Original Article

Mini Nutritional Assessment Short-Form as screening tool for osteoporosis in patients with chronic obstructive pulmonary disease

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Background and Objectives: Osteoporosis is a common complication of chronic obstructive pulmonary disease (COPD). It is impractical to measure bone mineral density (BMD) in all patients with COPD. This study aimed to investigate the relationship between Mini Nutritional Assessment Short-Form (MNA-SF), a simple nutritional status questionnaire, and osteoporosis, and to determine whether it can be used as a reliable screening tool for osteoporosis in patients with COPD. **Methods and Study Design:** Thirty-seven patients with stable COPD were enrolled in this prospective cohort study. Patients with MNA-SF scores >11 were defined as well-nourished, and those with scores of ≤11 being at risk for malnutrition. Body composition, BMD, and undercarboxylated osteocalcin (ucOC), a bone metabolism marker, were measured using bioelectrical impedance, dual energy X-ray, and electrochemiluminescence immunoassay, respectively. **Results:** Seventeen (45.9%) were classified as at risk for malnutrition, and 13 (35.1%) had osteoporosis. Patients at risk for malnutrition had significantly more osteoporosis and higher ucOC values than well-nourished patients (p=0.007, p=0.030, respectively). Patients with osteoporosis also had significantly lower body mass index (BMI) and fat-free mass index than those without osteoporosis (p= 0.007 and p=0.005, respectively), although FEV_1 % pred was not significantly different. MNA-SF (cutoff value; 11) had better sensitivity to identify the presence of osteoporosis than BMI (cutoff value; 18.5 kg/m^2) (sensitivity, 0.769; specificity, 0.708; sensitivity, 0.462; specificity, 0.875, respectively). **Conclusions:** MNA-SF was associated with osteoporosis and bone metabolism markers in patients with COPD. MNA-SF may be a useful screening tool for osteoporosis in patients with COPD.

Key Words: chronic obstructive pulmonary disease, osteoporosis, Mini Nutritional Assessment Short-Form, nutritional assessment

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease characterized by persistent respiratory symptoms and airflow limitation and is a systemic disease accompanied by many comorbidities.[1] Nutritional impairment is one of the most important comorbidities of COPD, and malnutrition is a prognostic factor independent of airflow limitation.[2] Therefore, it is important to assess the nutritional status of patients with COPD in daily clinical practice. The full Mini Nutritional Assessment (MNA) questionnaire is a well-established nutritional assessment tool for the elderly[3] and low scores has been reported to be associated with hospitalizations in patients with COPD.[4] However, because it takes 10-15 minutes to complete the full MNA, it is not widely used in clinical practice. Therefore, a more concise Mini Nutritional Assessment Short-Form (MNA-SF), which consists of six questions and can be administered in less than four minutes, has been developed[5] and validated.[6] The MNA-SF is recommended by the European Society for Clinical Nutrition and Metabolism for the nutritional assessment of elderly patients.[7] Currently, MNA-SF is utilized in patients with a variety of diseases, and we have reported that MNA-SF scores are associated with exacerbations in patients with COPD.[8]

Osteoporosis is highly prevalent in patients with COPD[9] and increases the risk of fractures, leading to the deterioration of activities of daily living in patients with COPD.[10] However, it is impractical to screen all patients with COPD for osteoporosis, including bone density. Therefore, the key is to efficiently detect patients with COPD who are at risk for osteoporosis. A recent meta-

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analysis reported that the risk factors for osteoporosis in patients with COPD were weight loss (body mass index (BMI) <18.5 kg/m^2), lower fat-free mass index (FFMI), and the presence of sarcopenia.[9] Nutritional status is certainly associated with osteoporosis, but mobility also affects its development. Therefore, the MNA-SF, which considers nutritional status as well as mobility and neuropsychological problems, may be better at identifying osteoporosis than BMI. The purpose of this study was to investigate the relationship between MNA-SF, an easy to perform questionnaire, and bone mineral density (BMD) and bone metabolism markers in patients with COPD, and to examine whether MNA-SF could be a screening tool for osteoporosis in patients with COPD.

