ORIGINAL ARTICLE

Bali Medical Journal (*Bali MedJ)* 2022, Volume 11, Number 1: 556-562
P-ISSN.2089-1180, E-ISSN: 2302-2914

Predictive factors and the relationship between the early detection of osteoporosis and pathological fractures in Indonesian menopausal women

Supriyatiningsih[1,3*], Meiky Fredianto[2,3], Muhammad Arifuddin[2,3], Amalia Rizki Hanif[3], Salwa Nabilah Cholfa[3], Sulistiari Retnowati[1,3], Ima Rismawati[4]

[1]Obstetrics and Gynaecology Department, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Indonesia;
[2]Surgical Department, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Indonesia;
[3]PKU Muhammadiyah Gamping, UMY Teaching Hospital, Indonesia;
[4]Muhammadiyah Maternal and Child Health Center, Universitas Muhammadiyah Yogyakarta, Indonesia;

*Corresponding author:
Supriyatiningsih;
Obstetrics and Gynaecology Department, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta;
supriyatiningsih_upi@yahoo.com

Received: 2022-03-04
Accepted: 2022-04-24
Published: 2022-04-30

ABSTRACT

Background: Estrogen deficiency in menopausal women induces bone loss and makes them prone to pathological fractures. Age, body mass index (BMI), parental history of osteoporosis, and smoking tobacco also increase bone loss and pathological fractures. This study aims to determine whether age, BMI, parental history of osteoporosis, and smoking tobacco can predict pathological fractures in menopausal women. Moreover, the relationship between the early detection of osteoporosis with pathological fracture incidence will also be determined.

Methods: This is an analytic observational epidemiological research with a cross-sectional retrospective design that involved 40 menopausal women. The data were collected from the patients' medical records 2020 in Obstetrics and Gynecology Clinic, Asri Medical Center (AMC) Muhammadiyah Hospital, Yogyakarta. The predictive factors for pathological fracture (age, BMI, parental history, smoking tobacco) were analyzed by using Fisher's exact test and the relationship between osteoporosis early detection, including bone mineral density (BMD) value, parathyroid hormone (PTH) levels, osteocalcin levels, and osteoporosis self-assessment tool for Asians (OSTA) score, with pathological fractures were investigated by using the chi-square test.

Result: Age has a significant relationship with the occurrence of pathological fractures in menopausal women (OR = 6.6, 95% CI: 1.128-8.604, p = 0.042), while BMI, parental history of osteoporosis, and smoking tobacco did not have a significant relationship with pathological fractures ($p > 0.05$). Early detection of BMD and PTH was also found to have a significant relationship to fracture incidence. Additionally, menopausal women with high PTH levels and osteoporosis BMD values are eight times and four times greater risk of acquiring fractures than menopausal women with normal BMD values and PTH levels.

Conclusion: Age can be a predictive factor for pathological fractures, and the early detection of PTH and BMD is related to the occurrence of pathological fractures in menopausal women.

Keywords: menopause, pathological fracture, osteoporosis, bone mineral density, parathyroid hormone.
Cite This Article: Supriyatiningsih., Fredianto, M., Arifuddin, M., Hanif, A.R., Cholfa, S.N., Retnowati, S., Rismawati, I. 2022. Predictive factors and the relationship between the early detection of osteoporosis and pathological fractures in Indonesian menopausal women. *Bali Medical Journal* 11(1): 556-562. DOI: 10.15562/bmj.v11i1.3258

INTRODUCTION

Natural menopause is defined as the absence of a menstrual period for 12 consecutive months after the last menstruation and is not caused by pathological conditions, such as chemotherapy, radiation, or surgical causes.[1,2] Women will likely experience natural menopause between the ages of 49 and 52.[3] Studies have found that menopause could be associated with estrogen level deficiency.[4] Estrogen deficiency impacts bone remodeling and causes women to be at least four times more likely to develop osteoporosis than men.[5] Moreover, follicle-stimulating hormone (FSH) significantly increases in menopausal women and stimulates bone resorption, leading to osteoporosis.[6] As an impact, bone remodeling, which is the final stage of bone healing, would be impaired.[7] Low bone mass followed by osteoporosis can develop bone fragility and increase the risk of fractures.[8] Bone loss in osteoporosis occurs over a gradual decline and worsens with time.[8]

