS of Medical Parasitology (Wijaya *et al.* 2016).

Figure 3. slide of *P. humanus capitis*

Data analysis

Data analysis in this study used descriptive statistics which were carried out by processing data in the form of tables and figures. All data were systematically arranged and then described to see the description of pediculosis in the research subjects. As for the image data, it is described to see the morphological characteristics of *P. humanus capitis* as a cause of pediculosis.

Results

Pediculosis examinations at the Al-Muhajirin Islamic Boarding School are conducted separately between female students in grades 7-1 and 7-2. The number of respondents who participated in this research was 49 female students from classes 7-1 and 7-2, but at the time of the research, three female students were not present in class 7-1, and 5 female students in class 7-2 so that the final number of respondents who participated in In this study, there were 41. The results of the P. humanus capitis examination on 41 female students at the Al-Muhajirin Islamic Boarding School can be seen in the table below:

Table 1. Results of examination of P. *humanus capitis* on the hair of female students in grades 7-1 and 7-2

Results	Number of Respondents	Percentage (%)
Positive	36	87,8 %
Negative	5	12,1 %
Total	**41**	**100 %**

Discussion

Based on the table above, it can be seen from the examination of 41 female student respondents that as many as 36 female student students (87.8%) tested positive for *P. humanus capitis*, and five female student students (12.1%) tested negative for *P. humanus capitis*. The positive presence of *P. humanus capitis*, as much as 87.8%, proves that the incidence of pediculosis in grade 7 female students at the Al-Muhajirin Islamic Boarding School, Central Cikarang, West Java, is still relatively high. The results of this research complement the results Nurdiani's (2020), which reported that as many as 6-12 years old children at the Sirojan Mustaqim Islamic Boarding School and the residents of RW 03 in Pondok Ranggon Village, Cipayung District, East Jakarta obtained results of 60 (77.93 %) women and 11 (33.33%) men tested positive for *P. humanus capitis*; The selection of research samples that focused more on girls refers to the results of research by Gumsah & Apriani (2021) which reported that examinations of children 3-12 years old resulted in 31 (76%) positive girls and 3 (33%) negative boys for pediculosis in Babakan Asem Village, Teluknaga District, Tangerang and research by Suhesti and Pramitaningrum (2020) which revealed that the percentage of children aged 3-12 years in one of the Cibitung housing complexes, Bekasi Regency was 28 (85%) women who tested positive for pediculosis capitis.

Another study that selected the location of Islamic boarding schools and female students was also carried out by Setyoasih and Suryani (2006), who stated that out of 84 female students at Muhammadiyah Boarding School Prambanan Sleman Yogyakarta, 43 (51.2%) female students were positive for pediculosis captis infestation. The findings of the incidence of pediculosis in Islamic boarding school children were also shown in the research of Ary *et al.* (2019), who reported that out of 193 students, 93 (48.2%) were infested with pediculosis with age and most being 13 years old and class VIII respectively amounting to 45 (48.4%) and 35 (37.6%) students at Madrasah Tsanawiyah. (MTs) at Islamic Boarding School X, East Mempawah District, West Kalimantan. The high incidence of pediculosis was also shown in Hapsari (2021), which showed that of the 48 female students living in Islamic boarding school dormitories, 31 (64.6%) were found to have *P. humanus capitis* at the PPAI An Nahdliyah Islamic Boarding School, Malang Regency.

According to Gumsah and Apriani (2021), the incidence of pediculosis capitis is influenced by personal hygiene and the environment. *Islamic boarding*

schools generally have a dominant environment for the spread of pediculosis capitis. This is because Islamic boarding schools have bedrooms with a high residential density, making it easier to spread pediculosis capitis from one female student to another. Several risk factors for supporting pediculosis capitis in Islamic boarding schools include sharing towels, not washing your hair twice a week, not changing bed sheets once a week, and using shared bedding, combs, and accessories.

