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Determining the hierarchy of risk factors for low-energy fractures in patients of an Osteoporosis Treatment Clinic

Dorota Lis-Studniarska[1,A-F], Marcin Studniarski[2,A,C-D,F], Aleksandra Zakrzewska[2,B-D,F], Robert Irzmański[3,A,E-F]

[1] *Central Clinical Hospital, Medical University, Łódź, Poland*
[2] *Faculty of Mathematics and Computer Science, University of Łódź, Poland*
[3] *Department of Internal Medicine, Rehabilitation and Physical Medicine, Medical University, Łódź, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. The medical records were examined of 222 patients of the Osteoporosis Treatment Clinic at the Central Clinical Hospital of the Medical University of Łódź, Poland. The influence was analyzed of 27 clinical risk factors on the occurrence of low-energetic fractures in this population. The aim of the research was to find possible dependencies between different risk factors, and the actual fractures that were recorded in the database.

Materials and Method. For each risk factor and for each category (e.g., patients with diabetes and patients without diabetes), the percentage was computed of patients who had incidents osteoporotic fractures, and the percentage of those without fractures. Student's t-test and Pearson's chi-squared test were used to find statistically significant risk factors.

Results. Statistically significant risk factors were found: age, chronic kidney disease, T-scores of the femoral neck and T-score of the lumbar spine, serum phosphate levels, FRAX-BMD, FRAX-BMI, and the type of diet.

Conclusions. Some observations concerning the influence of individual risk factors on the occurrence of fractures are consistent with those presented in the literature. However, it was also noticed that the patients with hyperthyroidism, rheumatic diseases, diabetes, cancer or gastrointestinal diseases, had a smaller percentage of fractures than the patients who did not have these diseases. This may be explained by the small number of those having these diseases, or by the fact that they had already received appropriate treatment.

Key words

risk factors, osteoporosis, fractures, medical records

INTRODUCTION

Osteoporosis is a disease that renders bones weak, brittle, and susceptible to fractures. Traditionally, osteoporosis is associated primarily with postmenopausal women, but it can also occur in men. Osteoporotic fractures most often occur in the spine, hips and wrists, but can also additionally affect other bones. Due to the aging of society, osteoporosis is a major civilization problem in many countries. Low-energy fractures, in addition to increased mortality, reduce the quality of life, generate disability, and costs of treatment and care for patients.

Osteoporotic hip fractures are a substantial cause of physical dysfunction and mortality, especially in the elderly. It is estimated that hip fractures will increase worldwide from 1.7 million in 1990 to 6.3 million by 2050.

Recent recommendations for the Polish population [1] describe the following three cases in which the diagnosis of osteoporosis should be made:

1) According to the WHO criteria from 1994, based on DXA examination of the femoral neck or lumbar spine of men and women, osteoporosis is diagnosed based on the BMD (bone mass density) value with a T-score equal to or less than –2.5 SD (standard deviation). This criterion applies to women after menopause as well as to elderly men.
2) For postmenopausal women, and men over the age of 50, the diagnosis of osteoporosis can also be made if a low-energy fracture has occurred at a major site, i.e. spine, hip, wrist, humerus, rib, or pelvis, and the T-score is ≤ –1.0.
3) For younger persons, the diagnosis of osteoporosis can be based on different criteria, including Z-score < –2.0.

Due to the aging of society, the number of osteoporosis cases increases every year. It is estimated that worldwide 6.1% of men and 22.1% of women over 50 years of age suffer from the disease. In Poland, according to National Health Fund data, the estimated number of osteoporosis patients in 2018 was 2.1 million, including 1.7 million women. In 2018, the highest registered morbidity values (number of people using services due to osteoporosis) were in the 65 – 69 age group, a total of 12,000 men and 123,000 women. The lowest recorded morbidity was in the group of people aged 50–54 – 24.5 thousand women and 3.8 thousand men.

In Poland, the amount of reimbursement of services due to osteoporosis in 2018 amounted to PLN 42 million for 222 thousand patients, while the value of medicines was PLN 47.6 million. 80% of the total reimbursement of services under Outpatient Specialist Care were consultations in

✉ Address for correspondence: Dorota Lis-Studniarska, Central Clinical Hospital, Medical University, Pomorska 251, 92-213 Łódź, Poland
E-mail: dorotamarialis@gmail.com

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rheumatology and osteoporosis treatment clinics. In the same year, 120,000 fractures were recorded – 20,000 of the humerus, 43,000 of the forearms, 34,700 of the proximal end of the femur, and 28,000 of the vertebrae. The value of reimbursement due to fractures was PLN 476 million, most of which was PLN 336 million spent on the treatment of femur fractures, which constituted 71% of the expenditure. The annual mortality rate after hip fractures in 2017 was 29.4%. Data from the National Health Fund from 2017 show that within 6 months of a fracture, only 2.5% of people in Poland underwent a densitometric test, and 2% filled a prescription for drugs registered for the treatment of osteoporosis [2].

Almost 60% of osteoporotic fractures occur without symptoms and often remain undiagnosed. Spinal DXA morphometry using fan beam cameras can be used for the assessment of T6-L4 vertebrae. This test can be used to evaluate moderate or severe fractures. However, it is only 50% sensitive for first-degree fractures. Radiological examination in the Th4-L4 range is performed in the lateral projection. Thanks to X-ray morphometry, the height of the vertebra is measured in the posterior, middle and anterior parts. The threshold for fracture is 20% reduction of the vertebra.

A widely used method to calculate the 10-year probability of a fracture caused by osteoporosis is FRAX (Fracture Risk Assessment Tool). The authors of [3] observed that a high fracture risk shown by FRAX was most often connected with densitometric criteria of osteoporosis. However, it was proved that the FRAX result underestimated the actual occurrence of hip fractures in the lowest deciles of scores, and overestimated this occurrence in the highest deciles of scores [4]. It is also known that FRAX underestimates the fracture risk for people having some specific diseases [5].

To compute FRAX scores, the following risk factors are used as input: age, gender, weight, height, past low-energetic fracture, hip fracture in parents, current tobacco smoking, taking glucocorticoids for more than 3 months, rheumatoid arthritis, secondary osteoporosis, taking 3 or more units of alcohol daily, femoral neck BMD. If the BMD measurement is not available, then the BMI (Body Mass Index) can be used instead. There are many other possible risk factors not taken into account in FRAX but mentioned in research papers [6]. It is therefore important to examine which of these factors have essential influence on the actual occurrence of fractures in patients. The presented article applies some simple statistical methods to analyze this problem.

The study involved the examination of the medical records of 222 patients of the Osteoporosis Treatment Clinic (OTC) at the Central Clinical Hospital of the Medical University in Łódź, Poland. The aim of the study was to find possible dependencies between different risk factors and the actual low-energetic fractures recorded in the database. The results could be important, especially for the Polish population where, according to the NHF (National Health Fund) 2019 report [1], only 6% of patients obtain adequate treatment.

