Vol. 10 No. 1 February 2022 – Mei 2022

MEDICINUS

JURNAL KEDOKTERAN
UNIVERSITAS PELITA HARAPAN

Diterbitkan oleh Fakultas Kedokteran, Universitas Pelita Harapan, Indonesia
ISSN 1978 - 3094
E ISSN 2622 - 6995

MEDICINUS

Journal of Faculty of Medicine
University of Pelita Harapan

Vol.10 No. 1
February 2022 – Mei 2022
ISSN 1978-3094
E-ISSN 2622-6995

Clinical Article

Case Report

Publish: March 2022

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Publish

February – June – October

Characteristics of NSAIDs Prescription in Elderly Knee Osteoarthritis Patients

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Citation: Wong Janetta, Lumbuun Nicolaski. Characteristics of NSAIDs Prescription in Elderly Knee Osteoarthritis Patients. Medicinus. 2022 February; 10(1):1-9
Keywords: Osteoarthritis; NSAID; Rationality; Prescription
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Online First : March 2022

Abstract

Introduction: The prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) as pharmacological therapy for OA was found to be imprecise. In 2018, the rationality of NSAIDs prescribed at Wolter Monginsidi Hospital, Manado showed as much as 100% proper indication, 77% proper dose, and 89% proper medication. This shows that the rationality of NSAIDs prescription is still irrational. Irrational prescribing has the potential to result in side effects or the incidence of drug-related problems

Aim: To determine the characteristics and the rationality of NSAIDs prescriptions in elderly knee OA.

Methods: This is a descriptive study of 108 medical records for the period January 2020-April 2021 at BS Clinic, Semarang, using purposive sampling method.

Result: Results showed the characteristics of elderly knee OA patients at BS Clinic were 74.1% women, 47.2% belonging to obese group, and 41.7% experiencing severe pain. Patient's age had a median value of 66 years. In the number of comorbidity, the median value was 1. The rationality of NSAIDs prescription was 95,4% proper diagnosis, 100% proper drug, 97.2% proper dose, and 99.1% proper indication with the incidence of side effects of NSAIDs prescribing was 1.9%.

Introduction

Elderly, in Law No. 13 of 1998, is defined as someone who has reached the age of 60 years and over. World Health Organization (WHO) defines elderly into the population group aged 60 years and over.[1,2] Statistics Indonesia shows that demographic data on the elderly in Indonesia in 2019 recorded 63.82% of 60-69 years, 27.68% aged 70-79 years, and 8.5% of elderly aged 80 years and above. The evidence of an increase in the elderly population every year has the various consequences on aspects of life, one of which is health.[3]

According to American College of Rheumatology (ACR), osteoarthritis (OA) is most common degenerative disease of joint cartilage. This disease affects knee, hip, and hand joints. Hence, OA becomes one of most common main causes of disability in elderly.[4] Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used pharmacological therapy in OA. NSAIDs are drugs that have analgesic, antipyretic, and anti-inflammatory properties by inhibiting the cyclooxygenase (COX) enzyme.[5] NSAIDs are commonly used in prescription so it is necessary to pay attention to the rationality of prescribing NSAIDs.

Drug rationality is defined by the compatibility of the diagnosis and drug administration with the reference used regarding diagnosis, dosage, and indications of usage.[6] Previous study in 2018 at Wolter Monginsidi Hospital, Manado, showed the rationality of NSAIDs prescription was found to be 100% proper indication, 77% proper dose, and 89% proper drug.[7,8] Another study in 2014 at the Subang District Hospital had the rationality of 100% proper diagnosis, 52% proper drug, 100% proper dose, 100% proper indication.[8]These studies show that administration of NSAIDs has not been fully rational. The rationality of NSAID prescribing needs to be a concern as the amount of elderly OA cases increase, which there is a danger of side effects if the prescribing pattern is inappropriate. Irrational prescribing of NSAIDs can lead to side effects such as gastrointestinal, cardiovascular, nephrotoxicity, cognitive deficits, and stroke. [5,9,10]

Although similar things have been studied, the rationality of NSAIDs prescription has not been completely perfect that can lead to the occurrence of side effects. In addition, the patient characteristics such as age, gender, presence of comorbid disease,body mass index (BMI), and degrees of painplay roles in NSAIDs prescription. Therefore, it is necessary to look further the characteristics of NSAIDs prescribed in elderly knee OA.

Objectives

This study aimed to determine the characteristics of NSAIDs prescribed in elderly knee OA in *Fasilitas Kesehatan Tingkat Pertama/FKTP* (general clinic) since the previous study focused on hospital prescriptions mostly given by specialists.

Material And Methods

Study Design

This research was a retrospective descriptive cross-sectional study design.

Sample

108 medical records of period January 2020to April 2021 were obtained from BS Clinic, Semarang. Sampling was carried out from December 2020 to April 2021.

Data Collection Method

Data were collected using purposive sampling method (total sampling) in the number of samples. 108 samples were taken and met the inclusion criteria consisting of (1) medical records of male and female OA outpatients aged 60 years;(2) medical records of patients who made the next visit at least a month after receivingNSAIDs. Meanwhile, OA patients who came but were referred to a higher-level health facility without receiving any treatment atthe clinic were excluded from the research data. Data such as name, gender, age, BMI, number of comorbidity, degree of pain, diagnostic statement, NSAIDs use (type, dosage, and prescription duration), and any side effect of prescription were obtained from medical records. Several data on the patient's pain degree in January-November 2020 period were completed through primary data collection of online interviews with the patients. All the collected data were recorded in Case Report Form (CRF).

Data Analysis

Data were analysed using Statistic Package for the Social Sciences 26th version. Univariate analyses were

performed to assess the characteristics and the rationality of NSAIDs prescription compared to literatures.

Results

Patient Characteristics

A total sample of 108 medical records was obtained from the data collection. Research obtained that 74.1% of OA patients were women. In the context of BMI, the largest amount of data was 51 people (47.2%) in the obese group. The median age was 66 years with the youngest of 60 years and the oldest of 92 years. Patients aged 60 years had the most frequent visit to the clinic. In the number of comorbidity, the median value was 1 with the smallest number of 0 means patients didn't have anycomorbidity and the most being 3 diseases. Numeric Rating Scale (NRS) was used to assess pain degree felt by the OA patients. The majority of the samples experienced severe pain with the prevalence of 41.7%.

Table 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	28	25.9
Female	80	74.1
BMI		
Underweight	7	6.5
Normal	28	25.9
Overweight	22	20.4
Obese	51	47.2
Pain degree		
Mild	20	18.5
Moderate	43	39.8
Severe	45	41.7
	Age	**Number of Comorbid**
Median	66	1
Mode	60	0
IQR	7	1
Min-Max	60-92	0-3

Prescription Characteristics

Based on 2016 ACR Revised Criteria for Early Diagnosis of Knee Osteoarthritis, the research found that NSAIDs prescriptions in BS Clinic had the level of proper diagnosis of 95.4%. 100% of proper drug obtained in this study referred to Rekomendasi IRA 2014. Based on British National Formulary (BNF) 80, research got 97.2% of proper dose and 99.1% of proper indication on NSAIDs prescription.

Table 2. Characteristics of Prescription

Characteristics	%
Proper Diagnosis	95.4
Proper Drug	100
Proper Dose	97.2
Proper Indication	99.1

Table 3. Types of NSAID prescribed

NSAIDs	Degree of Pain		
	Mild	**Moderate**	**Severe**
Celecoxib	1	4	1
Meloxicam	4	10	12
Ibuprofen	6	11	3
Diciofenac	9	18	29
Total	**20**	**43**	**45**

In the context of prescription duration, result showed the median value was 3 days with the shortest being 3 days and the longestwas 7 days

Table 4. Duration of NSAIDs Prescription

Duration of NSAIDs Prescription			
Median	**Mode**	**IQR**	**Min-Max**
3	3	0	3-7

Side Effects

Two (1.9%) out of 108 samples experienced the side effect of NSAIDs prescription manifested as dyspepsia. Table 5 showed the division of patient groups based on the administration of gastroprotective agent, given as proton pump inhibitor (PPI). About 84 samples did not get PPI, including those 2 samples with dyspepsia. As for 24 samples got PPI and didn't experience any side effect caused by NSAIDs prescription.

Table 5. Side Effects of NSAIDs Prescription

PPI	Side Effects	
	Dyspepsia	Nothing
Given	-	24
Not	2	82
Total	**2**	**106**

Discussion

Patient Characteristics

The gender distribution of knee OA patients at BS Clinic shows the largest number of data in the female group, which is 80 people (74.1%). This research resembles a study in 2020 at *RSUD dr. Mohamad Soewandhie* with a prevalence of OA in women by 77.9% and a research in 2015 at Subang District Hospital with a prevalence of OA in women of 63%.[8,11] Hence, it can be concluded that the gender characteristics of knee OA patients in *FKTP* correspond with those who come to the hospital in terms of more women than men.[12–15]

Fifty one (47,2%) out of 108 samples were categorized as obese group that resembles a study in 2014 at *Posyandu Lansia Surakarta* which showed the prevalence of knee OA in obese patients was 48.1%.[16] According to the findings, it can be concluded that knee OA patients who came to *FKTP* had the same BMI characteristics in the terms of being obese. The prevalence of this study increased in the obese group because the knee is a weight-bearing joint. Several studies have stated that obesity is one of the risk factors for knee OA due to increasing load in joint.[13] A study in 2016 proved that there was a significant relationship between BMI and the degree of joint damage in OA patients.[17]

This study has an age profile with a median value of 66 years, which is similar to a studyin 2014 by Hasiibi at *Puskesmas Susut, Bali* with the median age of 66.5 years. So that, OA patients who come to *FKTP* have the characteristics of same population average age.[18] Increasing age as the aging process contributes to the development of OA. Chondrocyte cells undergo aging through the degradation of cartilage and tissue by increasing the production of pro- inflammatory mediators in arthritis-affected joints.[19,20]

This study obtained data on the number of comorbidity with a median value of 1. This is in accordance with the CDC statement that most of joint disease patient suffers from one other chronic disease.[21] Hypertension was the most comorbidity as in 20 samples (15.3%). NSAIDs use has the side effect of increasing blood pressure. So that, prescribing in the patients with a history of hypertension needs to be considered. Research has also shown that aging factorscontribute to an increase in systolic pressure and heart rate due to increased stiffness of the arteries thereby reducing the reservoir function of the heart arteries.[22] NSAIDs work by inhibiting the COX enzymethat will decrease the rate of prostacyclin (PGI2) synthesis as a vasodilator and platelet inhibitor that are

produced in inflammatory conditions. Reduced amount of PGI2 will trigger an increase in blood pressure, leading to hypertension and thrombosis.[23]

In the assessment of pain degree, NRS was used in accordance with the study population that is elderly group. NRS has the advantage of being practically since any equipment isn't needed, is easy to understand, and isn't influenced by feelings of being disturbed due to the pain felt.[24,25] A study by Gallasch, et al. showed that NRS has a high level of reliability in the elderly population and is appropriate for all levels of education.[26] Measurement with Visual Analog Scale (VAS) is hampered by the need for equipment, the patient's level of education to understand measurement instructions, and the patient's medical history related to the visual acuity and cognitive function. Thereof, VAS is more difficult to be applied in the elderly population.[24,25] Verbal Rating Scale (VRS) has been shown to be influenced by conditions that affect patient's quality of life, such as the emotional feeling due to the pain felt or as the result of limitations in dailyactivities.[25]

Prescription Characteristics

The compatibility of the OA diagnosis in this study was 95.4%. This was based on the 2016 ACR criteria which states that patients are diagnosed with knee OA if they have symptoms of knee joint pain plus at least 3 out of 6 other symptoms, consist (1) patients aged >50 years; (2) morning joint stiffness <30 minutes; (3) crepitus; (4) bone tenderness; (5) joint enlargement; and/or (6) warmth isn't palpable on the joint surface.[27]

Several factors may influence the discrepancy in the diagnostic accuracy of this study. The diagnostic decision was made based on clinical complaints and physical examination which was not supported by a comprehensive supporting examination. Furthermore, the research population, which was the elderly could be a factor because doctors and patients themselves tend to perceive complaints as a natural process of aging. This is in line with the results of a 2014 study by Paskins, et al.[28] In addition, some patients may have undergone therapy or taken medication previously that it could affect the diagnosis due to differences in symptoms felt before and after the therapy. Besides, patients' own opinions and ideas based on disease information from the internet and the financial limitations in the cost of necessary health care could also hinder the diagnostic accuracy.