Osteoporosis in menopausal women is called post-menopausal osteoporosis, and it leads to an increased risk of fractures.[5,9] There are typically no symptoms of post-menopausal osteoporosis until there is a pathologic fracture, which is when a bone is broken due to low force, such as minor trauma or daily activities, that would not otherwise fracture in a normal bone.[8] The prevalence of osteoporosis in women aged 50-70 years was 23%, or one in three women developed osteoporosis in Indonesia in 2013. The prevalence of osteoporosis in women is two times greater than in men.[10] Fractures in post-menopausal women inevitably have subsequent negative impacts on their health as they can lead to disability, impaired quality of life, and pose a serious economic burden on individuals, families, societies, and health care systems

due to the high healthcare costs of the chronic disease.[9,11] The average cost for hospitalization following a hip fracture, as the most prevalent pathological fracture among older women, was $10,075, and the estimate for the total health and social care costs for 12 months following hip fracture was $43,669 per patient.[12,13] In Indonesia, the cost per hip fracture was reported to be as much as USD 5,000-9,000, with the total hip fracture incidence per year being 119/100,000.[14]

The WHO fracture risk assessment tool (*FRAX*®) is a tool that is used in many countries to assess the probability of acquiring a major fracture and the risk of hip fracture within ten years.[15] However, the estimated results of the tool can vary in each country as not every country has developed its own FRAX model to suit its needs.[16] Another test to predict and detect osteoporosis and pathological fracture incidence is bone mineral density (BMD).[17] The risk of fracture increases 2-fold for each standard deviation (SD) score reduction in BMD.[18] However, using BMD alone to assess the risk for fractures results in high specificity but low sensitivity. Therefore, this suggests that most fractures will occur in women who do not have osteoporosis, as defined with a T-score of ≤ -2.5.[18] Thus, BMD testing alone is not recommended for population screening, and other risk factors need to be assessed.[18]

Some studies mentioned that the risk factors of menopausal women for acquiring fractures included age, fracture history, parental history of femur fracture, gender, body mass index (BMI), glucocorticoid use, smoking habits, drinking habits, causes of secondary osteoporosis, and rheumatoid arthritis.[5,19–21] However, few studies about the predictive factors of pathological fracture among menopausal women in Indonesia have been conducted. Moreover, to the authors' knowledge, no study has investigated all predictive factors that cause pathological fractures among menopausal women in the country.[22,23] Studies related to osteoporosis and early detection by BMD value, osteocalcin levels, parathyroid hormone (PTH) levels, and OSTA (osteoporosis self-assessment tool for Asians) scores to prevent pathological fracture incidence are also limited in Indonesia. Therefore, this study aims to determine the factors that influence pathological fractures in menopausal women in Indonesia and investigate the relationship between the early detection of BMD, PTH levels, osteocalcin levels, and OSTA score with pathological fracture incidence.

METHODS

This study is an analytic observational epidemiological study with a cross-sectional retrospective design. The analyzed factors included age, BMI, parental history of osteoporosis (genetics), and smoking habits. Meanwhile, the early detection items of osteoporosis that were analyzed included BMD value, osteocalcin levels, PTH levels, and the OSTA score with the cut off used in BMD was ≥ -1.0, osteocalcin level was 10.1 ± 9.4 ng/mL, PTH level was 10-65 pg/mL, and OSTA score was < 0 (low osteoporosis risk). Data were collated by retrospective data collection of patients' medical records from February to December 2020 in Obstetrics and Gynecology Clinic, Asri Medical Center (AMC) Muhammadiyah Hospital, Yogyakarta.