The study was conducted with the consent of the Bioethics Committee at the Medical University of Łódź (Approval No. RNN/03/23/KE).

In a recently published paper [7], some methods of Artificial Intelligence (AI) were applied to the same data to find a method for predicting osteoporotic fractures and to determine the most important risk factors. The comparison of this research and [7] will be presented in the Discussion section below.

MATERIALS AND METHOD

The main aim of the study was to investigate which of the potential risk factors for osteoporosis and low-energy fractures have a significant impact on the occurrence of osteoporosis and fractures. The following possible risk factors were taken into account, selected because of their appearance in published papers or because they were deemed important by the staff of our clinic. Also included are the results of densitometric and laboratory tests normally prescribed to our patients. Below are brief descriptions of these factors, explaining their importance. The abbreviations in brackets will be used later in Table 4.

Gender. After menopause in the 6th decade of life, women experience a bone loss of 1–2% every year. The lack of estrogen leads to increased bone remodelling, which causes the bones to be less resistant to mechanical injuries. It is estimated that 16–18% of women over the age of 70 are at risk of hip fracture. Men reach the maximum bone mass about the age of 30; therefore, they will attain later the values indicating osteoporosis associated with the gradual loss of bones over the years. For men aged over 70, the risk of a hip fracture equals 5–6%, but the rate of mortality after such fractures is twice as high as in women. According to [8], osteoporosis is often underestimated in men.

Age. It is known that the risk of osteoporotic fractures increases with age. For example, in women, osteoporosis affects 1/10 of the population aged 60, 1/5 of the population aged 70, 2/5 of the population aged 80, and 2/3 of the population aged 90 [9].

Body Mass Index (**BMI**). Computed as follows: BMI = (weight-kg)/(height-m)^2. It was observed in [10] that a lower BMI was connected with a higher probability of fractures.

DXA neck T-score. The first test (Neck T-sc 1),

DXA spine T-score. The first test (Spine T-sc 1). T-scores describe bone density and are used to diagnose osteoporosis. A T-score (either neck of the femur or spine) equal to –2.5 or less in women after menopause and men over 50 is an indication of osteoporosis.

Phosphates. The first test (Phos 1) – phosphates serum level in mmol/l. Phosphorus is included in many drinks and foods and excessive consumption is associated with the use of highly processed food, and may lead to reduced absorption of iron, zinc and magnesium, and reduce bone mineral density. The absorption of phosphorus is between 60–70%. For proper calcium absorption, the ratio of calcium to phosphorus is important and should be 1.5:1 or 1:1 [11].

Vitamin D3. The first test (VitD3 -1) – vitamin D3 serum level in ng/ml. Vitamin D3 helps regulate calcium and phosphate metabolism and is found in fish, cod liver oil, egg yolk, dairy products. However, only 20% of the demand can be obtained from the diet; therefore, skin synthesis is important, which also decreases with age. For elderly people, supplementation of vitamin D3 should be applied all year round [11]. Cholecalciferol is then converted in the liver to 25(OH)D calcidiol. In the kidneys, after hydroxylation,

the active form 1,25(OH)2 D-calcitriol is produced. Older people with low exposure to UV rays and reduced skin synthesis of vitamin D3, often have low levels of this vitamin. In addition, 25(OH)D3, due to reduced renal activity of 1-alpha-hydroxylase, is not converted into the active form. The polymorphism of the vitamin D receptor (VDR) gene, although present in 2% of elderly people, may be responsible for low BMD.

Calcium. The first test (Cal 1) – calcium serum level in mmol/l. About 99% of calcium accumulated in the body is found in the bones; therefore, the peak bone mass depends on a proper supply of calcium. The demand for calcium in adults is about 1,000 mg per day. 10–40% of calcium is absorbed from the diet, but this amount decreases with age. In the Polish population, the supply of this element is 50–60%. Dairy products are among the foods with a high calcium content. Most patients in this study had adequate blood calcium levels without the need for additional supplementation. Among the factors facilitating the absorption of calcium are the proper functioning of the digestive tract, the secretion of appropriate amounts of hydrochloric acid, calcium deficiencies in the body, lactose, vitamin D3, and maintaining the correct ratio of calcium to phosphates in the food consumed. On the other hand, high pH in the stomach, functional disorders of the digestive tract, a large supply of fibre, phytates, oxalates, iron, magnesium, alcohol, animal proteins, and excess phosphates limit the absorption of calcium. When supplementing with calcium alone, there is no reduction in bone fractures, but the risk of heart attack and kidney stones increases [12].

Last menstrual period (Lm). Age at the last menstrual period for women. The authors of [13] have shown a high individual risk of low-energy fractures in non-obese females with untreated premature menopause.

Hypogonadism or premature menopause (<45 years) (Hg/Me). Peak bone mass is significantly lower in people with hypogonadism and delayed puberty before the age of 30. This applies to women with Turner syndrome, men with Klinefelter syndrome, and patients with resistance to androgens or estrogens. The degree of trabecular bone loss is proportional to bone mass. Hypogonadism, low testosterone levels, are risk factors for fractures in men [14], and those with prostate cancer undergoing ablative treatment are at particular risk. Bone resorption is particularly pronounced in postmenopausal women, which is associated with estrogen deficiency [13]. The increased rate of remodeling persists for many years, but is most evident in the first 10 years after menopause. The release of calcium from the bones is increased, which results in reduced secretion of parathyroid hormone. Low estrogen levels result in less calcium absorption in the intestines, and vitamin D3 metabolism decreases.

Secondary osteoporosis (SO) – means that the patient has one of the disorders listed in [9].

Strumectomy (St). According to [15], strumectomy considerably increases the long-term risk of osteoporosis.

Hyperthyroidism (Hy/th). Hyperthyroidism impairs bone strength and may cause fractures, particularly if untreated for a long time [16].

Rheumatic diseases (Rh/di). Rheumatic diseases greatly increase the risk of fractures caused by osteoporosis [17]. This is caused by the activation of osteoclastogenesis by pro-inflammatory cytokines. A heightened risk of falls may be caused by joint damage, atrophy, and muscle weakness. Other factors that increase bone resorption are cigarette smoking and alcohol abuse, especially in men treated rheumatologically. On the other hand, the use of TNF α inhibitors has a protective effect on bone metabolism [18].

Diabetes (Db). People with diabetes, especially type 1, are at greater risk of fractures (approximately 10 times). It is recommended to perform densitometric tests 5 years after the diagnosis of type 1 diabetes and repeat them every 2–5 years. Type 2 diabetes increases this risk 1.5 times. For people having type 2 diabetes, the fracture risk often does not correspond to the values of BMD [1]. Additionally, the increased risk of falls may be caused by some complications of diabetes, such as visual impairment, myopathy, neuropathy and obesity.

