Title Page

- **Manuscript title:** Prevalence, Risk Assessment, And Predictors of Osteoporosis among Chronic Obstructive Pulmonary Disease Patients.
- **Running title/Short title:** Osteoporosis among COPD patients.
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Conflict of Interest:

There is no conflict of interest to be declared.

PREVALENCE, RISK ASSESSMENT, AND PREDICTORS OF OSTEOPOROSIS AMONG CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS.

ABSTRACT:

Objectives:

This study aimed to detect the prevalence and investigate the predictors for low bone mineral density among COPD patients and test a new risk assessment tool for the early screening of osteoporosis among COPD patients.

Methods:

This study is a longitudinal observational study conducted from June-2019 until December-2020 at a tertiary care setting in Penang, Malaysia**.** Follow-ups were arranged every six months. During the study, patients' BMD was checked every visit, and the subjects' pulmonary parameters were recorded, including; mMRC dyspnea scores, CAT scores, spirometry results, exacerbations history, and SpO_2%. Furthermore, a novel risk assessment tool was validated in this study, and logistic regression was conducted to find low BMD predictors among COPD patients.

Results:

Based on T-score, more than 50% of subjects were osteoporotic based. The overall mean±SD for patients' age was 65.4±10.04. The overall mean±SD for patients' BMI was 23.32±5.43. Both FEV1% predicted, and FEV/FVC was significantly lower among osteoporotic subjects, and lower mMRC stages were observed among non-osteoporotic patients. For the novel risk assessment tool, a cutoff point of 34 made the optimum balance between sensitivity and specificity (0.867 and 0.087, respectively) with an AUC of 0.934. Furthermore, severe COPD patients were four times at higher risk of getting osteoporosis, FEV% predicted, and FEV/FVC was inversely related to the risk of osteoporosis. Patients with severe dyspnea had twice the risk of getting osteoporosis.

Conclusion:

Osteoporosis was prevalent among COPD patients. For a screening tool, the risk assessment tool showed good sensitivity and precision in detecting osteoporotic subjects among COPD patients. Severe COPD patients were significantly at higher risk of getting osteoporosis.

Keywords: Osteoporosis, COPD, Risk Assessment, Prevalence, Predictors.

What's known:

- COPD can be associated with osteoporosis.
- Osteoporosis is a silent disease; a large gap was observed between the number of osteoporotic patients and those diagnosed or treated.

What's new:

- The prevalence and the predictors of osteoporosis among COPD patients were detected.
- A novel risk assessment tool for early screening of osteoporosis was validated.

1. Introduction:

Chronic obstructive pulmonary disease (COPD) is among the leading causes of death worldwide [1]. It is a serious lung disease known for causing irreversible and progressive airway obstruction and severe breathing limitation that can lead to emergency intervention and hospital admission. COPD is often under-diagnosed. It is estimated that more than 300 million patients are suffering from COPD worldwide, and it is considered among the most common respiratory conditions in the world [2]. It can be associated with an exaggerated chronic inflammatory response in the airways after contact with smoke, air pollution, noxious fumes or gases, and cigarette smoking [3]. COPD is now considered a systemic condition associated with many comorbidities such as lung cancer, diabetes mellitus, atherosclerosis, muscle weakness, anxiety, depression, and osteoporosis [4–6].

Osteoporosis is one of the comorbidities that can be associated with COPD. The national osteoporosis foundation (NOF) in the United States of America has described osteoporosis as "A bone disease that occurs when the body loses too much bone, makes too little bone, or both. As a

result, bones become weak and may break from a fall or, in serious cases, from sneezing or minor bumps. Osteoporotic bones have lost density or mass and contain abnormal tissue structure. As bones become less dense, they weaken and are more likely to break" [7]. The causative mechanism and the link between these two diseases remain unclear; a recent meta-analysis indicated that osteoporosis is more prevalent among COPD patients than anticipated [6]. Osteoporosis can be asymptomatic; the low bone mineral density among osteoporotic patients increases the risk of fractures, most common of which are the wrist, hip, and spinal [8]. Furthermore, a vertebral fracture can reduce lung capacity by 9% [9]. The impaired capacity to move due to osteoporotic fractures was linked to a faster decline in COPD patients' pulmonary function [10], which put the patients in a vicious cycle and drastically impact the patient's quality of life. Osteoporosis is a silent disease, and the majority of patients are unaware of their condition until it is too late; studies have shown that there is a huge treatment gap between the number of patients who are at high risk of osteoporotic fractures and the number of those being treated [11,12].

