METHODOLOGY

Logistic regression in estimates of femoral neck fracture by fall

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Abstract: The latest methods in estimating the probability (absolute risk) of osteoporotic fractures include several logistic regression models, based on qualitative risk factors plus bone mineral density (BMD), and the probability estimate of fracture in the future. The Slovak logistic regression model, in contrast to other models, is created from quantitative variables of the proximal femur (in International System of Units) and estimates the probability of fracture by fall.

Objectives: The first objective of this study was to order selected independent variables according to the intensity of their influence (statistical significance) upon the occurrence of values of the dependent variable: femur strength index (FSI). The second objective was to determine, using logistic regression, whether the odds of FSI acquiring a pathological value (femoral neck fracture by fall) increased or declined if the value of the variables (T–score total hip, BMI, alpha angle, theta angle and HAL) were raised by one unit.

Patients and methods: Bone densitometer measurements using dual energy X–ray absorptiometry (DXA), (Prodigy, Primo, GE, USA) of the left proximal femur were obtained from 3 216 East Slovak women with primary or secondary osteoporosis or osteopenia, aged 20–89 years (mean age 58.9; 95% CI: −58.42; 59.38). The following variables were measured: FSI, T-score total hip BMD, body mass index (BMI), as were the geometrical variables of proximal femur alpha angle (α angle), theta angle (θ angle), and hip axis length (HAL).

Statistical analysis: Logistic regression was used to measure the influence of the independent variables (T-score total hip, alpha angle, theta angle, HAL, BMI) upon the dependent variable (FSI).

Results: The order of independent variables according to the intensity of their influence (greatest to least) upon the occurrence of values of the dependent FSI variable was found to be: BMI, theta angle, T-score total hip, alpha angle, and HAL. An increase of one unit of an independent variable was shown, with statistical significance, to either raise or decrease the odds of the dependent FSI variable. Specific findings were as follows: an increase by 1° of the α angle escalated the probability of FSI acquiring a pathological value by 1111 times; an increase by 1° of the θ angle was found to boost these odds 1231 times; an increase by 1 mm of the HAL was found to increase these odds by 1043 times; an increase by 1.0 kg/m^2 of the BMI raised the odds 1302 times; an increase by +1 standard deviation of the value of the T-score total hip subsequently decreased these odds 198 times.

Conclusion: The equation of the Slovak regression model makes it possible in praxis to determine the probability or absolute risk of femoral neck fracture by fall at those densitometrical workplaces without a program for measuring the FSI variable.

Keywords: osteoporosis, femoral neck fracture, logistic regression, absolute risk, bone densitometry, bone geometry, biomechanics

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Introduction

To determine the absolute risk of osteoporotic fractures in clinical osteology, the current value of bone mineral density (BMD), measured by bone densitometer dual energy X-ray absorptiometry (DXA) has been used and is still being used in some workplaces.

With new findings in clinical osteology, the estimate of absolute fracture risk has been improved by introducing different questionnaires. Evaluations are made according to the number of positive answers. Besides the questionnaire column for BMD value in the femoral neck area, other questions have been added, to establish the presence or absence of the patient's exposure to selected (chosen) risk factors. Individual questionnaires differ in the number and sorts of risk factors listed.[1–7]

The latest methods in estimating the probability (absolute risk) of osteoporotic fractures include logistic regression models. A logistic regression model is a special case of generalized linear model, where the random component is a variable with alternative distribution of probability, and a logit is used as a link function. Independent variables can be quantitative or qualitative. A dependent variable is categorical and largely qualitative. Most frequently we find the application of a binary logistic regression, where the dependent variable is dichotomous, acquiring only two values, 0 or 1. The value 1 denotes the occurrence of the investigated phenomenon (outcome), and the value 0, its absence.

The binary logistic regression model is used to predict the probability of a change in a categorically-dependent variable, conditional on the values of independent variables. In addition to supplying an estimate of conditioned probability, the model allows one to assess the degree of influence of selected independent variables upon the occurrence of values (categories) of the dependent variable.

In clinical osteology, it is possible by using a logistic regression model, to test the statistical significance of the influence of chosen risk factors and BMD values on incidence of osteoporotic fractures.

This paper offers a description of a Slovak regression model, which differs from previously published regression models by the nature of the selected independent variables and a dependent categorical variable, belonging to biomechanical and geometrical variables. The Slovak logistic regression model, in contrast to other models, is created using quantitative measures of the proximal femur and estimates the probability of fracture by fall. These quantitative variables are defined using the International System of Units (SI).