Neoplasma (Ne/pl). Cancer can impact the health of bones in numerous ways; in particular, bone metastases can lead to fractures. Some cancer treatments also have detrimental effects on bones and concerns especially hormone deprivation therapies for breast cancer and prostate cancer [19].

Gastrointestinal diseases (Ga). Disorders of the gastrointestinal tract, resection of the stomach and intestines, treatment with drugs that reduce the secretion of hydrochloric acid in the stomach, may reduce the absorption of necessary nutrients, including calcium. People with gastrointestinal diseases have a higher risk of osteoporosis and fractures [20].

Chronic kidney disease (Ki). This disease greatly increases the risk of fracture, caused by disturbed homeostasis of phosphorus and calcium. In the initial phase of the disease, there is a gradual retention of phosphorus in the body and impaired renal synthesis of vitamin D3. Moreover, the elevation in serum Parathyroid Hormone (PTH) is observed, which causes an increased bone resorption to maintain the balance of calcium [21].

Glucocorticoids (Gk). The drugs in this group are widely used for the treatment of various diseases. Taking glucocorticoids regularly for more than 3 months may result in the reduction of bone formation, increase of urinary calcium excretion, myopathy, hypogonadism, and other hormonal disorders. In patients over 50 years of age, preventive administration of anti-resorptive drugs may be considered when other risk factors for fractures are present, and in patients over 65 years of age, even when there are no other risk factors [1].

History of hip fractures in parents (Fam/hip). According to [22], the degree of bone remodeling may depend on genetic factors. It is estimated that genetic factors influence the occurrence of low-energy fractures in 25–35%. The occurrence of hip fractures in parents is one of the risk factors taken into account in FRAX [10].

Alcohol (Al). Alcohol increases the excretion of calcium in the urine, and may have a toxic effect on osteoblasts and the liver. Consequently, the production of vitamin D3 is

diminished [23]. The authors of [24] conclude that a high intake of alcohol causes a significant risk of fracture. The risk, however, is largely independent of BMD. No increase of fracture risk occurs in people who take no more than 2 units of alcohol daily; above this quantity there is a significant risk which is essentially the same for both men and for women.

Smoking (Sm). Smoking is widely considered a risk factor for osteoporotic fracture [25]. A decrease in bone strength is observed in smokers, more often in men than in women. It depends on the dose, years of smoking, and number of cigarettes smoked per day.

Coffee (Co). Number of cups drunk daily. There is no evidence that drinking coffee increases the risk of fractures in healthy people with adequate calcium intake [26]. Caffeine, like theine, causes the flushing out of calcium from the body. But in this case, the absorption of calcium from food increases. Therefore, providing appropriate amounts of calcium in food is very important.

Physical activity (Ph/ac). At least 30 min daily. Physical exercise has a positive impact on the prevention and treatment of osteoporosis. It increases muscle mass and osteoblast activity [27]. Skeletal muscle mass and function decrease with age, which in turn increases the risk of falls and fractures. Strength training can be applied at any age and is beneficial for reducing the risk of fractures.

Sun exposure (Su). At least 15 min daily. Exposure to sunlight is important because of the skin's synthesis of vitamin D3, which unfortunately decreases with age. In Poland, this synthesis can be effective from May to September, from 10:00 – 15:00, in sunny weather when, without sunscreen, at least the forearms and lower legs are exposed for at least 15 minutes. According to [28], older persons with restricted sun exposure are at a high risk for vitamin D deficiency.

Meat (Diet/Me). The correct supply of protein, 1,2 g daily for 1 kg of body weight [1], is important – no matter whether plant or animal. Excessive protein intake can result in increased bone loss of calcium and increased urinary excretion. One extra gram of protein, mostly animal, in the diet contributes to an increase in the excretion of 1 mg of calcium in the urine by acidification. It has been shown that lacto-ovo-vegetarians and pesca-vegetarians have a normal or even slightly higher supply of calcium than people using a mixed diet. Studies have shown that more osteoporotic fractures occur in countries with a high consumption of animal protein. A vegan diet, being more alkaline, reduces bone loss and the risk of fractures. Elevated levels of homocysteine are observed in people who consume animal products, which increases the risk of bone fractures. A plant diet is rich in protective ingredients: vitamin C, magnesium, potassium, phytochemicals, thanks to which it has antioxidant and anti-inflammatory effects and increases the production of collagen in the bones. Beta-carotene, lycopene and phytoestrogens, have a beneficial effect on the reduction of fractures. Studies have confirmed that a diet based on vegetables and fruits has protective effect on bones [11].

Salting (Diet/Sal). It is known that reduction of salt in the diet can help normalize blood pressure and reduce calcium excretion. On the other hand, a low-salt diet can result in a negative balance of calcium and magnesium, which could cause osteoporosis [29]. The recommended dose of salt is 2,000 mg, equal to about 1 teaspoon per day. Only about 15% of the consumed amount of sodium is in table salt, the rest is hidden in such products as ready-made spice mixes, stock cubes, marinades, dressings, powdered sauces, canned products, ready meals, crisps and cheeses.

RESULTS

Figures 1–4 and Tables 1–2 describe the basic characteristics of patients of the Osteoporosis Treatment Clinic whose data were taken into account. More information is given in Table 1 of [7], where the same group of patients is considered.

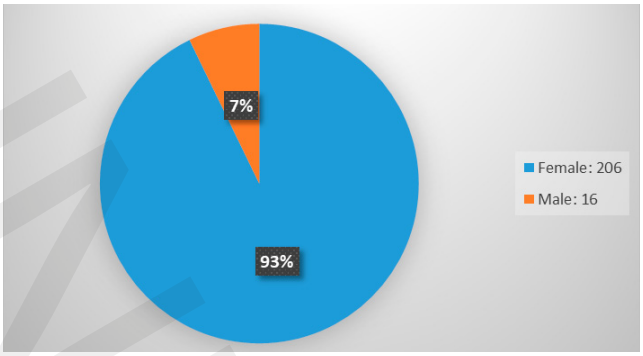

Figure 1. Structure of patients by gender

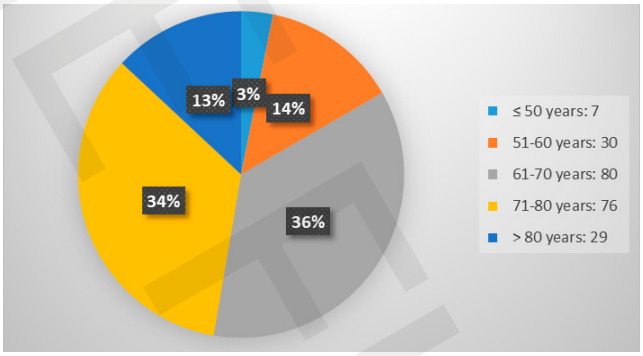

Figure 2. Structure of patients by age groups

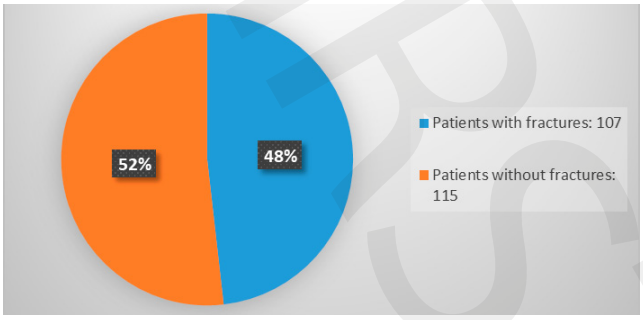

Figure 3. Structure of patients by occurrence of fractures

Tables 1 and 2 compare the data on actual fractures, with the probabilities computed by the FRAX calculator (in 2 versions: using BMD and using BMI). In these tables, N denotes the number of patients in a given group, and the percentages of patients with and without fractures in each row add up to 100%.

