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Study of Hip Fracture Risk using Tree Structured Survival Analysis

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In dieser Studie wird das Hüftfraktur-Risiko bei postmenopausalen Frauen untersucht, indem die Frauen in verschiedene Subgruppen hinsichtlich dieses Risikos klassifiziert werden. Frauen in einer gemeinsamen Subgruppe haben ein ähnliches Risiko, hingegen in verschiedenen Subgruppen ein unterschiedliches Hüftfraktur-Risiko. Die Subgruppen wurden mittels der Tree Structured Survival Analysis (TSSA) aus den Daten von 7.665 Frauen der SOF (Study of Osteoporosis Fracture) ermittelt. Bei allen Studienteilnehmerinnen wurde die Knochenmineraldichte (BMD) von Unterarm, Oberschenkelhals, Hüfte und Wirbelsäule gemessen. Die Zeit von der BMD-Messung bis zur Hüftfraktur wurde als Endpunkt notiert. Eine Stichprobe von 75 % der Teilnehmerinnen wurde verwendet, um die prognostischen Subgruppen zu bilden (Trainings-Datensatz), während die anderen 25 % als Bestätigung der Ergebnisse diente (Validierungs-Datensatz). Aufgrund des Trainings-Datensatzes konnten mittels TSSA 4 Subgruppen identifiziert werden, deren Hüftfraktur-Risiko bei einem Follow-up von im Mittel 6,5 Jahren bei 19 %, 9 %, 4 % und 1 % lag. Die Einteilung in die Subgruppen erfolgte aufgrund der Bewertung der BMD des Ward'schen Dreiecks sowie des Oberschenkelhalses und nach dem Alter. Diese Ergebnisse konnten mittels des Validierungs-Datensatzes reproduziert werden, was die Sinnhaftigkeit der Klassifizierungregeln in einem klinischen Setting bestätigte. Mittels TSSA war eine sinnvolle, aussagekräftige und reproduzierbare Identifikation von prognostischen Subgruppen, die auf dem Alter und den BMD-Werten beruhen, möglich.

In this paper we studied the risk of hip fracture for post-menopausal women by classifying women into different subgroups based on their risk of hip fracture. The subgroups were generated such that all the women in a particular subgroup had relatively similar risk while women belonging to two different subgroups had rather different risks of hip fracture. We used the Tree Structured Survival Analysis (TSSA) method to generate the subgroups based upon the cross-sectional data from 7,665 women enrolled in the Study of Osteoporotic Fractures (SOF). All of these women had forearm, os calcis, hip and spine bone mineral density (BMD) measurements. Time to hip fracture since BMD measurement was also recorded for these women and was treated as the outcome variable. A random sample consisting of 75 % (training data set) of women from the 7,665 available was used to generate the prognostic subgroups while the other 25 % (validation data set) was used to validate the results. Based on the training data set, TSSA identified four subgroups for whom the risk of hip fracture for an average of 6.5 years of follow-up was 19 %, 9 %, 4 % and 1 %. The rules to generate the subgroups were based on BMD of Ward's triangle, BMD of the os calcis, and BMD of the femoral neck, and age. We reproduced these results using the validation data set, showing the usefulness of the classification rules in a clinical setting. In conclusion, TSSA provided a useful, powerful and reproducible procedure for identification of meaningful prognostic subgroups based upon an individual woman's age and BMD measurements.
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Many potential risk factors for hip fractures, including bone mass measured at various skeletal sites and by different techniques, have been identified [1–8]. While all of these measurements are interrelated, the magnitude of the relationship differs [9, 10]. Given the choice of skeletal site, the technique to measure it and the interrelationship between these resulting measurements, it is important to find the measurement or the combination of measurements that "best" classifies an individual into the appropriate risk group for hip fracture [10]. The following analysis of the risk factors and subsequent classification scheme can be used: (1) to evaluate the risk factors and their combinations to measure risk of hip fractures; (2) to identify subgroups of patients such that the subgroups are homogenous within themselves and heterogeneous between each other with respect to the risk of hip fracture; and (3) to assess whether any single measurement can generate subgroups similar to subgroups generated by the combination of multiple measurements.