Objectives of the study

There were three main objectives of this study. The first was to determine, using logistic regression, the order of independent variables according to the intensity of their influence (statistical significance) upon the occurrence of values of the dependent FSI variable.

The second aim was to use logistic regression to determine whether there was a significant increase (or decrease) in the probability of a patient's FSI acquiring a pathological value (odds for femoral neck fracture by fall), if the value of the independent variables (T-score total hip, BMI, alpha angle, theta angle, and HAL) were raised by one unit. The final objective was to provide information to enable physicians engaged in osteological praxis to estimate the probability or absolute risk for femoral neck fracture by fall using a regression model equation, for Slovakian women, at those workplaces without a program for measuring the FSI variable.

Patients and methods

A sample of 3216 women from Eastern Slovakia with primary or secondary osteoporosis or osteopenia, aged 20–89 years (mean age 58.9; 95% confidence interval [CI]: −58.42; 59.38) were examined with the bone densitometer DXA (Table 1).

The BMD was determined in the standard region of interest (ROI), total hip left. BMD values were given in absolute numbers of grams of Ca-hydroxyapathite crystals per cm^2 (g/cm^2), as well as in relative numbers as a T-score (the number of standard deviations from the reference group of young healthy women) and a Z-score (the number of standard deviations from the relevant age group of healthy women). Osteoporosis or osteopenia were diagnosed in accordance with the World Health Organization's (WHO) criteria (Table 2).

To achieve measurement quality (QA), only two operators alternated in measuring with the DXA device and all women were measured with the same device. The following variables

Table 1 Characteristics of the sample of examined patients, investigated variables and applied methods

Number (n)	3216
Gender	Female
Age ($\bar{x}$, 95% CI)	58,90 ⟨58,42; 59,38⟩
Disease	Osteoporosis, osteopenia
Variables	FSI, age, BMI, angle alfa, angle theta, HAL, T-score total hip
Methods	Densitometry (DXA, GE, Prodigy – Primo)
Statistical analysis	Logistic regression

**Abbreviations:** CI, confidence interval; BMI, body mass index; FSI, femur strength index.

Table 2 WHO classification of bone density

Bone density	T-score
Normal	>−1.0 SD
Osteopenia	⟨−1.0; −2.5) SD
Osteoporosis	≤−2.5 SD

were measured on the left proximal femur: T-score total hip, alpha angle, theta angle, HAL, FSI. Patients' body mass index was also measured and their ages were recorded in the protocol.

Definitions of variables

Alpha angle (α) is an angle formed by the femoral shaft axis and the perpendicular. The alpha angle can acquire both positive and negative values in the population, depending on whether the femur is in a valgose or varose position[8] (Figure 1).
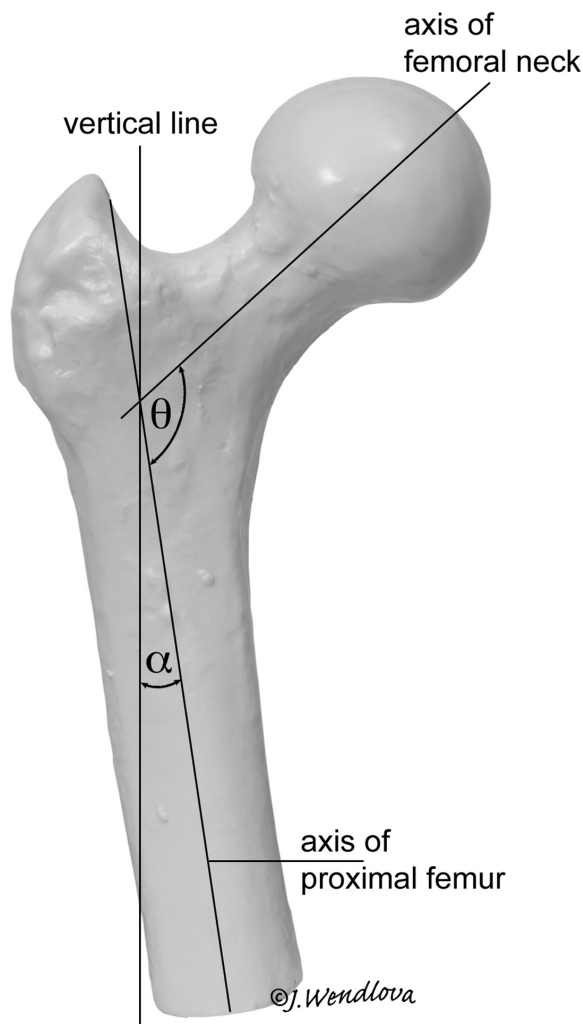
Figure 1 Angle alpha and angle theta.