Table 1. Percentages of patients with and without fractures by 10-year fracture probability – FRAX BMD

FRAX BMD osteoporotic fracture (F)	Total	With fractures		Without fractures	
		N	%	N	%
F ≤ 5%	54	7	13.0%	47	87.0%
5% < F ≤ 10%	82	37	45.1%	45	54.9%
F > 10%	86	63	73.3%	23	26.7%

Table 2. Percentages of patients with and without fractures by 10-year fracture probability – FRAX BMI

FRAX BMI osteoporotic fracture (F)	Total	With fractures		Without fractures	
		N	%	N	%
F ≤ 5%	46	5	10.9%	41	89.1%
5% < F ≤ 10%	95	41	43.2%	54	56.8%
F > 10%	81	61	75.3%	20	24.7%

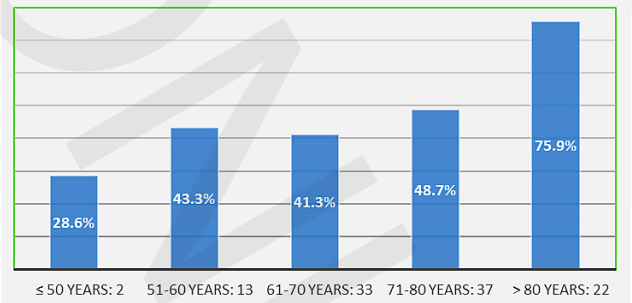

Figure 4. Percentages of patients with fractures in age groups

In order to draw conclusions several statistical hypotheses were tested using the Statistica software. First, the null hypothesis was tested, that the factors listed in Table 1 as well as the following variables are not linearly correlated:

- number of low-energetic fractures before treatment (Nu/l-e/fr);
- number of low-energetic fractures during treatment (Ne/l-e/fr);
- number of all low-energetic fractures (fr);
- occurrence of low-energetic fractures at any time (frNY) (1 – at least one fracture; 0 – no fractures);
- FRAX value based on BMD for osteoporotic fracture (BMD o/f);
- FRAX value based on BMI for osteoporotic fracture (BMI o/f);
- FRAX value based on BMD for hip fracture (BMD h/f);
- FRAX value based on BMI for hip fracture (BMI h/f).

This analysis indicated which pairs of variables can be rejected from the null hypothesis because the p-value was less than 0.05. Among these pairs, those with a correlation coefficient greater than 0.5 were selected (with a moderate or high correlation). This condition was met by the following pairs of variables:

- Height and weight;
- BMI and weight;
- BMI o/f and age;
- BMI h/f and age;
- Hg/me and SO;
- Neck T-sc and BMD o/f;
- Neck T-sc and BMD h/f;
- 4 FRAX variables – between each other in any pairs.

However, the above correlations are quite obvious and result from the way the individual values are calculated. For example, BMI was calculated from a formula using weight, and the Neck T-score used to calculate FRAX-BMD. No other significant relationships between risk factors or risk factors and fracture occurrence were detected.

Subsequently, the relationship between the number of fractures before and during treatment (fr variable) and FRAX values was checked. The highest correlation coefficient of 0.425189 was for BMD o/f. Here, too, the correlations were also low.

Table 3. Relationship between the number of fractures and FRAX values.

Correlations
Marked correlations are significant at p < ,05000
N=222 (Casewise deletion of missing data)

Variable	Means	Std.Dev.	fr	BMD o/f	BMI o/f	BMD h/f	BMI h/f
fr	0,76126	1,003043	1,000000	0,425189	0,396759	0,371432	0,329551
BMD o/f	10,82973	8,415420	0,425189	1,000000	0,758490	0,975217	0,704807
BMI o/f	11,03559	8,746813	0,396759	0,758490	1,000000	0,733915	0,942067
BMD h/f	5,09369	7,022018	0,371432	0,975217	0,733915	1,000000	0,732736
BMI h/f	6,29279	8,573559	0,329551	0,704807	0,942067	0,732736	1,000000

Below is a scatterplot of the data for 2 variables: fr (number of fractures) and BMD o/f (FRAX value for osteoporotic fracture using BMD). Blue circles indicate data for individual patients.

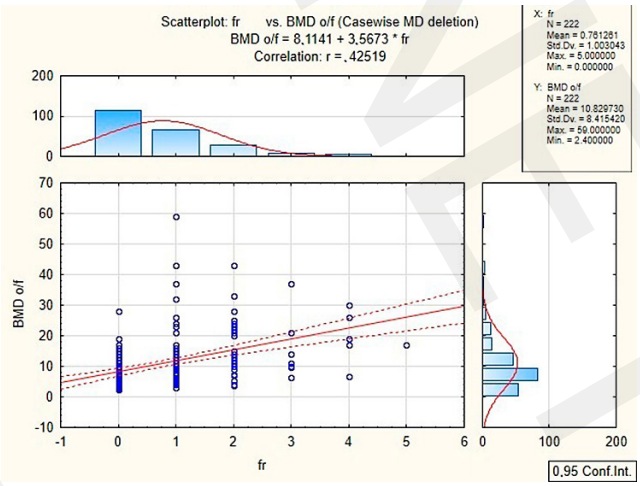

Figure 5. Scatterplot for fr and BMD o/f variables

Figure 5 shows that there is a large group of people who have fractures with a FRAX value below 10%, some even multiple fractures.

An attempt was made to use multiple regression to analyze the relationship between the number of fractures (as a dependent variable) and the considered risk factors (as independent variables). Although the different sets of the risk factors were investigated, the adjusted R-squared value was always less than 0.15, and no satisfactory result was obtained.

Student's t-test with frNY as the grouping variable was applied to compare means of different risk factors within the corresponding groups of patients (i.e., with fractures and without fractures). The sizes of both groups were very similar (Tab. 4).

The columns t-value and p are the results of this test. The numbers 0 and 1 in the column headers refer to the value of the frNY variable.