The link between COPD and osteoporosis is unclear and yet to be understood. In this study, we tried to detect the prevalence of osteoporosis among COPD patients in Malaysia, and we clinically evaluated the cases and investigated the possible predictors. We also tested and validated a novel osteoporosis risk assessment tool designed for the early identification of patients at high risk because standard mass testing for osteoporosis is neither practical nor cost-effective.

Methodology:

Study design and setting:

This study is a longitudinal observational study conducted from June-2019 until December-2020 at a tertiary care setting in Penang, Malaysia. Medical records, medical charts, laboratory reports, and detailed patient history have been screened to evaluate the patient's eligibility. The subjects' bone mineral density (BMD) was measured, then they were divided into groups; group A: Patients with COPD and Osteoporosis, and group B: Subjects with healthy BMD. All the health care facilities in the study are run publically by the ministry of health, Malaysia.

Participants:

To reduce the chance for selection bias, cases that met the inclusion criteria were coded and shuffled, then samples were selected randomly, and then subjects were invited to participate in the study. A competent pulmonologist and an investigator clinically examined all recruited subjects. In the first interview, all subjects were adequately informed about the study's details, roles, instructions, and written informed consent was obtained from them, then the baseline visit and two follow-ups were arranged every six months, the visits appointments were booked based on patients' convenience. The interviews and follow-ups took, on average, around 30 minutes to complete.

Tests and Measurements:

All tests and measurements were conducted during the patients' planned visits. Data collection tool has been developed to collect patients' information, including demographics, socioeconomic data, medical history, and clinical test results: The modified Medical Research Council (mMRC) dyspnea scores, COPD Assessment Test (CAT) scores, spirometry results, COPD severity, exacerbations history, and comorbidities (supplementary file-1). Also, patients' lifestyles and habits were recorded, like the level of activity, smoking history, drug use history. For the spirometry test, patients were requested not to take any short-acting bronchodilator 8 hours before the visit or any long-acting bronchodilator 24 hours before the visit; for those who took bronchodilator, only post-bronchodilator spirometry was performed. A well-trained nurse conducted the spirometry based on the American Thoracic Society (ATS) guidelines [13]; all recruited subjects were professionally diagnosed with COPD according to the latest GOLD guidelines [14].

BMD measurement:

The patients' bone mineral density (BMD) was tested every visit after making the respiratory examination and completing the follow-up interview. The BMD was measured using Quantitative Ultrasonography (QUS) at the calcaneus area (SONOST 3000, by OsteoSys Co., Ltd. Guro-Dong 152-848, Seoul, South Korea.). The results were expressed in T-Score and categorized based on WHO's criteria [15]. (Normal: T-score of -1.0 or above, osteopenia: T-score between -1.0 and -2.5, Osteoporosis: T-score of -2.5 or below, and Severe osteoporosis: T-score below -2.5+ Fracture).

Clinical Evaluation Tool (CET) for bone health:

Before conducting the BMD test, patients were interviewed to reduce the chance of being biased in the test's results. A unique closed-ended evaluation risk assessment tool was developed; the risk assessment was made by identifying risk factors for osteoporosis, then based on a simple additive scoring system, the patients' risk of being osteoporotic was estimated.

This tool was divided into two step; the first step consisted of 18 questions related to bone health, each of which carries specific points; from 1 to 3 (1: No, 2: I do not know/Not sure, 3: Yes), (supplementary file-2). The lowest possible is 18, while the highest possible score is 54. The total score was calculated, and the assumption was the higher the obtained score, the higher the risk for osteoporosis. The second step was the osteoporosis risk evaluation scale. Based on the obtained scores from the previous section, the cases were divided into two categories: 1-Non-Osteoporotic: (18-34) points, 2-Osteoporotic: (35-54) points.

Validation of the designed tool:

The designed tool's components and items were examined and evaluated by a panel of experts with medical research, clinical, and tools construction backgrounds. Receiver operator characteristic (ROC) analysis to determine the constructed diagnostic tool's sensitivity and specificity was conducted, results were analyzed to determine the best cutoff point of the obtained scores using SPSS (27.0; IBM corp.). The formulas that were used to calculate the sensitivity, specificity, and precision were as following [25]:

Sensitivity=$\frac{True\ Positive}{True\ Positive+False\ Negative}$=¿ [The number of patients with osteoporosis (T-score≤-2.5 at the calcaneus area)]/[The number of osteoporotic patients incorrectly classified as non-osteoporotic using the assessment tool+ The number of patients with osteoporosis (T-score≤-2.5 at the calcaneus area)]

1-specificty= $\frac{False\ Positive}{False\ Positive+True\ Negative}$ [The number of patients incorrectly classified with osteoporosis using the tool]/[The number of patients incorrectly classified with osteoporosis using the tool+The number of non-osteoporotic subjects(T-score>-2.5 at the calcaneus area)].

