Osteoporosis and Sarcopenia 11 (2025) 9–14

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: www.elsevier.com/locate/afos

Original article

A predictive nomogram for selective screening of asymptomatic vertebral fractures: The Vietnam Osteoporosis Study

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ARTICLE INFO

Keywords:
Osteoporosis
Vertebral fracture
Incidence
Risk factors
Predictive model
Nomogram

ABSTRACT

Objectives: Vertebral fractures are associated with disability and mortality, but most vertebral fractures are asymptomatic. The present study aimed to determine the incidence of and develop a predictive nomogram for asymptomatic vertebral fractures in Vietnamese adults.

Methods: This cohort study as a part of the Vietnam Osteoporosis Study involved 168 men and 287 women aged 50 years and older without a clinically diagnosed vertebral fracture. Their spine x-rays were taken at the recruitment and subsequent 2-year visit. Vertebral fractures were ascertained using the Genant's semi-quantitative method. We employed the Bayesian Model Averaging method to search for the optimal model for predicting asymptomatic vertebral fractures. A predictive nomogram was also developed to facilitate risk prediction.

Results: During a median of 2.38 years of follow-up, 13 men and 16 women developed an asymptomatic vertebral fracture, yielding the overall incidence rate of 28 fractures per 1000 person-years, or 33 fractures/1000 person-years in men and 24 fractures/1000 person-years in women, respectively. Most asymptomatic vertebral fractures were moderate, almost 1.5 times more common than mild fractures. The optimal model for predicting incident asymptomatic vertebral fractures included age, male sex and lower femoral neck T-score. The area under the receiver's operating characteristic curve was 0.91, with 95% CI ranging from 0.86 to 0.96.

Conclusions: Asymptomatic vertebral fractures were relatively common among adults in Vietnam. A simple model with sex, age and femoral neck T-score is helpful for selective screening of asymptomatic vertebral fractures in Vietnamese individuals.

1. Introduction

With rapid aging populations and increasing life expectancy [1,2], developing countries will experience an increased burden of chronic diseases, including osteoporosis and osteoporotic fractures [3]. Vertebral fracture, one of the most common manifestations of osteoporosis [4], is associated with substantially increased disability, mortality [5,6] and impaired quality of life [7,8]. Most vertebral fractures remain undiagnosed and unmanaged [9,10], and the identification of asymptomatic vertebral fractures remains a challenge.

Despite of the rapid increase in the aging population in developing economies, especially the Asian region, data on the incidence of vertebral fractures are scarce [4,11]. Only two population-based studies in lower- and middle-income countries report the incidence between 30.6 and 32.1 vertebral fractures per 1000 person-years in men and between 40.3 and 54.5 per 1000 person-years in women [12,13]. Furthermore, a previous report found that Asians have a higher risk of fractures than Caucasians [11]. Therefore, it is relevant to expand research in Asian populations to contribute to the global epidemiology of vertebral fractures and national healthcare strategies.

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https://doi.org/10.1016/j.afos.2024.12.002
Received 1 March 2024; Received in revised form 25 November 2024; Accepted 31 December 2024
Available online 8 March 2025

In Vietnam, a lower-middle-income country with one of the highest rates of aging in the world [14], the prevalence of asymptomatic vertebral fractures was approximately 25% [15]. However, there are no documentation on the incidence of vertebral fracture in Vietnam. Given its rapid aging population, Vietnam can serve as an excellent research context to determine the incidence of asymptomatic vertebral fractures, contributing to shaping the global epidemiology of vertebral fractures over the next 30 years as the population ages. Thus, the present study sought to determine the incidence of and risk factors for asymptomatic vertebral fractures in men and women over 50 years in Vietnam.

2. Methods

2.1. Study subjects

The present study is a part of the Vietnam Osteoporosis Study (VOS), in which protocol and procedures have been described in detail elsewhere [15,16]. Briefly, VOS is a population-based study initiated in 2015 in Ho Chi Minh City, Vietnam. The city, with a population of 10 million, is the central economic hub of the country. We contacted community organizations such as temples, churches, and senior citizens' organizations to attract the targeted populations. Study information was also introduced via television and newspapers. Individuals over 50 who agreed to participate in the study underwent tests and measurements at the Bone and Muscle Research Laboratory, part of Saigon Precision Medicine Research Center [17]. All individuals participated in the study voluntarily, and no financial incentives were provided, though they had their health and lipid profiles checked for free. The study's procedure and protocol were approved by the research and ethics committee of the People's Hospital 115, Ho Chi Minh City, Vietnam (approval number: 297/BV-NCKH). The study was conducted according to the ethical principles of the Declaration of Helsinki, and all participants gave written informed consent.

The current study included participants aged 50 years and older at the recruitment who had spine X-rays taken at baseline and a 2-year visit. None of the participants had any diseases that affected bone metabolism, such as renal failure, hypothyroidism, diabetes mellitus, malabsorption syndrome, or bone cancer. We also excluded individuals who had previous or current use of therapies that interfere with bone metabolism (eg, corticosteroids, antidiabetic medications, heparin, warfarin, thyroxin, and estrogen), mental illness, inability to answer the questionnaire, or did not agree to participate in the study.