Using p-values less than 0.05, the following risk factors (marked in red) were determined as those with mean values

Table 4. The t-test results

Variable	T-tests; Grouping: frNY: =iif(fr;1;0) Group 1: 1 Group 2: 0 Mean 1	Mean 0	t-value	df	p	Valid N 1	Valid N 0	Std.Dev. 1	Std.Dev. 0	F-ratio Variances	p Variances
Sex	0,94393	0,91304	0,88661	220	0,376254	107	115	0,23115	0,28300	1.499007	0,035551
Age	71,49533	67,38261	3,06611	220	0,002440	107	115	10,16781	9,81458	1,073276	0,709754
AgeK	2,59813	2,22609	2,86354	220	0,004594	107	115	1,00808	0,92775	1.180670	0,383710
Weight (kg)	63,60841	65,72174	-1,24719	220	0,213654	107	115	11,88054	13,26207	1.246092	0.252052
Height (m)	1.60551	1,62061	-1,61648	220	0.107423	107	115	0,06450	0.07388	1,311857	0.157804
BMI	24,61531	24,98298	-0,63253	220	0,527698	107	115	3,96251	4,64119	1,371886	0.100099
Lm	49,50980	51,14423	-1,49165	204	0,137336	102	104	6,82851	8,75937	1,645482	0.012657
Al.	0,16355	0,16522	-0,04874	220	0,961173	107	115	0,26400	0,24532	1,158078	0.441285
Sm	0,14486	0,07826	1,61253	220	0,108280	107	115	0,35027	0,26150	1.794097	0.002305
Co	0,89813	0,93478	-0,29099	220	0,771335	107	115	1,00094	0,87490	1,308888	0.158559
Gk	0,07009	0,10435	-0,90494	220	0,366488	107	115	0,25187	0,30705	1.486191	0.039611
Ph/ac	0,69159	0,72174	-0,49133	220	0,623681	107	115	0,46401	0,45010	1.062749	0.748499
Su	0,30841	0,33913	-0,48661	220	0,627017	107	115	0,46401	0,47549	1.050073	0,800216
Rh/di	0,06542	0,08696	-0,60072	220	0,548646	107	115	0,24843	0,28300	1.297712	0.175023
Db	0,09346	0,10435	-0,27016	220	0,787290	107	115	0,29244	0,30705	1.102386	0,612184
Ne/pl	0,12150	0,15652	-0,74990	220	0,454115	107	115	0,32824	0,36494	1.236118	0,269771
Hy/th	0,05607	0,06087	-0,15136	220	0,879833	107	115	0,23115	0,24014	1.079285	0,691815
Hg/me	0,11215	0,08696	0,62545	220	0,532325	107	115	0,31704	0,28300	1.254956	0,234002
Ga	0,25234	0,26087	-0,14478	220	0,885019	107	115	0,43640	0,44103	1,021347	0,913907
Ki	0,04673	0,00000	2,36357	220	0,018971	107	115	0,21205	0,00000	0,000000	1,000000
St	0,06542	0,13043	-1,62224	220	0,106183	107	115	0,24843	0,33826	1,853874	0,001430
SO	0,11215	0,09565	0,40136	220	0,688544	107	115	0,31704	0,29540	1.151839	0,458228
Diet/Me	0,98131	0,94783	1,49097	220	0,137402	107	115	0,09530	0,21331	5,010259	0,000000
Diet/Sal	0,42991	0,42174	0,15351	220	0,878140	107	115	0,41464	0,37808	1,202757	0,333038
Fam/hip	0,13084	0,08696	1,05005	220	0,294845	107	115	0,33881	0,28300	1,433292	0,059626
Neck T-sc1	-2,09100	-1,58302	-4,21435	204	0,000038	100	106	0,82427	0,90105	1.195001	0,371487
Spine T-sc1	-2,11731	-1,68962	-2,22850	208	0,026918	104	106	1,28957	1,48285	1,322216	0,156435
Phos1	1,20235	1,14375	2,14592	200	0,033084	98	104	0,22300	0,16192	1,896780	0,001489
VitD3-1	39,57596	38,44088	0,48006	216	0,631668	104	114	17,53457	17,34746	1,021689	0,909151
Cal1	2,43733	2,45800	-1,44364	209	0,150339	101	110	0,09876	0,10842	1,205235	0,344043
BMD o/f	14,68505	7,24261	7,32714	220	0,000000	107	115	9,96271	4,25072	5,493264	0,000000
BMI o/f	14,87383	7,46435	6,94871	220	0,000000	107	115	10,49276	4,38757	5,719158	0,000000
BMD h/f	7,81682	2,56000	5,99837	220	0,000000	107	115	8,89216	2,93804	9,160082	0,000000
BMI h/f	9,46355	3,34261	5,67855	220	0,000000	107	115	10,95505	3,56243	9,456635	0,000000

significantly different in the 2 groups of patients: age, chronic kidney disease, T-score of the femoral neck and T-score of the lumbar spine, serum phosphate level, FRAX-BMD and FRAX-BMI.

The AgeK variable is auxiliary and means assigning the patient to an age category (the value changes in 10-year intervals). Age categories are defined in the bottom line of Figure 4.

More information on 5 important risk factors are presented in Table 5. These factors are described divided into 2 groups: minimum one fracture or no fracture. For every factor there is information about mean, mean±SE (standard error) and mean±1.96SE. The interval [mean–1.96SE, mean+1.96SE] is referred to as the confidence interval. It can be interpreted that all future observations will be within this interval with 95% probability. If the confidence intervals for a minimum of one fracture and no fracture do not intersect, this means that this factor can be used to predict the low-energy fracture with high probability (only within the considered group of patients).

Table 5. Means of important risk factors

		RISK FACTORS				
		Age	Chronic kidney disease	Neck T-score	Spine T-score	Phospha-tes
Minimum one low-energetic fracture at any time	Mean + SE*1.96	73.42193	0.086908	-1.92944	-1.886946	1.246499
	Mean + SE	72.47829	0.067229	-2.00857	-1.99085	1.224873
	Mean	71.49533	0.046729	-2.091	-2.11731	1.202347
	Mean - SE	70.51237	0.026229	-2.17343	-2.24376	1.17982
	Mean - SE*1.96	69.56873	0.006549	-2.25256	-2.36516	1.158195
No low-energetic fractures at any time	Mean + SE*1.96	69.17643	0	-1.41148	-1.40733	1.17487
	Mean + SE	68.29782	0	-1.4955	-1.5456	1.159627
	Mean	67.38261	0	-1.58302	-1.68962	1.14375
	Mean - SE	66.46739	0	-1.67054	-1.83365	1.127873
	Mean - SE*1.96	65.58879	0	-1.75455	-1.97192	1.11263

Additionally, Pearson's chi-squared test was performed for categorical variables, i.e., having a finite set of values. This tests the null hypothesis that a categorical variable and the variable frNY are independent. If p was less than 0.05, this hypothesis can be rejected and it can be concluded that the variables are dependent.