METHODS

This was a prospective study of patients with already diagnosed COPD who regularly attended the Nara Medical University Hospital between September 2011 and March 2014. COPD was diagnosed when FEV_1/FVC was less than 0.7, based on the GOLD (Global Initiative for Chronic Obstructive Lung Disease) definition.[11] We excluded patients who had known heart disease, malignancy, cor pulmonale, or any other severe inflammatory or metabolic disease. Eventually, 37 patients with stable COPD agreed to participate in this study. Pulmonary function tests were performed in all patients. Vital capacity (VC), forced vital capacity (FVC), FEV_1, and residual volume (RV) were measured using a pulmonary function instrument with computer processing (FUDAC 70, Fukuda Denshi, Tokyo, Japan), and the FEV_1/FVC ratio was calculated. Lung volumes were determined using the helium gas dilution method, and the diffusing capacity for carbon monoxide (DLco) was measured by the single-breath method. The obtained values were expressed as percentages of the predicted values.[12] This study was approved by the Ethical Advisory Committee of Nara Medical University (No.447), and all patients provided written informed consent.

The MAN-SF consists of six items: weight loss over the past three months, appetite over the past three months, mobility, psychological stress, neuropsychological problems, and BMI or calf circumference.[5] MNA-SF classifies nutritional status as normal (scores >11), risk for malnutrition (8–11), or malnourished (<8). In this study, patients with an MNA-SF score of >11 were defined as well-nourished, and those with a score of ≤11 were at risk for malnutrition. The COPD assessment test (CAT) is a tool used to assess symptoms in patients with COPD.[13] The CAT consists of eight items scored from 0 to 5 (0=best, 5=worst) that include coughing, mucus production, chest tightness, capacity for exercise and activities, confidence, sleep quality, and energy levels. CAT scores range from 0 to 40. The ABCD classification of GOLD categorizes CAT scores of <10 (low symptoms) and CAT scores of ≥10 (high symptoms).11 In this study, we used the Japanese version of CAT.[14]

Body composition, including fat-free mass (FFM), fat mass (FM), and body fat percentage (% fat), was measured by bioelectrical impedance analysis (BIA) using the In Body 720 (InBody Co., Ltd., Japan). The FFM index (FFMI) and fat mass index (FMI) scores were calculated. BMD was measured using dual-energy X-ray absorptiometry (DXA). BMD values (g/cm^2) and T-scores (the number of standard deviations (SDs) of the comparison of the subject's BMD value with the mean BMD value of a young adult population of the same sex) were obtained from the average value from L1 to L4 of the lumbar spine. Osteoporosis was defined as a T-score ≤-2.5, according to the criteria of the World Health Organization. Undercarboxylated osteocalcin (ucOC), a bone metabolism marker, was measured using an electrochemiluminescence immunoassay.

Ethics approval and informed consent

This study was approved by the Ethical Advisory Committee at Nara Medical University (No.447), and all patients provided written informed consent.

Statistical analysis

Continuous variables are presented as median [quartile 1 - quartile 3]. Statistical significance was set at $p<0.05$. The chi-square test for categorical data and the Mann-Whitney U-test for non-parametric continuous variables were conducted for comparison between the two groups. Statistical analysis was performed using IBM SPSS Statistics version 20 for Windows (IBM Corp., Armonk, NY, USA).