Then we replaced the false-positive rates with precision, representing the proportion of positive results that were correctly classified because it does not include the number of true negative and cannot be affected by imbalance caused by the negative proportions.

Precision= $\frac{True\ Positive}{True\ Positive + False\ Positive}$= [The number of patients with osteoporosis (T-score≤-2.5 at the calcaneus area)]/[The number of patients with osteoporosis (T-score≤-2.5 at the calcaneus area)+ The number of non-osteoporotic patients incorrectly identified as osteoporotic using the assessment tool].

The generated area under the curve (AUC) was used to evaluate the constructed tool's performance compared to QUS results; AUC should not be ≤0.500 [16].

Inclusion and exclusion Criteria:

All male COPD patients above 40 years old who visited the respiratory clinic or the ward were included in the study. Female patients were excluded because of the drastic postmenopausal hormonal effect on osteoporosis development and prognosis. Patients with other severe conditions that might significantly impact bone health were excluded (cancerous diseases, hepatic malfunction, kidney disease, Paget's disease, mastocytosis, and osteogenesis imperfect, severe malabsorption), Patients with severe endocrinal disorders like Addison's disease, Cushing's syndrome, and Graves' disease were also excluded. COPD patients with TB were excluded unless they were successfully treated more than five years ago, because of its combined effect on the lungs and bone health. Patients who were already diagnosed with bone disease or who were on bone treatment or currently using bone supplementations were excluded.

Statistical Analysis:

The statistical analysis was conducted using the latest version of the Statistical Package for the Social Sciences (SPSS) (Version 27.0; IBM corp.). Descriptive analyses were done to identify the nature of the study population. Chi-square test was performed for categorical variables and t-test to compare the means in continuous variables; both tests were used to detect any significant difference between two points and establish an association. Linear regression was conducted to examine the relationship between the CET and T-score during the study. Logistic regression was performed to calculate the risk of having osteoporosis among COPD subjects. The adopted

statistical significance cut point was at $p<0.05$. Microsoft Excel and Word were used to store and arrange data and to generate figures and tables.

Sample size:

The sample size was calculated using Daniel's formula for prevalence with finite population corrections [17,18]. It was done on for a precision of 5% (d=0.05), 95% confidence, odds ratio (OR=34.48%) [19], and for Penang's population (N=1746300) based on 2018 census [20]. The total sample size was 323 subjects; however, we were able to recruit 380 cases.

Registration and Ethical Approval:

This study was registered with the National Medical Research Register with the following number: NMRR-19-239-46017, and ethical approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with the following number: KKM/ NIHEC/P19-528(11).

Results:

Based on eligibility criteria, 469 subjects were invited to participate in the study, out of which 93 declined or were reluctant, and we lost contact with 61 subjects; additional 65 patients more were recruited, and the total number of patients was 380 (figure 1). Out of subjects, 207(54.5%) were Chinese, 109 (28.7%) were Malay, and 63 (16.6%) were Indians; only one patient was of other ethnic group.

The total number of osteoporotic subjects in the study was 196 patients (51.6%), based on QUS T-score results. The overall mean±SD for patients' age was 65.4±10.04. The overall mean±SD for patients' BMI was 23.32±5.43 (Table 1). The majority of patients were with no university education and were from urban areas (60.5% and 76.3%, respectively), and the average income for most patients was above 400USD per month (1600RM). Only 16 (4.2%) patients consumed alcohol regularly (more than two units a day), more than 80% had a history of smoking, and 55% had a history of at least one comorbid associated with COPD.

