Research Article

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British Journal of Research
ISSN 2394-3718

2018
Vol.5 No.2:42

DOI: 10.21767/2394-3718.100042

Artificial Neural Networks (ANNs) as a Reliable Tool for the Assessment of Fracture Risk in Postmenopausal Women

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Received Date: May 03, 2018; **Accepted Date:** May 30, 2018; **Published Date:** June 02, 2018

Citation: Bonaccorsi G, Cervellati C, Grossi E, Fila E, Massari L, et al. (2018) Artificial neural networks (ANNs) as a reliable tool for the assessment of fracture risk in postmenopausal women. Br J Res Vol. 5 No. 2: 42.

Abstract

Artificial neural networks (ANNs) are a computational tool, based on highly non-linear mathematics models with potential applications in the prediction of osteoporotic fractures. Therefore, the present study aimed to evaluate the potential of ANNs analysis in the prediction of bone fragility fractures in post-menopausal women. ANNs prognostic performance in identifying vertebral morphometric deformity was compared with that of the widely used tool FRAX® in a sample of 587 Caucasian postmenopausal women underwent densitometry and morphometric analyses for the detection of vertebral fractures. The analysis of areas under the curve (AUCs) showed that sensitivity for ANNs (74%) almost doubled that found for FRAX ® (38%), with the latter presenting a specificity higher than the proposed tool (96 vs. 77%). Overall, ANN-based analysis was able to highlight high-risk patients with a global higher accuracy (74%) compared to that obtained by FRAX (67%). In conclusion, our data showed that compared to WHO's algorithm ANNs had higher sensitivity in identifying vertebral deformity, thus suggesting a "promising role" in the prediction of osteoporotic fracture in postmenopausal women. However, further studies on larger sample are needed to definitely establish the clinical reliability of ANNs.

Keywords: Artificial neural networks; FRAX; Osteoporosis; Fractures

Introduction

Postmenopausal osteoporosis (PO) represents one of the most important health issue, since its prevalence is associated with a worsening of life quality. Indeed, the major PO clinical outcome is fragility fractures (FFs) that increase mortality and add significant costs to the society [1]. FFs are the result of several distinct risk factors, which must be taken in consideration when individual's fracture risk is assessed [2].

Subclinical morphometric vertebral fractures (MVF) are considered the "first event" of osteoporosis and is one of the strongest clinical predictors of subsequent fractures. Thus, it may be more relevant for an appropriate assessment of future fracture risk to assess all the fractures.

During the last decades, classical clinical risk factors (CRFs) have been integrated with several mathematical algorithms, developed to predict the level of fracture risk with or without bone mineral density (BMD) data [3]. At present, the Fracture Risk Assessment Tool (FRAX®), created by the WHO Collaborating Centre for Metabolic Bone Diseases, is the most commonly used [4].

Concerns have been raised about its clinical accuracy and alternative algorithms have been developed to address the highlighted intrinsic drawbacks such as underestimation of the number previous fractures, not inclusion of spine BMD data and others. Nonetheless, these efforts have not yielded significant improvement in the overall reliability, most likely because they have not targeted the underlying problem. Mathematically

speaking, osteoporosis-related FFs can be regarded as a highly non-linear phenomenon and the currently used statistical models might be too simple to produce reliable outcomes. Thus, conceivably, other computational models able to analyze these types of interconnections should be considered.

Artificial neural networks (ANNs) represent one of the most meaningful examples in this context due to its successful application in many complex and diverse tasks in clinical medicine, such as clinical outcome predictions of head injury [5] and in predicting hip fracture mortality [6]. However, the use of ANNs was, to the best of our knowledge, never explored in predicting vertebral fracture.

The aim of the present study was to evaluate the ability of ANN-based methods in the identification of high-risk individual in terms of both clinical and subclinical vertebral FFs. To this end, we compared the performance of ANNs and FRAX in discriminating women who sustained previous vertebral fractures, as assessed by morphometric approach, from those who did not.

