Bratisl Lek Listy 2009; 110 (10)
614 – 619

PERSPECTIVES

New Approach to Probability Estimate of Femoral Neck Fracture by Fall (Slovak Regression Model)

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Abstract: *Patients and methods:* 3,216 Slovak women with primary or secondary osteoporosis or osteopenia, aged 20-89 years, were examined with the bone densitometer DXA (dual energy X-ray absorptiometry, GE, Prodigy – Primo), $\bar{x} = 58.9$, 95% C.I. (58.42; 59.38). The values of the following variables for each patient were measured: FSI (femur strength index), T-score total hip left, alpha angle – left, theta angle – left, HAL (hip axis length) left, BMI (body mass index) was calculated from the height and weight of the patients.
Results: Regression model determined the following order of independent variables according to the intensity of their influence upon the occurrence of values of dependent FSI variable: 1. BMI, 2. theta angle, 3. T-score total hip, 4. alpha angle, 5. HAL. The regression model equation, calculated from the variables monitored in the study, enables a doctor in praxis to determine the probability magnitude (absolute risk) for the occurrence of pathological value of FSI (FSI<1) in the femoral neck area, i. e., allows for probability estimate of a femoral neck fracture by fall for Slovak women.
Conclusion: 1. The Slovak regression model differs from regression models, published until now, in chosen independent variables and a dependent variable, belonging to biomechanical variables, characterising the bone quality. 2. The Slovak regression model excludes the inaccuracies of other models, which are not able to define precisely the current and past clinical condition of tested patients (e.g., to define the length and dose of exposure to risk factors). 3. The Slovak regression model opens the way to a new method of estimating the probability (absolute risk) or the odds for a femoral neck fracture by fall, based upon the bone quality determination. 4. It is assumed that the development will proceed by improving the methods enabling to measure the bone quality, determining the probability of fracture by fall *(Tab. 6, Fig. 3, Ref. 22).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: osteoporosi, femoral neck fracture by fall, logistic regression, absolute risk, probability, bone densitometry, bone geometry, biomechanics, bone quality.

To determine risk of osteoporotic fractures in clinical osteology, the current value of bone mineral density (BMD), measured by bone densitometer DXA (dual energy X-ray absorptiometry) has been used and is still being used in some workplaces (1–4).

With new findings in clinical osteology, the estimate of individual fracture risk has been upgraded by introducing different questionnaires and their evaluation according to the number of positive answers. Besides the questionnaire column for BMD value in the femoral neck area, other questions were added, establishing the presence or absence of the patient's exposure to selected (chosen) risk factors. Individual questionnaires differed in the number and sorts of risk factors (5–7).

The latest methods in estimating the probability (absolute risk) of osteoporotic fractures at present included 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. Dependent variables can always be both quantitative and qualitative. A dependent variable is always qualitative (categorial). Most frequently we find the applications of a binary logistic regression, where the dependent variable is dichotomous, acquiring only two values, 0 and 1, the value 1 indicating the occurrence of followed phenomenon, and the value 0 its absence.

The model of a binary logistic regression is used to predict the probability of an alteration of a categorial dependent variable (most frequently of the value 1), conditioned by the values of independent variables. In addition to the estimate of conditioned probability, the model allows to assess the influence of selected independent variables upon the occurrence of dependent variable values (categories).

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

The paper brings the description of a regression model, differing from previously published regression models, by the selection of independent variables and a dependent variable, belonging to biomechanical variable factors, characterising the bone quality. These variables are precisely defined for each patient in the SI system units. The Slovak regression model eliminates the inaccuracies of other models, which are not able to define pre-

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Tab. 1. Characteristic of sample of examined patients, followed variables and applied methods.

Number (n)	3126
Gender	female
Age ($\tilde{x}$, 95% K.I.)	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

cisely the current and past clinical condition of tested patient (e.g., to define the length and dose of exposure to risk factors).

Objective of the study

1. To determine the order of independent variables according to the intensity of their influence (statistical significance) upon the occurrence of values of the dependent *FSI* variable.
2. On the basis of chosen biomechanical independent variables of proximal femur to determine the probability of the occurrence of pathological values of the dependent *FSI* variable *(FSI<1)* in the femoral neck area for a Slovak patient, i.e., to estimate the probability of a femoral neck fracture by fall.