COPD among Osteoporotic and Non-osteoporotic Patients:

The overall mean SD of FEV1% predicted and FEV1/FVC ratios showed no significant difference between the baseline and final follow-up. However, during the study, both were significantly lower in osteoporotic subjects compared to the non-osteoporotic ones [FEV1% pred (baseline): 51.45±14.8 VS 61.85±16.1, FEV1% pred (final): 51.13±14.6 VS 61.79±15.7, FEV1/FVC (baseline): 62.9±16.2 VS 68.32±15.6, and FEV1/FVC (final): 62±16 VS 67.87±15.1] (Table 2). A statistically significant higher mean SD of the mMRC dyspnoea scale has been observed; The patients' overall score has increased between the baseline (2.1±0.77) and the final visit (2.33±0.82), and the score was significantly higher among osteoporotic patients at baseline and the final visit (2.38±0.81 and 2.46±0.87, respectively) compared to patients without osteoporosis (1.94±0.65 and 1.98±0.67). While the CAT score significantly increased in the last visit, the number of exacerbations was higher among osteoporotic patients. Patients' T-score was significantly higher in the last visit of the study, while the risk assessment tool showed higher scores among osteoporotic subjects.

The Risk Assessment Tool (CET):

Based on our sample, among the developed risk assessment tool components, the following factors showed a significant association with osteoporosis ($p<0.001$): a history of malnutrition or being severely underweight, using oral steroids for two consecutive months or more, and being frail and frequently falling (Figure 2). Factors like a history of broken bones due to minor falls, family history of bone diseases, regular alcohol consumption (more than two units per day), low physical activities (less than 30mintues a day) were significantly associated with osteoporosis ($p<0.01$), while the p-value for the frequent exposure to toxins and irritants was less than 0.05. Surprisingly, allergy to dairy products or eggs and a history of low calcium or vitamin D levels were not significant. Also, smoking and age did not show a significant difference among the recruited subjects.

The best cutoff point to optimize the tool's sensitivity and precision was between 34 and 35 points (34.5) of the score obtained. Where 86.7% of positive outcomes are correctly predicted or classified by the tool, while the 1-specificity at this point was 0.087, which means that around 9% of negative outcomes are incorrectly classified or identified as positive at this point (figure 3-A). For the same cutoff point, the precision was 0.914, and the recall was also 0.867 (figure-3-

B). The area under the curve (AUC) for the conducted test was 93.4%, and the overall model quality was above 0.5 (0.91) (figure-3-C).

Relationship between The Risk Assessment Tool (CET) and QUS's T-score:

To ensure that we have a linear relationship between the score obtained from the risk assessment tool and the QUS machine's score, we made a sector plot. In figure 4-A, the data showed positive linearity and homoscedasticity. As the tool's scores go up, the T-score goes up (the BMD of patients goes down because the obtained results in the T-score test are presented in negative values from -0.0 to -4.0). A statistically significant correlation has been observed between the tool and T-score, $p<0.01$. The prediction equation for T-score from the regression was $Y=1.15+0.11(X)$, and the $r^2=0.691$, which means 69.1% of the T-score was predictable by the tool.

The linear regression correlation was statistically significant between the tool's overall score and the overall T-score, $r(378)=0.832$, $p<0.001$. The bootstrapped 95 confidence interval for the slop to predict T-score from the evaluation score ranged from 0.1 to 0.12; thus, for each point increased score of the tool, the patients T-score score increased by about 0.10 to 0.12 points. The Durbin-Watson statistics were 1.4, which meets the assumption of dependence; the normal p-p plot of the standardized residual of the performed regression showed that the dots generally line up around the slop, so we have normality of residuals, figure 4-B.

Predictors for Osteoporosis among COPD Patients:

The conducted model was able to predict 69.2% of osteoporosis cases. Patients with severe COPD (GOLD C and D) were four times at higher risk of getting osteoporosis [OR: 3.917, 95 CI: (2.430-6.314), $p<0.001$] (Table 3). The results from FEV1% predicted and FEV1/FVC ratio were inversely statistically significant; the lower the spirometric values, the higher the risk of osteoporosis to predict osteoporosis [OR: 0.970, 95 CI: (0.954-0.986), p=0.001. and OR: 0.984, 95 CI (0.970-0.999), p=0.035, respectively]. Those who had more severe dyspnea (3rd stage and above) were at higher risk of osteoporosis; the mMRC dyspnea scale demonstrated a reasonable

predictability power [OR: 2.046, 95 CI: (1.122-3.733), P=0.02]. Other factors, including BMI, Age, Spo2, and CAT score, failed to predict the cases.

Discussion:

Osteoporosis was highly prevalent among COPD patients, 51% of subjects were osteoporotic. According to a recent meta-analysis, the pooled prevalence of osteoporosis among COPD patient was 37.62%, which is way lower than what we found in this study; however, looking at the included studies, we found that the range was so wide from 14% up to 66% [6], which put our finding at the upper end of the observed range. A meta-regression analysis of 57 studies came to a similar conclusion with 38% overall pooled prevalence [21]. The mean SD of BMI was close to Sakurai-Iesato's finding in Japan and lower than Graat-verboom's work in the Netherland [22,23], which is due to the increased obesity rates in Europe and the middle east compared to Asia [24]. Also, the average age was almost five years lower than both studies, which can be attributed to the aging population, especially in Japan [24].