Azim and Andrini (2018) explained that pediculosis capitis in Islamic boarding schools is more dominant in girls than boys. This is because girls tend to have longer hair than boys. Women with long hair are easier to serve as reservoirs for the survival and reproduction of *P. humanus capitis*. However, there is no relationship between gender and the incidence of pediculosis capitis, considering that many other factors can potentially cause pediculosis capitis. The research results of Mitriani *et al.* (2017) in boarding students for classes VII, VIII, and IX This is because class VII students still have poor knowledge about preventing pediculosis, the behavior of exchanging headscarves and sleeping equipment between students is not good.

Regarding the relationship between risk factors for pediculosis in students at Islamic boarding schools, Lukman *et al.* (2015) proved that gender, frequency of washing hair, use of shared combs or hair accessories, use of shared mats or beds, hair length and hair type were correlated with the incidence of pediculosis at the Miftahul Ulum Islamic boarding school, Jember with gender being the biggest risk factor in influencing the incidence of pediculosis capitis. This proves that although pediculosis can attack all genders, women are twice as susceptible to pediculosis capitis infestation compared to men because the majority of women have long, straight, or curly and loose hair, making it more difficult to clean and beneficial for *P. humanus capitis* to grow shelter and metamorphosis. Apart from that, female students more often exchange hair accessories and gather with other students, thus facilitating the transmission of *P. humanus capitis* easily and quickly.

Other evidence was presented by Sari *et al*. (2022), who reported that the use of combs and headscarves together was the risk factor that had the most influence on the incidence of pediculosis in junior high school students aged ≤ 15 years at the Subullussalam Islamic Boarding School, Palembang. Indirectly, using combs together causes eggs and adult tuma from students suffering from pediculosis capitis to stick to the comb and be transferred to other students. The use of the headscarf can

indeed reduce the risk of transmission of pediculosis because it avoids direct contact. However, using the headscarf by students suffering from pediculosis can increase the scalp's moisture, especially when the headscarf is worn when the hair is still wet, thus becoming an optimal habitat for the reproduction of *P. humanus capitis.* If another student wears the headscarf without cleaning it, the tuma attached to it can be transferred to other students. Therefore. After using the hijab, wash it immediately and dry it in the sun so that it can kill *P. humanus capitis.*

Another risk factor that influences pediculosis capitis is shown in research by Rohmaniah and Prajayanti (2022), which states that personal hygiene knowledge and attitudes have a significant correlation with the incidence of pediculosis capitis in female students at the Al-Manshur Popongan Islamic Boarding School, Klaten. Female students with good personal hygiene knowledge and attitudes, such as clean skin, hair, and clothing, tend not to be infected with pediculosis capitis. In contrast, female students with low personal hygiene knowledge and attitudes tend to be more easily infested with pediculosis capitis. As for students with good personal hygiene knowledge but with poor personal hygiene attitudes, such as still having the habit of exchanging personal items with other female students and not applying personal hygiene knowledge to their personal lives, the prevalence of pediculosis capitis tends to remain high. This attitude is supported by inadequate dormitory facilities between female students with good and poor knowledge of personal hygiene, which remains a risk factor that continues to trigger an increase in pediculosis capitis even though female students of more mature age have good personal hygiene knowledge and attitudes.

Setiyani *et al*. (2021); Nurcahyati and Rangkuti (2020) female students with poor personal hygiene knowledge of 61.9% and 63.6% tend to increase the percentage of pediculosis capitis incidents in Islamic boarding school environments in children aged 5-16 years by 74.5% and 69 .8%. The same results were also reported in the research of Pringgayuda *et al*. (2021), who stated that the percentage of personal hygiene knowledge in children aged 12-18 years at the Miftahul Falah Islamic boarding school Banyumas Pringsewu, Lampung caused an increase in the incidence of pediculosis capitis by 67.5%.