RESULTS

Mini Nutritional Assessment Short-Form

The characteristics of the participants are present in Table 1. Median values of age and BMI were 69 years and 20.4 kg/m^2, respectively. Among the included patients, 35 (94.6 %) were males. Of the total number of patients, 14 (37.8%) had mild to moderate airflow limitation and 23 (62.2%) had severe or very severe airflow limitation. In the MNA-SF classification, 20 patients (54.1%) were classified as well-nourished (MNA-SF score >11) and 17 patients (45.9%) were classified as at risk for malnutrition (MNA-SF score ≤11). No patients had previous fragility fractures. Patients at risk for malnutrition and well-nourished patients had similar rates of use of inhaled corticosteroids (p=0.324; 40.0% and 52.9%, respectively). No patient had been prescribed oral steroids regularly.

Patients at risk for malnutrition and well-nourished patients had similar ages (p=0.752) (Table 2). Patients at risk for malnutrition had significantly lower BMIs, FFMI scores, FMI scores, and % fat than those of well-nourished patients (p<0.001, p<0.001, p<0.001, p=0.002, respectively). Regarding pulmonary function variables and MNA-SF, patients at risk for malnutrition had significantly lower RV % pred and DLco % pred than well-nourished patients (p=0.008 and p<0.001; respectively); however, there was no significant difference in VC % pred and FEV_1 % pred between the two groups (p=0.149 and p=0.110, respectively).

Osteoporosis and body composition

Of the 37 patients, 13 (35.1%) had osteoporosis (Table 3). Patients with osteoporosis had significantly lower BMIs and FFMI scores than did those without osteoporosis, although FMI and %fat were not significantly different between the two groups (p=0.007, p=0.005, p=0.203, p=0.371, respectively). There was no significant differ-

Table 1. The characteristics of participating restaurants (n=90)

	Median [Q1–Q3] or n (%)
Number	37
Men/ women	35/ 2
Age, years	69.0 (65.0-77.0)
BMI, kg/m^2	20.4 (18.8-23.3)
GOLD stage, n	
I	2
II	12
III	19
IV	4
VC % pred, %	92.3 (84.9-105)
FEV_1% pred, %	46.7 (37.5-61.2)
RV% pred, %†	137 (111-171)
DL_{CO}, % pred, %†	39.3 (31.9-53.6)
CAT	16 (10-22)
MNA-SF	
Well-nourished, n (%)	20 (54.1%)
At risk of malnutrition, n (%)	17 (45.9%)

BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; VC: vital capacity; FEV_1: forced expiratory volume in 1 second; RV: residual volume; DL_{co}: diffusing capacity for carbon monoxide; CAT: COPD assessment test; MNA-SF: mini nutritional assessment short form.
†Missing data for RV %pred. and DLco %pred., n=35.

ence in lung function variables such as FEV_1 % pred, RV %pred, and DLco % pred other than VC between the two groups (p=0.089, p=0.824, p=0.073, p=0.046, respectively). In terms of bone metabolism markers, ucOC was significantly elevated in patients with osteoporosis compared to that in those without osteoporosis. In the relationship between nutritional status assessed by MNA-SF and osteoporosis, patients at risk for malnutrition had significantly more osteoporosis than did well-nourished patients (p=0.007; 58.9% and 15.0%, respectively), and patients at risk of malnutrition had significantly lower BMD than well-nourished patients (p=0.005) (Figure 1). Moreover, patients at risk for malnutrition had significantly higher ucOC values (p=0.030). Conversely, COPD severity (FEV_1 % pred) was not correlated with BMD and ucOC (r= 0.255, p=0.153, r=- 0.311, p=0.061, respectively).

Identification of osteoporosis by BMI and MNA-SF

Of the 13 patients with osteoporosis, 10 were at risk for malnutrition and three were well-nourished, as assessed via the MNA-SF, with a significant difference between the groups (p=0.005, sensitivity: 0.769, specificity: 0.708) (Table 4). When BMI of 18.5 kg/m^2 was used as the cut-off value for the presence of osteoporosis, statistical significance remained, but the sensitivity was much weaker than that observed when MNA-SF was used as the cut-off (p=0.023, sensitivity: 0.462, specificity: 0.875). There was no association between the presence of CAT symptoms and the presence of osteoporosis (p=0.26).