In the performed test, the relationships between frNY and the following variables were obtained:

- Ki: $\chi^2 = 5.5$; $p = 0.02$, contingency coefficient 0.16;
- Diet/Me: $\chi^2 = 4.66$; $p = 0.03$, contingency coefficient 0.14;
- AgeK: $\chi^2 = 11.81$; $p = 0.01884$, contingency coefficient 0.23.

The contingency coefficient indicates how strongly the variables are related, and assumes values between 0 and 1. The greater this is, the stronger the relationship. Thus, it can be seen that the variables are dependent on each other, but in a weak way. On the basis of the chi-square test, the type of diet (Diet/Me) can be added to the group of significant risk factors. In the group of vegetarians, no one had fractures, but this group was small, only 5 people.

DISCUSSION

Literature review. The authors of many scientific articles describe and compare the use of different methods of diagnosing osteoporosis and determining the risk of fractures. The methods used include simple assessment tools – FRAX, and AI methods. In [4], comparison was performed between 3 fracture risk calculators (FRAX, Garvan, QFracture) and 2 classifiers, where the first was based on femoral neck BMD T-score alone, and the second on age plus femoral neck BMD T-score. These assessment tools were applied to a population of older men and the authors concluded that the second classifier was as good as the mentioned risk calculators. On the other hand, review papers [6] and [30] focus on AI methods. The authors of [6] collected 50 publications, starting from the 1990s, devoted to using AI to estimate the risk of fractures and osteoporosis. In a Table on page 14, they list 48 inputs that may be risk factors for fractures and 12 AI methods used so far with this aim. In [30], 58 articles were cited, 15 of which were reviewed in detail, presenting in special Tables the main characteristics of the described studies, e.g. the country, number of patients examined, percentage of women among the patients, type of data, AI method used, what the research was supposed to predict, and the result obtained. In the discussed works, the input factors were mainly the results of densitometry or X-ray tests, without considering other risk factors.

Some other articles could be described as reports of individual studies. The paper [31] discussed the use of neural networks and deep learning for the classification of X-ray images of bones in order to diagnose osteoporosis. In [32], the influence of 4 factors (age, gender, height, weight) on the risk of fractures was studied. The aim of the study was to assign patients to one of 2 groups (osteoporosis and no osteoporosis). The authors tested 20 different classifiers to select the most important factors from the point of view of classifying patients into particular groups. In [33], the random forest model was applied to investigate the influence of 15 factors on fracture risk; these factors included vitamin D level, smoking, coffee drinking.

Another approach was presented in [34] in which the authors used data mining methods to obtain knowledge from clinical records which would enable them to predict the individual risk of osteoporosis, without using any equipment for measuring bone strength. They considered 6 uncontrollable and 7 controllable risk factors; the latter ones connected mainly with diet and lifestyle. The aim of the paper [35] was to construct a classifier that distinguished an osteoporotic person from a healthy one, based on bone mineral density values. In [36], the concept of fuzzy sets was applied to construct an expert system to decide whether a patient had osteopenia, osteoporosis, or was in normal condition. The system was tested on 20 patients. In [37], fuzzy sets were also used where the following factors were considered as input variables: age, age at menopause, coffee consumption, BMD at the femoral neck, BMI, and BMD of the ward.

In each of 3 recent papers [27, 38, 39], the authors used several AI methods simultaneously to predict the risk of osteoporosis in various groups of patients (e.g. in [38], for breast cancer patients). In [38], the performance of 6 AI models was compared with that of FRAX and OSTA (Osteoporosis Self-Assessment Tool for Asians). Paper [39] compared 4 AI methods with OSTA. The authors of [27] applied 8 classification methods to divide patients into 3 categories: healthy, osteopenia and osteoporosis; the results were then compared with the results of DXA tests. Generally, it follows from the analysis carried out in these 3 works that different AI algorithms produce the best results for different groups of patients. There is no algorithm which is best for all situations.

The authors of [40] compared FRAX with the following AI algorithms for predicting fracture risk: CatBoost, SVM, and logistic regression. It was shown that only CatBoost had better performance than FRAX.

A new deep-learning method for osteoporosis prediction was presented in [41]. This model provides individualized risk assessment for each person with an explanation of feature contributions.

RESULTS

Analysis of the available medical documentation shows that women accounted for 93% of the patients of the Osteoporosis Treatment Clinic where the current study was conducted. Low-energy fractures were reported in 49% of the women. Among men, this percentage was lower and amounted to 37%. The largest percentage of fractures was in the group of patients aged over 80 (75.9%), the smallest – for those aged up to 50 (28.6%).

In the study population, T-score ≤ –2.5 was found in 53% of patients, of whom 56% had a low-energy fracture. Among the remaining patients (with a T-score higher than –2.5), fractures were found in 39%.

In the current study, a large group of people with a FRAX value below 10% (medium and low fracture risk) had fractures, and some had multiple fractures. The FRAX calculator was designed to be a simple, common and easy-to-use tool, both in primary health care and in specialist clinics. Recent papers have described the limitations of FRAX that should be taken into account when interpreting the results [5]. For example, the risk factors entered into FRAX cannot be gradated. To overcome this deficiency, an improved version of FRAX called FRAXplus® was developed in 2023. This version allows modification of the probability score obtained from conventional FRAX estimates, taking into account the following risk factors: (1) recent occurrence of an osteoporotic fracture (< 1 year), (2) higher than average oral glucocorticoid intake, (3) trabecular bone examination (TBS), (4) number of falls in the previous year, (5) duration of type 2 diabetes, (6) current information on lumbar spine BMD, (7) hip axis length [42].

Hypogonadism, including premature menopause (before the age of 45) and secondary osteoporosis increased the risk of fractures in the analyzed group, which is consistent with the data presented in the literature [13, 14]. In this population, all patients with chronic kidney disease had fractures. Since the group was small (only 5 people), it is difficult to draw any definite conclusions from this fact. However, it is known from the literature that kidney diseases significantly increase the risk of fractures [21]. Of the 6 patients with elevated phosphate levels (i.e. more than 1.45 mmol/L), as many as 5 had fractures.

Among the Clinic patients, 9% were chronically taking glucocorticoids at a dose > 5 mg/day (no specific dose expressed as prednisolone was given), 40% of them had a low-energy fracture (compared to 49% of patients not taking glucocorticoids).

No increase in bone fractures was observed in people with rheumatic diseases. On the contrary, the percentage of people with fractures is even lower in the group of people with rheumatic diseases than in the group of other patients. This is somewhat contradictory to the observations in [17]. However, it should be taken into account that the group of patients with rheumatic diseases is rather small (17 people).