A different case occurred in the research of Analdi and Santoso (2021), which reported an infestation of female students at the Anshor Al-Sunnah Islamic Boarding School, Riau, in Classes VIII, IX, and X who had good personal hygiene behavior of

88.2%. In this case, transmission of pediculosis capitis occurs through direct contact between female students, so prevention efforts are no longer carried out. However, effective treatment is needed to break the chain of pediculosis capitis transmission. Treatment and mitigation efforts were demonstrated in the research of Khamaruddin *et al.* (2020) who reported that before treatment and control efforts were carried out, the percentage of cases of pediculosis capitis in 60 students of Al-Hamid Islamic Boarding School, East Jakarta was 69%, but after treatment and control efforts were carried out in the form of a policy of shaving hair, cleaning hair 3x a week, and administering medication for head lice was able to reduce the incidence of pediculus capitis by 33% or a decrease of 36%.

The environmental conditions at the Al-Muhajirin Islamic Boarding School are inadequate, with the number of female students in one bedroom reaching 15 to 25 children. The facilities in the room only have one fan, which causes the female students' rooms to become damp and hot during the day. How mattresses, blankets, and headscarves are placed in a pile and mess, and the habit of female students exchanging headscarves is thought to be the cause of the high incidence of pediculosis capitis in this study.

The examination for pediculosis capitis in the study was carried out using a single-use comb (disposal comb), which aims to prevent the migration of lice from one child to another, in addition to preventing false positives from occurring in children who are not infected with pediculosis capitis. Pediculosis capitis examination is carried out in a room that has good lighting. The student's hair is first combed to avoid tangles, making it easier to examine *P. humanus capitis*. Female students who have long, tangled hair are combed using a comb with a sparse density so that it does not cause pain when combing. The entire head and hair are examined carefully, especially the temples, nape, and behind the ears. Students are declared positive for *P. humanus capitis* infection if one *P. humanus capitis* egg/nymph/adult is found in the scalp area. The spread of head lice is limited to the skin or hair area of the head, especially at the back of the head and near the ears in children. The results of P. humanus capitis found in the head area of the female students at the Al-Muhajirin Islamic boarding school can be seen in the image below.

Figure 4. A. *P. Humanus capitis* adult (female). B. *P. humanus capitis* adult (male). C. *P. humanus capitis* nympha phase

Figure 4 shows that adult *P. humanus capitis* has short antennae that are long and thin (filiform) with five segments and has three pairs of legs consisting of coxa, femur, tibia, and tarsus. The length of the front, middle, and hind legs is almost the same. The tip of the tarsus is shaped like claws, which grasp the hair shaft.

The difference between male and female *P. humanus capitis* can be seen in the shape of the abdomen, where the abdomen of the male *P. humanus capitis* is slimmer with a rounded tip of the abdomen. In comparison, the abdomen of the female *P. humanus capitis* is larger, with the tip forming the shape of the letter V.

The male *P. humanus capitis* his genitals. Namely, the aedagus (penis), while the female *P. humanus capitis* has a terminal portion called the gonopod and uterine gland which functions to secrete a cement fluid like glue (called nit) which functions to place the eggs in the hair so that they do not come off easily.

According to Wijaya *et al*. (2016), adult pediculus has a size of 1-3 mm. The size of the nymph is smaller than the adult pedicle. The difference is visible in the size of the abdomen due to the increase in abdominal segments. Pediculus is incapable of flying because it does not have wings, but its movement is fast, up to 23 cm/minute.

The advantage of this research is that the selection of Islamic boarding schools as endemic locations and female students as sample objects for pediculosis capitis examinations is precisely able to provide information about the incidence of pediculosis capitis in Bekasi Islamic boarding schools. The limitations of this study are that the number of Islamic boarding school locations does not cover a large area, the use of a cross-sectional design, and an analysis of the risk factors that cause pediculosis in the research locations has not been carried out.

Conclusion

The conclusion from this study is that the percentage of pediculosis capitis in female students is high, so it is necessary to take countermeasures in the form of head lice medication and education about personal hygiene for class 7 female students at Al-Muhajirin Islamic Boarding School, Central Cikarang, West Java.