The respondents were 40 menopausal women that were gathered through total sampling. The inclusion criteria used in this study are menopausal women who had complete data of their age, height and weight, parental history of osteoporosis, smoking history, and fracture history, and also had undergone the process for the early detection of osteoporosis such as BMD value, osteocalcin levels, PTH levels, and OSTA score. In this study, we choosed 50 years old as the cut off for the grouping because primary osteoporosis, bone loss that occurs due to a decrease in the hormone estrogen in postmenopausal women and older women, generally occurs at 50 years.[10] The exclusion criteria were patients with primary hyperthyroid and metabolic bone diseases such as Paget's disease, multiple myeloma, and Cushing syndrome.

After selecting eligible respondents through the patients' medical records, important data that could be further analyzed were noted. The Fisher's Exact Test was used to analyze the relationship between each risk factor with the incidence of pathological fracture, and the chi-square test was used to determine the relationship between the early detection of osteoporosis with fracture incidence. Furthermore, diagnostic tests were applied to each early detection variable's specificity, sensitivity, NPV (negative predictive value), and PPV (positive predictive value).

RESULTS

Forty menopausal women were included in the study, and most of the menopausal women sampled were more than 50 years old (80%). None of them are in the underweight category of BMI, and the majority are in the category of normal weight (67.4%), followed by overweight (23.3%). The majority of the respondents (76.7%) stated that their parents had fractures, and 60% of respondents confirmed that they had a history of fractures without mentioning the specific types or regions. Lastly, 72.1% of the respondents never smoked tobacco (Table 1).

Age has a significant relationship with pathological fractures in menopausal women, with a p-value of less than 0.05 ($p < 0.05$). Meanwhile, other risk factors, such as BMI, parental history of fractures, and smoking tobacco, have p-values of > 0.05, which means that there is no significant relationship between these factors and pathological fractures in menopausal women in this study (Table 2).

Most of the respondents (65%) who underwent BMD early detection were found to have acquired osteoporosis, and 76.9% of them had fractures. Most of the respondents also had normal levels of osteocalcin (65%), but most of the respondents who had fractures were in the group with high osteocalcin levels (71.4%) compared with those who did not acquire fractures (28.6%). Meanwhile, among respondents with normal osteocalcin levels, there was only a slight difference between those who acquired fractured and those who did not (53.8% and 46.2%, respectively). There were also slightly more respondents with high levels of PTH than those with normal levels of PTH. Among those with high PTH levels, 76.2% experienced fractures, and 23.8% did not. Moreover, early detection by OSTA showed that 52.5% of respondents have

a low risk for osteoporosis, with 61.9% of them acquiring fractures, while 47.5% have a high risk of obtaining osteoporosis, with 57.9% of them acquiring fractures (Table 3).

Table 4 shows the diagnostic test results for the early detection of osteoporosis through BMD, PTH, osteocalcin, and OSTA scores. The results revealed that the sensitivity and specificity of the BMD test are 83.33% and 62.50%, respectively; the PPV is 76.90%, and the NPV is 71.42%. The diagnostic test of osteocalcin early detection resulted in a sensitivity value of 41.67%, a specificity value of 75%; a PPV of 71.42%; and an NPV of 46.15%. The PTH diagnostic test reported a sensitivity value of 66.67%, a specificity value of 68.75%, a PPV of 76.19%, and an NPV of 57.89%. Moreover, the sensitivity, specificity, PPV, and NPV of OSTA were 45.83%, 50%, 57.89%, and 38.09%, respectively.

DISCUSSION

Predictive factors of pathological fracture

Age

Table 2 shows the correlation between the predictive factors of pathological fractures and their occurrence. The age variable has a significant value of less than 0.05 ($p < 0.05$), which means there is a significant relationship between age and pathological fracture. This result is in line with previous studies, which generally showed that the older the age, the higher the incidence of pathological fractures, particularly in women.[8,12,24] Age was also one of the significant risk factors for hip fracture in both older females and males aged > 65 years.[25] Additionally, an audit from International Osteoporosis Foundation (IOF) in 2013 reported that 23% of Indonesian women between 50-80 years old have osteoporosis and that this figure has increased to 53% for individuals in the age range of 70-80 years old.[14] However, the report involved both women and men; meanwhile, this study involved only menopausal women.