Theta angle (θ) is an angle formed by the femoral neck axis and the femoral shaft axis (Figure 1).

HAL is a distance (in mm) from the beginning point of the greater trochanter protuberance to the pelvis inner rim, measured in the femoral neck axis[8] (Figure 2).

FSI characterizes the strength of the femoral neck when stressed by compressive forces during a fall. It is defined as a ratio of estimated elastic limit in compression of the femoral neck to the expected compressive stress of a fall on the greater trochanter and adjusted for the patient's age, height and weight.[8]

BMI is calculated using the following equation:

$$\frac{weight(kg)}{height^2(m^2)}$$

Statistical analysis

A model of logistic regression was used.[9–13] The results of a clinical study, including 3 216 Eastern Slovakian female patients, were used to set up the model. To analyze the data from the sample the statistical methods were applied using a statistical analysis program, SAS® Enterprise Guide 4.0 (SAS Institute, Cary, NC).

The structure of the Slovak regression model

The dependent variable in the model was the FSI variable. The FSI values were categorized as follows: FSI > 1 (normal values); in the regression model these values were replaced by the 0 category, categorized FSI ($FSI_{category} = 0$). FSI < 1 (pathological values); in the regression model these values were replaced by the 1 category, categorized FSI ($FSI_{category} = 1$). A binary variable was produced with the working title $FSI_{category}$ in the

Figure 2 Hip axis length.

outputs from the SAS Enterprise Guide. The sample was found to include 470 (14.51%) of patients with pathological values of FSI ($FSI_{category}$ = 1) and 2 746 (85.37%) of patients, whose FSI values could be considered normal ($FSI_{category}$ = 0) (Table 3).

Independent variables, short listed for the regression model included: BMI, age, alpha angle, theta angle, HAL, and T-score total hip. The method of stepwise regression was applied in the selection of the most optimal subset of independent variables for use in a regression model. Age was excluded from the list of chosen independent variables.

The model with the variables BMI, alpha angle, theta angle, HAL, and T-score total hip was determined to be statistically significant as a whole. At the significance level of α = 0.01 and on the basis of the likelihood ratio test, test score and Wald test, we can reject the zero hypothesis that the model as a whole is not statistically significant meaning all regression coefficients equal zero. Instead we can accept an alternative hypothesis that the model as a whole is statistically significant, meaning at least one regression coefficient does not equal zero (Table 4).

The ability of the model to differentiate between the patients with normal and those with pathological values of FSI, based on the values of independent variables, was verified using the Hosmer–Lemeshow test. At the significance level of α = 0.01, we accepted the zero hypothesis meaning the model is adequate to the data. This was tested against an alternative hypothesis that the model is not adequate to the data (Table 5).

Results

Table 6 contains independent variables arranged according to the intensity of their influence upon the occurrence of values of the dependent FSI variable. These were evaluated using the Wald's test of statistical significance. All selected independent variables were found to affect the dependent FSI variable with statistical significance already at the level of α = 0.001.

The regression model equation allows a probability estimate of the occurrence of pathological values of FSI [P ($FSI_{category}$ = 1)] in the femoral neck area, ie, the absolute

Table 3 Frequency of occurrence of categorized FSI variable ($FSI_{category}$) in sample

Response profile			
Ordered value	$FSI_{categor}$	Total frequency	In %
1	1	470	14,61
2	0	2746	85,37

Abbreviation: FSI, femur strength index.

Table 4 Testing model's statistical significance

Testing global null hypothesis: $\beta = 0$			
Test	Chi-square	DF	P
Likelihood ratio	658.1840	5	<0.0001*
Score	564.5674	5	<0.0001*
Wald	431.7499	5	<0.0001*

Abbreviations: p, probability; DF, degree of freedom.
Notes: *Statistical significance

risk estimate of femoral neck fractures caused by fall and the relation is valid for the population of Slovak women.