2.2. Data collection

A standardized questionnaire was used to collect demographic and clinical data. The anthropometric parameters included age, smoking, history of falls, weight, standing height, leg, and back muscle strength. Body weight was measured using an electronic balance in indoor clothing without shoes. Height was determined without shoes on a portable stadiometer with a mandible plane parallel to the floor. The body mass index (BMI) was derived as the weight in kilograms divided by the square of the height in meters. Back strength and leg muscle strength was measured using the Oversize Platform BLC Dynamometer (3B Scientific., Atlanta, GA, USA).

Standard lateral and anterior-posterior lumbar spine radiographs (FCR Capsula XLII, Fujifilm Corp., Tokyo, Japan) were taken with a 101.6 cm tube-to-film distance and were centered at L2. Genant's semi-quantitative method [18] was used to diagnose a vertebral fracture. The first author (HTN) and the co-author (TTN) independently read the radiographs; whereas the corresponding author (LTHP) reread the radiographs to address any discrepancy between the first two readings. The kappa coefficient among readers was 0.78.

The severity of vertebral fractures (mild, moderate, or severe) was determined using the Genant's semi-quantitative criteria, in which the reduction in vertebral anterior, middle, and/or posterior height was 20%–25%, 25%–40%, and over 40% classified as mild (grade 1), moderate (grade 2), and severe (grade 3) vertebral fractures, respectively [18].

The Hologic Horizon densitometer (Hologic Corp., Bedford, MA, USA) was used to measure bone mineral density (BMD) for all participants at the femoral neck (FN) and lumbar spine (LS). Before every measurement, the densitometer was calibrated using a standard phantom. The precision errors (%CV) were 1.8% and 1.5% for the femoral neck BMD and lumbar spine BMD, respectively. BMD was transformed into a T-score as the difference between an individual's BMD and the population mean taken as aged between 20 and 30 years, and then standardized by the standard deviation. The population mean and standard deviation were derived from the local Vietnamese population [19]. According to the World Health Organization (WHO), an individual with a T-score ≤ -2.5 is considered to have osteoporosis.

2.3. Definition

The incidence of vertebral fractures was determined by the number of new fractures or increased severity of fractures documented in the second radiograph over 100 people. We used Wilson's score technique [20] to estimate the 95% confidence interval (CI) for the population incidence. We also determined the incidence of vertebral fractures by sex and age groups (50–59, 60–69 and 70+ years old).

2.4. Statistical analysis

We employed the Bayesian Model Averaging (BMA) method to search for the optimal model for predicting asymptomatic vertebral fractures. The BMA method has been consistently found to be more robust than the stepwise model-building method in the selection of an optimal prediction model [21,22]. In the presence of m variables, regression analysis was carried out for 2^m competing models in the BMA. The regression coefficients were averaged over all possible models. A uniform prior probability was given to each model, and together with the likelihood of each model, the posterior probability of the best model was determined by using the Bayesian theorem. The advantages of this method is that it eliminates insignificant variables, and it reflects the uncertainty of model selection [23]. The included variables in the BMA analysis were age, gender, body mass index, history of falls, smoking, back muscle strength, leg muscle strength, and T-score at the femoral neck and lumbar spine.

The receiver operating characteristic curve analysis and its corresponding area under the curve were used to assess the discriminative performance of the prognostic models [24]. The 95% CI of the area under the curve was estimated using the bootstrap method with 100 iterations of 10-fold cross-validation samples. The calibration of prognostic models was assessed through the Brier score. We also developed a predictive nomogram to facilitate the implication of the prediction model in clinical practice using the *rms* software package [25]. The analyses were conducted using the R Statistical Environment [26].

3. Results

The study included 455 individuals (168 men and 287 women) whose average age was 62.4 (SD: 6.27), ranging from 50 to 87 years old. There was no significant difference in age between the sexes, whereas men were more likely to be current smokers than women (31.0% vs 0.7%, $P < 0.001$) (Table 1). There were statistical differences in lumbar spine T-score in men compared to women (-0.98 vs -1.32, $P = 0.002$); men also had a significantly higher femoral neck T-score than women (-0.84 vs -1.38, $P < 0.001$).

During a median follow-up of 2.38 years (IQR: 2.15–2.5), 29 participants developed at least one incident vertebral fracture, yielding the incidence of vertebral fractures was 28 fractures per 1000 person-year (95% CI: 19–40). There were no significant differences in the

Table 1
Baseline characteristics of 455 participants stratified by sex.