Traditionally, the relationship of various risk factors to "time to hip fracture" has been studied [6, 7] using multiple regression techniques, including the Cox proportional hazard model [11]. These studies have been very useful in identifying risk factors and quantifying associated risks for hip fracture. A point to note for these analyses is that the effect of a SD reduction in BMD is the same for all individuals regardless of values of their other risk factors. This may be resolved by adding interactions of risk factors into the regression models. However, it is not commonly used and may be complicated for model interpretation. When the goal of a study is to identify subgroups and study the effect of the risk factors in these subgroups, the Cox model is not the most appropriate method. Tree structured survival analysis (TSSA) provides an alternative to study the effects of the risk factors [12] on time to hip fracture, which in our case are different bone mass measurements. Different from a Cox or a logistic model, TSSA evaluates the relationship between the risk factors and the outcome through recursive partitioning of patients according to their risk factors and then compared the resulted hip fracture risk of these partitions. There is no need of any linear relation in TSSA. The method not only identifies a set of significant risk factors, but also provides a simple procedure to identify subgroups of participants with the estimate of associated risk. The method has been used in many different medical areas. Segal and Bloch [13] applied TSSA to a rheumatoid arthritis survival study and a hip prosthesis failure study. Segal et al [14] compared several survival analysis techniques, including TSSA, in the evaluation of HIV progression. Altman, et al [15] used TSSA to predict survival in systemic sclerosis (scleroderma) and to develop a classification system for disease prognosis. Sevin, et al [16] used TSSA to propose a prognostic substaging for disease-free-survival of early stage cervical carcinoma patients. The advantages and disadvantages of TSSA have been extensively discussed by Segal et al [13, 14].

Encouraged by the successful use of TSSA in diverse medical areas, we used TSSA to study the effects of age and BMD measurements on time to hip fracture.

Methods

Subjects

From 1986 to 1988, 9,704 white women aged at least 65 years were recruited for the Study of Osteoporotic Fractures (SOF). At baseline of the study, BMD of the calcaneus,

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distal radius and proximal radius were measured using single X-ray absorptiomety (SXA) scanners. At the second visit, about 8,000 women were measured using dual x-ray absorptiometry (DXA) scanners for BMD at the PA-spine (L1–L4) and proximal femur (neck, trochanter, intertrochanter, Ward's triangle, total hip regions of interest). Overall, there were 7,665 women from the study who had all the previously mentioned BMD measurements. Time to hip fracture since the second visit was also recorded for each of the subjects. More details about the study and the data can be found elsewhere [6, 7].

In this paper included above mentioned 7,665 women. For women without a hip fracture, the last examination was considered as a censoring time for hip fracture, otherwise the time to hip fracture was noted. In addition to the BMD measurements, age at the second visit was also included in the analysis as a risk factor. It is very important to emphasize that our primary outcome is time to hip fracture after the second visit. In the paper, we also use the term "survival " to refer to free of hip fracture since the second visit and the term "survival probability" to refer to the probability of free of hip fracture. Therefore, the term "survival analysis" in our current contents had nothing to do with death.

Statistical Methods

The TSSA is an exploratory, non-parametric statistical method to do risk analysis that requires no assumption about the relationship between the risk factors (age and BMD) and the outcome (time to hip fracture). The method is an extension of tree based techniques (such as CART [17]) for comparing simple regression data to data that involves censoring. The method itself involves splitting a group of patients into two subgroups according to the values of a selected variable. A split partitions the group into patients with values lower than a particular cutoff point and those with values greater than this cutoff point. For example, the splitting based on femoral neck BMD will be determined by whether an individual's femoral neck BMD is above or below a particular threshold value. In every group of the tree that is to be subdivided, all the risk factors (including age and all BMD) are examined, and the "best" one is selected, along with its splitting value, by the computer algorithm based on the log-rank test statistics. The larger the value of the test statistics, the larger the difference in survival distribution of the two resulting subgroups. The optimal split is finally selected such that the two resulting subgroups have the largest difference in survival profiles. As is typical this splitting procedure generates a large sized survival tree with many subgroups. Subsequently, an algorithm, described in detail by Segal [12], is used to reduce the large tree to a desirable size. Finally, based on the cutoff points and each subject's risk factor values, the subject is classified into a subgroup with each subgroup having different risk of hip fracture.

Two TSSA analyses were performed for the data. The first tree analysis used risk factors of age and all the BMD measures and was referred as Model 1 in the paper. The second tree analysis focused only on age and hip BMD measures and was referred as Model 2. The results of the two tree analyses were used to assess the effect of DXA measurements other than hip BMD in identifying high risk individuals.