This is also supported by research in 2018 by Egerton, et al., published the factors that hindered the accuracy of diagnosis in GPs' practice were as follows[29]

1) Doctors tend to underestimate the patient's complaints.[28,29]
2) Gaps in the knowledge and abilities of doctors.[29,30]
3) Lack of access and awareness to update references or guidelines related to diagnosis.
4) Time-limited consultation.[30,31]

The results showed that the accuracy of the NSAIDs types of knee OA patients at the BS Clinic was 100% that resembles the research at *RSUP dr. Soeradji Tirtonegoro, Klaten* in 2018 with 100% drug type accuracy.[32] As seen that NSAIDs prescribing in *FKTP* corresponds hospital prescriptions in terms of the accuracy of NSAIDs type. The selection of

NSAIDs in this study was based on COX-2 selective, in the form of celecoxib and meloxicam that were administered to patients with a history of GI and cardiovascular and in patients without contraindications. While the non- selective prescribed as ibuprofen and diclofenac sodium were administered to patients with a history of cardiovascular given with gastroprotective agent (PPI) and in patients without contraindications.

The dosing accuracy profile in this study was 97.2% in 105 of 108 prescriptions, which is comparable to a study in 2014 at *Apotek X Kuningan* with an exact dose of 94.45%. The discrepancy occurred in 3 prescriptions with meloxicam given as 3 x 7.5 mg/day while the recommended dose in the literature is 7.5-15 mg/day.

The accuracy of indications in this study was 99.1%, which resembles a similar study at the Subang District Hospital with 100% proper indication.[8] A prescription of diclofenac sodium was given inappropriate. It was prescribed to a patient with a stroke that is classified as cerebrovascular disease which is included in the contraindication of diclofenac sodium. Diclofenac has the highest COX-2 selectivity compared to other types in non-selective group. In turn, increases the inhibition rate of prostacyclin production and causes vasoconstriction. In addition, renal action-induced hypertension may occur due to volume expansion. NSAIDs also induce thrombosis due to platelet aggregation due to inhibition of prostaglandin production.[23,33]

Research obtained the median value of prescription duration in this study was 3 days as well as being the shortest duration and the longest was 7 days. NSAID is a dose-response agent where the amount of dose affects the side effects of the prescription. Research in 2017 by Al Khaja, et al. showed that NSAID prescriptions are recommended with the shortest duration to minimize side effects that may arise withlong-term use.[34]

In the study, it was found that two (1.9%) patients experienced side effect in the form of dyspepsia and were not given PPI asgastroprotective agent. This study is comparable to a study in 2020 which stated that the most common side effects of NSAIDs is in the GI system.[35,36] Gastroprotective agents should be given to patients on NSAID treatment, especially those with GI history. The selection of PPI is based on its mechanism of action that reduce gastric acid production for 36 hours and is recommended to be given in the smallest dose NSAID prescriptions.[35,37,38]

Acknowledgements

The researcher would like to thank Dr. dr. Nicolaski Lumbuun, Sp.FK and BS Clinic, Semarang, for their roles in this research so that the research can be completed verywell.

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Comparison of Early Postoperative Pain between Lightweight Mesh and Heavyweight Mesh in Lichtenstein Hernia Repair for Geriatric Patients at Rumah Sakit Siloam Karawaci from January 2018 - December 2019

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Citation: Sidharta Nicholas Axel, Irawan Andry, Siregar Jeremia Immanuel, Hardjo Lugito Nata Pratama. Comparison of Early Postoperative Pain between Lightweight Mesh and Heavyweight Mesh in Lichtenstein Hernia Repair for Geriatric Patients at Rumah Sakit Siloam Karawaci from January 2018 - December 2019**.** Medicinus. 2022 February; 10(1):10-15
Keywords: Inguinal hernia; Complications; Heavy weight mesh; Light weight mesh
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Online First : March 2022

Abstract

Background: Inguinal hernias are one of the most often cases in surgery. Inguinal hernias are usually found in males rather than females. There are two types of meshes in inguinal hernia repairs: heavyweight and lightweight mesh. There werestill a lot of differences in the outcome of each mesh that was used. Therefore, with various different post operative pain results from past research, the author expressesan interest to conduct a research on this topic towards geriatric patients**.**

Methods: In this cross-sectional comparative study, 45 patients using heavyweight mesh and 45 patients using lightweight mesh herniorrhaphy with Lichtenstein technique in inguinal hernias at RS Siloam Karawaci Lippo Village and RSU were reviewed retrospectively. Patient's data were taken from medical record using purposive-sampling method. Early Postoperative pain on day 1 until 7 were classified following the Visual Analogue Scale (VAS). Incidence of postoperative infection and seroma were assessed in both groups. Collected samples will be processed using Pearson's Chi-Squared test.

Result: This study shows that there is a significant difference between the use of lightweight mesh in reducing moderate early postoperative pain for men above the age of 60 years old (p = 0.025) rather than the use of heavyweight mesh. Incidence of other postoperative complications such as infection and seroma have no statistically difference between both groups.

Conclusions: The use of lightweight mesh has the advantage in reducing early postoperative pain from herniorrhaphy using Lichtenstein technique rather than heavyweight mesh in men above 60 years old.

Introduction

Inguinal hernias are one of the most common cases in surgery. About 75% of hernia cases are from inguinal hernias. Inguinal hernias usually occur more often in men (27%) rather than in women (3%)[1]. Inguinal hernia is an abnormal protrusion of intra abdominal contents through the myofascial plain of the transversalis and oblique muscles.[2] Patients with hernias are often found in late conditions because oftheir lack of knowledge of the diseases and the high cost of the operations. However,the hernias should be repaired as soon as possible to prevent further complications. If surgery is not conducted, strangulated hernias might be the source of infection that could cause death. Several studies have been conducted and showed that overweight or obese men have a lower risk of having an inguinal hernia than men with normal weight.[3]

Hernias might grow and contract that can cause an obstruction which will cause clinical symptoms such as pain, discomfort, and vomit.[4] There are two types of surgery to repair hernias; anterior approach and posterior approach. In the anteriorapproach, the surgeon will dissect the patient's abdomen and cover the abdominal wall using a surgical mesh. Whereas the posterior approach, a laparoscopic camera is inserted through the patient's umbilicaland a surgical mesh will be used to coverup the abdominal wall. Both types are used based on each of the surgeon's skills and the facilities that are provided in hospitals.[5]

Two types of surgical mesh are used in hernia repair; heavyweight mesh and lightweight mesh.[6] Some studies show both surgical mesh doesn't have any differencein postoperative pain, infection, the formation of seroma, and recurrence of hernia repair.[7] But other studies show that lightweight mesh has more advantages in reducing chronic postoperative pain.[8]

No studies have been done to look for any difference of early postoperative pain from the usage of lightweight mesh and heavyweight mesh for hernia repair both genders at the age above 60 years old specifically in South East Asia. The aim of this study is to know the difference in early postoperative pain from the usage of lightweight mesh and heavyweight mesh for hernia repair both genders at the age above 60 years old.

Material And Methods

Study Design

This study used a retrospective cross-sectional design, reviewing patients who came to Rumah Sakit Siloam Karawaci Lippo Village and Rumah Sakit Umum Siloam between January and December 2019 with a diagnosed of inguinal herniaand has done inguinal hernia repair using either lightweight mesh or heavyweightmesh with Lichtenstein technique. The exclusion criteria were patients with incarcerated or strangulated hernias and a history of right iliac fossa (RIF) pain.

Data Collection

A total of 90 medical records of patients diagnosed with inguinal hernia that underwent Lichtenstein procedure was collected. Analysis was retrospectively conducted, dividing patients into twogroups, group A consists of patients using heavyweight mesh with a non-absorbable polypropylene mesh on a dimension of 7.5 cm x 15 cm for hernia repair and group B consists of patients using lightweight mesh with a partially absorbable polypropylene mesh on a dimension of 6 cm x 11 cm for hernia repair. Demographic data and clinical manifestations of patients were collected from the medical record. Signs and symptoms that were collected are early postoperative pain at seven days, infection, and the formation of seroma. The pain score was assessed by the Visual AnalogueScale (VAS) on day 1 until 7 by the nurse during each visit at the postoperative room. Pain score was classified as mild VAS score1-3, moderate VAS score 4-7, and severe VAS score >7. Details regarding preoperative characteristics such as intraoperative findings, type of anesthesia, and postoperative complication wererecorded on the medical records.

Statistical analysis

The collected data was analysed and compared using Pearson's Chi-squared test.

The measurements were done by using the Statistical Package for Social Sciences (SPSS) version 24.0. A *P* value <0.05 was considered as statistically significant for all analyses.

Results

From January 2018 to December 2019, 90 patients were diagnosed with inguinal hernia that perform Lichtenstein technique for their hernia repair from Rumah Sakit Siloam Karawaci Lippo Village and Rumah Sakit Umum Siloam were included in the study. All of the patients were consecutively examined for 1 year after surgical operation.

From a total of 90 patients, they were divided into two groups. Group A consists of 45 patients using heavyweight mesh for hernia repair and group B consists ofpatients using lightweight mesh for hernia repair. The demographic characteristics of both groups can be seen in Table 1.

All patient's medical records that were used in this study were Indonesians and aged between 6 until 79 years old. The majority ofpatients with inguinal hernia were male (87.8%) rather than female (12.2%) patients, with most of them being above 60 years old.

All patients included in this study have beendiagnosed with inguinal hernia through history and physical examination findings. Patients usually come with groin pain, stretching of the tissue around hernia that can lead to a burning sensation in the groin. Patients may experience a dragging sensation in the groin, especially at the end of the day after doing activities a whole day. Inguinal hernias are easily diagnosed through valsalva maneuver where the patient was asked to strain down while the physician observes for bulges. All patients from both groups had done hernia repair using Lichtenstein technique with lightweight mesh and heavyweight mesh under general anesthesia.

Table 1. Patient characteristics

	Group A Heavyweight mesh n (%)	Group B Lightweight mesh n (%)
Gender		
Male	37 (82.2)	42 (93.9)
Female	8 (17.8)	3 (6.8)
Male > 60 years old		
Mild pain	8(17.8)	15 (33.3)
Moderate pain*	6 (13.3)	1 (2.2)
Female > 60 years old		
Mild pain	3 (6.8)	1 (2.2)
Moderate pain*	0	0

*:p value <0.05

A total of 37 male patients from group A were collected in this study. We found that 8 patients (17.8%) had early mildpostoperative pain and 6 patients (13.3%) had early moderate postoperative pain after inguinal repair using Lichtenstein technique.3 female patients (6.8%) out of 8 female patients from group A had early mild postoperative pain after hernia repair.

Group B consists of 42 male patients (93.9%) and 3 female patients (6.8%). Atotal of 15 male patients (33.3%) had early mild postoperative pain and one patient (2.2%) had early moderate postoperative pain after inguinal repair using Lichtenstein technique. One female patient (2.2%) had early mild postoperative pain after hernia repair. No female patients from both groups had moderate pain with VAS score 4-7 after inguinal hernia repair for 7 days.

Table 2. Early pain incidence at 7 days

Early pain VAS score	Number	Percentage
Mild (1-3)	37	41.1
Moderate (4-6)	7	7.7
Severe >7	0	0

When Patients Were Divided Into Groups OfMild VAS (1-3), Moderate VAS (4-7), AndSevere VAS (>7) score, it was found thatthe majority of patients in Rumah Sakit Siloam Karawaci Lippo Village and RSUhad early mild postoperative pain for a totalof 37 patients (41.1%) and 7 patients (7.7%) had moderate postoperative pain after inguinal hernia repair. No patients from bothgroups had severe postoperative pain after inguinal hernia with Lichtenstein technique (Table 2).

During the study, there were two patients in group A who had a formation of wound seroma after the operation and signs of infection. However there are no statistically differences between the two groups (p value = 0.50). No recurrence of inguinal herniawere reported in either group after a year of follow up. (Table 3).

Table 3. Surgical outcomes in both groups

	Group A Heavyweight mesh n (%)	Group B Lightweight mesh n (%)	P Value
Seroma	2 (4.44)	1 (2.22)	0.50
Recurrence	0	0	1.0
Wound Infection	2 (4.44)	1 (2.22)	0.50

*:p value <0.05

Discussion

Since the Lichtenstein technique was introduced for hernia repair, the recurrence rate has dropped sharply.[9] According to scientific literature, hernia mesh repair has proven successful in reducing the frequency of hernia recurrence. Polypropylene heavyweight mesh has become the standard prosthetic mesh for inguinal hernia repair. However, because of its low biocompatibility, it causes foreign body reaction and chronic discomfort after surgery such as pain.[10] To minimize the effects of those reactions, biodegradable mesh was invented to lower the content of polypropylene and is partially absorbable to maintain strength and rigidity after wound healing.[11]

For those reasons, this study focused on the early pain assessment and discomfort of patients rather than the recurrence. To measure early pain, we used VAS tomeasure the severity of pain after surgery. Based on the results, we found that partially absorbable lightweight polypropylene mesh is safe for inguinal hernia repair and improved the quality of life after surgery especially for male patients above the ageof 60 years old.