Estimated values of OR (odds ratio) are given in Table 7. None of the estimated 95% CI contains the value of 1. Therefore, it holds true for each independent variable that one unit of change of a given variable affects, with statistical significance, a change in probability (either an increase or decrease of the odds) that the FSI dependent variable acquires pathological values. The increase of independent variable values for BMI, alpha angle, theta angle, and HAL was shown to boost the odds. For instance, if the value of the BMI increases by one unit (+1.0 kg/m^2) and the values of the remaining independent variables do not change, the odds that dependent variable $FSI_{category}$ achieves a value of 1 (ie, pathological value of FSI < 1) increases 1.302 times, according to the regression model. In the same way, it is possible to interpret the estimated values of alpha angle, theta angle, and HAL.

The increase of values in the independent variable T-score total hip was shown to lead to a reduction of the odds that the FSI acquires pathological values. More specifically, if the T-score total hip value increases by one unit (+1 SD) and the values of remaining independent variables do not change, the odds that dependent variable $FSI_{category}$ acquires the value of 1 (ie, pathological value of FSI < 1) declines to the level 0.505 of the original values or 1.98 times.

Discussion

In the past few years, several papers have been published about regression models created with the aim of determining a probability estimate for osteoporotic fractures with a future prognosis of five, ten, or more years.[14–16] However,

Table 5 Testing model's quality

Hosmer and Lemeshow Goodness-of-Fit test		
Chi-square	DF	P
12.6364	8	0.1250

Notes: a = 0.01, P > a (0.1250 > 0.01).
Abbreviation: DF, degrees of freedom.

Table 6 Independent variables and their measured influence on the FSI

Analysis of maximum likelihood estimates

Variable	DF	Estimate β	Standard error	Wald chi-square	P
Intercept	1	−40.7612	2.4387	279.3576	<0.0001*
BMI	1	0.2639	0.0148	316.6411	<0.0001*
Angle theta left	1	0.2082	0.0173	145.0853	<0.0001*
T-score total hip left	1	−0.6824	0.0603	127.9164	<0.0001*
Angle alpha left	1	0.1051	0.0177	35.0879	<0.0001*
HAL left	1	0.0423	0.00959	19.4942	<0.0001*

Abbreviations: BMI, body mas index; DF, degrees of freedom; FSI, femur strength index; HAL, hip axis length.
Notes: *Wald's test of statistical significance.

their authors admit that these regression models have their inaccuracies and shortcomings. For instance, the exposure to some risk factors (ie, smoking, alcohol consumption, secondary diseases negatively affecting the bone metabolism, increased osteoresorption, glucocorticoid usage, etc) is not precisely defined. Furthermore, there is no possibility to include into the specification of these regression models, the amount of or length of exposure to these qualitative risk factors on an individual patient basis. Another disadvantage of previous regression models is that they were created without involving the population aged ≥80 years, even though it is known that it is just this group which most often suffers from femoral neck fractures, as well as other fractures. Likewise, the risk estimate of fractures with the prognosis for five or ten years is not the most appropriate one, as most fractures happen by fall and not spontaneously. Finally, these regression models do not take into consideration whether the osteoporotic patient (male or female) exercises regularly according to the instructions of a rehabilitator including exercises for balancing the muscular dysbalance;[17] exercises with simulated disruption of balance with the aim to improve the coordination movements, and exercises with the correct techniques for falling (distribution of the energy of fall into several consequent phases of the movement). The risk of a fall for an osteoporotic patient, who does not

exercise regularly the aforementioned exercises and instead exhibits a sedentary lifestyle, is higher than for a patient practicing regular physical activity following the instructions of a rehabilitator.

Correctly estimating the probability (absolute risk) of a femoral neck fracture

Previously-used regression models have been based on various qualitative risk factors and on only one characteristic of the bone quality, the BMD. Criteria for some risk factors cannot be defined so precisely as to fully meet the physician's requirement for individual characteristics of the tested patient so the newer regression models often get entangled in adding more and more risk factors, belonging primarily to the category of qualitative independent variables. The inaccuracy of these qualitative risk factor definitions is often combined with incorrect estimates of spontaneous fracture risk with a prognosis for different future time intervals and not with the prognosis of fracture risk by fall. By contrast, the Slovak regression model is based on an assumption that all risk factors, without direct necessity of their knowledge, listing, and characteristics, share in the formation of the resulting bone quality and it is this bone quality which determines the absolute risk of fracture by fall. Therefore, in the Slovak regression model we focused on as accurate a determination as possible (considering our diagnostic limitations) of the material properties of bones, ie, their strength and elasticity. The bone quality was determined by biomechanical quantitative variables. Falls usually happen by a certain stereotypical mechanism, allowing the use of biomechanics to calculate accurately the magnitude of impact force by fall upon the hip.[18] This impact force magnitude is taken into account in the biomechanical-dependent FSI variable. Therefore, in the Slovak regression model an estimate is made for fracture probability by fall and not with the prognosis of spontaneous fracture in the future. It can happen that after getting