Due to the exploratory nature of TSSA, the results generated from these analyses need to be validated. We addressed this by dividing our data set into two parts. The first data set called the training data set, consisted of 5,776 women (75 %) and was generated randomly from the whole data set of 7,665 women. The second data set included the remaining 1,889 women and was called the validation data set. The choice of 75/25 % split was arbitrary. We used the training set to generate the survival trees. Thus, we purposely over sample the training data set so that there were more hip fracture incidences for tree construction. These trees were then applied to the second data set to examine: (1) whether the survival profile of patients in the validation data set matched the survival profile generated by the training data set; (2) whether BMD measurements in other skeletal sites in addition to the hip added any information regarding hip fracture.

All statistical calculations were performed using a statistical software package S-plus [18]. TSSA was calculated by an S-plus function provided by Dr. Segal. Comparisons of two survival curves were based on graphical presentations of 95 % confidence bands of Kaplan-Meier survival curves. The more efficient a classification scheme is, the more difference in survival profiles for the resulted subgroups, and correspondingly, the larger the log-rank test statistics. Therefore, we used difference in log-rank test statistics to compare two classification systems that were applied to the same subjects. We used S-plus bootstrap

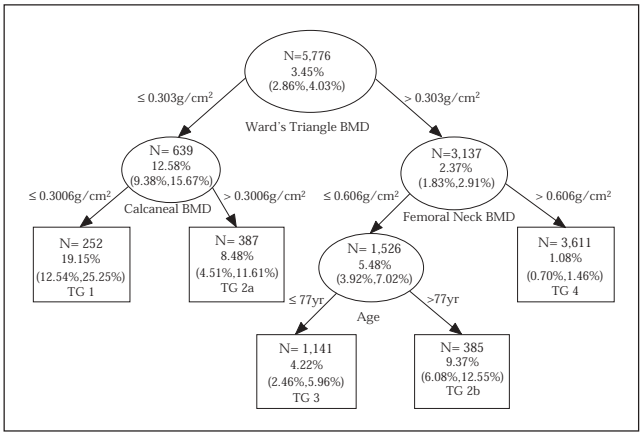

Figure 1. The Tree Structured Survival Analysis Using Age and All BMD Variables (Model 1). The variables, corresponding cut-off points for splitting, number of subjects in each resulting subgroup, and the corresponding probability of hip fracture in a 6.5 year follow up period. Terminal groups TG2a and TG2b were combined due to their similar survival profiles.

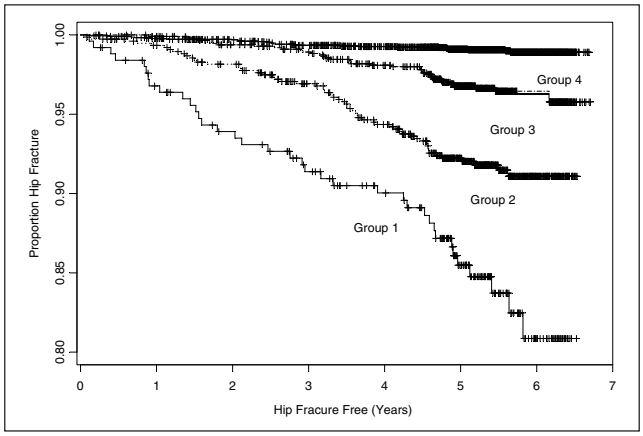

Figure 2. Kaplan-Meier survival curves for hip fractures. The differences in survival probability in the four groups increase with the length of follow up. After 6.5 years, the probability of no hip fracture was 80.86 % for TG1 versus 98.92 % for TG 4.

function to derive statistical significance of such a difference of two log-rank test statistics [19].

Results

Construction of Model 1

Table 1 summarized characteristics and relative risk of fracture by the univariate Cox proportional hazards model for women used for training (5,776) and validation (1,889) purposes as well as their combination (7,665) in the paper. This group of women is very similar to the whole SOF study population [6, 7].

The results of Model 1 are presented in Figure 1. In this figure, we show the variables, the corresponding cutoff points for splitting, the number of subjects in each resulting subgroup, and the corresponding probability of hip fracture during a 6.5 year follow-up period. The terminal groups (no further splitting of the group), noted as TG in the figure, are denoted by rectangles.