Characteristics of the cohort of examined patients, followed variables and applied methods

A cohort of 3,216 Slovak women with primary or secondary osteoporosis or osteopenia, aged 20–89 years, were examined with the bone densitometer DXA (GE, Prodigy – Primo) (Tab. 1).

All women were examined with the same bone densitometer DXA (GE, Prodigy – Primo). The *BMD* was determined in the standard region of interest (ROI) – total hip left. *BMD* values were given in absolute numbers in *g of Ca-hydroxyapathite crystals for cm^2 (g/cm^2),* as well as in relative numbers as T-score (the number of standard deviations from the reference group of young healthy women) and Z-score (the number of standard deviations from the relevant age group of healthy women). Osteoporosis or osteopenia were diagnosed in accordance with the WHO criteria:

Classification of bone density	T- score:
Normal	>-1.0 SD
Osteopenia	<-1.0; -2.5) SD
Osteoporosis	≤-2.5 SD

To achieve the measurement quality (QA), only two operators alternated in measuring with the DXA (GE, Prodigy – Primo) device. Patients were randomly selected from the region of the East Slovakia, to make the examination location accessible to them (city of Kosice), so that the requirement of measuring all women with the same device could be met. The following biomechanical variables were measured with the DXA device: *T-score total hip left, alpha angle – left, theta angle – left, HAL left, FSI, BMI (body mass index)* was calculated from the height and weight of the patients, and the age of patients was recorded in the protocol.

Definitions of variables

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

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 whether the femur is in a valgose or varose position (Fig. 1) (8).

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 (Fig. 2) (8).

FSI – characterizes the strength of femoral neck, stressed by compressive forces during a fall. It is defined as a ratio of the elastic limit in pressure for the femoral neck (σ_E) with normal BMD values and current tension in pressure, developed in the femoral neck during a fall (σ_C) (8).

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

Statistical analysis (9–13)

Logistic regression.

The results of a clinical study, including 3,216 Slovak patients, were used to set up a model. To analyze the data of the cohort of women statistical methods were applied using statistical programme systems SAS® *Enterprise Guide 4.0.*

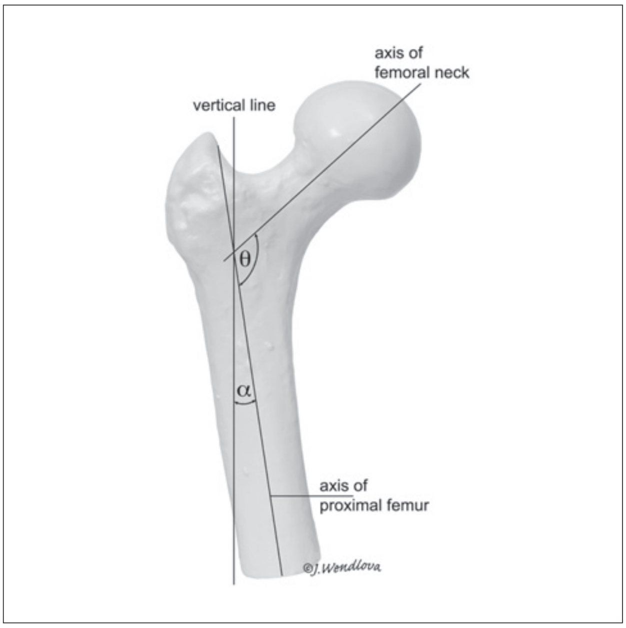

Fig. 1. Angle alfa and angle theta.

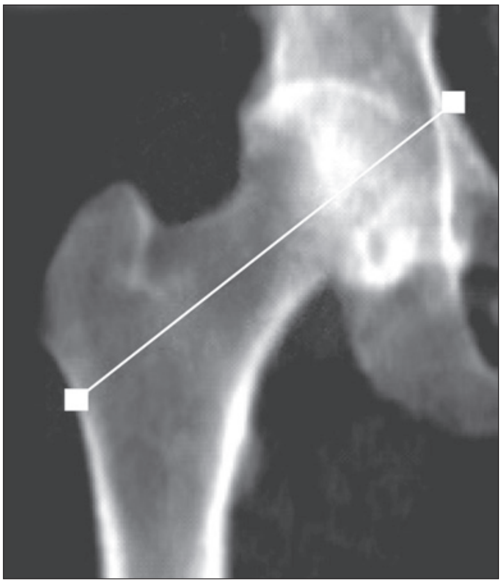

Fig. 2. HAL - hip axis length.