According to this research, the frequency of early postoperative complications (seromaand wound infection) in both groups were the same. All of these results are in accordance with other researchers.[3,12,13]

There were no significant differences between both groups for inguinal hernia recurrence. Findings in this research did not differ results from other investigations.[8,14,15] However, the work of O'Dwyer, et al concluded that hernia recurrences were statistically significantly higher in lightweight mesh groups compared to heavyweight groups after three years after surgery. This research couldn't correlate with the frequency of hernia recurrence because each patients were observed for a total of one year after surgery.[12] H.Paajanen's scientific research compared lightweight meshes against heavyweight meshes and found that none of both groups had any differences in reducing pain after surgery under local anesthesia. However, in this research, all surgical procedures were done under general anesthesia.[7]

Mesh was introduced to help repair inguinal hernias. However, it is also a risk factor for development of postoperative pain. Early postoperative pain after inguinal herniorrhaphy with Lichtenstein technique can be defined as pain that only exists after surgery in less than three months. Symptoms include unpleasant feelings such as burning sensation in the surgical area. Some factors that can contribute to the pain are damage to nerves, psychological factors, and even a patient's fear.

Mechanisms such as nerve entrapment or nerve trauma are the most common cause for postoperative pain from this inguinal hernia repair.[6] Based on our findings, lightweight mesh has proven to reduce postoperative pain in male patients at the age above 60 years old rather than the use of heavyweight mesh. Although lightweight mesh has shown to reduce early postoperative pain, recent studies have reported that in the long-term follow up, the difference between the usage of lightweight mesh and heavyweight mesh are significantly reduced.[16,17] Over time, the pain tolerance of patient's will increase until the disappearance or relief from their symptoms in which the act of surgical exploration can be avoided. The new biosynthetic lightweight mesh provides better tissue integration, collagen deposition, and a sustainable neovascularization compared to polypropylene heavyweight meshes.[7] Our findings are similar to other scientific articles where lightweight mesh significantly reduces early postoperative pain.[8,9,16]

Conclusion

This study has proven that the use of lightweight mesh has the advantage in reducing early postoperative pain from herniorrhaphy using Lichtenstein technique rather than heavyweight mesh in menabove 60 years old. Surgical techniques with a systematic identification and preservation of inguinal region nerves should be considered to prevent chronic groin pain. Treatment for postoperative painis done by drugs such as steroid or other steroid-like drugs, anesthetics drugs, and surgical exploration of the groin with total neurectomy of all three nerves.

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Failure Factors & Prediction Model of Indonesian Medical Doctor Proficiency & Competency Test (UKMPPD) within COVID-19 Pandemic

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Citation: Salim Jonathan, Arnindita Jannatin Nisa,Tandy Sutiono, Wibisono Jacobus Jeno, Wibisono Maria Georgina. Failure Factors & Prediction Model of Indonesian Medical Doctor Proficiency & Competency Test (UKMPPD) within COVID-19 Pandemic. Medicinus. 2022 February; 10(1):16-26
Keywords: UKMPPD; Indonesia; Failure factor; COVID-19; ABO blood
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Online First : March 2022

Abstract

Background: Coronavirus Disease 2019 drastically modulate the healthcare world. The pandemic's immense transmission and lethality rate enforce the Indonesian Medical Doctor Proficiency & Competency Test to discard practical measures and rely only on a written exam. These with pandemic social and physical restrictions impede prospective doctors' learning opportunities leading to easier failure. Henceforth, the present study has high urgency to identify and manage failurefactors, especially in the pandemic.

Methods: The cross-sectional study examines 75 clinical medical students through purposive analysis with an online questionnaire in August 2021. Data are analyzed with Chi-Square, Mann-Whitney, and binary logistics.

Result: Respondents have an average age of 24.15 (1.322) years old, majorly female (82.7%), and pass as first takers (86.7%) with 1.27 (0.949) off-campustutelage. The significant factors for the test failure are depression and economic status. The study developed a failure prediction model with the area under the curve 0.845, cut-off 366.5, 80.0% sensitivity, and 84.6% specificity.

Conclusion: Intrinsic, extrinsic, and academic factors have significant roles in the failure outcome. For this reason, preparation is crucial not only among individuals but also institutions. The study also provides feedback about the importance of mental health and economic status for Indonesian medical students.

Introduction

The global community has declared and agreed to the right to equitable health among all individuals. World Health Organization (WHO) 1946 constitution depicts that the most fundamental human right is unrestricted access toward the highest healthcare standards among all individuals.[1] Health is defined as a state of complete physical, mental, and social well-being along with the absence of disease or disability. Moreover, the 1948 Universal Declaration of Human Rights explains that the healthcare right also includes primary living supports, namely: food, clothing, shelter, health, social services, and security in the event of employment termination, illness, disability, divorce, old age or other events beyond the individual's control.[2] Indonesia, as the 4th most populated country, has a firm stance in the equity and healthcare of its citizens. The Republic of Indonesia 1945 Constitution states thateveryone has the right to live in physical and spiritual prosperity, have a residence, have a good and healthy living environment, and have the right to obtain healthcare services.[3] Every individual has a fundamental right to healthcare, including healthcare workers. Medical doctors reported having several barriers in accessing health facilities: embarrassment, peer pressure, feeling of self-care failure, over/under/misdiagnosis anxiety, time and

financial limitation, social and occupational stresses, etc.[4] Fortunately, it is observed that medical doctors have lower mortality rates compared to other professions. Medical professionals have an average age of death at 78.9 (14.1) years, which is higher than the global community (73.5 years) and Indonesian citizens (men: 70 years & women: 74 years). [5–7] Yet, among the professionals, depression presents within 27% of medical students, 29% of health administrative personnel, and 60% of clinical practice doctors.[8] The alarming rate of mental issues signifies that greater emphasis should be sown on the health of medical professionals.

Indonesia has 190075 registered doctors with the Indonesian Doctors Association (IDI), forming a doctor-to-population ratio of 0.4:1000.[9,10] The rate is still very distinct from the WHO recommendation of 1:1000, and the 2018 global annual rate of 1.566:1000.[11] Thereafter, the spread ofmedical doctors in Indonesia is also not equal. 57.2% of medical personnel, for instance, are located within Java.[11] These pose a massive gap in healthcare that threatens equitable health. The imbalance of doctors to the population triggers an overwhelming burden within the healthcare personnel and system. Consequently, burnout is on the rise, and medical performance is depleting. These, with the drastic escalation of patients due to the Coronavirus Disease 2019 (COVID-19) pandemic, conceive an atrocious situationof national pre-healthcare collapse (i.e., the circumstances where healthcare within the country cannot proceed as expected due to crisis in its implementation, system, workforce, or logistic).

Multidisciplinary efforts to increase the number of medical doctors in Indonesia are made through establishing educational programs at new universities. Although having sixty-seven faculty of medicine within universities across the nation, geographicfactors and distinct local tradition sometimes inflect differences in the exertion of the medical curriculum. Subsequently, the national standardization of competence among the prospective doctors is carried out through the Indonesian Medical Doctor Proficiency & Competency Test (UKMPPD) to mitigate the after-mentioned problem. All materials tested in the UKMPPD are factored in the 2019 Indonesian National Standard for Medical Profession Education (SNPPDI) compiled by the Indonesian Medical Council (KKI). The exam consists of two stages: a computer-based test (CBT) that tests theoretical measures and an Objective Structured Clinical Examination (OSCE) that tests clinical skills. Since the 2020 and the COVID-19 pandemic, UKMPPD is only carried out with the CBT stage.

Dwiyanti et al. affirmed the relationship between UKMPPD results with the cumulative grade point average (GPA) and pre-UKMPPD selection test scores.[12] While a study by Khadafianto in Yogyakarta found that aspects in medical assessments (i.e., written exams, Objective Structured Long Examination Record (OSLER), and the Mini-Clinical Evaluation Exercise (mini c- ex)) were associated with UKMPPD CBT outcome.[13] Similarly, score from Clinical Integration Assessment (CIA), Benchmark (BM), and *Asosiasi Institusi Pendidikan Kedokteran Indonesia* tryout can be taken as valid predictors for UKMPPD CBT score.[14]

UKMPPD results are influenced by various factors, including demographics, mental health, and academic performance of examinees. Meanwhile, changes in medical education due to physical and social restrictions during the pandemic

indirectly play a significant role in the outcome of UKMPPD. From August 2020–May 2021, the UKMPPD failure rate showed a polarizing trend from 17.63% to 32.48%.[15] As far as the author's knowledge, no previous studies have observed the UKMPPD failure factors and prediction models. The current study aims to analyze UKMPPD failure factors during the COVID- 19 pandemic.

Methods

Study Design

The present study utilizes a cross-sectional design in September 2021. The current study followed the International Review Board (IRB) and Helsinki Declaration ethical protocols by obtaining clinical ethical approval from Pelita Harapan University Ethics Committee with certification 163/K- LKJ/ETIK/IX/2021. The respondents have agreed, understood, and signed the informed consent before continuing the study. The sample size is computed through 5% alpha and 80% power.

Subject Collection & Enrollment

Using an online questionnaire on Google Form, the data are gathered through purposive sampling of the medical profession students from all medical faculty universities around Indonesia. All Indonesian respondents over 18 years old and who have taken the UKMPPD at least once can fill the online questionnaire distributed through Line, WhatsApp, Telegram, Kaskus, and other social media or forums.

Data Measurement

The online questionnaire is divided into four sections: demographic, UKMPPD, depression, and sleep quality. The level of depression is measured through part of the Depression Anxiety and Stress Scale (DASS-21), whereas the sleep quality uses Pittsburgh Sleep Quality Index (PSQI). Both instruments have decent validity and reliability for their capabilities.

Statistical Analysis

The study analyzes respondents' data through descriptive statistics, while the UKMPPD failure factors through Chi-Square, Mann-Whitney, and binary logistics. Significance describes as present in p-value < 0.05.

Result

The data collection in September 2021 generates 75 qualified respondents with a 100% participation rate which are medical university students with an average age of 24.15 (1.322) years old, predominantly female (82.7%), and pass the UKMPPD (86.7%) as the first takers (86.7%). The respondents claim to adopt studying at 1.27 (0.949) off-university academy in preparation for the exam. Likewise, it was observed that they have disproportionate mental health and sleep quality, where 22.6% have depression, and 70.7% have poor sleep quality. Other features are portrayed in **table 1**.

Tabel 1. Demographic Characteristics

Characteristics	Frequency	
	n (%)	X (SD)
Age		24.15 (1.322)
Gender		
Female	13 (17.3)	
Male	62 (82.7)	

Marriage status		
Never	64 (85.3)	
Married/Divorced	11 (14.7)	
Blood Group		
A	15 (20.0)	
B	18 (24.0)	
AB	15 (20.0)	
O	27 (36.0)	
Economic Status		
≥ average	52 (69.3)	
≤ average	23 (30.7)	
Occupation		
No	19 (25.3)	
Working	56 (74.7)	
Family of Doctor		
Yes	23 (30.7)	
No	52 (69.3)	
Grade Point Average		3.50 (0.415)
Study Duration		
Normal	61 (81.3)	
Longer	14 (18.7)	
Exam Status		
First-Taker	65 (86.7)	
Re-Taker	10 (13.3)	
Off-Campus Tutelage		1.27 (0.949)
Exam Location		
Own University	59 (78.7)	
Other University	16 (21.3)	
Depression Level		6.77 (5.298)
Normal	58 (77.3)	
Mild	6 (8.0)	
Moderate	10 (13.3)	
Severe	1 (1.3)	
Extremely Severe	0 (0.0)	
Sleep Quality		9.20 (3.956)
Good	22 (29.3)	
Poor	53 (70.7)	
Exam Result		
Pass	65 (86.7)	
Fail	10 (13.3)	

Abbreviation: SD: standard deviation

Numerous factors have a significant effect on the potential failure of UKMPPD (**table 2**). On intrinsic factors, students who failed were 2.02 years older (p: 0.009), and the majority had AB blood type (80.0%). On the other hand, UKMPPD failure is also based on extrinsic factors where it is more commonly found in students who are married or divorced (70.0%), have lower middle economic status (80.0%), working (80.0%), and come from a family of doctors.(70.0%).