The terminal groups 2a and 2b (TG2a and TG2b) had very similar survival profiles (Kaplan-Meier survival curves, not shown) over the whole follow-up period. As a result we combined them into risk group 2. The final classification of all the subjects into four different risk groups is reported in Table 2 and their corresponding Kaplan-Meier survival curves in Figure 2. As shown by Figure 2, the differences in the probabilities of no hip fracture (survival probability) among four groups increase with the length of follow-up. At the end of 6.5 years, the probability of hip fracture (1 – survival probability) was 19.14 % for Group 1, in contrast to 1.08 % for Group 4. Their ratio was the relative risk reported in Table 2. Similarly, we presented ratios of probabilities of hip fracture for Groups 2 and 3 in reference to Group 4 in Table 2. Also note that the survival probability decreased substantially faster in Group 1 compared to the other groups, especially after 5 years.

Construction of Model 2

Model 2 examined classification using age and hip BMD measures. It resulted in a tree in Figure 3 that was very similar to Model 1 except for the terminal groups TG1 and TG2a. The split for TG1 and TG2a in Model 1 was based on calcaneal BMD and was replaced in Model 2 by age of 76. The survival probabilities for TG1 and TG2a of Model 2 were not significantly different from Model 1 as the Kaplan-Meier curves of each model were within the 95 % confidence bands of the alternative model (Figure was not shown). In addition, a 95 % bootstrap confidence interval of the difference between Model 1 and Model 2 in log-rank test statistics comparing survival profiles of TG1 and TG2a was (–19.51, 17.56), which showed splits of TG1 and TG2a in Models 1 and 2 were not statistically different. It was interesting to notice that age, instead of any other BMD measurement at the hip, replaced calcaneal BMD as the most competitive splitting in Model 2.

Table 1. Summary statistics and univariate Cox proportional hazards analysis for hip fracture in a study of 7,665 women

	Training Data N = 5776			Validation Data N = 1889			Total Data N = 7665		
Variables	Mean	SD	RR* (95 %CI)	Mean	SD	RR* (95 %CI)	Mean	SD	RR* (95 %CI)
Length of follow-up (years)	5.2	1.1		5.205	1.1		5.2	1.1	
Hip fracture incidence rate (%)**	2.89			3.18			2.96		
Age at the second visit (years)	73.4	5.1	1.1 (1.1, 1.2)	73.4	4.9	1.1 (1.1, 1.2)	73.4	5.1	1.1 (1.1, 1.2)
Distal radius BMD (g/cm^2)	0.363	0.084	1.6 (1.3, 1.9)	0.366	0.085	1.6 (1.2, 2.1)	0.363	0.084	1.6 (1.4, 1.8)
Proximal radius BMD (g/cm^2)	0.637	0.103	1.5 (1.3, 1.8)	0.637	0.104	1.4 (1.1, 1.7)	0.637	0.103	1.5 (1.3, 1.7)
Calcaneal BMD (g/cm^2)	0.407	0.092	2.1 (1.7, 2.4)	0.408	0.096	2.0 (1.5, 2.6)	0.407	0.093	2.0 (1.8, 2.4)
PA spine L1–L4 BMD (g/cm^2)	0.854	0.167	1.6 (1.3, 1.9)	0.864	0.172	1.4 (1.1, 1.9)	0.857	0.169	1.5 (1.3, 1.8)
Femoral neck BMD (g/cm^2)	0.650	0.111	3.1 (2.6, 3.8)	0.650	0.109	2.3 (1.7, 3.0)	0.650	0.110	2.9 (2.4, 3.4)
Ward's triangle BMD (g/cm^2)	0.428	0.111	2.8 (2.4, 3.3)	0.429	0.107	2.3 (1.8, 3.1)	0.428	0.110	2.7 (2.3, 3.1)
Intertrochanteric BMD (g/cm^2)	0.885	0.160	2.6 (2.2, 3.1)	0.886	0.159	2.1 (1.6, 2.8)	0.885	0.160	2.5 (2.1, 2.8)
Trochanteric BMD (g/cm^2)	0.558	0.103	2.6 (2.2, 3.1)	0.558	0.101	2.2 (1.7, 2.9)	0.558	0.102	2.5 (2.2, 2.9)
Hip total BMD (g/cm^2)	0.758	0.131	2.7 (2.3, 3.2)	0.759	0.130	2.1 (1.6, 2.8)	0.759	0.131	2.6 (2.2, 3.0)

* RR is the relative risk for hip fracture that is defined as one standard deviation decrease in BMD measurements and as a one-year increase in age.
** Hip fracture incidence rate is the percentage of subjects who observed hip fracture during the follow-up period.