DISCUSSION

The main findings of the present study are as follows: 1) Patients with COPD at risk for malnutrition by MNA-SF had lower BMD and FFMI as well as higher serum concentrations of ucOC compared to well-nourished patients; 2) MNA-SF (<11) was superior to BMI (<18.5 kg/m^2) in terms of its sensitivity in identifying osteoporosis in patients with COPD.

Patients with COPD have lower BMDs than those of healthy people,[15] and are at a higher risk of osteoporotic fractures, one of the factors that reduce physical activity. Therefore, in clinical practice, there is a need for the early detection of patients with COPD at risk for osteoporosis. Bones respond to nutritional status and mechanical loading. Physical exercise reportedly significantly improves the BMD of the lumbar spine and femoral neck of patients and to relieve pain,[16] making it an important factor in the prevention of osteoporosis. In addition to nutrition and exercise, age,[17] smoking,[18] exacerbations,[19] and steroid use[20] have been implicated in osteoporosis in COPD patients. Multiple factors must be considered when screening for osteoporosis in patients with COPD.

The MNA-SF includes nutritional status, mobility, and neuropsychological problems in its metrics. In this study, six of the nine patients with COPD with weight loss (BMI <18.5 kg/m^2) had osteoporosis and weight loss (BMI <18.5 kg/m^2) was associated with osteoporosis (Table 4). However, of the twenty-eight patients with COPD without weight loss (BMI ≥18.5 kg/m^2), seven had osteoporosis, and BMI alone could detect only about half of the patients with osteoporosis. On the other hand, only three patients with COPD assessed as being well-nourished using MNA-SF had osteoporosis. Therefore, screening for osteoporosis based on the BMI alone may result in more patients with osteoporosis being missed.

As in previous reports,[9] FFMI also correlated with BMD in this study (p=0.003, r=0.521). However, special equipment is required to measure FFMI, and not all medical institutions can measure it. However, we found no correlation between the %FEV_1 and BMD. A previous systematic review reported that a decrease in FEV_1 was associated with an increased risk of osteoporosis.[15] However, a recent meta-analysis revealed that a lower FEV_1 value was not a significant risk factor for osteoporosis in patients with COPD.[9] Nutritional status and mobility may be more important than the COPD stage in assessing osteoporosis in patients with COPD. Therefore, nutritional

Table 2. Mini nutritional assessment short-form

	Well nourished (n=20)	At risk of malnutrition (n=17)	*p* value
Age, yr	69.5 (65-76)	69 (64-80)	0.752
BMI, kg/m^2	23.3 (21.8-24.1)	17.7 (16.8-19.1)	<0.001
FFMI, kg/m^2	16.9 (16.0-17.1) †	14.0 (13.8-14.8)	<0.001
FMI, kg/m^2	6.9 (5.0-8.1) †	3.8 (2.7-4.3)	<0.001
% body fat, %	28.8 (22.9-32.4) †	20.8 (16.3-23.9)	0.001
VC %pred., %	96.5 (89.9-108)	90.0 (79.9-100)	0.149
FEV_1% pred, %	51.6 (42.8-64.4)	43.3 (35.1-49.0)	0.110
RV% pred, %†	115 (98.9-139)	167 (146-198) ‡	0.008
DL_{CO}, % pred, %†	47.8 (38.2-61.1)	30.4 (20.7-40.2) ‡	<0.001
CAT	15 (8.3-20.3)	19 (14-23)	0.167

MNA-SF: mini nutritional assessment short form; BMI: body mass index; FFMI: fat-free mass index; FMI: fat mass index; VC: vital capacity; FEV_1: forced expiratory volume in 1 second; RV: residual volume; DL_{co}: diffusing capacity for carbon monoxide; CAT: COPD assessment test.
†Missing data for FFMI. FMI and % body fat, n=18.
‡Missing data for RV %pred. and DLco %pred., n=15.