Table 2. Failure Factors of UKMPPD

Factor	Pass UKMPPD		OR CI95	P Value
	Yes	No		
Age	23.88 (0.801)	25.90 (2.424)		0.009
Gender			1.227 (0.229-6.583)	0.552
Female	54 (83.1)	8 (80.0)		
Male	11 (16.9)	2 (20.0)		
Marriage status			35.583 (6.573-192.644)	< 0.001
Never	61 (93.8)	3 (30.0)		
Married/Divorced	4 (6.2)	7 (70.0)		
Blood Group				< 0.001
A	14 (21.5)	1 (10.0)		
B	17 (26.2)	1 (10.0)		
AB	7 (10.8)	8 (80.0)		
O	27 (41.5)	0 (0.0)		
Economic Status			13.333 (2.552-69.665)	0.001
≥ average	50 (76.9)	2 (20.0)		
≤ average	15 (23.1)	8 (80.0)		
Occupation			19.636 (3.661-105.325)	< 0.001
No	54 (83.1)	2 (20.0)		
Working	11 (16.9)	8 (80.0)		
Family of Doctor			0.140 (0.032-0.606)	0.007
Yes	16 (24.6)	7 (70.0)		
No	49 (75.4)	3 (30.0)		
Grade Point Average	3.54 (0.412)	3.29 (0.385)		0.051
Study Duration			19.333 (4.049-92.319)	< 0.001
Normal	58 (89.2)	3 (30.0)		
Longer	7 (10.8)	7 (70.0)		
Exam Status			576.000 (33.044-10040.563)	< 0.001
First-Taker	64 (98.5)	1 (10.0)		
Re-Taker	1 (1.5)	9 (90.0)		
Off-Campus Tutelage	1.37 (0.894)	0.60 (1.075)		0.006
Exam Location			14.519 (3.161-66.694)	< 0.001
Own University	56 (86.2)	3 (30.0)		
Other University	9 (13.8)	7 (70.0)		
Depression Level	5.75 (4.187)	13.40 (7.058)		0.001
Normal	55 (84.6)	3 (30.0)		< 0.001
Mild	5 (7.7)	1 (10.0)		
Moderate	5 (7.7)	5 (50.0)		
Severe	0 (0.0)	1 (10.0)		
Extremely Severe	0 (0.0)	0 (0.0)		
Sleep Quality	8.45 (3.540)	14.10 (2.961)		
Good	22 (33.8)	0 (0.0)		< 0.001
Poor	43 (66.2)	10 (100.0)		0.024

Meanwhile, the academic component has an essential relation to UKMPPD. Students with more prolonged professions, re-takers status, little to no off-university tutoring, and those taking exams at other universities are at higher risk of not passing the UKMPPD ($p< 0.05$). Additionally, the level of depression and sleep quality also contributed to the failure of UKMPPD ($p < 0.001$ and 0.024). All students who did not pass had poor sleep quality, and 70.0% of failed students had depression.

Table 3. UKMPPD Failure Factors Regression

Factor	Estimate	Odds Ratio		CI_{95}	p-value
		Crude	Adjusted		
Age	0.584		1.794	0.491-6.558	0.377
Marriage Status	-0.897	35.583	0.408	0.007-23.464	0.664
Economic Status	4.231	13.333	68.761	1.103-4287.859	0.045
Family of Doctor	-2.767	0.140	0.063	0.002-1.911	0.112
Off-Campus Tutelage	0.404		1.498	0.303-7.398	0.620
Exam Location	3.204	14.519	24.622	0.735-824.872	0.074
Depression Score	0.435		1.546	1.068-2.236	0.021

Abbreviation: CI: confidence interval

T**able 3** shows that through binary regression controlling for factors, significance is only observed in economic status (odds ratio (OR): 68,761, 95% confidence interval (CI_{95}): 1.103-4287,859, p: 0.045) and depression score (OR: 1.546, CI_{95}: 1.068-2.236, p: 0.021), while other factors are just confounders. The UKMPPD failure prediction was also developed into the following probability equation:

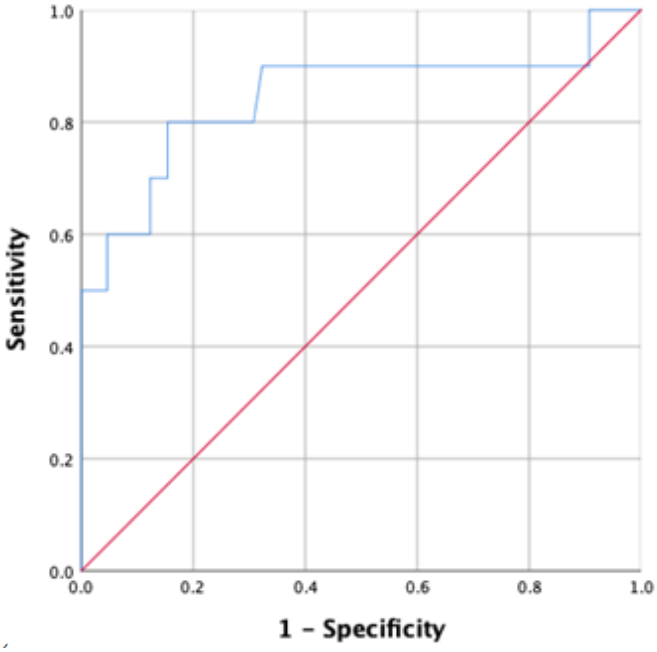
UKMPPD Failure Probability =

$$1/(1+e^{-(-22.055+0.584*\text{age}-0.897*\text{marriage}+4.231*\text{economy}-2.767*\text{family of doctor}+0.404*\text{tutor}+3.204*\text{exam location}+0.435*\text{depression score})})$$

Nevertheless, the after-mentioned equation is entirely unsuitable for daily application. Thus, the UKMPPD failure prediction model was made based on a regression score with an area under the curve 0.845, cut-off 366.5, sensitivity 80.0%, dan specificity 84.6%. (**table 4**). The probability of contrasting different diagnostic rates of UKMPPD failure can be seen in **figure 1**.

Table 4. UKMPPD Failure Prediction Model

Factor	Multiplier/Selection	Score
Age	Age *4	
Marriage status	Married/Divorced: 0	
	Never Narried: 1	
Economic Status	≥ average: 0	
	≤ average: 21	
Family of Doctor	Yes : 0	
	No: 13	
Off-Campus Tutelage	Tutelage number *1	
	Own University: 17	
Exam Location	Other University: 0	
Depression Score	Score *28	



Gambar 1. ROC Curve of UKMPPD Failure Model

Discussion

Reflecting upon the data collection on 75 Indonesian prospective medical doctors in August 2021, the UKMPPD passing rate is 86.7%. This is in line with the findings of Intan et al. with an 89.09% passing rate in February–May 2019.[16] The rate is satisfactory as it exceeds the national rate from August 2020 to May 2021 (67.52-82.37%).[15]

The intrinsic factor certainly has a profound role in this study. There was an age difference of 2.02 years old between those who failed and passed the UKMPPD. The failure minority also has mostly AB blood type. Mahat et al. corroborate the notion that medical students with AB blood had the lowest scores compared to others (60.3 (10.73)).[17]

ABO blood group was not directly related to the failure. However, it determines the personality in facing challenges or exams and learning methodologies. Blood typing has a significant correlation with his/her ability to be understood (p: 0.002), multiple personality ($p < 0.001$), optimism (p: 0.002), big-hearted ($p < 0.001$), and genius-look ($p< 0.001$).[18,19] Different personalities when learning materials and tackling exams contribute more to the passing rate than expected. For example, extroverted people can help teach their slow peers; further, optimism may become a “temporary” cure for people with mental issues (i.e., depression, anxiety, stress, and panic) agony. Subsequently, these relationships between ABO and UKMPPD indicate differences at the genetic level.

Nevertheless, significance was also found in extrinsic factors: sleep quality, marital status, occupation, and family doctor. Marriage comes with various responsibilities. With the increase in family members, married individuals must invest more time in their partners and households. This reduces the time and concentration of medical students to study and pass the UKMPPD. Beard et al., in their regression, found that marital status had a negative significance on individual academic performance (-0.36 and $p < 0.05$).[20]

For similar reasons, employment status renders someone to have lower academic performance. A recent study by Douglas et al. found that at least 62% of undergraduate students have a job.[21] This situation triggers a decrease in concentration and study time in each individual. Mardelina and Muhson described an essential difference between work, learning activities, and achievement (Δ: 0.16 and 0.10 at p: 0.01).[22]

Moreover, the failure in UKMPPD is also regulated by the quality of sleep. Although not directly related to sleep quality (p: 0.875), academic performance was correlated with components of sleep willingness, time to sleep, bedtime, and hypnotic state ($p < 0.05$).[23] Problems in sleep will interfere with individual academics due to the role of sleep in memory consolidation, concentration, awareness, and stress control. During the rapid eye movement (REM) cycle, slow 10-16 Hz brain waves bridge memory integration between the hippocampus and the long- term memory in the neocortex.[24] These waves occur only during sleep, where there are fluctuations in synchronization of membrane potential among the hyperpolarization and depolarization of cortical neurons.[25] Moreover, inadequate sleep will also rob the energy for individuals to enact their daily activities and studies.People with less than needed sleep (sleep deprivation) can solicit alertness-wakefulness concern (e.g.,

reduced concentration, slower thought process, and depression) while also simultaneously manifesting physical problems (e.g., hypertension, infection due to impaired immunity, obesity, decreased sex drive, andcardiovascular diseases).

Off-campus tutelage, exam locations, participant status, and length of study certainly play a substantial role in the UKMPPD. Individuals with adequate tutoring have more adequate opportunities and learning materials. Abulyatama University medical students had 54.3% passing students who took off-campus tutelage, while 22.9% failed students did not.[26] The tutelage has a high bearing because it enables the prospective medical doctors to learn more UKMPPD materials, especially hand-picked high yield materials with cutting-edge learning methods specific to each tutelage, for example, tacky mnemonics, distinct keywords, and high prevalent topics.

Further, the location of exams at other universities and re-taker status put pressure on individuals. The participants had to remember the UKMPPD material and the layout of the new exam room, and the burden from mental disorders and peers. The 90.0% rate of failure in re-takers is in line with the 2019 study, where it was similarly found that 77.78% of all those who failed UKMPPD were re-takers.27 Nonetheless, only economic status and depression scores were significant after multivariate regression control, while other factors are proven to be confounders.

The relationship between depression and individual academic ability has been examined in numerous studies. Ikhsan et al. found a correlation between individuals' depression levels and passing the block exam (p: 0.004).[28] Meanwhile, Ekawati et al. found that 23.80% of students were depressed doing their thesis.[29]

Depression in prospective medical doctors can be triggered either by internal factors (genetic and experience) or external factors (peer pressure, academic pressure, illness, drugs, and hormones). The workload and academic burden within the medical profession certainly deepen the depression level in every individual. Riandini et al. found that excessive workload for medical students in the pediatrics department was significantly associated with academic stress (OR: 8.569, CI95: 1.914-38.350, p: 0.005).[30] Incidentally, depression within clinical students was different from that of pre-clinical medical students (p:0.018), in which there were 42.5% with mild depression and 5.0% with major depression.[31]

These hormonal instabilities will negatively modulate individuals' perceptions of themselves and their surroundings. They will feel isolated, difficult to enjoy life, and interfere in daily activities. Amotivation, anhedonia, and irritability due to this dopamine disorder concoct difficulties in learning, sleeping, eating, and activities leading to academic setbacks and UKMPPD failure. A study at the Malang Islamic University corroborates these findings by showing a solid and significant correlation between depression and the UKMPPD passing rate (r: 0.675 and $p < 0.001$).[27]

On the other hand, a prominent role for the UKMPPD comes from economic status. Thecost of continuing studies in the medical major is not negligible. Based on thegovernment regulations by the Minister of Research, Technology and Higher Education (Permenristekdikti) No. 18 of 2018 article 26, institutions may determine their educational costs but have to remain

affordable and within the range defined by the government.[32] If the particular institution adopts class c fees in selecting operational cost programs, then the education fee ranges from 150-300 million rupiah. Gadjah Mada University charges a single tuition fee (UKT) for medical majors ranging from 45-65 million rupiah for undergraduates and professionals based on the Gadjah Mada University Chancellor Decree of 515/UN1.P/KPT/HUKOR/2021.[33] The after- mentioned cost does not include fees of the semester, buildings, laboratories, internships, and many others.

Consequently, financial maturity is absolute for individuals who study medicine and their families. Individuals from lower-middle- income families may view these costs as a challenge that disrupt learning. A part-time job or working with parents to earn an income dreadfully reduces study time, interferes with concentration, and consumes energy. Economic incapacity additionally restricts a person from using technology or tutoring to achieve academic success. Razak et al. portray that students' financial conditions affect academic performance tremendously (B: 0.201 and $p < 0.001$).[34] Meanwhile, some medical students may opt to flunk the UKMPPD not to become a financial burden to themself and their families.