Table 2. Classification of subjects into four groups according to risk of hip fracture, based on results of TSSA. The original terminal groups TG2a and TG 2b were combined into Group 2 due to their similar survival profiles.

Risk Group	Terminal Group	% of Subjects (N = 5,776)	Definition	Relative Risk* and 95 % CI
1	TG1	4.36 %	Ward's triangle BMD ≤ 0.303 and calcaneal BMD ≤ 0.3006	18.0 (11.2, 28.6)
2	TG2a or TG2b	13.37 %	(Ward's triangle BMD ≤ 0.303 and calcaneal BMD > 0.3006) or (Ward's triangle BMD > 0.303 and femoral neck BMD ≤ 0.606 and age > 77 years old)	8.8 (5.8, 13.4)
3	TG3	19.75 %	Ward's triangle BMD > 0.303 and femoral neck BMD ≤ 0.606 and age ≤ 77 years old	3.5 (2.2, 5.6)
4	TG4	62.52 %	Ward's triangle BMD > 0.303 and femoral neck BMD > 0.606	1

* Relative risk for hip fracture within 6.5 years follow-up when the risk group 4 was the reference group.

Validation of the Trees

As shown above, TSSA has produced a simple classification scheme that divides women into different risk groups with the maximum differences in their risk for hip fracture. One concern, however, was that the results may not be reproducible on a newly collected data set or another data set with similar characteristics. In Figure 4, we plotted the Kaplan-Meier survival curves of Model 1 and the corresponding 95 % confidence bands (solid lines) for the four groups generated by validation data set. On each of the four plots, we also plotted the survival curves from Figure 2 (dotted lines).

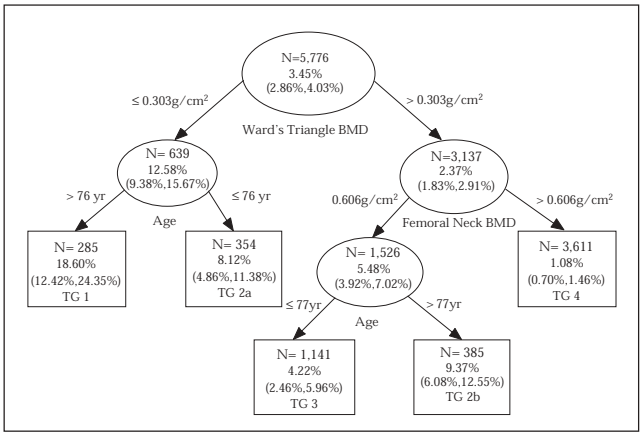

Figure 3. The Tree Structured Survival Analysis Using Age and Hip BMD Variables (Model 2). The variables, corresponding cut-off points for splitting, number of subjects in each resulting subgroup, and the corresponding probability of hip fracture in a 6.5 year follow up period. Terminal groups TG2a and TG2b were combined due to their similar survival profiles.

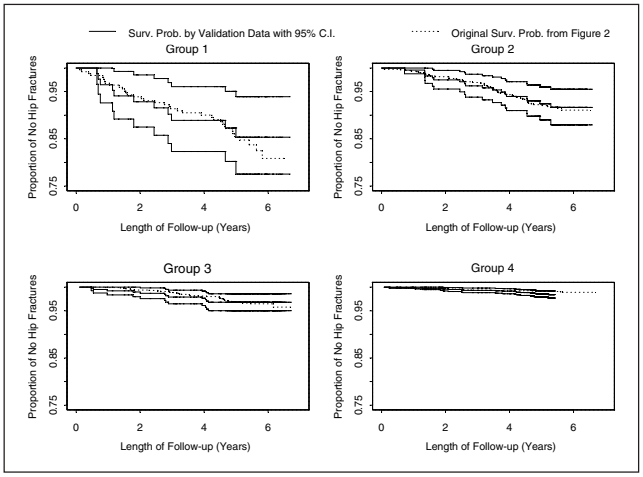

Figure 4. Reproducibility of TSSA classification. Kaplan-Meier survival curves and the corresponding 95 % confidence bands (solid lines) for the four groups generated by classifying women in the validation data set according to the classification scheme in Table 2. On each of the four plots, we also plotted the survival curves from Figure 2 (dotted lines). All the dotted lines were within the 95 % confidence bands of the observed survival curves from the validation data set.