Factors such as: diabetes, neoplasma, diseases of the gastrointestinal tract, thyroidectomy, hyperthyroidism (analyzed individually) did not increase the number of fractures.

According to Lalonde, a pro-health lifestyle and environmental factors are responsible for the health of the society to the greatest extent (approx. 70% in total) [43].

In this study, it was found that people who drink alcohol in small amounts are less likely to suffer a low-energy fracture than non-drinkers. Excessive alcohol consumption (> 3 units per day) is a risk factor for fractures and is included in the FRAX calculator. However, some studies show that drinking moderate amounts of alcohol, together with a healthy lifestyle, can have a positive effect on BMD [44, 45].

Smoking proved to be an important risk factor for fractures. 65.2% of smokers had such an incident, compared with only 46.4% of non-smokers. This confirms the observations in [25].

Drinking more than 3 cups of coffee a day was a risk factor for fractures, while 1–2 cups reduced the risk. Caffeine can increase the excretion of calcium, while with the correct supply, the body regulates the absorption of this element from the intestines. A recent review [46] showed that the lowest relative risk of hip fracture is found in those who consume 2–3 cups of coffee per day.

Physical workout and sun exposure (UV rays) proved to have a protective effect, reducing the risk of fractures.

Some related studies have been conducted previously in the Polish population [24, 47], although both the methods of fracture risk assessment and the results obtained in these two studies are different from the current study. In [47], the influence of different risk factors on lumbar spine BMD was examined and showed that the significant risk factors were: age, BMI, year of menopause, and family history of osteoporosis. In [24], the risk of fractures was computed by FRAX, and by using Logistic Regression it was shown that the most significant risk factors were: smoking, past gynaecological surgical procedures and corticosteroid therapies.

Another study, based on the same dataset as the present study, was described in [7]. Its aim was to examine the possibility of applying some basic methods of AI to predict whether a patient would have an osteoporotic fracture. This goal was not fully achieved; however, it was possible to identify the following risk factors that are important for an optimal prediction model: age, chronic kidney disease, neck T-score, and phosphates level. Note that these 4 risk factors were also found to be statistically significant in the cuurent study.

Limitations of the study. There are several essential limitations which could have influenced the results of statistical analysis:

Only patients attending the Outpatient Clinic participated in the study; this group was not representative for the general population of the Łódź region.

The number of men was small compared to women.

There were very small groups of patients having specific comorbid diseases.

CONCLUSIONS

The study examined possible dependencies between different risk factors of osteoporotic fractures, and between risk factors and actual fractures for patients of an Osteoporosis Treatment Clinic in Łódź, Poland. It was found that the only statistically significant risk factors were: age, chronic kidney disease, T-score of the femoral neck and T-score of the lumbar spine, serum phosphate levels, FRAX-BMD, FRAX-BMI, and the type of diet. Therefore, the results of the analysis of only these parameters can be used in the form of statements, and the rest are only presumed. However, other risk factors can also have some influence for the probability of fractures. In the surveyed group of people, it was somewhat unexpected that the patients with hyperthyroidism, rheumatic diseases, diabetes, cancer or gastrointestinal diseases, had smaller percentages of fractures than those who did not have these diseases. This may be explained either by the small numbers of patients having these diseases, or by the fact that these patients were under the care of specialists and receiving appropriate treatment. In addition, treatment with TNF α inhibitors may prevent bone resorption in patients with rheumatoid arthritis.

REFERENCES

1. Głuszko P, Sewerynek E, Misiorowski W, et al. Guidelines for the diagnosis and management of osteoporosis in Poland. Update 2022. Endokrynol Pol. 2023;74(1):5–15. https://doi.org/10.5603/EP.a2023.0012
2. NFZ o zdrowiu. 2019. Osteoporoza, Centrala Narodowego Funduszu Zdrowia, Departament Analiz i Strategii, Warszawa. https://ezdrowie.gov.pl/pobierz/1911_nfz_o_zdrowiu_osteoporoza (access: 2024.01.19).
3. Leslie WD, Majumdar SR, Lix LM, et al. High fracture probability with FRAX usually indicates densitometric osteoporosis: implications for clinical practice. Osteoporos Int. 2012;23:391–397. https://doi.org/10.1007/s00198-011-1592-3
4. Gourlay ML, Ritter VS, Fine JP, et al. Comparison of fracture risk assessment tools in older men without prior hip or spine fracture: the MrOS study. Arch Osteoporos. 2017;12:91. https://doi.org/10.1007/s11657-017-0389-1
5. Miedany IE. FRAX: re-adjust or re-think. Arch Osteoporos. 2020;15:150 https://doi.org/10.1007/s11657-020-00827-z
6. Cruz AS, Lins HC, Medeiros RVA, et al. Artificial intelligence on the identification of risk groups for osteoporosis, a general review. BioMed Eng OnLine. 2018;17:12. https://doi.org/10.1186/s12938-018-0436-1
7. Lis-Studniarska D, Lipnicka M, Studniarski M, et al. Applications of artificial intelligence methods for the prediction of osteoporotic fractures. Life. 2023;13:1738. https://doi.org/10.3390/life13081738
8. Rinonapoli G, Ruggiero C, Meccariello L, et al. Osteoporosis in men: a review of underestimated bone condition. Int J Mol Sci. 2021;22(4):2105. https://doi.org/10.3390/ijms22042105
9. Johnston CB, Dagar M. Osteoporosis in older adults. Med Clin N Am. 2020;104:873–884. https://doi.org/10.1016/j.mcna.2020.06.004
10. FRAX Fracture Risk Assessment Tool. https://frax.shef.ac.uk/FRAX/index.aspx (access: 2023.08.30)
11. Tucker KL. Osteoporosis prevention and nutrition. Curr Osteoporos Rep. 2009;7:111–117 https://doi.org/10.1007/s11914-009-0020-5
12. Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30:3–44. https://doi.org/10.1007/s00198-018-4704-5
13. Bagur AC, Mautalen CA. Risk for developing osteoporosis in untreated premature menopause. Calcif Tissue Int. 1992;51(1):4–7. https://doi.org/10.1007/BF00296207
14. Golds G, Houdek D, Arnason T. Male hypogonadism and osteoporosis: the effects, clinical consequences, and treatment of testosterone deficiency in bone health. Int J Endocrinol. 2017;2017:4602129. https://doi.org/10.1155/2017/4602129
15. Hung CL, Yeh CC, Sung PS, et al. Is partial or total thyroidectomy associated with risk of long-term osteoporosis: a nationwide population-