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Effect of Musical Therapy on Malondialdehyde Levels on Male Mice Brain Tissue

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ABSTRACT

Introduction: An example of a non-pharmacological therapy that is currently being developed is music therapy. The serenity created from classical music and *murottal* therapy is good for therapy performance, accelerating the healing process, and also reducing stress levels.
Objective: This study aimed to examine the effects of classical music "Mozart" and *Murottal* Al-Qur'an therapy on mice malondialdehyde levels
Methods: This study used 24 male BALB/c strain mice (10-12 weeks), in a true experimental setting using the Post-Test-Only Control Group Design. Four groups of mice were created: K (control), P1 (*murottal* Al-Qur'an), P2 (classical music "Mozart"), and P3 (combination therapy). Statistical analysis was used with a significance of $p < 0.05$.
Results: According to study findings, the P2 group had the highest average malondialdehyde level meanwhile the lowest average malondialdehyde levels were found in Group P1. The test results showed no significant relationship ($p = 0.213$)
Conclusions: The findings of this study showed that there was no significant correlation between malondialdehyde levels when "Mozart" classical music and Murrotal treatment were given. The group who received the classical music "Mozart" nevertheless, had higher malondialdehyde levels, according to the findings.

Introduction

In the current era, the human body is very vulnerable to exposure to free radicals. The free radicals can come from inside and outside the human body itself. Free radicals originate from normal metabolic processes in the body such as phagocytosis, aerobic metabolism, prostaglandin (PGs) synthesis, or certain external factors such as ionizing radiation (IR), xenobiotics, and pollutants (Fang et al., 2002; Mfotie Njoya, 2021). Free radicals damage various cell components, including deoxyribonucleic acids, membrane lipids, and proteins (Dobyns et al., 2006). All these factors involved in free radical production will

activate different pathways to induce oxidative stress.

Previous research has proven the influence of the Al-Quran on the behavior of mice. The Al-Quran recitation can improve conditions of depression at a hearing frequency of 60 decibels (dB) but triggers conditions of aggression at a frequency of 80 dB (Algristian et al., 2022). Mice-model of cancer that were exposed to the Al-Quran recitation at a therapeutic frequency were also able to prevent the development of cancer cells (Muhammad et al., 2022). Until now there has been no research comparing reading the Al-Quran recitation and music on individual health conditions. This research tries to make this comparison.

Music is a form of art that can be a crucial factor in human life. Not only does it serve as entertainment, but it can also influence human physiological and psychological processes (Rebecchini, 2021). In the medical context, music has been associated as one of the flexible treatment methods, aiming to improve various aspects of human health and well-being (Gooding, 2018; Yinger, 2018). Through several studies that have been conducted, music therapy has shown several benefits for human health, such as being able to improve the quality of life in mental illness patients, improve cognitive skills, reduce anxiety, and so on (Gropper & Miller, 2020).

Quality music therapy generally uses sounds that are calm, simple, and have a regular tempo (Saraswati, 2014). One type of music that can be used as therapy is *Murottal* Al-Qur'an. The sound of the *Murottal* Al-Qur'an has a constant and regular rhythmic characteristic and is quieter. Another type of music that can be used is classical music which consists of a combination of several instruments such as violin, piano, cello, and so on. This type of music is also known to have a calming, relaxing, and relaxing impression (Burrai et al., 2020) related to the impact of listening to classical music showed an improvement in the quality of life in heart failure patients. through the above background, research is needed regarding the effect of *murottal* Al-Qur'an and classical music "Mozart" listened to adult *Mus musculus* on brain tissue malondialdehyde levels.

Methods

Research design

This study is a true experimental study using male mice as experimental animals. The research design this time is a post-test-only control group design which aims to analyze the impact of giving Al-Qur'an *murottal* therapy, classical music "Mozart", and a combination of both on Malondialdehyde levels in mice.

Experimental animals

This study used male mice (*Mus musculus* strain BALB/c) obtained from the pharmacology laboratory, faculty of medicine, Hang Tuah University, Surabaya. A total of 24 mice (*Mus musculus*) with BALB/c strain. To minimize the homeostatic changes that occur during transportation and the hormonal changes caused by environmental changes, experimental animals will be acclimated for a week before treatment. The 24 mice were then separated into 4 groups (n=6): Group K (control group), Group P1 (Murotal Al-Qur'an treatment), Group P2 ("Mozart" classical music treatment), and Group P3 (combination of treatments).