On the contrary, the present study bridges individuals and institutions with the curriculum of the medical profession and the need for doctors in Indonesia. Urgent and strict revisions on the medical curriculum amid the current COVID-19 pandemic are vital. Even actions such as identifying the influencing factors of UKMPPD may be the ray of light for Indonesia to see more competent doctors in the future, which can help fight the pandemic. The upsurge of decent medical doctors within the fourth most populated Southeast Asia archipelago hoped to restore the healthcare system, the equitable spread of healthcare personnel, and the medical trust of the citizens to the doctors.

However, the study has limitations on its design, the minimal number of samples, and the use of online questionnaires, leading to recall and selection bias. Yet, these things cannot be denied or salvaged because of the impact of the COVID-19 pandemic restrictions. Further studies on the topic may include greater sample size and prospective nature to open up a more accurate frontier in determining the malefactor failure factors and finally giving Indonesia the healthcare system it needs.

Conclusion

Various intrinsic, extrinsic, and academic factors have significant roles in the failure of UKMPPD. For this reason, UKMPPD preparation is crucial among individuals and institutions. The study also provides feedback to individuals and institutions about the importance of mental health and economic status for Indonesian medical students.

Disclaimer

There is no conflict of interest within the authors, nor between the authors to any external body. All funding incurred within the present study is financed through the authors' accounts without any help from an outside group or grants from an independent party. Further, the authors declare no acknowledgment present.

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The Correlation of Insomnia and Anxiety in Students of The Faculty of Medicine, University of Pelita Harapan

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Citation: Dhinata Kinley, Lumbuun Nicolaski. The Correlation of Insomnia and Anxiety in Students of The Facultyof Medicine, University of Pelita Harapan**.** Medicinus. 2022 February; 10(1):27-33
Keywords: Anxiety; Insomnia; Stress; Childhood Trauma; Medical Students
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Abstract

Background and Aim: Insomnia and anxiety are common disorders with high prevalence rate especially in medical students. Moreover, many confounding factors playing a role in influencing anxiety. Most studies does not include or measure other confounding factors of anxiety into the analysis. This requires research which examines insomnia and anxiety assessing the contribution of the factors influencing anxiety.

Methods: A cross-sectional study methodology with linear regression analysis on a sample of students from the Faculty of Medicine, University of Pelita Harapan using the DASS-21 questionnaire to assess anxiety and ISI to assess insomnia.

Results: Prevalence rates of insomnia was 34.29% and anxiety 32.38% in Pelita Harapan University medical student. From the results of the bivariate linear regression, a weak relationship between insomnia and anxiety ($r = 0.322$; $p = 0.000$) is seen. In multivariate results, there were confounding stress variables ($r = 0.565$; $p= 0.000$) and trauma ($r = 0.250$; $p = 0.005$) which contributed greatly to anxiety (In order of largest).

Conclusion: There is a weak correlation and anxiety. Moreover, high prevalence rate of anxiety in medical students may be contributed heavily not only by insomnia but also stress and childhood trauma.

Introduction

Anxiety is the most common psychiatric disorder and arises because of tension, fear, or discomfort stemming from the anticipation of internal or external danger situations. In the world, anxiety has reached a prevalence rate of 13.6-28.8% and 15.2% in Indonesia alone which in a period of 5 years, the number of anxiety cases rose by 20% and is predicted to continue to increase.[1–3] However in medical students, anxiety rate reaches 35.2%; much higher than the general population.[4] The high prevalence of anxiety in the general population and medical students can be supported by the many precipitating factors or etiology of anxiety itself. This includes gender, chronic illness, personal and family depression, stress, grades, academic years and childhood trauma.[5,6]

Insomnia is a disorder of dissatisfaction with the quantity or quality of sleep due to difficulty or inability to maintain sleep, fall asleep or return to sleep.[7] Insomnia is the most common sleep disorder where as much as 10-15% of the world's adult population has been diagnosed with primary insomnia with 1/3 of reporting dissatisfaction with sleep. In Indonesia alone, 33.3% of the population suffers from mild insomnia and 11.0% of the population with clinically significant insomnia symptoms.[8,9] A prevalence of 60% in medical students in Indonesia was also found.[10]Increased risk of developing mental disorderssuch as GAD or depression; and chronic diseases, is also more visible in insomnia patients where coronary heart disease, hypertension, diabetes and obesity are among the biggest causes of death in Indonesia and in the world.[11]

There have been many studies that prove anxiety as a cause of insomnia [12,13] However, it is also known that insomnia can also cause anxiety, although research on this is still new and scanty.[14–16] Moreover, there are very few national studies addressing anxiety with insomnia in the medical student population. Even from several national studies that were found, no one had studied insomnia with anxiety in a multivariate manner to calculate anxiety confounding variables.

Due to doubts, lack of research and the magnitude of the impact of insomnia and anxiety on Indonesian medical students, researcher wanted to further dissect the correlation between insomnia and anxiety in medical student. This study is structured as a positive effort to increase the contribution and form a foundation for next research on insomnia with anxiety.

Methods

Ethical Considerations

Researchers maintain sample data confidentiality and apply for ethical permission to the ethics committee of the Faculty of Pelita Harapan University with protocol number 52122020.

Study Design and Sampling

A cross-sectional study of 105 medical students from the University of Pelita Harapan carried out in January 2021-March 2021. Samples are selected non randomly using purposive sampling.

Inclusion Criteria: Students of the Faculty of Medicine, Universitas Pelita Harapan batch2016-2020.

Exclusion Criteria: Long-term use of medication such as allergy medications, antipsychotics, antidepressants, cortico-steroids, or selective serotonin reuptake inhibitors (SSRIs).

Data Collection

Data is collected by self-administered questioner and phone interview (for DASS-21). Subject information about initial (Name), age, gender, medical year, GPA, chronic disease, family history of depression, childhood trauma and ISI (Insomnia Severity Index), are collected by self-administered questioner while DASS-21 which contains depression, anxiety and stress severity questions are phone interviewed after self- administered questioner is completed.

In Insomnia Severity Index (ISI), insomnia is categorized according to the severity scale into several categories. ISI contains only 7 question points which could easily be filled out and interviewed by researchers without a psychiatric or present. With a Cronbach value of 0.988, the ISI can be guaranteed its reliability and its validity has also been tested in the Indonesian population.[17] The ISI itself has 7 question points, each of which has 5 answers to choose from, namely: none, a little, moderate, severe, and very severe. each answer has a different value; none (0 points), little (1 point), moderate (2 points), severe (3 points) and very severe (4 points). From all the answers to the ISI questions, the scores are added up to produce a numerical value on a scale of 0-28. The higher the number, the more severe the degree of insomnia.[18]

Depression Anxiety Stress Scales (DASS) is a tool used to assess the depression, anxiety, and stress. DASS is often used for research due to its validity, reliability, ease of assessment or implementation.[19] Clinically, It can provide a complementary role in clinical diagnosis. DASS could help detecting the severity of depression, anxiety and stress in patients and progression of the disease, medication or treatment given. In research, the DASS can be used with both lay and professional examiners and is suitable for all ages.[20] There are 2 DASS questionnaires that have been translated into Indonesian, namely: DASS-21 and DASS-42. In addition to being tested for validity, DASS has a high reliability, Cronbach's alpha of 0.912 for DASS-21[21] and 0,948 for DASS-42[22]. DASS-21 contains 21 different questions with 7 questions assessing each scale. These scales are then added

together to produce numerical values that can be interpreted into 5 ordinal scales, namely, normal, mild, moderate, severe and very severe.[20,23]

Data Analysis

Statistical analysis is carried out using SPSS version 24. Sample descriptive of variables were shown using percentage (for prevalence), median and IQR (Interquartile Range). Insomnia and anxiety prevalence are calculated using descriptive data and summarized in percentage.

Bivariate analysis was conducted to determine correlation between insomnia and anxiety using simple linear regression determining r and r^2.

Multivariate analysis of variables uses multiple linear regression to determine cofounders and contribution size. However before determining cofounders, variables are eliminated from the highest partial significancy to meet statistical assumptions. This assumption includes model's total significance of <0.05 and variable partial correlation of <0.2. to determine contribution size of variable towards anxiety, partial correlation is used.

Linearity, homoscedasticity, collinearity, existence assumption are all met. However, normality and independence assumption are not met. Therefore, the author uses simple bootstrapping of 3000 sample using Meisner twister number generator to assume normality of data.

Results

Characteristics of participants

A total of 105 research samples met researchcriteria. Most of the study samples were women. Although relatively even distribution of academic year 1, 2, 3, only 10 (9.52%) samples came from year 4 and 6 (5.71%) from year 5. A median age of 20 (19–20) and an average GPA of 3.3 (3–3.5). This may indicate a relatively small spread or variation in age and GPA in sample population. There were 6 (5.71%) students who suffered from chronic diseases and did not use medications as listed in the exclusion criteria. There are 5 (4.76%) samples who has depression in the family and 15 (14.29%) suffering from childhood trauma.

Table 1. Demographic Sample

	n	%	Median (IQR)
Gender			
Female	74	70.48%	
Male	31	29.52%	
Academic Year			
2020	28	26.67%	
2019	24	22.86%	
2018	37	35.24%	
2017	10	9.52%	
2016	6	5.71%	
Age			20 (19–20)
GPA			3.3 (3–3.5)
Chronic Disease			
No	99	94.29%	
Yes	6	5.71%	
Depression in Family			
No	100	95.24%	
Yes	5	4.76%	
Trauma			
No	90	85.71%	
Yes	15	14.29%	

Prevalence of Insomnia and Anxiety

Of the 105 research samples, there were 36 samples (34.29%) affected by insomnia and 34 samples (32.38%) affected by anxiety.

Table 2. Prevalence of Insomnia and Anxiety

	n	%
Insomnia		
ISI 0-7 (-)	69	65.71%
ISI 8-28 (+)	36	34.29%
Anxiety		
DASS-21 Anxiety 0-3 (-)	71	67.62%
DASS-21 Anxiety 4-21 (+)	34	32.38%

Relationship between Insomnia and Anxiety

To find out the conclusion of the research hypothesis, it is necessary to do

a bivariate linear regression analysis between insomnia and anxiety. Seen in the summary model table, correlation coefficient R is 0.322 with p-value of 0.000. This indicates a weak degree of correlation between insomnia and anxiety. This statistical model accounts for 10.4% of anxiety cases.

Table 3. Bivariate Regression Summary Model

Model[b]	R	R^2	Sig.
1	.322[a]	.104	.000

a. Predictors: (Constant), Insomnia
b. Dependent Variable: Anxiety

Multivariate Linear Regression

After removing variables from the highest partial correlation, confounding variables were obtained namely stress and trauma variables. Other variables such as age, gender, batch, GPA, chronic illness, depression in the family and depression are eliminated due to not meeting multivariate regression criteria.

As seen in multivariate model, the correlation coefficient R is 0.598. This shows a moderate level of correlation between predictors (Stress, Trauma, Insomnia) and levels of anxiety. This statistical model of stress, trauma, and insomnia can only explain 33.8% of anxiety.

Table 4. Multivariate Regression Summary Model

Model[a,b]	R	R^2	Adj R^2
3	.598[a]	.357	.338

a. Predictors: (Constant), Stress, Trauma, Insomnia
b. Dependent Variable: Anxiety

From the Partial Correlation of each variable, it can be seen the influence of these variables on anxiety. Stress, trauma and insomnia respectively have the largest contribution of all the variables studied.

Table 5. Partial Correlation of Variables

Model		Partial Correlations
3	Insomnia	.104
	Stress	.475
	Trauma	.221

In Pearson's table, r coefficient on stress variable is 0.565 with a p-value of 0.000 (significant). The r trauma coefficient is 0.250 with a p-value of 0.005 (significant).

From the coefficient of r variable, it can be determined that stress is moderately correlated, and trauma is weakly correlated with anxiety.

Table 6. Pearson Correlation of Cofounders

Var[a]	r	Sig	BCa 95% CI[b]	
			Lower	Upper
Stress	.565	.000	.440	.678
Trauma	.250	.005	.021	.471

a. Dependent Variable: Anxiety
b. Unless otherwise noted, bootstrap results are based on 3000 bootstrap samples

Discussion

Prevalence of Insomnia and Anxiety

Globally, Anxiety has reached a prevalence rate of 13.6-28.8% and 15.2% in Indonesia.[1–3] Medical students however, reaches 35.2%.[4] these results are similar to the prevalence obtained.