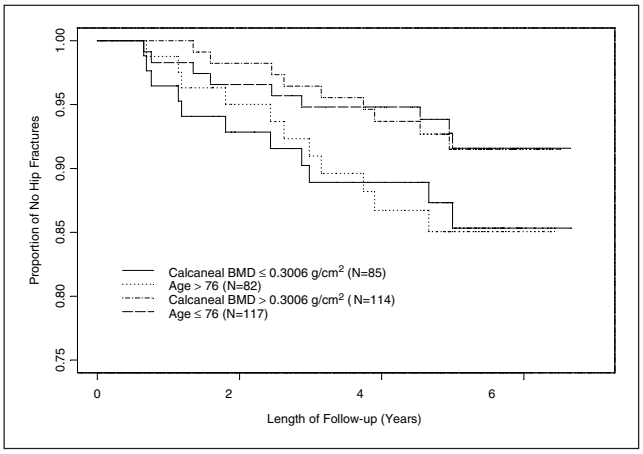

Figure 5. Survival curves for women with low Ward's BMD (n=199), showing the difference between TG1 and TG2a

Because of the small number of hip fracture incidence in this data set, the 95 % confidence bands were wide and it was hard to assess the goodness of fit. All the dotted lines were within the 95 % confidence bands of the observed survival curves from the validation data set. In addition, the proportions of women in the four groups were 4.50 %, 12.76 %, 20.54 %, and 62.20 %, which are very similar to the proportions given in Table 2 for the training data set (Chi-squared test, $p > 0.05$). The corresponding probability of hip fracture in 6.5 years follow-up for Groups 1 to 4 was 14.7 %, 8.3 %, 3.2 %, and 2.0 % respectively, for the validation data. The risks between Group 3 and 4 in the validation data differed less than that of the training data after 5 years follow-up. However, the difference was still within statistical variation. Overall, the results suggested that the TSSA results on different data sets were in general agreement with the data set that generated the tree, as long as these data sets were sampled from similar population of the training data set.

Finally, to see the effect of additional BMD measurements and to confirm the replacement of calcaneal BMD by age in the training data set in Model 2, we needed to compare TG1 and TG2a in Models 1 and 2 for the validation data. Among 20 women who had hip fractures and low Ward's triangle BMD (≤ 0.303), four were in the higher risk group according to Model 1 but in the lower risk group according to Model 2, while the opposite was true for another group of four women. The remaining 12 women were classified the same by either criterion. Figure 5 shows the corresponding survival curves of the two different splits (resulted in TG1 and TG2a) for women in the validation set. Because we had only a small number of fractured subjects, we did not have sufficient power to detect any statistically significant differences between the two models. However, one can still judge from the figure that the differences between the two models are minimal and that age can be a good surrogate split for calcaneal BMD.

Discussion

TSSA was able to provide a classification based on BMD at Ward's triangle, neck, and calcaneus, as well as age. However, as the alternative tree construction showed, age could replace calcaneal BMD in defining a woman's risk of hip fracture without losing significant information. As a result, there is a strong suggestion that there exists no clinical advantage of measurement of calcaneal BMD in addition to BMD of hip for assessment of hip fracture risk. This does not mean that calcaneal BMD alone is not a useful measurement for risk assessment. Several studies have shown the effectiveness of calcaneal BMD for predicting vertebral fracture [20] and hip fracture [6]. However, our data do not support the measurement of calcaneal BMD if hip BMD has already been obtained. Other BMD sites such as the radius and PA spine were not significant independent predictors of risk in the TSSA. This may differ in a study of younger women.

Another limitation of using calcaneal BMD is that the time to fracture was calculated from visit 2 while calcaneal BMD was measured in the first visit. As a result, the calcaneal BMD was obtained two years before hip BMD measures. More recent calcaneal BMD may change the result. However, we don't have any data for verification.