based study. World J Surg. 2018;42:2864–2871. https://doi.org/10.1007/s00268-018-4573-2
16. Delitala AP, Scuteri A, Doria C. Thyroid hormone diseases and osteoporosis. J Clin Med. 2020;9(4):1034. https://doi.org/10.3390/jcm9041034
17. Lee JH, Suh YS, Koh JH, et al. The risk of osteoporotic fractures according to the FRAX model in Korean patients with rheumatoid arthritis. J Korean Med Sci. 2014;29(8):1082–1089. https://doi.org/10.3346/jkms.2014.29.8.1082
18. Hu Z, Zhang L, Lin Z, et al. Prevalence and risk factors for bone loss in rheumatoid arthritis patients from South China: modeled by three methods. BMC Musculoskelet Disord. 2021;22(1):534. https://doi.org/10.1186/s12891-021-04403-5
19. Ye C, Leslie WD. Fracture risk and assessment in adults with cancer. Osteoporos Int. 2023;34:449–466. https://doi.org/10.1007/s00198-022-06631-4
20. Oh HJ, Ryu KH, Park BJ, et al. Osteoporosis and osteoporotic fractures in gastrointestinal disease. J Bone Metab. 2018;25(4):213–217. https://doi.org/10.11005/jbm.2018.25.4.213
21. Lima GAC, Paranhos-Neto FP, Pereira GRM, et al. Osteoporosis management in patient with renal function impairment. Arq Bras Endocrinol Metab. 2014;58(5):530–539. https://doi.org/10.1590/0004-2730000003360
22. Trajanoska K, Rivadeneira F. Genomic medicine: lessons learned from monogenic and complex bone disorders. Front Endocrinol. 2020;11:556610. https://doi.org/10.3389/fendo.2020.556610
23. Wnęk D. Dieta w osteoporozie. Medycyna Praktyczna https://www.mp.pl/pacjent/dieta/diety/diety_w_chorobach/191330,dieta-w-osteoporozie (access: 2023.08.30).
24. Nawrat-Szołtysik A, Miodońska Z, Zarzeczny R, et al. Osteoporosis in Polish older women: risk factors and osteoporotic fractures: a cross-sectional study. Int J Environ Res Public Health. 2020;17(10):3725. https://doi.org/10.3390/ijerph17103725
25. Al-Bashaireh AM, Haddad LG, Weaver M, et al. The effect of tobacco smoking on bone mass: an overview of pathophysiologic mechanisms. J Osteoporos. 2018;2018:1206235. https://doi.org/10.1155/2018/1206235
26. Berman NK, Honig S, Cronstein BN, et al. The effects of caffeine on bone mineral density and fracture risk. Osteoporos Int. 2022;33:235–1241. https://doi.org/10.1007/s00198-021-05972-w
27. Fasihi L, Tartibian B, Eslami R, et al. Artificial intelligence used to diagnose osteoporosis from risk factors in clinical data and proposing sports protocols. Sci Rep. 2022;12:18330. https://doi.org/10.1038/s41598-022-23184-y
28. Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. Eur J Rheumatol. 2017;4(1):46–56. https://doi.org/10.5152/eurjrheum.2016.048
29. DiNicolantonio JJ, Mehta V, Zaman SB, et al. Not salt but sugar as aetiological in osteoporosis: a review. Mo Med. 2018;115(3): 247–252.
30. Ferizi U, Honig S, Chang G. Artificial intelligence, osteoporosis and fragility fractures. Curr Opin Rheumatol. 2019;31(4):368–375. https://doi.org/10.1097/BOR.0000000000000607
31. Grace SJ, Kumar DS, Gautam R, et al. Osteoporosis detection using deep learning. Int J Mod Trends Sci Technol. 2019;05(03):17–20.
32. Iliou T, Anagnostopoulos C-N, Anastasssopoulos G. Osteoporosis detection using machine learning techniques and feature selection. Int J Artif Intell Tools. 2014;23(5):1450014. https://doi.org/10.1142/S0218213014500146
33. Moudani W, Shahin A, Chakik F, et al. Intelligent predictive osteoporosis system. Int J Comput Appl. 2011;32(5):28–37. https://doi.org/10.5120/3901-5468
34. Sathawane KS, Tuteja RR. Data mining in clinical records to foretell the risk of osteoporosis. Int J Res Advent Technol. 2015;3(6):24–31.
35. Devikanniga D, Raj RJS. Classification of osteoporosis by artificial neural network based on monarch butterfly optimisation algorithm. Healthc Technol Lett. 2018;5(2):70–75. https://doi.org/10.1049/htl.2017.0059
36. Reshmalakshmi C, Sasikumar M. Fuzzy inference system for osteoporosis detection. IEEE 2016 Global Humanitarian Technology Conference; Oct. 13–16; 2016;675–681. https://doi.org/10.1109/GHTC.2016.7857351
37. Shubangi DC, Shilpa K A survey on detection and diagnosis of osteoporosis. Int J Eng Sci Invention. 2017;6(10):30–35.
38. Ji L, Zhang W, Zhong X, et al. Osteoporosis, fracture and survival: Application of machine learning in breast cancer prediction models. Front Oncol. 2022;12:973307. https://doi.org/10.3389/fonc.2022.973307
39. Bui, HM, Ha, MH, Pham, HG, et al. Predicting the risk of osteoporosis in older Vietnamese women using machine learning approaches. Sci Rep. 2022;12:20160. https://doi.org/10.1038/s41598-022-24181-x
40. Kong SH, Ahn D, Kim B, et al. A novel fracture prediction model using machine learning in a community-based cohort. JBMR Plus (WOA). 2020;4(3):e10337. https://doi.org/10.1002/jbm4.10337
41. Suh B, Yu H, Kim H, et al. Interpretable deep-learning approaches for osteoporosis risk screening and individualized feature analysis using large population-based data: model development and performance evaluation. J Med Internet Res. 2023;25:e40179. https://doi.org/10.2196/40179
42. Discover the advantages of FRAXplus®. https://fraxplus.org/frax-plus (access: 2024.01.22).
43. Tulchinsky TH. Marc Lalonde, the health field concept and health promotion. Case Studies in Public Health. 2018;523–41. https://doi.org/10.1016/B978-0-12-804571-8.00028-7
44. Williams FMK, Cherkas LF, Spector TD, et al. The effect of moderate alcohol consumption on bone mineral density: a study of female twins. Ann Rheum Dis. 2005;64(2):309–310. https://doi.org/10.1136/ard.2004.022269
45. Godos J, Giampieri F, Chisari E, et al. Alcohol consumption, bone mineral density, and risk of osteoporotic fractures: a dose-response meta-analysis. Int J Environ Res Public Health. 2022;19(3):1515. https://doi.org/10.3390/ijerph19031515
46. Zeng X, Su Y, Tan A, et al. The association of coffee consumption with the risk of osteoporosis and fractures: a systematic review and meta-analysis. Osteoporos Int. 2022;33:1871–1893. https://doi.org/10.1007/s00198-022-06399-7
47. Filip RS, Zagórski J. Osteoporosis risk factors in rural and urban women from the Lublin Region of Poland. Ann Agric Environ Med. 2005;12(1):21–26.