The structure of the Slovak regression model

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

The cohort included 470 (14.51 %) patients with pathological values of *FSI* ($FSI_{categor}=1$) and 2,746 (85.37 %) patients, whose *FSI* values could be considered as normal ($FSI_{categor}=0$) (Tab. 2).

- *Independent variables,* shortlisted for the regression model, included: *BMI, age, alpha angle – left , theta angle – left, HAL left, T-score total hip – left.*

The method of stepwise regression was applied in the selection of the best subset of independent variables. The variable of age was struck off the list.

- *Testing the statistical significance of the model*

The model with the variables *BMI, alpha angle – left , theta angle – left, HAL left, T-score total hip – left* is 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 H_0: the model as a whole is not statistically significant (all regression coefficients equal zero), and accept an alternative hypothesis H_A: the model as a whole is statistically significant (at least one regression coefficient does not equal zero) (Tab. 3).

Tab. 2. Frequency of occurrence of categorized FSI variable ($FSI_{categor}$) in cohort.

Response Profile			
Ordered value	$FSI_{categor}$	Total frequency	In %
1	1	470	14.61
2	0	2746	85.37

Tab. 3. Testing of model's statistical significance.

Testing Global Null Hypothesis: β=0			
Test	Chi-Square	DF	p
Likelihood Ratio	658.1840	5	<.0001*
Score	564.5674	5	<.0001*
Wald	431.7499	5	<.0001*

p – probability, DF – degree of freedom, * – statistical significance

Tab. 4. Testing model's quality.

Hosmer and Lemeshow Goodness-of-Fit Test		
Chi-Square	DF	p
12.6364	8	0.1250

α=0,01, p>α (0,1250>0,01)

Tab. 5. Estimated model's variables and testing of their statistical significance.

Analysis of Maximum Likelihood Estimates					
Variable	DF	Estimate β	Standard Error	Wald Chi-Square	p
Intercept	1	-40.7612	2.4387	279.3576	<.0001*
BMI	1	0.2639	0.0148	316.6411	<.0001*
angle theta left	1	0.2082	0.0173	145.0853	<.0001*
T-score total hip left	1	-0.6824	0.0603	127.9164	<.0001*
angle alpha left	1	0.1051	0.0177	35.0879	<.0001*
HAL left	1	0.0423	0.00959	19.4942	<.0001*

- *Verification of model quality*

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 by the Hosmer-Lemeshow test. At the significance level of α=0.01 we accepted the zero hypothesis H_0: the model is adequate to the data. This was tested against an alternative hypothesis H_A: the model is not adequate to the data (Tab. 4).

Results

The Table 5 contains independent variables arranged according to the intensity of their influence upon the occurrence of val-

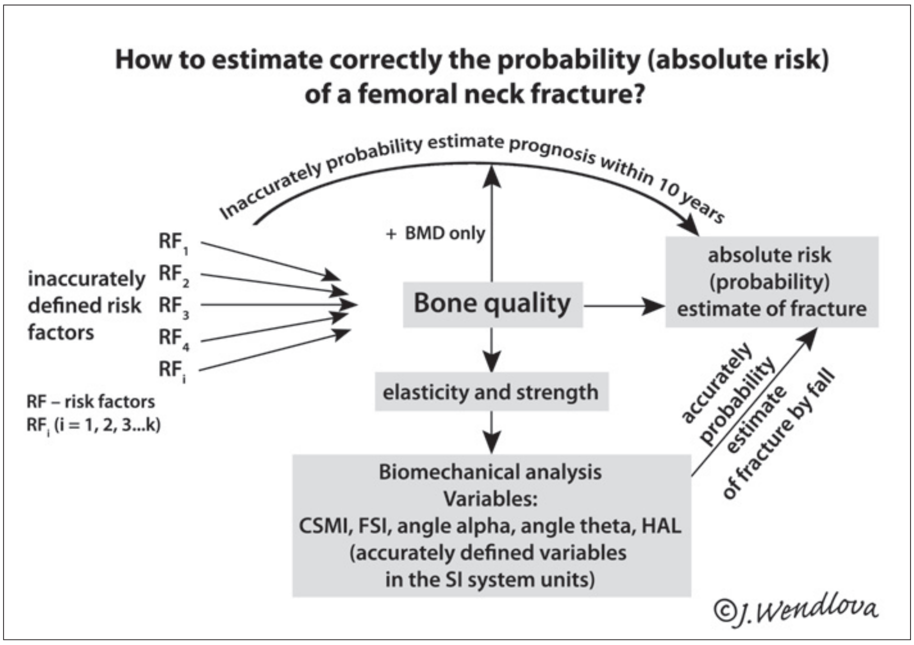

Fig. 3. How to estimate correctly the probability (absolute risk) of a femoral neck fracture?