In people older than 60 years of age, hip fractures generally occur from a fall or slip.[25] These accidents can occur due to the physical, sensory, and cognitive changes associated with aging in combination with environments that are not adapted for older people.[26] Bone loss is also a major factor contributing to the increase in fracture rate with aging.[8] Moreover, low levels of estrogens in menopausal women significantly increase bone resorption and induce accelerated bone loss.[4]

Body Mass Index

A prospective cohort study proved that either low BMI or obesity might increase the risk for hip fracture.[21] In our study, no respondent had a low BMI, which may lead to the insignificant result of this study regarding the statistical relationship

Table 1. Data of the respondents' characteristics.

Risk factors	Frequency (n = 40)	Percentage (%)
Age		
< 50 years old	8	20
≥ 50 years old	32	80
BMI		
Underweight (<18.5)	0	0
Normal (18.5 to <25)	29	67.4
Overweight (25.0 to <30)	10	23.3
Obesity (30 or higher)	1	2.3
Parental history of osteoporosis		
Yes	33	76.7
No	7	16.3
Smoke tobacco		
Yes	9	20.9
No	31	72.1
Fracture history		
Yes	24	60
No	16	40

Notes: BMI, body mass index

Table 2. The analyzed results between each predictive factor and fractures.

Variables	Fractures (n = 40)				p-value	OR	CI 95%
	Yes		No				
	n	%	n	%			
Age							
≥ 50 years old	22	68.8	10	31.3	0.042*	6.600	1.128 – 8.604
< 50 years old	2	25	6	75			
BMI							
Normal (18.5 to <25)	16	55.2	13	44.8			
Overweight (25.0 to <30)	8	72.7	3	27.3	0.473	0.462	0.101 – 2.100
Obesity (30 or higher)	1	100	0	0			
Parental history of fractures							
Yes	20	60.6	13	39.4	1.000	1.154	0.221 – 6.019
No	4	57.1	3	42.9			
Smoke tobacco							
Yes	8	88.9	1	11.1	0.610	7.500	0.835 – 67.347
No	16	51.6	15	48.4			

Notes: *p value <0.05; OR, odds ratio; BMI, body mass index

Table 3. **Early detection and fracture history.**

Variables	Frequency	Fracture history		OR	p-value	CI 95%
		Yes	No			
BMD						
Osteoporosis	26 (65%)	20 (76.9%)	6 (23.1%)	8.333	0.003*	1.906 – 36.440
Normal	14 (35%)	4 (28.6%)	10 (71.4%)			
Osteocalcin levels						
High	14 (35%)	10 (71.4%)	4 (28.6%)	2.143	0.279	0.532 – 8.625
Normal	26 (65%)	14 (53.8%)	12 (46.2%)			
PTH levels						
High	21 (52.5%)	16 (76.2%)	5 (23.8%)	4.400	0.028*	1.134 – 17.069
Normal	19 (47.5%)	8 (42.1%)	11 (57.9%)			
OSTA score						
High risk	19 (47.5%)	11 (57.9%)	8 (42.1%)	0.846	0.796	0.238 – 3.004
Low risk	21 (52.5%)	13 (61.9%)	8 (38.1%)			

Notes: *p-value <0.05; OR, odds ratio; BMD, bone mineral density; PTH, parathyroid hormone; OSTA, osteoporosis self-assessment tool for Asians

Table 4. **Diagnostic test results of early detection item.**

Variables	Sensitivity	Specificity	PPV	NPV
BMD	83.33%	62.50%	76.90%	71.42%
PTH	66.67%	68.75%	76.19%	57.89%
Osteocalcin	41.67%	75%	71.42%	46.15%
OSTA score	45.83%	50%	57.89%	38.09%

Notes: PPV, positive predictive value; NPV, negative predictive value; BMD, bone mineral density; PTH, parathyroid hormone; OSTA, osteoporosis self-assessment tool for Asians

between BMI and fracture incidence ($p > 0.05$) (Table 2). The majority of respondents (67.4%) had a normal BMI, 23.3% had an overweight BMI, and only 2.3% were in the obesity range. The study results showed that a low BMI is likely to increase hip fracture incidence than a normal BMI, while overweight or obese had a lower risk for hip fracture.[25]