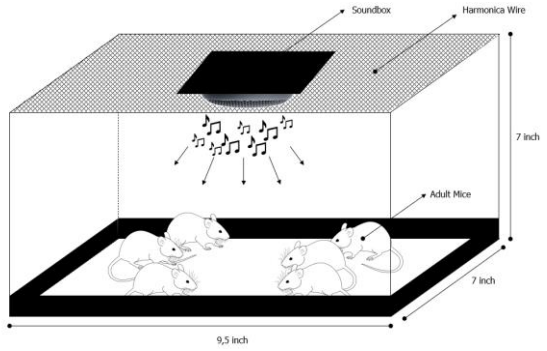

Figure 1. Treatment cage. Each treatment cage contained 6 mice with a soundbox placed on top of the cage facing down.

Treatment procedure

Furthermore, a sound source was placed above each group's cage at an effective distance of approximately 40 cm (Figure 1). According to the various experimental treatments, previously prepared mice were placed into isolation cages in various rooms. Three soundboxes/tape recorders using Al-Qur'an Murrotal sound therapy (sura Al-Fatiha and Al-Baqarah by Qori' Al-Mathrud) and the well-known "Mozart" ("Sonata in D for two pianos, KV448-Allegro con spirito") music sound therapy was used for the treatment of mice for two hours every day for a total of 20 days.

Mice malondialdehyde level measurement

On the 21st day, the mice will be dissected and the right cerebral hemisphere tissue will be taken, and then placed in an Eppendorf tube. MDA levels were measured using the TBARS spectrophotometry method with a wavelength of 532 nm.

Data analysis

The value of Malondialdehyde levels of each mouse in the group obtained will be subjected to statistical tests. The significance of the data will be evaluated in this study using the One-Way ANOVA test. Post hoc Mann Whitney-U was used to determine which groups were different in terms of variables. The value of $p < 0.05$ is considered to indicate a statistically significant difference.

Results and Discussion

This study aimed to prove whether or not exposure to "Mozart" classical music and *murottal* Al-Qur'an music had any effects. *Murottal* Al-Qur'an therapy is one of the

non-pharmacological therapies that has been developed in recent years. *Murottal* Al-Qur'an treatment has been the topic of research that has been successful in showing a good effect on several illness problems, including high blood pressure (hypertension), levels of stress and anxiety, and depression. (Irmachatshalihah et al., 2019; Yunus et al., 2021; Zahra et al., 2019)

We obtained an average value of malondialdehyde levels that varied through each group through the results of the tests carried out in each group. The P2 group, or the group that received Mozart music, had the highest average malondialdehyde level, with a value of 341.33 and 184.06—with a total of 204.83 45.50, group P1, who received the *murrotal* Al-Quran therapy, had the lowest average number of malondialdehyde levels. The analysis findings were further investigated by doing a One-way ANOVA test, which showed that there was no significant correlation between Mozart classical music and *murottal* Al-Qur'an treatment on increasing mice malondialdehyde levels ($P > 0.05$).

Observation results showed that mice induced by *murottal* Al-Qur'an therapy tended to be calmer and less aggressive than other groups. Meanwhile, the combined group had the most aggressive and hyperactive tendencies, as evidenced by the injuries found in almost every combined treatment group. Table 1 shows the findings of the overall observation of the study subjects' behavior.

According to Figure 2, the P1 group's average MDA level was the lowest among all the test groups, at 204.83 nmol/g. The result indicates the group of mice exposed to the Murrotal Al-Quran therapy method does not experience stress. The same outcomes were found in Kurniasari's research from 2017; one group of mice ($n = 5$) exposed to the Murrotal Al-Quran for two hours each day had an average MDA level of 0.42 nmol/mL. Kurniasari et al., 2017)

Several other scientists have widely researched the use of classical music as a method of music therapy. A prior study found that when it comes to improving mice's (Mus musculus) spatial memory, Mozart's and Murotal's classical music have the same effect. However, when mice are given both approaches, their spatial memory is superior and their level of aggression is higher (Muhammad et al., 2023).