Methods

Study design

The present study involved a group of women who referred for osteoporosis management between 2013 to 2014 at the Menopause and Osteoporosis Center of the University of Ferrara, a city in the North East of Italy. This study was designed and performed according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) and was conducted according to the guidelines for Good Clinical Practice (European Medicines Agency). Written informed consent was obtained from each patient before inclusion in the study.

Each participant underwent measurement weight, standing height and evaluation of demographic data, medical history and all clinical risk factors included in FRAX® (**Table 1**) by trained personnel. Inclusion criteria were: postmenopausal status, age between 40 and 90 years old (age range indicated for FRAX evaluation), Caucasian ethnicity, no osteoporosis treatment and low T-score and/or a clinical indication to perform vertebral morphometry in accordance to NOF guidelines.

Among the potential 1,154 individuals who accessed the ambulatory clinic a total of 587 eligible women (median: 62; range 43-88 years) with complete data-records have been enrolled.

BMD measurement

BMD measurements have been performed at both spine and femoral sites by DXA (Hologic Discovery; software version APEX 3.3.0.1., Bedford MA, USA) according to manufacturer and International Society of Clinical Densitometry (ISCD) guidelines. Precision error percentage (%) for BMD was 0.1 at lumbar spine, femoral neck and total hip. For lumbar spine BMD, L1-L4 vertebrae have been selected for the analysis.

Vertebral fracture assessment (VFA)

DXA technology (Hologic Discovery) allowed acquiring images of the lateral thoraco-lumbar spine at the point-of-service of bone density evaluations in order to detect moderate to severe vertebral fractures. The Genant visual semi-quantitative method was exploited to diagnose vertebral osteoporotic fractures and to assess their grade and level of severity. The algorithm based qualitative assessment (ABQ) [7], developed to differentiate vertebral fractures from other causes of vertebral deformities, is also been applied.

Fracture risk assessment tool

The individual 10-year fracture risk has been assessed through FRAX method (available online, http://www.shef.ac.uk/FRAX), keeping in consideration the CRFs for osteoporosis collected in the medical history, prior fragility fractures only, and the T-score for femoral neck BMD. The output is a 10-year probability of developing hip fracture and a 10-year probability for a major osteoporotic fracture to occur (clinical vertebral, humerus, wrist, hip or shoulder fracture).

Artificial neural networks analysis

In the present evaluation, we specifically worked with the family of supervised ANNs, a type of network which tackles issues while an external, objective target output can be fixed, allowing the system to learn by examples thanks to a preliminary "calibration" through a training set" – that is, a suitable sub-sample of the whole database.

The sample selected for the analysis is relatively large, as it is required by the nature of the research question, to allow enough variability to make meaningful inferences as to the predictive capacity of the single variables. Multivariate analysis was carried out with supervised ANN, according to the method already adopted in Penco et al. [8] The choice of a relatively unusual and sophisticated inferential technique such as ANN is motivated by the fact that the underlying relation to be estimated among our independent sample variables and the dependent variable (the presence of vertebral fracture) is extremely complex and there is no reliable a-priori statistical model to refer to. ANNs self-adjust their structure as they learn from their own errors, are able to handle a very high number of variables simultaneously, irrespective of their underlying degree of non-linearity, and lead to structurally robust results even when the underlying statistical process is not well understood, thereby allowing to deal with many sources of inferential trouble such as outliers, collinear interactions among variables, hidden variables, and so on [9].

In particular, we work with the family of Supervised ANNs, that is to say, with ANN that tackle problems where an external, objective target output can be fixed, so that they learn by examples (the training set, that is, a suitable sub-sample of the whole database), calculating an error function during the training phase, and adjusting the connection strengths in order to minimize the error function until a satisfactory and stable level of accuracy in the prediction/classification task is reached. This type of ANNs thus computes a function of the form: y =

f(x,w*), where x is the input, y is the output and w* is the set of ANN weights (the function parameters) that encode the ANN's approximate reconstruction of the structure of the function.