The FEV1% predicted and FEV1/FVC ratios were significantly lower among osteoporotic patients than the non-osteoporotic ones, similar to a Taiwanese study. This study's logistic regression showed that BMI was not a predictor for osteoporosis, which was identical to our findings [25]. In our work, osteoporotic patients had more severe dyspnea and suffered from more frequent exacerbations. Similarly, In Greece, they found that COPD patients without any comorbidities had a better FEV1 predicated and significantly better performance on the mMRC dyspnea score throughout the study from the baseline to the final follow-up [26]. Vardar-yagli et al, found that kinesiophobia was strongly associated with more severe dyspnea and patients with comorbidities suffered from more severe fatigue and dyspnea than healthy subjects [27].

A significant association with osteoporosis has been observed among most of the enlisted risk factors. In Shanghai, they found that being underweight or malnourished and low-level activities were significantly associated with osteoporosis, which matches our findings [28]. A recent study from Sweden indicated that smoking was associated with an increased risk of osteoporosis and fractures [29]; however, in a regression meta-analysis, the researchers have reached inconclusive results regarding the effect of smoking [21]. They have also found that patients with low lung function parameters (FEV1% predicted and FEV1/FVC) and those at higher stages of GOLD criteria were at higher risk of osteoporosis. Furthermore, the significant risk factors for

osteoporosis among COPD patients included low BMI, frequent exacerbations, the use of steroids, systemic inflammation, low vitamin D, lack of physical activities, and hyperthyroidism [21]. Even though old age was a significant risk factor in five studies, heterogeneity was observed (I^2=72%, p=0.006), and sensitivity analysis revealed that the evidence was not strong. Similar to our findings, among male subjects in Taiwan, a higher prevalence of osteoporosis was observed among COPD patients, and lower BMI was associated with osteoporosis; after binary regression, low BMI was an insignificant risk factor, unlike severe COPD [25]. Although lactose intolerance has been associated with low BMD, according to Yahya and her colleagues, only low calcium level was significantly associated with low BMD ($\beta = 0.006$; $p = 0.033$) [30]. Also, it has been found that among patients above 65 years, factors such as slipping, falling, and being weak significantly increased the risk of getting fractures [31].

A few risk evaluation tools for osteoporosis were developed in the past; however, they were designed for postmenopausal women. Recent research has shown that most of these tools were lacking precision (ranging from 0.04 to 0.12) among Malaysian, and the Simple Calculated Osteoporosis Risk Estimation (SCORE) had the best balance between recall and precision among the tested tools, and the area under the curve was the highest (0.072-0.161) [32]. The Age, Body Size,No Estrogen (ABONE) and Osteoporosis Risk Assessment Instrument (ORAI) tools included information about age, body weight, estrogen use. The Osteoporosis Self-assessment Tool (OST) used information about weight and age. The SCORE was based on race, rheumatoid arthritis, trauma history after 45, estrogen therapy, and weight [33]. On the other hand, The Fracture Risk Assessment Tool (FRAX) focused on the risk of fractures in the next 10 years. In the USA, the National Osteoporosis Foundation (NOF) recommended not to use this tool without BMD measurement to assess postmenopausal women's bone health included [34]. A study has tested FRAX without BMD, and they found its sensitivity to be 33.3% with a specificity of 86.4% and an AUC of 60% at a threshold of ≥9.3 % [33], while the AUC in our findings was around 90%.

Etinberg et al, found that FRAX was the predictability of fractures varied a lot. Although the addiction of BMD test results to the tool's calculations improved the FRAX risk estimate (AUC for hip fractures: from 0.69 without BMD to 0.77 with BMD), it did little to improve its predictive performance [35]. After conducting a systematic review of the available tools'

performance, Crandall concluded that none of the tools was optimal in identifying osteoporotic patients [33].