In this study, we found that the group that was treated with classical music "Mozart" had a malondialdehyde level of 341.33 ± 184.06, which was the highest among the other groups. This increase in malondialdehyde levels indicates that the mice in the P1 group experienced stress due to the classical music of "Mozart". Apart from these results, we realize that the

effectiveness or success rate of using this therapy method varies in different cases. Research on classical music therapy (Guétin et al., 2009) on anxiety, depression, and mood experienced by 13 patients with traumatic brain injury for 20 weeks. The results showed that music therapy was able to improve patient mood in patients from the first session to the next. The provision of music therapy also significantly reduced anxiety and depression starting from week 10 to week 20 (the end of the study).

The results of the observation of the behavior of the *murottal* Al-Qur'an and Mozart group mice were better than the combined and control groups during the study period and the malondialdehyde level test. Mice who were given Koran therapy showed the lowest level of aggressiveness and were the calmest than the other treatment groups. This can be attributed to the optimal effect of dopamine and endorphins in the Qur'an group compared to other groups. Both have the potential to create a calmer state in mice and tend to be less obsessive. Amanah & Esterlita Purnamasari, 2015; Olshansky et al., 2008) According to research by Kent Berridge, the two systems of "want" (dopamine) and "liking" (opioids) are complementary. The dopamine system is stronger than the opioid system. This system will make a person continue to seek satisfaction over and over again and continue to feel less so that they always want more than before. Berridge & Robinson, 1998)

Apart from the results obtained from this study, we realize that there are limitations in this study, one of which is the natural process that occurs biochemically in the body of mice. So that researchers cannot directly control the biomolecular changes that occur during the study. Another limitation is the genetic dominance in each mouse that is derived also cannot be controlled optimally.

Table 1. Test results for malondialdehyde levels and observation of animal behavior

Group	Total (n)	MDA Level (nmol/g)*	General Behavior	
			Aggressiveness	Agility
K	6	218,67 ± 89,06	++	++
P1	6	204,83 ± 45,50	-	+
P2	6	341,33 ± 184,06	+	++
P3	6	266,33 ± 108,76	+++	+++
P - Value		0,213		

Notes: + (low), ++ (medium), +++ (high). *) The results of the one-way ANOVA test showed insignificant results (P > .005) for both variables with Sig. of 0.213 in the malondialdehyde level. Data are shown as mean ± SD.

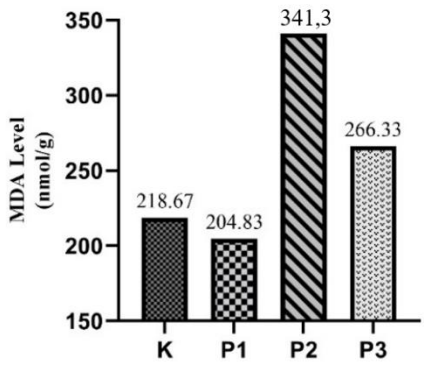

Figure 2. The average level of malondialdehyde levels in all study groups, Group K = Negative control (n = 218.67), P (1) = mice treated with Murrotal Al-Quran (n = 204.83), P (2) = Mice were treated with "Mozzart" classical music, P(3) = mice were given a combination of Al-Quran Murrotal and Classical Music treatment

Conclusion

This study shows new insights into non-pharmacological therapeutic methods using classical music "Mozart". Based on the findings of this study, classical music therapy "Mozart" has the highest average score of malondialdehyde levels which indicates stress. Meanwhile, the group that was given Al-Qur'an *murottal* therapy had the lowest average score of malondialdehyde levels. Other findings on the general behavior of rats showed that the *murottal* Al-Qur'an treatment group showed calmer behavior, while the group with combined therapy treatment showed aggressive behavior. Therefore, further research is needed to determine other factors that affect the aggressiveness of experimental animals.

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Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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