Parental history of osteoporosis

Although osteoporosis and fractures related to estrogen deficiency among menopausal women are influenced by genetic factors, fracture incidence across ethnic and racial groups still varies.[4,5] Table 2 showed that the p-value for parental history of osteoporosis regarding fracture incidence was > 0.05, which means that both variables did not have a significant relationship in this study. However, a study that researched 50-year-old-menopausal women showed that parental history of hip fracture could increase the risk of femur fracture.[27] Moreover, genetic factors could affect the age of natural menopause, and this is supported by the differences in age at natural menopause among women of different ethnicities and in developed and developing countries.[28] Genetics also contribute to the susceptibility to osteoporosis in a complex way, where several genes are involved in controlling osteogenesis by acting on the target cells, which are influenced by age, nutrition, hormones, and environment (ethnicity).[20]

However, susceptibility varies with the location of osteoporosis and related fractures; some genes may affect wrist fractures, hip fractures, vertebral fractures, or other locations.[20] Currently, there is limited epidemiologic information regarding osteoporosis fractures and their determinants in Asian women, and the existing literature would only discuss certain types of fractures, such as osteoporosis and vertebral fractures in Japan and hip fractures in China.[4,29,30] This study does not mention specific types of fractures, either the fractures of the respondents or their parents. Therefore, further clinical studies are needed for ethnically and geographically distinct populations by using a specific tool developed for assessing specific fractures based on ethnicity among menopausal women in Indonesia.

Tobacco use

Numerous studies have reported that smoking has a role in increasing the risk of pathological fractures, one of which is a meta-analysis study that reviewed 10 cohort studies and found that smoking habits can lead to osteoporosis in later life. The fracture risk calculator, the FRAX® Tool, estimates an individual's 10-year probability of incurring a fracture, and smoking is one of the assessed aspects due to its possibility of causing fractures. Tobacco content in cigarettes can interfere with the bone formation process (ossification) and reduce estrogen levels.[16,31] Conversely, this study showed an insignificant relationship between smoking and fracture incidence ($p > 0.05$). This difference could be due to our study's lack of study samples. The weakness of this study lies in the small number of samples

because the participants were only selected from one reproductive and menopausal center. However, there is an interesting fact that active smokers have a higher risk of hip fracture than individuals who no longer smoke.[25] Quitting smoking for ten years or more can increasingly reduce the incidence of fractures.[32]

The early detection of osteoporosis and pathological fractures

Table 3 shows that BMD has a significant relationship with fractures with a p-value of 0.003 ($p < 0.05$). Menopausal women within this study who were categorized as osteoporosis patients by the BMD test had an 8-fold higher risk for fractures than menopausal women who had normal BMD scores (OR = 8.333; CI 95% = 1.906-36.440). It indicates that the BMD test is a robust predictor of whether an individual will have a fracture. It is in line with another study result of a large clinical BMD database in Canada which reported that the BMD test is a strong predictive and good early detector for osteoporosis incidence and pathological fractures.[17] The sensitivity of the BMD examination was 83.33%, which means that of the patients who obtained a positive diagnostic test result, 83.33% of them had pathological fractures. The specificity of the BMD test is 62.50%, which means that 62.5% of all healthy patients will have a negative diagnostic test result. The PPV is 76.90%, which indicates that 76.90% of patients with a positive BMD test would get pathological fractures. Meanwhile, the NPV is 71.42%, which means that 71.42% of patients with a negative test would not obtain fractures.