ues of a dependent *FSI* variable, evaluated by the *Wald's* test of statistical significance. All selected independent variables 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* $(P (FSI_{categor}=1))$ in the femoral neck area, i.e., the probability estimate of femoral neck fractures, caused by fall (the relation is valid for the population of Slovak women).

Estimated values of *OR (odds ratio)* are given in the Table 6. None of the estimated 95% confidence intervals *(CI)* contains the value of 1. Therefore, it holds true for each independent variable that one unit change of a given variable affects with statistical significance the change of the odds (increase or reduction of the odds) that the *FSI* variable acquires pathological values. The growth of values in the variables *BMI, alpha angle – left, theta angle – left, and HAL left* increases the odds. If the value of the *BMI* variable increases by one unit (+1.0 kg/m^2) and the values of remaining variables do not change, the odds that *FSI* acquires in the regression model the value of 1 (i.e., pathological value of *FSI<1*) increase 1.302 fold. In the same way it is possible to interpret the estimated values of variables *alpha angle – left, theta angle – left, and HAL.*

Tab. 6. Regression model allows to interpret the values of independent variables through OR (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

The increase of values in the variable *T-score total hip – left* leads to the reduction of the odds that the *FSI* variable acquires pathological values. If the value of the variable *T-score total hip* increases by one unit (+1 SD) and the values of remaining variables do not change, the odds that *FSI* acquires the value of 1 (i.e., pathological value of *FSI<1*) decline to the level 0.505 of the original values, i.e., decline about 1.98 fold.

Discussion

In the past few years several papers were published about regression models created with the aim to determine a probability estimate (absolute risk) for osteoporotic fractures with the prognosis for five, ten or more years (14–16). However, their authors admit that these regression models have their inaccuracies and shortcomings. The exposure to some risk factors is not precisely defined, as for example: smoking, alcohol consumption, secondary diseases negatively affecting the bone metabolism (increased osteoresorption), glucocorticoid usage, etc. There is no possibility to include into the specification of the regression model within these qualitative risk factors the length of exposure to a risk factor and in some the size of its dose according to an individual data from the patient. Another disadvantage of regression models is the fact that they were created without involving the population of the age ≥80 years, even though it is known that just this group most often suffers from femoral neck fractures as well as other fractures. 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 sponta-

neously. The regression models do not take into consideration whether the osteporotic patient (male or female) exercises regularly according to the instructions of a rehabilitator:
• exercises for balancing the muscular dysbalance
• exercises with simulated disruption of balance aiming at improvement of coordination movements
• exercises with the correct techniques of falling (distribution of energy of the fall into several consequent phases of the movement)

The risk of a fall for an osteoporotic patient, who does not exercise regularly the abovementioned exercises and prefers a sedentary lifestyle, is higher than for a patient with a regular physical activity according to the instructions of a rehabilitator.

How to estimate correctly the probability (absolute risk) of a femoral neck fracture? (Fig. 3)

Previously used regression models have been based on various risk factors and only on one characteristics of the bone quality – BMD. Criteria for some risk factors cannot be defined so precisely as to meet fully the physician's requirement for a real individual characteristics of the tested patient, and so the new regression models get entangled in adding more and more new risk factors, belonging primarily to qualitative independent variables. The inaccuracy of risk factors definitions is joined by incorrect estimate of the spontaneous fracture risk with the prognosis for different future time intervals and not with the prognosis of fracture risk by fall. We based the Slovak regression model 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 the bone quality determines the absolute risk of fracture by fall. Therefore, in the regression model we focused on as accurate determination as possible (considering our diagnostic possibilities) of material properties of bones - their strength and elasticity. The bone quality was determined by biomechanical quantitative variables. Falls usually happen by a certain stereotypical mechanism, allowing biomechanics to calculate accurately the magnitude of impact force by fall upon the hip (17). 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 the fracture probability by fall and not with the prognosis of spontaneous fracture in the future. It can happen that after getting the prognosis of absolute risk of a spontaneous fracture, say, within 5 years, on the next day the patient can fall and suffer a fracture of a vertebra or a femoral neck.