Our results have shown that increased severity of COPD was associated with a higher risk of osteoporosis. Patients with more advanced COPD stages were at higher risk of osteoporosis; however vertebral deformities were not significantly associated with FEV1% [36]. Furthermore, In a longitudinal study, it has been noticed that the increased exacerbation rates were independently associated with the progression of osteoporosis among COPD patients [37]. This has been attributed to the exaggerated inflammatory response among COPD patients and increased hypoxia and oxidative stress, besides the imbalanced protease/antiprotease system [38]. Moreover, the regression has shown the partial pressure of oxygen *(*PaO2) and the frequency of exacerbation were significant predictors for low BMD *(*R2 = 0.09, p = 0.03 and R2 = 0.20, p = 0.007, respectively). A recent Japanese study investigated the correlation between COPD severity indicators and bone biomarkers. They found that the mean SD of FEV_1/FVC and %FEV_1 were significantly lower among COPD patients and were associated with decreased bone formation and caused osteogenesis malfunctioning among middle-aged and older adults [39].

Strengths and limitations:

There are a few limitations to this study. The developed risk assessment tool might be prone to recall bias since many of its components depend on patient's self-reporting. Furthermore, the recruited subjects were COPD patients from Penang only, limiting the generalization of findings. Unlike QUS T-score results, which were sensitive to patients' BMD changes, the tool could not detect changes in patients' bone health during the study. Nonetheless, this tool was sensitive enough and served its purpose in identifying high-risk subjects that should be forwarded for further examination. Furthermore, using a complex combination of major risk factors with different marking levels gave the tool unique flexibility. By putting a value on patients' ignorance of their condition, it was less prone to skewness, which reduces the chances of overlooking osteoporosis risk factors.

Although this tool was initially designed for COPD patients, it utilizes common risk factors that can be adapted for other populations. Moreover, the tested sample size was adequate, which gives a close enough picture and a realistic image of the presented topic. This study also provides a good insight into COPD patients' bone health in Malaysia and opens the door for more investigations

and comparative studies in the future. Importantly, this study gives a good insight for medical practitioners who are worried about their patients' bone health, and the developed tool might help in decision making whether to recommend more advanced quantitative expensive diagnostic test like DXA or not.

Conclusion:

Osteoporosis was prevalent among COPD patients. For a screening tool, the risk assessment tool showed good sensitivity and precision in detecting osteoporotic subjects among COPD patients. Severe COPD patients were significantly at higher risk of getting osteoporosis. Also, patients with lower spirometric results or higher mMRC scores were at higher risk of being osteoporotic.

References:

1. WHO | Burden of COPD. In: WHO [Internet]. World Health Organization; [cited 4 Mar 2021]. Available: https://www.who.int/respiratory/copd/burden/en/
2. World COPD Day - November 18th | NIOSH | CDC. 13 Nov 2020 [cited 4 Mar 2021]. Available: https://www.cdc.gov/niosh/newsroom/feature/WorldCOPD-Day11-18.html
3. Leap J, Arshad O, Cheema T, Balaan M. Pathophysiology of COPD. Critical Care Nursing Quarterly. 2021;44: 2–8. doi:10.1097/CNQ.0000000000000334
4. Inoue D, Watanabe R, Okazaki R. COPD and osteoporosis: links, risks, and treatment challenges. Int J Chron Obstruct Pulmon Dis. 2016;11: 637–648. doi:10.2147/COPD.S79638
5. Sundqvist M, Andelid K, Ekberg-Jansson A, Bylund J, Karlsson-Bengtsson A, Lindén A. Systemic Galectin-3 in Smokers with Chronic Obstructive Pulmonary Disease and Chronic Bronchitis: The Impact of Exacerbations. Int J Chron Obstruct Pulmon Dis. 2021;16: 367–377. doi:10.2147/COPD.S283372
6. Bitar AN, Syed Sulaiman SA, Ali IAH, Khan I, Khan AH. Osteoporosis among Patients with Chronic Obstructive Pulmonary Disease: Systematic Review and Meta-analysis of Prevalence, Severity, and Therapeutic Outcomes. J Pharm Bioallied Sci. 2019;11: 310–320. doi:10.4103/jpbs.JPBS_126_19
7. Learn What Osteoporosis Is and What It’s Caused by. In: National Osteoporosis Foundation [Internet]. [cited 4 Mar 2021]. Available: https://www.nof.org/patients/what-is-osteoporosis/
8. Cai S, Yu H, Li Y, He X, Yan L, Huang X, et al. Bone mineral density measurement combined with vertebral fracture assessment increases diagnosis of osteoporosis in postmenopausal women. Skeletal Radiol. 2020;49: 273–280. doi:10.1007/s00256-019-03280-3