Osteocalcin is considered a bone formation marker.[33] This study reveals no significant relationship between osteocalcin and fractures ($p = 2.143$). On the contrary, another study showed that increased levels of bone turnover marker (BTM) in menopausal women correlated with rapid bone loss and was associated with a higher risk of fracture.[34] BTM can help detect menopausal women with a higher risk of fracture and has been used to predict fracture risks, including vertebrae, hip, and multiple fractures.[33] However, it is worth noting that patients with high PTH levels had more fractures, although the *p*-value was insignificant. It may be due to the small number of respondents in this study. The sensitivity of osteocalcin is 41.67%, which means that 41.67% of patients who obtained positive diagnostic test results have pathological fractures. The specificity of osteocalcin is 75%, which indicates that 75% of healthy patients will have a negative diagnostic test result. The PPV is 71.42%, which means that the probability of patients with a positive test who would have the fracture is 71.42%, and the NPV of osteocalcin is 46.15%, which indicates 46.15% of patients with a negative test would not have the fractures.

This study shows a significant relationship between PTH and fractures (*p*-value of 0.028). Menopausal women with high PTH levels have a greater risk for fractures by 4-fold than menopausal women with normal PTH levels (OR = 4.400; CI 95% = 1.134-17.069). The other result also stated that PTH levels would increase with age.[35] The measurement of bone markers (PTH), combined with BMD and other risk factor assessments, can improve the accuracy of risk fracture identification.[36] The results of PTH diagnostic tests show that the sensitivity is 66.67%, which means that 66.67% of the patients with positive diagnostic tests experienced fractures. The specificity of PTH is 68.75%, which means that 68.75% of healthy patients will have a negative diagnostic test result. Moreover, the PPV of PTH is 76.19%, which means that the probability of patients with positive test results who would experience fractures is 76.19%. Meanwhile, the NPV of PTH is 57.89%; this indicates that the probability of patients with a negative test result who were healthy was 57.89%.

Table 3 shows no significant relationship between OSTA score and fracture incidence (*p*-value 0.796). Conversely, a study reported that patients with a high-risk OSTA score were 8.3 times higher to experience fractures than patients with low OSTA scores.[37] The sensitivity of the OSTA score was 45.83%, which means that as much as 45.83% of patients who obtained positive diagnostic results have obtained fractures, and the specificity of the OSTA score was 50%, so 50% of all healthy patients will have a negative diagnostic test. The PPV of the OSTA score was 57.89%, which means that the probability of patients with a positive test result who truly have fractures was 57.89%, while the NPV was 38.09% which means that the probability of patients with a negative test result who have no fractures was as much as 38.09%. However, another study result also suggested that OSTA scores have high sensitivity but low specificity and low positive predictive value in identifying osteoporotic women. Therefore, its use for the general population can have a high false-positive rate.[38]

CONCLUSION

This study showed that age has a significant relationship with pathological fracture incidence. The group of age ≥ 50 years old has a 6.6 times greater risk of fracture than the < 50 years aged group. Therefore, age is a predictive factor for pathological fractures in menopausal women. Early detection of BMD and PTH also has a significant relationship with the incidence of fractures, as menopausal women with osteoporosis category results have an eight times greater risk for osteoporosis than individuals with results from the normal category. Menopausal women with high PTH levels also have a fracture risk of four times greater than those with normal PTH levels. Therefore, early detection of BMD and PTH are robust predictors and modalities of early detection.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

FUNDING

This study was funded by the Center for Research, Publication, and Community Development Universitas Muhammadiyah Yogyakarta with grant number 034/PEN-LP3M/I/2020 NO.81.

ETHICS APPROVAL

All participants' identities were encrypted; therefore, this study did not require the informed consent of the study's population with approval from the Research Ethics Committee, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta (No. 080/EC-

KEPK FKIK UMY/III/2019).

AUTHORS CONTRIBUTION

Supriyatiningsih contributes to study concepts and design, defining intellectual content, literature search, data acquisition and analysis, statistical analysis, manuscript preparation, editing, and review, and this study's guarantor. Meiky Fredianto contributes to study concepts and design, defining intellectual content, data analysis, statistical analysis, manuscript preparation, editing, and review. Muhammad Arifuddin contributes to manuscript editing. Amalia Rizki Hanif and Salwa Nabilah Cholfa contribute to literature searching, data acquisition and analysis, statistical analysis, and manuscript preparation. Sulistiari Retnowati contributes to manuscript editing. Ima Rismawati contributes to literature search, manuscript preparation, and manuscript editing.