Table 7 The Slovak regression model allows interpretation of the values of independent variables through odds ratio values

Odds ratio estimates

Variable	Point estimate	95% Wald confidence limits	
T-score total hip left	0.505	0.449	0.569
angle alpha left	1.111	1.073	1.150
angle theta left	1.231	1.190	1.274
HAL	1.043	1.024	1.063
BMI	1.302	1.265	1.340

Abbreviations: BMI, body mas index; HAL, hip axis length.
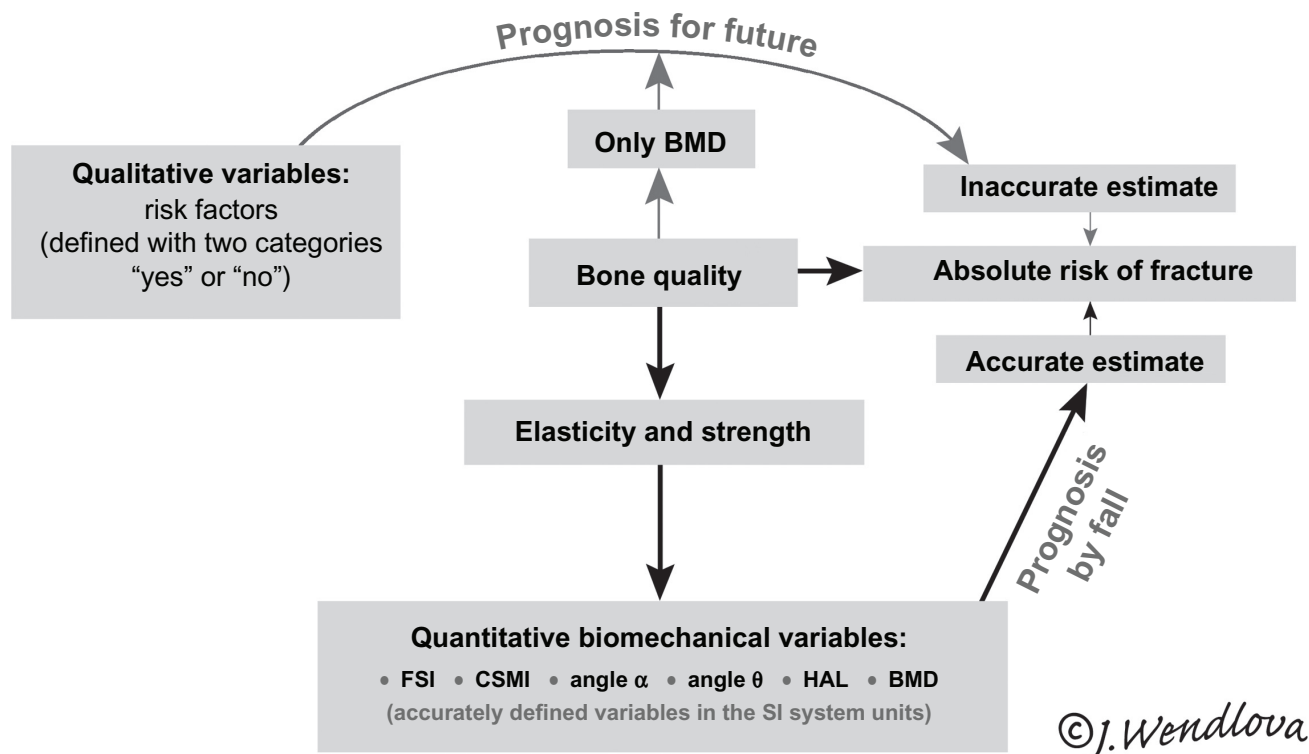
Figure 3 Two possibilities for estimating the probability (absolute risk) of a femoral neck fracture in current osteological praxis.
Abbreviations: BMD, bone mineral density; CSMI, cross-sectional moment of inertia; FSI, femur strength index; HAL, hip axis length.

the prognosis of absolute risk of a spontaneous fracture, for instance, within 5 years, a patient can fall the next day and suffer a fracture of a vertebra or the femoral neck.