Around 44.3% of indonesians suffers from insomnia.[8,9] Research from Other University medical students reported a higher prevalence of insomnia reaching the majority of medical students.[10] This could be caused by differences in sampling time of the study where the comparison study may take samples on the days before or during the exam. As a result, most students experienced higher mental stress and insomnia than usual. Although to confirm and prove, the need for information on time of data collection which is not explained further by the comparative study.[24]

Relationship between Insomnia and Anxiety

On bivariate analysis, another study using bivariate analysis and the same questionnaire, found similar results (r=0.655; p=0.000).[25] A relatively large difference in r when compared to the results of the study is seen. However, comparative studies were conducted in another country with different population characteristics and different ways of interpreting the DASS-21 questionnaire. This makes the prevalence of anxiety and insomnia also different in the two studies, making the correlation coefficient results different between the two studies. This is evident in the very high prevalence of anxiety in supporting studies (66.9%) and relatively different insomnia (27.7%).[25]

Multivariate Linear Regression

Anxiety is a multifactorial disorder which is greatly impacted by many variables not only insomnia. This needed a more holistic approach to measure the impact of insomnia after correcting for other confounding variables. Multivariate linear regression is the great tool needed to assess the weight of these multiple cofounders affecting anxiety directly.

On multivariate analysis, comparison study found that there was a moderate correlation (r=0.512; p<0.000) between stress and anxiety and a weak correlation (r=0.25; p<0.05) was also found in trauma with anxiety.[26,27] When compared with R from the combined model regression table, it can be seen that r stress value is close to the R value of the combined model. This can indicate a large contribution of the stress variable alone when compared to other variables in the combined regression model. Moreover, results of the multivariate regression coefficient of the partial correlation section conclude that stress is the biggest contributor to anxiety.

Other variable not included in the final multivariate regression such as: age,gender, batch, GPA, chronic illness, depression in the family and depression could be regarded not as cofounders but as variables which doesn't affect anxiety significantly.

Limitations

Although this research benefits from controlling confounders and uses interview to obtain DASS data from samples, cross-sectional study is used as this research's methodology. Thus, could not clearly determine cause and effect. Moreover, this research uses purposive sampling which potentially cause selection bias. With this, more research will be needed to address other cofounders of anxiety such as: diet or exercise which may contribute to anxiety in medical students.

Acknowledgements

The author would like to thank all participants.

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The Relationship Between Breastfeeding Pattern and the Risk of Postpartum Depression of Mothers in Tangerang

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Citation: Tancherla Angeline, Widjaja Melanie. The Relationship Between Breastfeeding Pattern and the Risk of Postpartum Depression of Mothers in Tangerang**.** Medicinus. 2022 February; 10(1):34-41
Keywords: Breastfeeding pattern; Postpartum depression; Mother
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Online First : March 2022

Abstract

Background and Aim: Postpartum depression (PPD) has a negative impact on mothers and children, such as breastfeeding (BF) disturbance. However, the relationship between BF pattern and PPD is still unclear due to contrasting results, and no related study has been done in Indonesia. Therefore this study is conducted to evaluate the relationship between BF pattern and the risk of PPD of mothers in Tangerang.

Method: This is an analytic observational study with a cross-sectional design. The samples of this study are 58 mothers that fulfill the inclusion criteria. Samples are chosen by purposive sampling method. Data collection is conducted from January to April 2020. The results were analyzed using SPSS program version 22.0 with Chi- Square method.

Results: There were 37 samples (63.8%) without PPD risk and 21 samples (36.8%) with PPD risk. Among 37 samples without PPD risk, 70.3% had exclusive BF and 29,7% had non-exclusive BF. Among 21 samples with PPD risk, 14.3% had exclusive BF and 85,7% had non-exclusive BF. Chi-Square analysis result showed that there is a significant association between BF pattern and PPD risk (p=0.0001), with an OR of 0.071 (95% CI: 0.17-0.289).

Conclusion: Breastfeeding pattern has a significant association with PPD risk. Exclusive BF has a protective effect on the risk of PPD at one month postpartum.

Introduction

Postpartum depression (PPD) is a common medical complication of pregnancy and childbirth. The definition of PPD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) is a mood disorder that can occur during pregnancy and within four weeks postpartum.[1] Symptoms of PPD include feelings of loneliness, sleep disturbances, decreased appetite, and emotional changes.[2] The incidence rate of PPD in Indonesia is still unclear, because no institution had conducted the research, and there are still many mothers with PPD who are not diagnosed properly. The study conducted at Dr. Soetomo Hospital in Surabaya in 2006 had found that the incidence of PPD was 22.35%.[3] A research at Haji Adam Malik General Hospital Medan in 2009 had found that the incidence of PPDwas 16%.[4]

Postpartum depression can last for years. Approximately 25-50% of mothers experience PPD that lasts more than seven months.[5] Long-term PPD harms maternal mental health and causes social problems, even leading to problems after recovery.[5-8] Postpartum depression is also associatedwith an increased risk of chronic medical disorders and behaviours, such as smoking and alcohol abuse.[9–11] Postpartum depression also negatively impacts. children's cognitive, social and physical development. Mothers who suffer from PPD will also encounter economic burden, because they require large costs for health care, and can cause losses in productivity due to absence from work, early retirement, or long-term unemployment.[12,13]

Postpartum depression can also cause interference in breastfeeding. Initially, the relationship between

breastfeeding and PPD was described as unidirectional, with PPD leading to lower rates of breastfeeding initiation and early cessation of breastfeeding.[14] Recently, several studies had found that the relationship may be bidirectional. Reports showed that PPD can reduce breastfeeding rates, and conversely, no initiation of breastfeeding can increase PPD risk. Several studies had shown an association between a longer duration of breastfeeding and a lower prevalence of PPD.[15–17] Other studies had reported that breastfeeding is a protective factor against PPD and assists faster recovery from PPD symptoms.[18] There were also several studies about the relationship between breastfeeding and PPD that had different conclusions. Some researchers had reported that there is no relationship between breastfeeding and PPD. Meanwhile, two studies had found that breastfeeding mothers have a higher risk of developing depression.[19–21]

The effect of breastfeeding on the risk of PPD is still not well understood, due to contrasting conclusions from various studies. Several studies showing the positive effect of breastfeeding have small samples and only a few have controlled for confounding factors such as socioeconomic factors, relationship quality, and stressful life events.[22,23] Most of the studies conducted did not control for maternal mental health conditions previously.[24] Compared to the number of studies on the relationship between PPD and initiation of breastfeeding, only few had analysed the relationship between breastfeeding patterns and the risk of PPD, especially in Indonesia. For this reason, this study was done to know whether the pattern of breastfeeding can affect the risk of PPD in mothers in Tangerang, Indonesia.

Methods

This is an analytic observational study with a cross-sectional study design. A purposive sampling method was conducted in 5 public health centre's (Pusat Kesehatan Masyarakat) in Tangerang from January until April 2020. The samples included in this study were mothers in Tangerang who were in 4 weeks postpartum period. The exclusion criteria were mothers with a previous history of PPD or any mental disorders, mothers who obtained a score of ≥ 10 in Edinburgh Postnatal Depression Scale (EPDS) during the third trimester of pregnancy, mothers who gave birth to a premature, congenitally ill, or dead baby, or baby treated in NICU (Neonatal Intensive Care Unit). Initially, mothers who were in the third trimester of pregnancy were recruited and the risk of PPD was assessed using the EPDS questionnaire. Mothers who were in the third-trimester pregnancy that scored ≥ 10 in EPDS (having the risk of PPD), have ever been diagnosed or treated for mental disorders were excluded from this study. After 4 weeks postpartum, the included samples were assessed using the EPDS questionnaire again.

The primary data used in this study were obtained through questionnaires, which included the EPDS. The EPDS consists of ten questions that assess the patient's mood over the past week. In each question, respondents were asked to choose from a series of possible responses. Each response was given a score of 0-3. A total score of 10, or any positive response to "thoughts of hurting myself had crossed my mind", means that the mother is more likely to have PPD. Demographic data collected include age, marital status, occupation, income, and education. Data were analysedusing SPSS program version 22.0 with Chi- Square method.

Results

A Total Of 58 Mothers Who Fulfilled The Inclusion And Exclusion Criteria Were Included In This Study. The Respondents' Age Were Between 22-38 Years, With An Average Of 28.05 Years. All Respondents Were Married, And 56 (96.55%) Were Housewives. There Were 5.17% With Middle-Income, 82.76% With High-Income, And 12.07% With Very High-Income

(According To The Classification Of Central Statistics Agency (Badan Pusat Statistik)). Respondents' Education Consisted Of Primary Education (17.24%), Secondary Education (72.41%), Higher Education (10.35%). There Were 29 Respondents (50%) Who Gave Exclusive BF (Up To One Month), 22 Respondents (37.93%) Who Fed Breast Milk And Formula Milk, And Seven Respondents (12.07%) Who Did Not BF At All (Only Fed Formula Milk). The Following Table Contains The Demographic Data Of The Respondents.

Tabel 1. Demographic Data of Study Respondents

	n	Percentage (%)
Age (years)		
20-25	9	15,52
26-30	39	67,24
>30	10	17,24
Status		
Married	58	100
Occupation		
Working	2	3,45
Unemployed	56	96,55
Income		
< Rp. 1.500.000 /month (Low)	-	-
Rp. 1.500.000-2.500.000 /month (Middle)	3	5,17
Rp. 2.500.000-3.500.000 /month (High)	48	82,76
> Rp. 3.500.000 /month (Very High)	7	12,07
Education		
Primary Education	10	17,24
Secondary Education	42	72,41
Higher Education	6	10,35
Breastfeeding Pattern (1 month)		
Exclusive Breastfeeding	29	50
Non-exclusive Breastfeeding (with formula milk)	22	37,93
Did not Breastfeed	7	12,07

From the data obtained, it was found that 37respondents (63.8%) had no risk for PPD, and 21 respondents (36.8%) had a risk for PPD at 4 weeks postpartum. Among 37 respondents who were not at risk, there were 70.3% who gave exclusive breastfeeding, 27% who gave breast milk with complementary feeding (formula milk), and 2.7% who did not breastfeed at all. Among 21 respondents who were at risk, 14.3% gave exclusive breastfeeding, 57.1% gave breast milk with complementary feeding (formula milk), and 28.6% did not breastfeed at all. Data regarding breastfeeding patterns and PPD risk is shown in Table 2 below.

Table 2. Comparison of Breastfeeding Patterns with Risk of Postpartum Depression among Respondents (3 x 2 Table)

Breastfeeding Pattern	PPD Risk (EPDS)				Total
	No Risk for PPD(Total Score <10)		Risk for PPD (Total Score ≥10)		
	n	%	n	%	
Exclusive BF	26	70,3	3	14,3	29
Non-exclusive BF (with complementary feeding)	10	27	12	57,1	22
Did not BF	1	2,7	6	28,6	7
Total	37		21		58

To analyse the relationship between breastfeeding patterns and the risk of PPD, a 3 x 2 table was created and the analysis was carried out using the Chi-square test. Based on these results, it was found that there were more than 20% of the number of cells that had an expected value (E value) of less than five, so this 3 x 2 table did not meet the Chi-Square criteria. Therefore, the category of 'non-exclusive breastfeeding' was merged with 'did not breastfeed' to increase the expected frequency. The following table is a 2 x 2 table of the results combining the two categories (Table 3).

Table 3. Analysis of Breastfeeding Patterns with the Risk of Postpartum Depression (2x2 Table)

Breastfeeding Pattern	PPD Risk (EPDS)				P-value	OR (95% CI)
	No Risk for PPD(Total Score <10)		Risk for PPD (Total Score ≥10)			
	n	%	n	%		
Exclusive BF	26	70,3	3	14,3	0.0001	0.071 (0.17-0.289)
Non-exclusive BF	11	29,7	18	85,7		

The results of the Chi-Square analysis showed that there was a significant relationship between breastfeeding patterns and the risk of PPD at 4 weeks postpartum (p=0.0001). Based on the results of the odds ratio (OR) analysis, it was found that the value of OR was 0.071 (95% CI: 0.17- 0.289). These results indicated that respondents with exclusive breastfeeding pattern had an odds of 0.071 times to be at risk of PPD at 4 weeks postpartum. The practice of exclusive breastfeeding is protective against the risk of PPD.

Discussion

From the results of this study, we found that the practice of exclusive breastfeeding of mothers in Tangerang is still lacking. Many mothers did not understand the importance of exclusive breastfeeding, therefore they did not practice it correctly. Some mothers had never heard of PPD and they did not know that they might carry the risk of having PPD. This is due to the lack of knowledge and education regarding mental health in the society.