REFERENCES

1. Holloway D. Menopause Symptom Management in the United Kingdom. Nurs Clin North Am. 2018;53(2):263–77.
2. Roman Lay AA, do Nascimento CF, Horta BL, Dias Porto Chiavegatto Filho A. Reproductive factors and age at natural menopause: A systematic review and meta-analysis. Maturitas. 2020;131(April 2019):57–64.
3. Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Heal. 2019;4(11):e553–64.
4. Yoo JE, Shin DW, Han K, Kim D, Yoon JW, Lee DY. Association of Female Reproductive Factors with Incidence of Fracture among Postmenopausal Women in Korea. JAMA Netw Open. 2021;4(1):1–14.
5. Ji M-X, Yu Q. Primary osteoporosis in post-menopausal women. Chronic Dis Transl Med. 2015;1(1):9–13.
6. Lizneva D, Yuen T, Sun L, Kim S min, Atabiekov I, Munshi LB, et al. Emerging concepts in the epidemiology, pathophysiology, and clinical care of osteoporosis across the menopausal transition. Matrix Biol. 2018;71–72(2017):70–81.
7. Ansari M. Bone tissue regeneration: biology, strategies and interface studies. Prog Biomater. 2019;8(4):223–37.
8. Sozen T, Ozisik L, Calik Basaran N. An overview and management of osteoporosis. Eur J Rheumatol. 2017;4(1):46–56.
9. Francisco Baccaro L, Marques Conde D, Costa-Paiva L, Mendes Pinto-Neto A. Clinical Interventions in Aging Dovepress The epidemiology and management of post-menopausal osteoporosis: a viewpoint from Brazil. Clin Interv Aging. 2015;10:583–91.
10. Ministry of Health Republic of Indonesia. Situasi osteoporosis di Indonesia (the situation of osteoporosis in Indonesia). 2020.
11. GDP 2019 Fracture Collaborators. Global, regional, and national burden of bone fractures in 204 countries and territories , 1990 – 2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet Heal Longev. 2021;2(September):580–92.
12. Povoroznyuk V V., Grygorieva N V., Kanis JA, McCloskey E V., Johansson H, Strafun SS, et al. Epidemiology of Hip Fractures in Two Regions of Ukraine. J Osteoporos. 2018;2018.
13. Williamson S, Landeiro F, Mcconnell T, Javaid MK. Costs of fragility hip fractures globally: a systematic review and meta-regression analysis. Osteoporos Int. 2017;
14. International Osteoporosis Foundation. The Asia-Pacific Regional Audit-Epidemiology, Costs, and Burden of Osteoporosis in 2013. International Osteoporosis Foundation. 2013.
15. Noor N, Nik K, Hatta M, Lokman M, Daud A, Ibrahim M, et al. Fracture risk prediction in post-menopausal women with osteopenia and osteoporosis: preliminary findings. Enferm Clin. 2018;28:232–5.
16. Lekamwasam S. The diversity of Fracture Risk Assessment Tool (FRAX)-based intervention thresholds in Asia. Osteoporos Sarcopenia. 2019;5(4):104–8.
17. Leslie WD, Brennan-Olsen SL, Morin SN, Lix LM. Fracture prediction from repeat BMD measurements in clinical practice. Osteoporos Int. 2015;27(1):203–10.
18. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al. UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1).
19. Zhou H, Mori S, Ishizaki T, Takahashi A, Matsuda K, Koretsune Y, et al. Genetic risk score based on the prevalence of vertebral fracture in Japanese women with osteoporosis. Bone Reports. 2016;5:168–72.
20. Al Anouti F, Taha Z, Shamim S, Khalaf K, Al Kaabi L, Alsafar H. An insight into the paradigms of osteoporosis: From genetics to biomechanics. Bone Reports. 2019;11(July):100216.
21. Kim SH, Yi SW, Yi JJ, Kim YM, Won YJ. Association Between Body Mass Index and the Risk of Hip Fracture by Sex and Age: A Prospective Cohort Study. J Bone Miner Res. 2018;33(9):1603–11.