The structure of the Slovak regression model and its solution represents a new approach to the probability (absolute risk) estimate for femoral neck fractures by fall, and this model is the first of its kind in the world literature. In the Slovak regression model, BMI is the statistically most significant independent variable affecting the dependent FSI variable. It means that BMI significantly influences the probability of fracture by fall. The explanation is simple. We put the values of variables for height and weight into the equation for the calculation of impact force by fall (17). It holds true that the higher the weight or height of the patient, the bigger the impact force applied to the hip, increasing the probability of fracture by fall. If the patient has higher values of variables alpha angle, theta angle, HAL than the mean value (m) in the Slovak population , her probability of femoral neck fracture by fall is also higher.

The age was not decisive in our regression model; therefore, the programme excluded it from the model. For the regression model it was sufficient to give a current value of T- score total hip (BMD) and FSI value, characterising the bone quality. BMD and FSI values are, however, age-dependent, but their value can be at any age affected by exposure to a number of risk factors; therefore, even at a younger age it can acquire very low pathological values, e.g., depending on the length of exposure of the patient to diseases pathologically increasing osteoresorption (e.g., thyreotoxicosis, chronical hepatopathy, chronical pancreatitis, etc.). The bone quality diminishes with aging (positive correlation), primarily with the assumption of physiological aging of bones without any influence of exposure to other risk factors, which can reduce the bone quality in young people to the quality values of bones of old people. Geometric variables of proximal femur (alpha angle, theta angle, HAL) + a variable of bone quality: BMD total hip (T-score total hip) + BMI variable enable us to estimate the probability of the occurrence of pathological values of FSI in the femoral neck area. The values of the dependent FSI variable, lower than 1, increase the probability of a fracture in the femoral neck area by fall (18–22). The lower the value of the FSI variable than 1, the bigger the probability (p) for a fracture by fall. The equation of the Slovak regression model makes it possible in praxis to determine the probability for a finding of pathological values of FSI at those densitometrical workplaces, not having a programme for measuring the FSI variable. The doctor puts into the regression model equation (given in Excel® programme) the current values of the patient: the standardized BMD (sBMD) – T score total hip, BMI, angle alpha, angle theta, HAL.

Summary

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

The Slovak regression model:
- estimates the probability (absolute risk) of a fracture by fall, does not estimate the probability (absolute risk) of a spontaneous fracture in the future
- estimates the probability (absolute risk) of a fracture on the basis of the values of biomechanical variables of proximal femur, determining the bone quality,
- allows precisely defined values of each tested patient to be put into the programmed equation of the Slovak regression model, as they are given in the units of the International System of Units (SI).
- a patient with probability (p) value of $p > 50$ % has an increased risk of a femoral neck fracture by fall

- from the aspect of the Slovak economic strategy it is possible to use the established frequency of pathological FSI values in a selected sample for the estimate of expected frequency of pathological values in the Slovak population of osteoporotic women; as regards these patients, it is necessary to take into account increased costs of a complex intensive therapy of osteoporosis as the prevention of femoral neck fractures by fall.

Conclusion

The regression model can be helpful in the Slovak strategy of health economics as it may determine the patients with increased risk of femoral neck fractures by fall. For these risk patients it is necessary to apply an intensive complex therapeutical intervention (drug therapy, kinesitherapy, nutritional therapy, wearing a hip protector) which proves to be effective in the prevention of costs reimbursement for the therapy of femoral neck fractures.

We assume that the methods of estimating the probability (absolute risk) and the odds of femoral neck fractures by fall will be constantly improved, and in the future there will be an enhancement of accuracy of the methods enabling the measurement of the bone quality which determines the probability of fractures by fall. It would confirm the growing importance of the application of the laws of biomechanics of the skeleton in the clinical and osteological praxis, aiming at the increase of the accuracy of diagnostic methods and, finally, the increase of the effectiveness of therapeutical 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 the clinical osteology.

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Received March 2, 2009.
Accepted June 26, 2009.