Table 3. Osteoporosis

	Osteoporosis (+) (n=13)	Osteoporosis (-) (n=24)	*p* value
Age, yr	69 (64-77)	69.5 (65-76)	1.000
BMI, kg/m^2	18.8 (16.8-20.1)	22.0 (19.1-23.9)	0.007
FFMI, kg/m^2	13.9 (13.7-15.7)	16.1 (14.8-16.9) †	0.005
FMI, kg/m^2	7.5 (7.2-8.5)	8.8 (7.9-9.3) †	0.203
% body fat, %	23.3 (17.3-25.6)	23.4 (19.4-32.3) †	0.371
VC %pred., %	90.0 (79.9-99.0)	98.6 (89.5-113)	0.046
FEV_1% pred, %	43.3 (35.1-47.4)	51.6 (40.7-65.7)	0.089
RV% pred, %†	133 (105-174) ‡	137 (113-166) §	0.824
DL_{CO}, % pred, %†	33.7 (23.0-42.3) ‡	41.9 (34.4-59.3) §	0.073
$_{uc}$OC, ng/mL	4.4 (2.9-8.2)	2.8 (1.9-3.8)	0.004
CAT	16 (14-21)	15 (8.3-22)	0.460

MNA-SF: mini nutritional assessment short form; BMI: body mass index; FFMI: fat-free mass index; FMI: fat mass index; VC: vital capacity; FEV_1: forced expiratory volume in 1 second; RV: residual volume; DL_{co}: diffusing capacity for carbon monoxide; ucOC: under-carboxylated osteocalcin; CAT: COPD assessment test.
†Missing data for FFMI. FMI and % body fat, n=22.
‡Missing data for RV %pred. and DLco %pred., n=12.
§Missing data for RV %pred. and DLco %pred., n=23.

Table 4. Identification of osteoporosis

	Osteoporosis (+), n	Osteoporosis (-), n	*p* value
MNA-SF			0.005
Well nourished	3	17	
At risk of malnutrition	10	7	
BMI (kg/m^2)			0.023
≥18.5	7	21	
<18.5	6	3	
CAT			0.26
<10	2	9	
≥10	11	15	

MNA-SF: mini nutritional assessment short form; BMI: body mass index; CAT: COPD assessment test.

assessment by MNA may be a screening tool for osteoporosis, and that BMD measurement should be performed when patients with COPD are diagnosed as being at risk for malnutrition (MNA-SF <11).

Vitamin K deficiency leads to bone fragility and is a risk factor for fractures. In addition to nutritional disorders, COPD directly affects vitamin K deficiency. Osteocalcin, a bone matrix protein synthesized by osteoblasts, is not incorporated into the bone matrix and is released into the blood as ucOC in vitamin K-deficient conditions because glutamate residues are not converted to γ-carboxyglutamate residues. Therefore, elevated serum ucOC levels indicate vitamin K deficiency in the bone.[21] Vitamin K deficiency is caused by inadequate intake, malabsorption of fats, and use of coumarin anticoagulants. In the elderly, vitamin K absorption from the intestinal tract is thought to be reduced due to decreased secretion of bile salts and pancreatic juice and decreased dietary fat intake, and the elderly reportedly require higher vitamin K intake.[22] Patients with COPD reportedly have reduced vitamin K levels compared to those of smokers and nonsmokers.[23] Patients with COPD may be more susceptible to vitamin K deficiency due to the presence of genetic polymorphisms encoding proteins involved in the