22. Yusuf SA. Hubungan antara usia dengan bone densimetry pada wanita menopause alami. Trisakti; 2015.
23. Humaryanto, Syauqy A. Gambaran Indeks Massa Tubuh dan Densitas Massa Tulang sebagai Faktor Risiko Osteoporosis pada Wanita [The Profile of Body Mass Index and Bone Mass Density Scan as Osteoporosis Risk Factor among Female]. J Kedokt Brawijaya. 2019;30(3):218–22.
24. Bergh C, Wennergren D, Möller M, Brisby H. Fracture incidence in adults in relation to age and gender: A study of 27,169 fractures in the Swedish Fracture Register in a well-defined catchment area. PLoS One. 2021;15(12 December):1–18.
25. Abey-Nesbit R, Schluter PJ, Wilkinson T, Thwaites JH, Berry SD, Jamieson HA. Risk factors for hip fracture in New Zealand older adults seeking home care services: A national population cross-sectional study. BMC Geriatr. 2019;19(1):1–13.
26. World Health Organization. Falls. World Health Organizarion. 2021;
27. Cipriani C, Pepe J, Bertoldo F, Bianchi G, Cantatore FP, Corrado A, et al. The epidemiology of osteoporosis in Italian post-menopausal women according to the National Bone Health Alliance (NBHA) diagnostic criteria: a multicenter cohort study. J Endocrinol Invest. 2018;41(4):431–8.
28. Park CY, Lim JY, Park HY. Age at natural menopause in Koreans: Secular trends and influences thereon. Menopause. 2018;25(4):423–9.
29. Shimizu Y, Sawada N, Nakamura K, Watanabe Y, Kitamura K, Iwasaki M, et al. Menstrual and reproductive factors and risk of vertebral fractures in Japanese women: the Japan Public Health Center-based prospective (JPHC) study. Osteoporos Int. 2018;29(12):2791–801.
30. Peng K, Yao P, Kartsonaki C, Yang L, Bennett D, Tian M, et al. Menopause and risk of hip fracture in middle-aged Chinese women: A 10-year follow-up of China Kadoorie Biobank. Menopause. 2020;27(3):311–8.
31. Hernigou J, Schuind F. Tobacco and bone fractures: A review of the facts and issues that every orthopaedic surgeon should know. Bone Jt Res. 2019;8(6):255–65.
32. Shen GS, Li Y, Zhao GY, Zhou H Bin, Xie ZG, Xu W, et al. Cigarette smoking and risk of hip fracture in women: A meta-analysis of prospective cohort studies. Injury. 2015;46(7):1333–40.
33. Greenblatt MB, Tsai JN, Wein MN. Bone Turnover Markers in the Diagnosis and Monitoring of Metabolic Bone Disease. Clin Chem. 2017;63(2):464–74.
34. Szulc P, Delmas PD. Biochemical markers of bone turnover: Potential use in the investigation and management of post-menopausal osteoporosis. Osteoporos Int. 2008;19(12):1683–704.
35. Younes M, Hachfi H, Ouertani D, Hassine Neffati F, Ben Hammouda S, Jguirim M, et al. Utility of biochemical markers of bone turnover in diagnosis of osteoporosis and fracture risk prediction. Tunisie Medicale. 2014;92(5):304–10.
36. Kuo TR, Chen CH. Bone biomarker for the clinical assessment of osteoporosis: Recent developments and future perspectives. Biomark Res. 2017;5(1):5–13.

37. Rau C, Wu S, Kuo P, Chen Y, Chien P. Epidemiology of Bone Fracture in Female Trauma Patients Based on Risks of Osteoporosis Assessed using the Osteoporosis Self-Assessment Tool for Asians Score. Int J Environ Res Public Heal. 2017;14(1380).

38. Pongchaiyakul C, Nguyen ND, Eisman JA, Nguyen T V. Clinical risk indices, prediction of osteoporosis, and prevention of fractures: Diagnostic consequences and costs. Osteoporos Int. 2005;16(11):1444–50.