In order to cut down of the number of irrelevant variables in the database (i.e., the variables that do not carry any meaningful information for the prediction task), which cause a loss in the power of our inferences, we have employed a special 'artificial organism' called TWIST [10], suitably designed for sorting out the most relevant variables for the sake of prediction/ classification. It consists of a combination of two already known systems: T&T and IS. The T&T system is a robust data re-sampling technique that is able to arrange the source sample into sub-samples, all of which possessing a similar probability density function. In this way, the database is split into two or more sub-samples in order to train, test and validate the ANN models as effectively as possible on the basis of the available data. The IS system is an evolutionary 'wrapper' system that selects variables in order to minimize their number while preserving the actual amount of task-relevant information contained in the data-set. The combined action of these two systems allows us to increase substantially the inferential power of our ANN system, while circumventing at the same time a few major technical issues. Both systems are based on a Genetic Algorithm, the Genetic Doping Algorithm (GenD) developed at Semeion Research Centre (Rome, Italy) [11]. **Figure 1** described the TWIST system at work during the variables selection task.

The TWIST pre-processing singles out the variables that prove to be most significant for the prediction/classification task, while producing at the same time the training set and the testing set, which are extracted from a probability distribution very close to the one that provided the best performance in the task. As to the prediction/classification task, it is carried out by means of a supervised, multilayer Perceptron, with four hidden units [12]. The protocol scheme is reported in **Figure 1**.

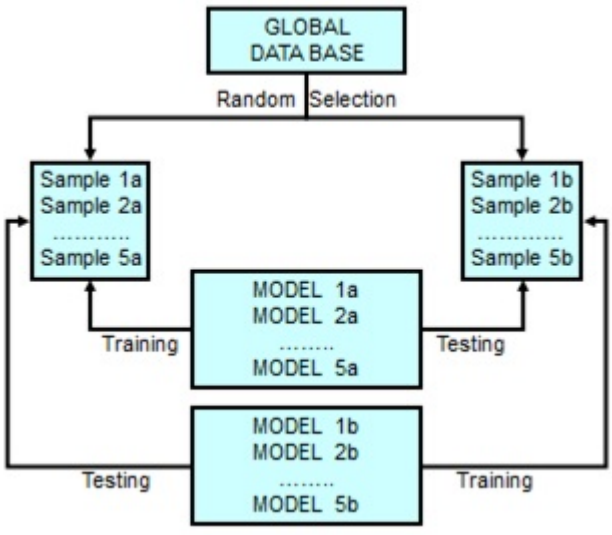

Figure 1: Validation protocol scheme for ANN.

A multivariate analysis has been carried out on supervised ANN, according to the method adopted by Penco et al. [10]. In order to decrease the number of irrelevant variables in the database (i.e., those variables which do not carry any meaningful information with regards to the prediction task), which may cause a loss the predictive power of our inferences, we made use of a special "artificial organism" called TWIST [13], suitably designed for sorting out the most relevant variables for the sake of prediction/classification.

The pre-processing task of the TWIST system isolates the variables which are proven to be the most significant for the prediction/classification task; at the same time, the system produces the training set and the testing set, which are extracted from a probability distribution very close to the one that provided the best performance in the task. Two-fold crossover training –testing it is performed by means of a supervised multi-layer perceptron with four hidden units in two independent experiments.

The data set for ANNs included 24 variables (15 clinical parameters and 9 BMD values). Among these factors, TWIST system selected a subset of 17 variables including 10 clinical parameters, considered also by FRAX® (age< 59 years, pre-menopause/peri-menopause, spontaneous menopause, menopause age (years), years in menopause (years), BMI (Kg/m²), no smoking, light smoking (<10 cig/die), heavy smoking (>10 cig/die), Corticosteroids and 7 BMD data (vertebral osteopenia, vertebral osteoporosis, normal femoral neck BMD, femoral neck osteoporosis, normal total hip BMD, total hip osteopenia, total hip osteoporosis).