We used only age and BMD measurements in our analyses. The risk factors and their cut-off points of the tree splits were selected only by statistical algorithm instead of clinical judgement in this paper. As a result, the final tree may depend on the effect of the training sample and could be altered slightly without significantly loss of statistical optimum. Like any step-wise selection procedures in regression analysis, the tree only reported one "optimum" setting while there may be many equal or near optimum settings available. For example, Model 2 was as optimum as Model 1. Thus, as a statistical based algorithm, our classification tree had its limitations and combination of other clinical information will be helpful.

There are many other important risk factors for hip fractures [7] that need to be evaluated but were not addressed here. For example, age could be a surrogate for other factors such as bone quality, the frequency of falls, or perhaps the ability to protect oneself during a fall. This needs to be investigated further. In addition, the classification schemes developed by TSSA did not consider the cost-effectiveness of the various exams.

The Cox proportional hazards model has traditionally been used in osteoporosis studies to evaluate the association of BMD and hip fractures [4, 6, 7]. This paper reports the first time that TSSA was used to study such associations. These two methods are not competitors but complimentary tools in the analysis of hip fracture risks [13, 14].

The Cox model is useful because it allows one to estimate the relative risk of hip fracture associated a decrease in BMD and/or increase in age. However, it does not estimate individual's risk of hip fractures. As a result, logistic regression or parametric survival analysis has been used to estimate hip fracture risk for given risk factors. Logistic regression doesn't deal with censoring data with similar efficiency as other survival analysis methods (Cox model, parametric survival analysis, and TSSA). While the logistic regression model and other parametric survival models have advantage of being parsimonious, they have the disadvantage of not being dichotomous and of being parametric, which makes classification of homogeneous group relatively complicated. TSSA, on the other hand, is a non-parametric method and as such avoids parametric or semi-parametric assumptions. It provides simple yet powerful dichotomous criteria to identify subjects with high risk of hip fractures. The dichotomous, however, limits TSSA's ability to make distinction within classes. For our study, a woman can jump her risk of hip fracture from Group 3 to Group 2 on her 77^{th} birthday without any bone loss, which showed this limitation of TSSA.

The primary goal of this paper was to define homogeneous risk groups for hip fracture, which was TSSA designed for. Alternatively, we can classify subjects according to the level of relative risk calculated by the Cox proportional hazards model. For that purpose, we generated a classification scheme of four risk groups according to the relative risk calculated from the training data. The four groups were constructed to have similar proportions of subjects according to TSSA Model 1. We then applied such relative risk based classification to our validation data in a similar way of TSSA did in the paper. The log-rank test statistics for the Cox model based classification was 10.92 ($p < 0.0001$) while the TSSA classification had a log-rank statistics of 56.97 ($p < 0.0001$). The 95 % bootstrap confidence interval of differences in log-rank test statistics was (–97.15, –3.69), which indicated a significantly less efficiency of the Cox model based classification scheme than the TSSA one. While both classification schemes stratified subjects and identified high-risk subjects, there was no overlap in their Groups 1 and 2 and very low agreement in their Group 3. Thus, it suggested that two algorithms utilized different characteristics of study subjects.

Although TSSA has the advantages of effective classification and simple interpretation, especially in a clinical setting, a formal statistical framework allowing statistical inference has yet to be established. In addition, the methodology is driven by the observed data. For that reason, it is important to test whether the classification can be reproduced in elsewhere. Like many other statistical models, our results can only extrapolate to its sampling population. Our validation data is a random sample of the study population. Therefore, we don't know if the results can be extended to population different of SOF. In addition, the validation has only small number of hip fracture incidences, which makes the power of detecting lack of fit very low.

With above mentioned limitations, the results from this analysis should be interpreted carefully. Our results are useful in suggesting variables and cutoff values to put into more traditional epidemiologic models such as logistic regression and proportional hazard models. The classification scheme may also be useful to epidemiologists in identifying high-risk population and developing appropriate preventive strategies. As shown in this analysis, about 65 % of women aged 65 and older have only minimum risk of hip fractures. Femur scans can effectively identify these women. Resources and efforts to prevent hip fractures can, therefore, be directly toward women at higher risk. We hope that this study will lead to the validation of hypotheses that were generated in this paper and that it has provided a direction and tool for future studies.

In conclusion, TSSA is an exploratory data analysis technique that uses multiple risk factors to provide a powerful and understandable classification procedure. It is useful in the evaluation of risk factors and identification of homogeneous subpopulations (with respect to the risk of hip fractures) within a population.

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