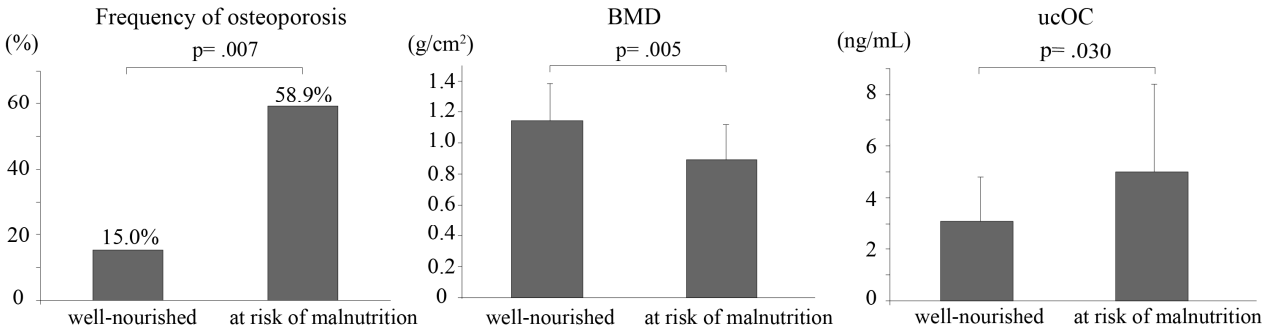
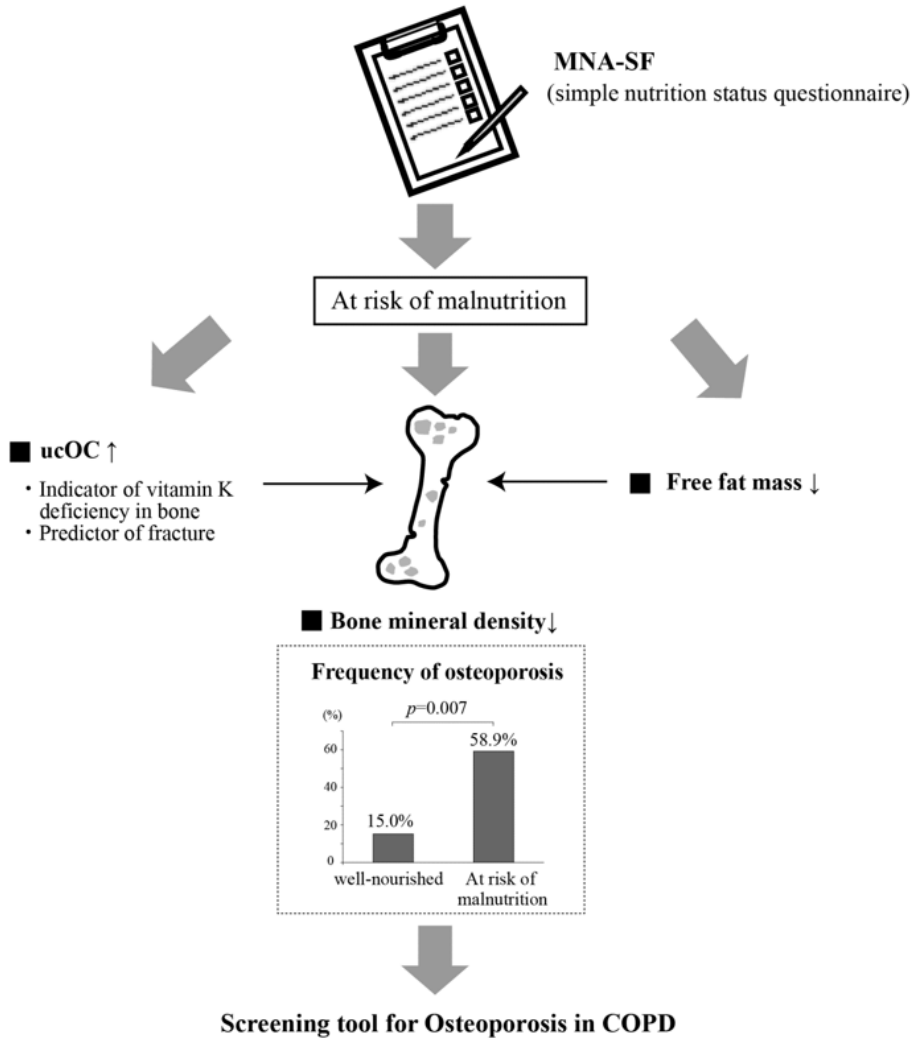


Figure 1. Frequency of osteoporosis, BMD and ucOC levels by nutritional status. BMD: bone mineral density; ucOC: undercarboxylated osteocalcin.