Statistical analysis

Data were shown according to their distribution as means of standard deviation (SD), which have been evaluated using the Kolmogorov-Smirnov test. The ability of FRAX and ANNs to discriminate between those patients who previously experienced any fractures and those who did not has been reported in terms of areas under the receiver operating characteristics (ROC) curves (AUC). SPSS 16.00 for Windows (Chicago, Illinois, USA) was used for statistical analysis. P values minor than 0.05 have been considered statistically significant.

Results

Postmenopausal women with and without concomitant fractures: comparison of CRFs

In the sample as whole (n=587), the overall prevalence of vertebral fractures was 51% (300/587).

As shown in **Table 1** women with no fractures were significantly younger than those with a fracture and had significantly lower prevalence of known fractures at spine/hip and at other skeleton sites, respectively. As expected, major and femoral FRAX® values were lower in no fractures group compared to the others (p<0.001 for both comparisons), while

BMD at femoral neck, spine and total hip were all significantly higher (p<0.001 for all).

Table 1: CRFS and DXA parameters in participants according to vertebral fractures prevalence.

	No Fractures (n 287)	V Fractures (n 300)	p
CRFs			
Age (years)	61 ± 7.5	66 ± 8.2	<0.001
BMI, kg/m^2	24.4 ± 3.9	24.8 ± 3.8	NR
BMI <19, n (%)	13	10	NR
Parental history of fractures, n (%)	15	21	NR
Smoking, n (%)	17	22	NR
Rheumatic disorders, n (%)	2	4	NR
Alcohol, n (%)	0	0	NR
Glucocorticoids, n (%)	4	2	NR
Secondary osteoporosis, n (%)	18	25	NR
Previous spine/hip fractures, n (%)	3	11	<0.05
Other prevoius fractures, n (%)	14	8	<0.05
Major FRAX	7.8 ± 5.8	10.6 ± 7.4	<0.001
Femoral FRAX	2.6 ± 3.6	4.4 ± 5.6	<0.001
DXA parameters			
Spine BMD (g/cm²)	0.721 ± 0.099	0,696 ± 0,099	<0.01
Spine T-score	-3.1 ± 0.9	-3,4 ± 1.0	<0.01
Femoral neck BMD (g/cm²)	0.627 ± 0.091	0,601 ± 0,089	<0.01
Femoral neck T-score	-2.0 ± 0.8	-2,2 ± 0.8	<0.01
Total hip BMD (g/cm²)	0.749 ± 0.097	0,720 ± 0,093	<0.01
Total hip T-score	-1.6 ± 0.81	-1,8 ± 0.8	<0.01
Data were presented as: n(%) for categorical and mean ± standard deviations for continuous variables.			

ANNs vs. FRAX®: comparison of the relative accuracy

The ability of ANNs to distinguish women with at least one morphometric vertebral fracture with those without vertebral fractures was evaluated through ROC curves.

As shown by **Figure 2**, the AUC of ANN evaluated by means of back propagation was 0.701 (95% confidence interval [CI]: 0.664-0.738) vs. 0.643 (95%CI: 0. 604 – 0.682) of FRAX® evaluated by means of logistic regression. **Table 2** shows a summarizing data indicating data of sensitivity, specificity and global accuracy of detecting a fracture, evidencing that sensitivity was higher for ANNs than for FRAX® (71 vs. 38%), whilst the specificity was higher for FRAX® compared to ANN (96 vs. 77%).

ANNs allowed identifying women with at least one vertebral fracture with an accuracy that resulted to be higher for ANNs compared to FRAX® (74 vs. 67%).