Several studies had analysed the relationship between PPD and initiation of breastfeeding. The studies showed that mothers who experienced PPD would have a shorter duration of breastfeeding, and the condition of PPD in mothers could be a predictor for breastfeeding initiation and the risk of breastfeeding cessation before six months.[14,25,26,27,28]

Studies by Mezzacappa et al and Figueiredo et al reported that mothers who breastfed had a reduced risk of PPD up to three months postpartum.[18,29] A cohort study by Ystrom et al showed that mothers who exclusively breastfed had a lower risk of PPD and early cessation of breastfeeding can increase maternal anxiety and depression.[28] Field et al stated that breastfeeding has an antidepressant effect.[30] This can be an explanation that exclusive breastfeeding is protective against the risk of PPD in this study (OR = 0.071, 95% CI: 0.17-0.289).

Several researchers had found that breastfeeding can have a protective effect on maternal psychological health because breastfeeding can reduce stress responses.[16,17,31] A study by Mezzacappa and Katkin showed that the lactogenic hormones, namely oxytocin and prolactin, have anxiolytic (anxiety lowering) and antidepressant effects.[16] Based on studies by Groer and Davis [32], Heinrichs et al [31], Nierop et al [33], and Tu et al [34], lactation could cause a decreased stress response, especially to cortisol. It was found that there was a decrease in the stress response of total cortisol and free cortisol in mothers who breastfed compared to mothers who did not breastfeed. These results indicated that lactation decreases neuroendocrine responses to stress and is associated with decreased PPD symptoms.

According to Taylor et al, the diurnal cortisol pattern also has an effect on decreasing PPD symptoms. Based on the study by Taylor et al, mothers who were depressed had high cortisol levels when they woke up but did not experience an increase from waking up to 30 minutes. In non-depressed mothers, a significant increase in cortisol levels was found from waking up to 30 minutes.[35] The results supported that PPD is affected by dysregulation of the HPA axis. As previously described, lactation and breastfeeding can help regulate neuroendocrine responses and diurnal cortisol secretion patterns, therefore the stability of diurnal cortisol secretion can reduce PPD symptoms.

Another factor related to breastfeeding is the regulation of sleep cycles of both mother and baby. Breastfeeding can help mothers reduce fatigue and symptoms of depression. According to Doan et al, mothers who breastfeed exclusively had longer sleep duration (a mean of 45 minutes longer) and fewer sleep disturbances than mothers who breastfeed non-exclusively.[36] Based on studies by Posmontier et al and Goyal et al, mothers with PPD had poorer sleep quality than mothers without PPD.[37,38] From the results of these studies, it can be

concluded that breastfeeding improves sleep quality in mothers, thereby reducing the risk of PPD.

Based on the results in this study, there wasa significant relationship between breastfeeding patterns and the risk of PPD (p=0.0001) at one month postpartum. Breastfeeding was protective against PPD (OR=0.071, 95% CI: 0.17-0.289). These results are in accordance with the results of other studies (Figueredo et al. 2014 [18]; Hamdan et al. 2012 [39]; Dunn et al. 2006 [40]). A cohort study by Figueredo et al on 181 pregnant women in Portugal found that mothers who exclusively breastfed for up to three months had a lower EPDS score ($p < 0.001$).[18] A cohort study by Hamdan et al on 137 postpartum mothers in Saudi Arabia reported that mothers who breastfed exclusively for up to two and four months had a lower EPDS score ($p < 0.0037$; $p < 0.0001$) and had a lower risk of developing PPD at four months postpartum ($p < 0.0025$).[39] According to a cohort study by Dunn et al on 524 postpartum mothers in Canada, exclusive breastfeeding for up to six weeks postpartum was the most protective against the risk of PPD.[40]

Conclusion

Based on the results of this study, it was found that the practice of exclusive breastfeeding in Tangerang is still lacking and many mothers were unaware that they might carry the risk of PPD. This study was conducted to evaluate the relationship between breastfeeding patterns and postpartum depression in mothers in Tangerang. The analysis results indicated that there is a significant relationship between breastfeeding patterns and the risk of PPD at 4 weeks postpartum. Respondents with exclusive breastfeeding patterns had a lower risk of PPD than respondents with non-exclusive breastfeeding patterns. The results of the analysis showed that exclusive breastfeeding was protective for the mother against the risk for PPD at 4 weeks postpartum.

Based on the shortcomings of this study, the researchers suggest that future studies can analyse the factors that are influenced by breastfeeding, such as neuroendocrine or hormonal factors, sleep cycle regulation, and sleep quality, since these factors can be related to the presence of symptoms and the PPD risk. Future studies are expected to control for confounding variables, such as socioeconomic factors, relationship quality, and social environment. Researchers also suggest that future research can be carried out in a longer period, namely for six months, in order to evaluate the effect of exclusive breastfeeding appropriately.

Acknowledgments and affiliations

None.

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The Role of Bone Scintigraphy and Parathyroid Scintigraphy on Multiple Osteolytic Lesions Which Misdiagnosed as Primary Bone Tumor (Giant Cell Tumor)

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Citation: Prasetyo Nora A., Darmawan Budi, Affandi Erwin, S. Kartamihardja A. Hussein. The Role of Bone Scintigraphy and Parathyroid Scintigraphy on Multiple Osteolytic Lesions Which Misdiagnosed as Primary Bone Tumor (Giant Cell Tumor). Medicinus. 2022 February; 10(1):42-49
Keywords: Bone scintigraphy; Parathyroid scintigraphy; Multiple osteolytic lesions; Primary bone tumor; Giant cell tumor
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Online First : March 2022

Abstract

Brown tumor is a non-neoplastic lesion that resulting from abnormal bone metabolism. It can be manifest in prolonged or untreated hyperparathyroidism. The clinical symptoms, radiological and histopathological examination were similar with giant cell tumor and can be mimicking metastases; or even misdiagnosed with giant cell tumor and mistreated the patient. Biochemical examination of calcium levels and parathyroid hormone should be included in the routine assessment of patients with multiple osteolytic lesions. A multidiscipline approach is needed.Throughout this case report, we would like to report the important role of Nuclear Medicine and Molecular Theranostic imaging modality in 38-year-old male with multiple osteolytic lesions, which was first diagnosed as giant cell tumor and differential diagnosis bone metastases but turnout to be a metabolic bone disease (brown tumor) with parathyroid adenoma as etiology.

Introduction

Primary bone tumors could be manifest as malignant or benign tumor. One of benign primary bone tumor is giant cell tumor.[1] Brown tumor is one of the differential diagnoses of giant cell tumor. It is a metabolic bone disease which could be found in hyperparathyroidism patients. Further imaging often requested by clinician to evaluate patient's condition thoroughly especially when multiple osteolytic bone lesions were found because giant cell tumor and brown tumor show similar clinical symptoms, radiologic, and histopathologic finding but the management is very different.[2,3]

European Society of Musculoskeletal Radiology (ESSR) declare that imaging modalities has a very important role to diagnosis bone tumors. Imaging modalities have two complementary types: morphological that depends mainly on structural changes and functional modalities that depend on the physiological changes.[4]

Throughout this case report, we would like to report the role of imaging modality in nuclear medicine as functional modality in 38-year-old male with multiple osteolytic lesions, which was first diagnosed as giant cell tumor and differential diagnosis bone metastases but turnout to be a metabolic bone disease (brown tumor) with parathyroid adenoma as etiology.

Case illustration

Mr. WS, a 38-year-old male, was referred to Department of Nuclear Medicine and Theragnostic Molecular Dr.

Hasan Sadikin General Hospital Bandung to undergo bone scintigraphy. He was referred with thoracal myeloradiculopathy (Th-VIII) and primary bone tumor as working diagnosis with metastasis and osteosarcoma as differentialdiagnosis.

He came with pain and swelling of all extremities, especially upper right extremity, as main complaint. These were preceded by intermittent pain for 2 years ago. Initially, pain was felt on right leg for 3 months, and then it was felt moving between all of the extremities. Movement of the extremities was limited by these pain sensations. Right upper extremity started to get swollen 10 months ago, whereas the left leg started 3 months ago. There were no radiating pain and numb sensation felt. There was 10 kg weight reduction in 3 months. History of broken left shoulder due to trauma 10 years ago. Patient said that there was stone when he urinated and sometimes it was mixedwith blood in the last 3 years.

Vital sign and generalized status of the patients were within normal limit. Deformity and hard mass were found on middle of left forearm, proximal of upper right arm, and proximal to middle of left leg (Figure 1).

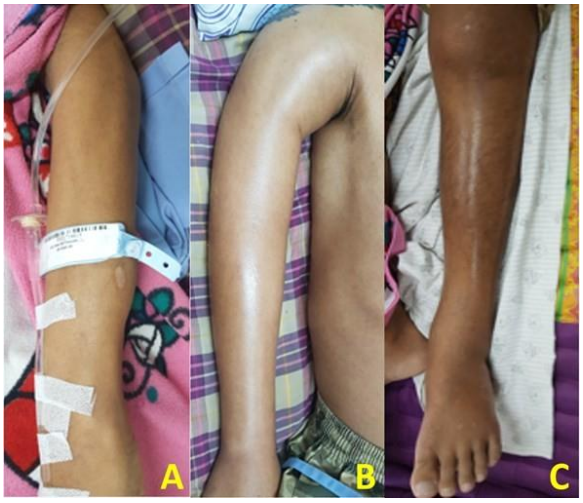

Figure 1. Deformity and hard mass on middle proximal of left forearm (A), proximal of upper right arm (B), and proximal to middle of left leg (C).

Bone biopsy from proximal right humerus showed a result of giant cell tumor. Biochemical evaluation showed a result high level of calcium ion 6.54 mg/dL (Normal range: 4.5 – 5.6 mg/dL) with normal kidney function. The radiographic imaging X-ray result of right shoulder and left forearm showed as a soft tissue mass with multiple lytic lesion which destruct the diaphysis-metaphysis-epiphysis of proximal humerus, scapula, and diaphysis of ulna (Figure 2).

Figure 2. The radiographic imaging of right shoulder (A) and left forearm (B)

Patient was referred to our Nuclear Medicine and Molecular Theranostic Department to perform bone scintigraphy. From bone scintigraphy (Figure 3) we found a diffuse increase of radioactivity uptake on the skull. There was also an inhomogeneous radiopharmaceutical uptake on both humerus, right antebrachial, left iliac crest, distal right femur, and both proximal of tibia. It also showed multiple hotspots on left clavicle, both anterior of costae-I, anterior of right costae-V and left costae-VI, posterior of left costae-IX and XI, left antebrachial, both metacarpals and phalanges, left metatarsal, both ischia, both the head of femur, also both sacroiliac joints. Retention of radiopharmaceutical was seen in right kidney and left kidney was not visualized. These patterns of radioactivity uptake are characteristics of metabolic bone disease with obstruction process of the rightkidney.

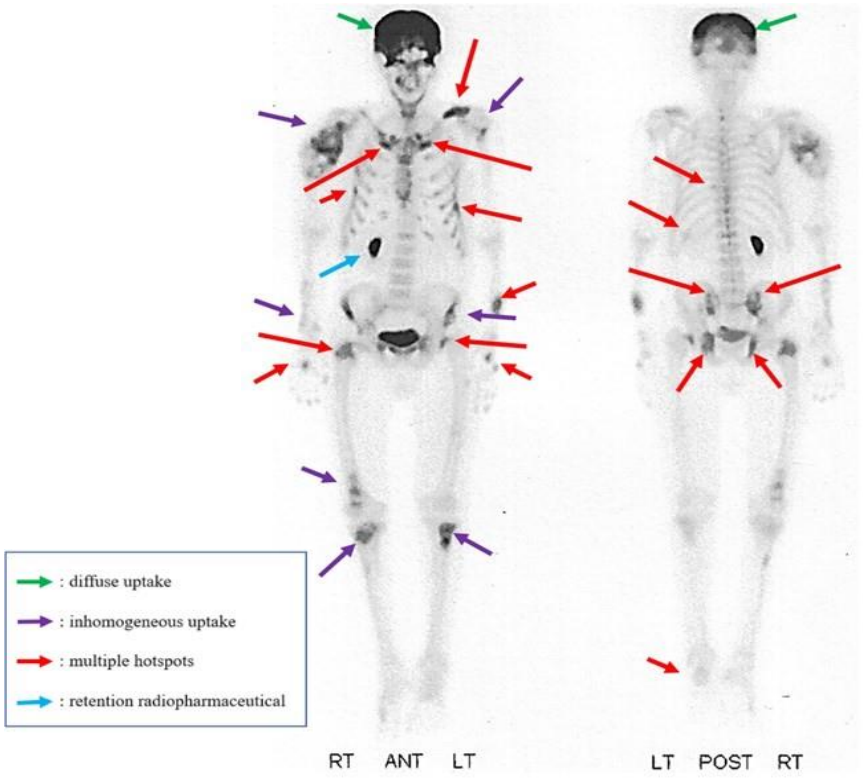

Figure 3. Bone scintigraphy findings

Afterward, patient was suggested to undergo another biochemical evaluation and it showed a high level of parathyroid hormone (PTH) 1,147 pg/mL (Normal range: 15-65 pg/mL), and low level of total vitamin D-25-OH 2.3 ng/mL (Normal range: 30-100 ng/mL).