9. Morseth B, Melbye H, Waterloo S, Thomassen MR, Risberg MJ, Emaus N. Cross-sectional associations between prevalent vertebral fracture and pulmonary function in the sixth Tromsø study. BMC Geriatrics. 2013;13: 116. doi:10.1186/1471-2318-13-116

10. Ozcakir S, Sigirli D, Ursavas A, Uzaslan E. COPD and Osteoporosis: Associated Factors in Patients Treated with Inhaled Corticosteroids . In: International Journal of Chronic Obstructive Pulmonary Disease [Internet]. Dove Press; 9 Oct 2020 [cited 4 Mar 2021] pp. 2441–2448. doi:10.2147/COPD.S274728

11. Kanis JA, Svedbom A, Harvey N, McCloskey EV. The Osteoporosis Treatment Gap. Journal of Bone and Mineral Research. 2014;29: 1926–1928. doi:https://doi.org/10.1002/jbmr.2301

12. Curtis EM, Moon RJ, Harvey NC, Cooper C. Reprint of: The impact of fragility fracture and approaches to osteoporosis risk assessment worldwide. International Journal of Orthopaedic and Trauma Nursing. 2017;26: 7–17. doi:10.1016/j.ijotn.2017.04.004

13. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200: e70–e88. doi:10.1164/rccm.201908-1590ST

14. pavelka. Updates in COPD: The 2019 GOLD Guidelines. In: College of Pharmacy - University of Minnesota [Internet]. 16 Apr 2019 [cited 4 Mar 2021]. Available: https://www.pharmacy.umn.edu/degrees-and-programs/postgraduate-pharmacy-residency-program/news-events-and-publications/curbside-consult-volume-17-issue-1-first-quarter-2019/updates-copd-2019-gold-guidelines

15. Lewiecki EM. [Table, Table 1. World Health Organization criteria for classification of patients with bone mineral density measured by dual-energy X-ray absorptiometry (3).]. MDText.com, Inc.; 23 Apr 2018 [cited 4 Mar 2021]. Available: https://www.ncbi.nlm.nih.gov/books/NBK279049/table/osteoporosis-clinic.classifica/

16. Fawcett T. An introduction to ROC analysis. Pattern Recognition Letters. 2006;27: 861–874. doi:10.1016/j.patrec.2005.10.010

17. Metcalfe C. Biostatistics: A Foundation for Analysis in the Health Sciences. 7th edn. Wayne W. Daniel, Wiley, 1999. No. of. pages: xiv+755+appendices. Price: £28.95. ISBN 0-471-16386-4. Statistics in Medicine. 2001;20: 324–326. doi:10.1002/1097-0258(20010130)20:2<324::AID-SIM635>3.0.CO;2-O

18. Daniel WW, Cross CL. Biostatistics: A Foundation for Analysis in the Health Sciences. John Wiley & Sons; 2018.

19. Subramaniam S, Chan C-Y, Soelaiman I-N, Mohamed N, Muhammad N, Ahmad F, et al. Prevalence and Predictors of Osteoporosis Among the Chinese Population in Klang Valley, Malaysia. Applied Sciences. 2019;9: 1820. doi:10.3390/app9091820

20. Department of Statistics Malaysia Official Portal. [cited 8 Sep 2020]. Available: https://www.dosm.gov.my/v1/

21. Chen Y-W, Ramsook AH, Coxson HO, Bon J, Reid WD. Prevalence and Risk Factors for Osteoporosis in Individuals With COPD: A Systematic Review and Meta-analysis. Chest. 2019;156: 1092–1110. doi:10.1016/j.chest.2019.06.036

22. Sakurai-Iesato Y, Kawata N, Tada Y, Iesato K, Matsuura Y, Yahaba M, et al. The Relationship of Bone Mineral Density in Men with Chronic Obstructive Pulmonary Disease Classified According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Combined Chronic Obstructive Pulmonary Disease (COPD) Assessment System. Internal Medicine. 2017;56: 1781–1790. doi:10.2169/internalmedicine.56.6910

23. Graat‐Verboom L, Borne BE van den, Smeenk FW, Spruit MA, Wouters EF. Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures. Journal of Bone and Mineral Research. 2011;26: 561–568. doi:https://doi.org/10.1002/jbmr.257

24. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92: 6–10. doi:10.1016/j.metabol.2018.09.005

25. Lin C-H, Chen K-H, Chen C-M, Chang C-H, Huang T-J, Lin C-H. Risk factors for osteoporosis in male patients with chronic obstructive pulmonary disease in Taiwan. PeerJ. 2018;6. doi:10.7717/peerj.4232