The structure of the Slovak regression model and its solution represents a new approach to the probability or absolute risk estimate for femoral neck fractures by fall, and this model is the first of its kind in the world literature. In this model, BMI is, statistically, the most significant independent variable affecting the FSI. This means that BMI significantly influences the probability of femoral neck fracture by fall. The explanation is simple. We put the values for height and weight into the equation for the calculation of impact force by fall and this equation is part of the equation for FSI calculation.[18] It holds true that the higher the weight or height of the patient, the greater the impact force applied to the hip, which then increases the probability of fracture by fall. Likewise, if the patient has higher values of variables alpha angle, theta angle, and HAL than the mean value (μ) in the Slovakian population, it follows that her risk of femoral neck fracture by fall is also higher.

The patient's age was not decisive in our regression model; therefore, the program excluded it from the model. For our model, it was sufficient to give a current value of T-score total hip, BMD, and FSI value, characterizing the

bone quality. BMD and FSI values are age-dependent, but their value can be affected at any age by exposure to a number of risk factors. Therefore, even at a younger age it can demonstrate very low pathological values depending on the length of patient's exposure to diseases which increase osteoresorption (eg, thyreotoxicosis, chronical hepatopathy, chronical pancreatitis, etc).

Geometric variables of proximal femur (alpha angle, theta angle, HAL) + BMD (T-score total hip) + BMI variables enable us to estimate the probability of the occurrence of pathological values of FSI in the femoral neck area. Values of FSI, lower than 1 increase the probability of a fracture in the femoral neck area by fall.[19–23] The lower the value of the FSI variable compared to 1, the greater the probability for a fracture by fall. The equation of the Slovak regression model makes it possible, in praxis, to determine the probability for a patient demonstrating a pathological value of FSI at those densitometrical workplaces without a program for measuring the FSI variable. To determine absolute risk of a femoral neck fracture by fall, the doctor enters the patient's current BMI, angle alpha, angle theta, HAL, standardized BMD, and T-score total hip values into the regression model equation (given in Microsoft Excel®; Microsoft, Redmond, WA).

Summary

With the Slovak regression model we have opened the way for a new method of estimating the absolute risk or odds for a femoral neck fracture by fall, based upon bone quality determination.

Benefits of the Slovak regression model are that it may be used to: estimate the present quality status of femoral neck by means of FSI value; estimate the probability of femoral neck fracture by fall on the basis of the values of quantitative biomechanical variables of proximal femur, given in SI units; eliminate the inaccuracies of other models, based on less precisely defined qualitative variables plus BMD, which do not allow one to determine the probability of femoral neck fracture by fall; determine that a patient with probability value of $P > 50\%$ has an increased risk of a femoral neck fracture by fall.

We do not foresee any great differences between the Middle and Western Slovakian female population and the investigated Eastern Slovakian female population. Therefore, we assume that the female sample from Eastern Slovakia is representative of all Slovak women with osteoporosis and osteopenia. We propose that the Slovak regression model can be used to estimate the probability of femoral neck fracture in the Slovakian female population as a whole.

Conclusion

The Slovak regression model can be helpful in that country's strategy of health economics as it may determine the patients with increased risk of femoral neck fractures by fall. For these at-risk patients it might be necessary to apply intensive complex therapeutic interventions (ie, drug therapy, kinesitherapy, nutritional therapy, wearing a hip protector) which have proven to be effective in the prevention of cost-reimbursement for the treatment of femoral neck fractures.

We assume that the methods of estimating the probability of femoral neck fractures by fall will continue to improve and in the future there will be an enhancement in the accuracy of those methods enabling the measurement of the bone quality, which can then be used to determine the probability of these kinds of fractures. This would confirm the growing importance of applying the laws of biomechanics of the skeleton in clinical and osteological praxis, aiming to advance the accuracy of diagnostic methods, and increasing the effectiveness of therapeutic methods.

We are glad to make our contribution with the Slovak regression model to a new view on the problem of estimating the absolute risk of femoral neck fractures by fall in clinical osteology.

Disclosure

The author declares that she has no competing interests, financial or otherwise.

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