And then, parathyroid scintigraphy was performed (Figure 4). It showed a pathologic radioactivity uptake on single hyperfunction parathyroid gland at inferior and posterior aspect of right thyroid lobe. It was concluded as a parathyroid adenoma located at inferior and posterior aspect of right thyroid lobe.

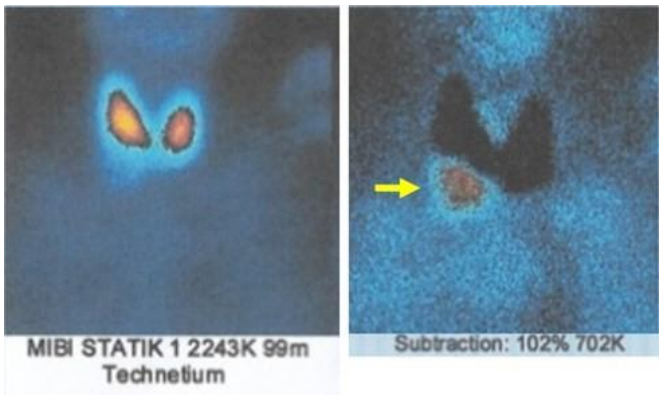

Figure 4. Parathyroid scintigraphy

Patient directly underwent parathyroidectomy procedure after the diagnosis of parathyroid adenoma has been made. Surgeon found the parathyroid adenoma at inferior and posterior aspect of right thyroid lobe, as seen on parathyroid scintigraphy. Histopathology report showed parathyroid adenoma. Patient's condition is improving after parathyroidectomy was done, and patient undergo therapy for hypocalcemia.

Case Discussion

Brown tumor is a non-neoplastic lesion that resulting from abnormal bone metabolism (imbalance of osteoclast and osteoblast activity that bone resorption exceeding bone formation) such in hyperparathyroidism case. It can be manifest in prolonged or untreated hyperparathyroidism (primary, secondary, or tertiary). There is female predominance compare to males, and the incidence increases with age (most cases reported in more than 50 years old and greater in post-menopausal women). The clinical symptoms can be asymptomatic swelling or with bone pain, pathologic fracture, hypercalcemia (renal stones). From radiological examination show osteolytic lesions mimicking metastases; their differential diagnosis includes primary bone metastasis, chondroma, aneurysmal bone cyst, osteosarcoma, and giant cell tumor. Diagnostic dilemma arises when multiple osteolytic lesions appear at different area of the skeletal, as in our case report. Because brown tumor and giant cell tumor have similar clinical, radiological, and histopathological finding, we need including brown tumor as differential diagnosis of multiple osteolytic bone lesions, in order to avoid unnecessary and harmful surgical interventions. Biochemical examination of calcium levels, and parathyroid hormone should be included in the routine assessment of patients with multiple osteolytic lesions. A multidiscipline approach is needed.[5,6]

Primary bone tumor could manifest as malignant or benign lesions. Several benign bone tumor could show high intensity radiopharmaceutical uptake, thus malignancy has to be ruled out. One of the benign tumor with such characteristic is giant cell tumor.[1] Giant cell tumor is originated from fibrous tissue of bone marrow. It emerged between the age of 10-70 years old (most frequently between 20-40 years old) with tendency towards female. The most frequent affected region would be metaphysis-epiphysis part of the long bone. Giant cell tumor mainly will emerge on knee (50%), radius, and humerus. It has high recurrency rate and often affecting surrounding tissue. The tumor consist of giant cell, which resemble osteoclast and anaplastic stromal cell, with a little bit of osteoid and collagen component.[7] One of the differential diagnosis of giant cell tumor is brown tumor, which is often found on hyperparathyroidism patients. Giant cell tumor and brown tumor have similar histopathology, thus imaging is should be requested by clinician, especially when multiple osteolytic lesions were found.[2,3]

In present case report, 38-years-old male with history of multiple bone mass and sensation of pain with movement. There were multiple osteolytic lesions on the long bones (diaphysis-metaphysis-epiphysis of proximal humerus and diaphysis of ulna) on radiographic imaging X-ray. Thus, bone biopsy was performed on right humerus, and the result was giant cell tumor. Because of multiple osteolytic lesions and giant cell tumor resembling a malignancy condition, the clinician reffered the patient to undergo whole body bone scintigraphy to find out whethere there were another osteolytic lesions.

Bone consists of protein and mineral with mainly composed of collagen, calcium, and pyrophosphate. Around 5 – 10% of the bone undergo regeneration during young adult period. Most of the calcium (99%) which are contained in the bone are in the form of hydroxyapatite. Later, the bone will be stabilized in adult

skeleton, and actively maintaining the equilibrium through modeling and remodeling process. These processes require the serum calcium homeostasis. In condition where the disease disrupt the calcium homeostasis, clinical symptoms of metabolic bone disease manifest.[8]

Metabolic bone disease (MBD) is a group of clinical manifestation which leads to the mineralization impairment, mass, and the deformity of the bone. It is often characterized by extreme bone abnormalities which will improve after treatment according to the etiology. Bone mineral equilibrium is influenced by several minerals, including calcium, phosphor, magnesium, and vitamin D. Although metabolic bone disease are common, it is difficult to diagnose based on clinical condition and conventional radiological modality.[8,9] Some of the disease that can cause metabolic bone disease are renal osteodystrophy, hyperparathyroidism, and vitamin D deficiency in osteomalacia and Paget's disease.[1] One of the causes of MBD is the over excretion of parathyroid hormone (PTH) which trigger bone resorption process thus resulting in hypercalcemia and hypophosphatemia.[9] This was first discovered by Friedrich Schlaugenhaufer in 1915. Blood examination is usually performed to screen hypercalcemia. MBD could be evaluated by bone scintigraphy.[7]

European Society of Musculoskeletal Radiology (ESSR) declare that imaging modalities has a very important role to diagnosis bone tumors. Imaging modalities have two complementary types, either morphological that depends mainly on structural changes (radiographic, ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI)) or functional modalities that depend on the physiological changes (bone scintigraphy). Radiographic imaging assessment is needed to check the pattern of bone destruction, zone of transition, periosteal reaction, cortical destruction, soft tissue / joint involvement, and the location of the bone tumor (predilection). Bone scintigraphy is useful for local / distant staging of bone tumors, and in case of primary bone tumor, bone scintigraphy could help in diagnosis because has specific features as we seen in this present case.[4,10]

Bone scintigraphy is one of the imaging modalities in nuclear medicine. Radiopharmaceutical, ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP), will be injected intravenously 3 hours before a whole-body scan is performed. Radiopharmaceutical ^{99m}Tc-MDP will bind to crystalline hydroxyapatite and amorphous calcium phosphate thus resulting uptake of radioactivity at the site of mineralized bone. Several factors that influence radioactivity uptake by ^{99m}Tc-MDP are blood flow, vitamin D level, parathyroid hormone level, corticosteroid, intraosseous tissue pressure, and blood vessel permeability.[10]

In the early stages of metabolic MBD, bone scintigraphy shows diffuse radioactivity uptake. In line with the disease progressivity, bone scintigraphy has well recognized features, such as a focal radioactivity uptake in bones with high bone turnover (fractures or pseudofractures) and brown tumor. It will also show "superscan" pattern (increase bone and soft tissue uptake ratio, faint or absent radioactivity uptake in the kidney) - a classic characteristic of MBD on bone scintigraphy- and higher radioactivity uptake on the axial bones as well as proximal part of the long bones. Diffuse radioactivity uptake on the periarticular areas, calvaria, mandible, sternum, and costochondral junction also classical bone scintigraphy finding inMBD.[1,9]

This patient underwent bone scintigraphy and it showed a diffuse increase radioactivity uptake on calvaria, inhomogeneous radioactivity uptake on long bones (both humerus, both antebrachial, both metacarpals and phalanges, both femurs, both the proximal of tibia, left metatarsal), and multiple hotspots on the surrounding area of the joint (both the head of femur, both

sacroiliac joints). It also showed "superscan" pattern - left kidney was not visualized (the retention of radiopharmaceutical in right kidney can be cause by kidney stone). This increase uptake on a whole-body bone scintigraphy, the elevated serum calcium, patient's history of stone excretion in urine were the clues that pointed our attention toward metabolic bone disease (brown tumor) with hyperparathyroidism as suspected aetiology in this patient. As biochemical examination showed a high level of parathyroid hormoneand low level vitamin D with normal kidney function, we conclude the high possibility of adenoma parathyroid in this patient.

Primary, secondary, and tertiary hyperparathyroidism will cause the increase of calcium and parathyroid hormone. All type of hyperparathyroidism will increase the bone resorption process thus increasing osteoblastic activity that cause increasing radioactivity uptake of MDP.[9] Parathyroid adenoma is the main cause of primary hyperparathyroidism (in 80% of all cases). Parathyroidectomy show high success rate in primary hyperparathyroidismmanagement, thus an imaging modality to localize the affected parathyroid gland is necessary to be performed to reduce the morbidity of the parathyroidectomyprocedure.[6,7]

Several traditional non-invasive modalities, such as computed tomography (CT), ultrasonography (USG), and magnetic resonance imaging (MRI), not been considered very useful for preoperative localization because could not determine the hyperfunctioning parathyroid gland or the surrounding tissue. The most sensitive, cost-effective, and non-invasive modality in determining the hyperfunctioning parathyroid gland is parathyroid scintigraphy (±80–100% vs 46–76% (CT) vs 36–76% (USG) vs 50–78% (MRI)).[7] Parathyroid scintigraphy could show falsenegative as well as false positive result. The hyperfunctioning parathyroid gland that are too small and multiple parathyroid adenomas could cause a false negative result. Whereas follicular thyroid adenoma, thyroid cancer, benign neoplasm, and metastasis could cause false positive result.Consumption of calcium channel blocker could activate the p-glycoprotein which could increase the washout of the radiopharmaceutical, thus leading to falsenegative result.[11]

Parathyroid scintigraphy using ^{99m}Tc- Sestamibi subtraction method was done on this patient, and it showed a single hyperfunction parathyroid gland at inferiorand posterior aspect of right thyroid lobe. This patient directly underwent parathyroidectomy procedure after the diagnosis of parathyroid adenoma has been made, and the location of hyperfunctioning parathyroid gland has been determined. Histopathology result after the parathyroidectomy procedure showed that it was indeed parathyroid adenoma.

In case of primary and secondary hyperparathyroidism, after parathyroidectomy usually hypocalcemia occurs temporarily, and the function of parathyroid gland will be normal in 1 week. However, persistent, and heavy hypocalcemia could be occurred in several cases even though parathyroid hormone has returned to normal.[9] After parathyroidectomy procedure, the patient's condition is improving, and patient undergo therapy for hypocalcemia.

Gosavi, et al. introduced an algorithm for diagnosis and treatment of primary hyperparathyroidism and exclusion of other giant cell lesions. Patient with asymptomatic or bone pain with osteolytic lesions on radiograph and giant cell in histopathology, should do a biochemical investigation such as parathyroid hormone and serum calcium, and perform parathyroid scintigraphy to localized the pathologic parathyroid gland prior surgery.[6] If needed, a whole body bone scintigraphy could be use to look for other skeletal lesions.[4]

Conclusion

In case of multiple osteolytic lesions, history taking, clinical evaluation, imaging modality, histopathological examination, and biochemical investigation are useful to find the etiology. The nuclear medicine imaging modalities, such as bone scintigraphy -tofind specific features of the radiopharmaceutical uptake- and parathyroid scintigraphy -the most sensitive, cost-effective, and non-invasive modality in determining the hyperfunctioning parathyroid gland- are useful and have an important role in cases of multiple osteolytic lesions with hyperparathyroidism as it'setiology. Brown tumor and giant cell tumor have similar clinical, radiological and histopathological finding. Therefore, it is important to provide the pathologist with all the appropriate laboratory and clinical data, not only the bone specimens. Biochemical investigation that useful on all patients with bone tumors are serum calcium and parathyroid hormone. This could help to identify tumor such as brown tumors.

Acknowledgement

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The authors declared that all the images and figures in this manuscript are author's own work andpatient has given his consent for this case report to be written.

Signature,

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