26. Tryfon S, Maniakos N, Ginis A, Markou I-L. Evaluation of pulmonary function and dyspnea index in Greek COPD patients with at least one metabolic comorbidity versus the population of the study without comorbidities – AEOLOS study. Endocrine Abstracts. Bioscientifica; 2020. doi:10.1530/endoabs.70.EP42

27. Vardar-Yagli N, Calik-Kutukcu E, Saglam M, Inal-Ince D, Arikan H, Coplu L. The relationship between fear of movement, pain and fatigue severity, dyspnea level and comorbidities in patients with chronic obstructive pulmonary disease. Disability and Rehabilitation. 2019;41: 2159–2163. doi:10.1080/09638288.2018.1459886

28. Q Z, W C, G W, X S. Prevalence and contributing factors of osteoporosis in the elderly over 70 years old: an epidemiological study of several community health centers in Shanghai. Ann Palliat Med. 2020;9: 231–238. doi:10.21037/apm.2020.02.09

29. Li H, Wallin M, Barregard L, Sallsten G, Lundh T, Ohlsson C, et al. Smoking-Induced Risk of Osteoporosis Is Partly Mediated by Cadmium From Tobacco Smoke: The MrOS Sweden Study. Journal of Bone and Mineral Research. 2020;35: 1424–1429. doi:https://doi.org/10.1002/jbmr.4014

30. Yahya NFS, Daud NM, Makbul IAA, Aziz QASA. Association of calcium intake, lactose intolerance and physical activity with bone health assessed via quantitative ultrasound among young adults of a Malaysian university. Arch Osteoporos. 2021;16: 14. doi:10.1007/s11657-020-00874-6

31. Yu W-Y, Hwang H-F, Chen C-Y, Lin M-R. Situational risk factors for fall-related vertebral fractures in older men and women. Osteoporos Int. 2021 [cited 7 Mar 2021]. doi:10.1007/s00198-020-05799-x

32. Toh LS, Lai PSM, Wu DB-C, Bell BG, Dang CPL, Low BY, et al. A comparison of 6 osteoporosis risk assessment tools among postmenopausal women in Kuala Lumpur, Malaysia. Osteoporosis and Sarcopenia. 2019;5: 87–93. doi:10.1016/j.afos.2019.09.001

33. Crandall CJ. Risk Assessment Tools for Osteoporosis Screening in Postmenopausal Women: A Systematic Review. Curr Osteoporos Rep. 2015;13: 287–301. doi:10.1007/s11914-015-0282-z

34. Crandall CJ, Schousboe JT, Morin SN, Lix LM, Leslie W. Performance of FRAX and FRAX-Based Treatment Thresholds in Women Aged 40 Years and Older: The Manitoba BMD Registry. Journal of Bone and Mineral Research. 2019;34: 1419–1427. doi:https://doi.org/10.1002/jbmr.3717

35. Ettinger B, Ensrud KE, Blackwell T, Curtis JR, Lapidus JA, Orwoll ES, et al. Performance of FRAX in a cohort of community-dwelling, ambulatory older men: the Osteoporotic Fractures in Men (MrOS) study. Osteoporos Int. 2013;24: 1185–1193. doi:10.1007/s00198-012-2215-3

36. Graumam RQ, Pinheiro MM, Nery LE, Castro CHM. Increased rate of osteoporosis, low lean mass, and fragility fractures in COPD patients: association with disease severity. Osteoporos Int. 2018;29: 1457–1468. doi:10.1007/s00198-018-4483-z

37. Kiyokawa H, Muro S, Oguma T, Sato S, Tanabe N, Takahashi T, et al. Impact of COPD Exacerbations on Osteoporosis Assessed by Chest CT Scan. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2012;9: 235–242. doi:10.3109/15412555.2011.650243

38. Sarkar M, Bhardwaj R, Madabhavi I, Khatana J. Osteoporosis in Chronic Obstructive Pulmonary Disease. Clin Med Insights Circ Respir Pulm Med. 2015;9: CCRPM.S22803. doi:10.4137/CCRPM.S22803

39. Tsukamoto M, Mori T, Nakamura E, Okada Y, Fukuda H, Yamanaka Y, et al. Chronic obstructive pulmonary disease severity in middle-aged and older men with osteoporosis associates with decreased bone formation. Osteoporosis and Sarcopenia. 2020;6: 179–184. doi:10.1016/j.afos.2020.11.003