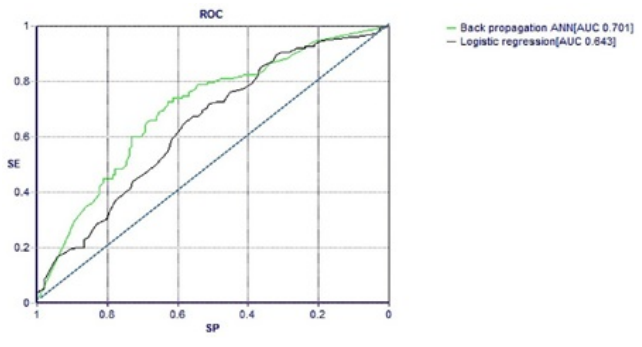

Figure 2: ROC curve of ANN vs FRAX®.

Table 2: Sensitivity, specificity and global accuracy of FRAX and ANNs.

Model	Sensitivity	Specificity	Global accuracy
FRAX®	38.00%	96.00%	67.00%
ANNs	71.02%	77.12%	74.04%

Discussion

The international guidelines underline the importance of a comprehensive assessment of osteoporotic fracture probability, particularly in people having a normal BMD or in the range of osteopenia.

Several risk prediction tools that integrate the weight of clinical risk factors (CRFs) for fracture risk, with or without information on BMD, have been developed in the last decades. Artificial Neural Networks (ANNs) could represent an alternative way compared to traditional statistic because it's a kind of mathematical model that try to better integrate BMD values, CRFs and fragility fractures. This procedure subsequently allows to calculate an error function during the training phase and to adjust the connection strengths in order to minimize the error function until the system reaches a satisfactory and stable level of accuracy in the prediction/classification task.

The choice of a relatively unusual and sophisticated inferential technique such as ANN is motivated by the fact that the nature of the underlying relation to be estimated between our independent variables and the dependent ones (such as the presence of vertebral fractures) is extremely complex and there is no reliable a-priori statistical model to refer to so far. ANN systems automatically self-adjust their structure as they learn from their own errors, are able to manage a very large number of variables simultaneously irrespective of their intrinsic level of non-linearity. Moreover, ANNs have been ideated in order to lead to structurally robust results even in presence of not well understood underlying statistical processes, therefore allowing to deal with several sources of inferential trouble such as outliers, collinear interactions among variables, hidden variables and many others [13].

In this study, we evaluated the clinical reliability of ANNs in identifying subjects at higher risk of FFs by comparing the statistical outcomes with those obtained by the widely used FRAX. In our post-menopausal population, the ANN-based analysis has been able to highlight patients with morphometric vertebral fractures with a global higher accuracy (74%) compared to what observed through the use of FRAX (67%).

Therefore, the potential applications of these novel prediction tools can be promising. In this sense, ANNs may putatively assist clinicians in making complex decisions, overcoming many of the intrinsic limits of current data-analysis models thanks their major advantage of being able to predict complex, highly non-linear phenomena. Medical decisions may thus potentially be managed with reliability and high accuracy even in presence of apparently not predictable scenarios.

Strength of ANNs are their sensitivity, higher than that of FRAX®. This characteristic made ANNs more suitable for the screening of people having a sub-clinical or asymptomatic vertebral fracture and this could be of importance since not clinical spine fractures are associated with higher mortality risk, repeated hospitalizations and poor quality of life.

The findings of our study should be interpreted within its limitations. First, its cross-sectional design does not allow giving any definitive conclusion regarding the direction of our findings. Second, standardized coefficients and odds ratios corresponding to each variable for the ANNs, cannot be calculated, and the interpretability might be limited at the level of individual variables. Third, a selection bias (since these women were referred to a center specialized in osteoporosis) should be not excluded. Finally, we did not include men and if our findings can be applied to this gender should be explored.

Conclusion

In conclusion, our data showed that compared to WHO's algorithm, ANNs had higher sensitivity and accuracy in identifying vertebral deformity, thus suggesting a "promising role" in the prediction of osteoporotic fracture in postmenopausal women. However, further studies in larger populations and with a longitudinal design are needed to definitely establish the clinical reliability of ANNs.

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