Graphical abstract. Mini Nutritional Assessment Short-Form (MNA-SF) may be valid screening tool for osteoporosis in patients with chronic obstructive pulmonary disease.

vitamin K cycle and increased demand for vitamin K activation by accelerated elastin degradation.[23] Thus, various factors may predispose elderly patients with COPD to vitamin K deficiency in the bones. In this study, patients at risk for malnutrition by MNA-SF had significantly higher serum ucOC levels than those who were well-nourished. Elevated ucOC levels have been reported to be a predictor of hip fracture independent of bone mass.[24] Therefore, the MNA-SF may also have the potential to predict future bone fractures.

The present study had some limitations. Most of the patients in this study were men. However, most of the large clinical trials of COPD in Japanese patients comprised mostly men, such as the present study.[25,26] Although the sample size of this study is small, the strength of this study is that the results can be easily applied in a clinical setting. Prospective longitudinal studies are needed to better determine whether patients with COPD at risk for malnutrition measured by MNA-SF will develop bone fractures in the future.

Conclusion

COPD is often complicated by osteoporosis, and osteoporosis in patients with COPD is more likely to be caused by nutritional disorders than by the COPD itself. The risk of osteoporosis may increase if MNA-SF scores among COPD patients are at risk for malnutrition. MNA-SF may be a simple tool to identify patients with osteoporosis and may be frequently used in clinical settings.

AUTHOR DISCLOSURES

None of the authors have any financial conflicts of interest to declare as it relates to the contents of this manuscript.

REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195:557-82. doi: 10.1164/rccm.201701-0218PP.
2. Cavaillès A, Brinchault-Rabin G, Dixmier A, Goupil F, Gut-Gobert C, Marchand-Adam S et al. Comorbidities of COPD. Eur Respir Rev. 2013;22:454-75. doi: 10.1183/09059180.00008612.
3. Guigoz Y, Lauque S, Vellas BJ. Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med. 2002;18:737-57. doi: 10.1016/s0749-0690(02)00059-9.
4. Benedik B, Farkas J, Kosnik M, Kadivec S, Lainscak M. Mini nutritional assessment, body composition, and hospitalisations in patients with chronic obstructive pulmonary disease. Respir Med. 2011;105(Suppl 1):S38-43. doi: 10.1016/s0954-6111(11)70009-9.
5. Rubenstein LZ, Harker JO, Salvà A, Guigoz Y, Vellas B. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). J Gerontol A Biol Sci Med Sci. 2001;56:M366-72. doi: 10.1093/gerona/56.6.m366.
6. Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T et al. Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging. 2009;13:782-8. doi: 10.1007/s12603-009-0214-7.
7. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015;34:335-40. doi: 10.1016/j.clnu.2015.03.001.
8. Yoshikawa M, Fujita Y, Yamamoto Y, Yamauchi M, Tomoda K, Koyama N, Kimura H. Mini Nutritional Assessment Short-Form predicts exacerbation frequency in patients with chronic obstructive pulmonary disease. Respirology. 2014;19:1198-203. doi: 10.1111/resp.12380.
9. Chen YW, 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;156:1092-110. doi: 10.1016/j.chest.2019.06.036.
10. Gazzotti MR, Roco CM, Pradella CO, Nascimento OA, Porto EF, Adas M, Lazaretti-Castro M, Jardim JR. Frequency of osteoporosis and vertebral fractures in chronic obstructive pulmonary disease (COPD) patients. Arch Bronconeumol (Engl Ed). 2019;55:252-7. doi: 10.1016/j.arbres.2018.10.010.
11. Global strategy for the diagnosis mapC. Global initiative for chronic obstructive lung disease (GOLD); 2017. [cited 2022/01/20]; Available from: http://goldcopd.org.
12. Kubota M, Kobayashi H, Quanjer PH, Omori H, Tatsumi K, Kanazawa M. Reference values for spirometry, including vital capacity, in Japanese adults calculated with the LMS method and compared with previous values. Respir Investig. 2014;52:242-50. doi: 10.1016/j.resinv.2014.03.003.
13. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. Eur Respir J. 2009;34:648-54. doi: 10.1183/09031936.00102509.
14. Tsuda T, Suematsu R, Kamohara K, Kurose M, Arakawa I, Tomioka R, Kawayama T, Hoshino T, Aizawa H. Development of the Japanese version of the COPD assessment Test. Respir Investig. 2012;50:34-9. doi: 10.1016/j.resinv.2012.05.003.
15. Graat-Verboom L, Wouters EF, Smeenk FW, van den Borne BE, Lunde R, Spruit MA. Current status of research on osteoporosis in COPD: a systematic review. Eur Respir J. 2009;34:209-18. doi: 10.1183/09031936.50130408.
16. Yan Y, Tan B, Fu F, Chen Q, Li W, Chen W, He H. Exercise vs conventional treatment for treatment of primary osteoporosis: A systematic review and meta-analysis of randomized controlled trials. Orthop Surg. 2021;13:1474-87. doi: 10.1111/os.13036.
17. Graat-Verboom L, van den Borne BE, Smeenk FW, Spruit MA, Wouters EF. Osteoporosis in COPD outpatients based on bone mineral density and vertebral fractures. J Bone Miner Res. 2011;26:561-8. doi: 10.1002/jbmr.257.
18. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int. 2001;68:259-70. doi: 10.1007/bf02390832.
19. 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. 2012;9:235-42. doi: 10.3109/15412555.2011.650243.
20. Ryan CS, Petkov VI, Adler RA. Osteoporosis in men: the value of laboratory testing. Osteoporos Int. 2011;22:1845-53. doi: 10.1007/s00198-010-1421-0.
21. Sokoll LJ, Sadowski JA. Comparison of biochemical indexes for assessing vitamin K nutritional status in a healthy adult population. Am J Clin Nutr. 1996;63:566-73. doi: 10.1093/ajcn/63.4.566.
22. Tsugawa N, Shiraki M, Suhara Y, Kamao M, Tanaka K, Okano T. Vitamin K status of healthy Japanese women: age-related vitamin K requirement for gamma-carboxylation of osteocalcin. Am J Clin Nutr. 2006;83:380-6. doi: 10.1093/ajcn/83.2.380.
23. Piscaer I, van den Ouweland JMW, Vermeersch K, Reynaert NL, Franssen FME, Keene S et al. Low vitamin K status is associated with increased elastin degradation in chronic obstructive pulmonary disease. J Clin Med. 2019;8:1116. doi: 10.3390/jcm8081116.
24. Vergnaud P, Garnero P, Meunier PJ, Bréart G, Kamihagi K, Delmas PD. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. J Clin Endocrinol Metab. 1997;82:719-24. doi: 10.1210/jcem.82.3.3805.
25. Ichinose M, Taniguchi H, Takizawa A, Grönke L, Loaiza L, Voß F, Zhao Y, Fukuchi Y. The efficacy and safety of combined tiotropium and olodaterol via the Respimat(®) inhaler in patients with COPD: results from the Japanese sub-population of the Tonado(®) studies. Int J Chron Obstruct Pulmon Dis. 2016;11:2017-27. doi: 10.2147/copd.S110389.
26. Suzuki M, Makita H, Ito YM, Nagai K, Konno S, Nishimura M. Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study. Eur Respir J. 2014;43:1289-97. doi: 10.1183/09031936.00110213.