Factor	Men (N = 168)	Women (N = 287)	P-value
Age, yrs	62.03 (6.27)	62.59 (6.27)	0.356
Body mass index, kg/m^2	23.27 (3.30)	23.20 (3.02)	0.827
Current smoking (Yes)	52 (31.0%)	2 (0.70%)	<0.001
History of falls (Yes)	10 (5.95%)	27 (9.40%)	0.193
Leg muscle strength, kg	63.9 (27.8)	32.2 (18.8)	<0.001
Back muscle strength, kg	51.4 (23.3)	25.9 (15.5)	<0.001
T-score at the lumbar spine	−0.98 (1.12)	−1.32 (1.07)	0.002
T-score at the femoral neck	−0.84 (0.94)	−1.38 (0.93)	<0.001

Values are expressed as mean (standard deviation) otherwise described. P-values were derived from unpaired T-test for continuous variables and Chi-square test for categorical variables.

incidence of vertebral fractures between men and women, though men had the point-estimated incidence slightly higher than women (33 fractures/1000 person-years versus 24 fractures/1000 person-years). We also documented the highest incidence of vertebral fracture amongst individuals aged 70 years or older (Table 2).

Among the 30 incident vertebral fractures, there were 11 "brand-new" fractures and 19 more severe fractures, while the majority (56.7%) of fractures were in grade 2. Furthermore, the number of grade 2 fractures accounts for the highest proportion, over 1.5 times higher than grade 1 fractures (Table 3).

We employed the BMA method to search for the optimal prediction model with the fewest predictors and maximal predictive performance. We found that Model I had the highest posterior probability (0.61) and the fewest variables (3 variables), as well as a good Brier score among the three models under consideration. Model I was consequently deemed the optimal model. This model includes femoral neck T-score, sex, and age. Specifically, every 5-year age increase meant 80.0% higher odds of vertebral fractures, a half standard deviation decrease in femoral neck T-score equated to 219% higher odds of vertebral fractures, and being male was associated with a nearly sixfold increase in those odds (Table 4). The receiver operating characteristic curve analysis indicates that the prediction model had an AUC of 0.91, with 95% CI ranging between 0.86 and 0.96 (see Fig. 1).

Figure 2 represents a nomogram that can be used to predict the risk of vertebral fractures for an individual with a specific risk profile. For instance, a 75-year-old woman with a femoral neck T-score of −2.0 would have a 25% risk of sustaining a vertebral fracture within 2 years of follow-up. Nonetheless, if her femoral neck T-score is −2.5, her risk of vertebral fracture within 2 years should be increased up to 55%.

4. Discussion

This is the first prospective population-based study to determine the incidence of asymptomatic vertebral fractures in Vietnam. Amongst these healthy community-dwelling individuals aged 50 and over we found that the incidence of vertebral fractures was 28 per 1000 person-years, with men tending to have a greater risk than women.

The incidence of vertebral fractures varies significantly between studies. The observed incidence in this study is relatively higher than that reported in Korea [27] and Japan [28]. South Korea is considered one of the countries with a low risk of osteoporosis and osteoporotic fractures [29]; meanwhile, Vietnam has a high prevalence, with 1/4 of the population over 50 years old having a vertebral fracture [15]. Japan recorded a high incidence in the past [30] but currently has a decreasing trend [28]. The previous low incidence rate may also be due to the survey being conducted in hospital patients, and some patients with vertebral fractures may not come to clinical attention [28]. Besides, the current results are higher than our recent report [31], which shows that the real burden of vertebral fractures in the Vietnamese population in the future is very worrying. On the other hand, the differences in the age group of the research subjects and the method of diagnosing vertebral fractures influence the findings on the incidence of vertebral fractures. In contrast, our data were comparable to that of Thailand where the overall incidence of vertebral fractures was 39.7 per 1000 person-years [13] using the same method as ours.

The incidence of vertebral fracture in our study was higher than that in Caucasian population. Indeed, while Vietnamese women had a 2-fold higher incidence compared with Caucasian women, Vietnamese men had a 6-fold higher incidence compared with Caucasian men [32]. Our

Table 2
Incidence of asymptomatic vertebral fractures stratified by sex and age group.

Factors	Number of people with fractures, N/total	Follow-up time (years), median (IQR)	Incidence, person-years	95% CI
Any vertebral fracture	29/455	2.38 (2.15–2.5)	28/1000	19–40
By sex				
Men	13/29	2.36 (2.18–2.49)	33/1000	23–46
Women	16/29	2.38 (2.07–2.51)	24/1000	15–35
By age				
50–59	3/29	2.36 (2.18–2.49)	8/1000	4–15
60–69	11/29	2.38 (2.09–2.51)	20/1000	12–30
70+	15/29	2.47 (2.23–2.51)	126/1000	105–149

Table 3
Characteristics of the incident vertebral fractures stratified by grade.

Factors	N/total	%
The number of the vertebral fractures had increased severity		
New fractures	11/30	36.7
Increased severity	19/30	63.3
Grade of fractures		
Grade 1	11/30	36.7
Grade 2	17/30	56.7
Grade 3	2/30	6.6

Table 4
Predictors of the risk of vertebral fractures: logistic regression models from the Bayesian Model Averaging analysis.

Predictor	Unit of Comparation	Odds Ratio	95% CI
Model I			
Sex	Male	5.67	2.0–16.1
Age	+5	1.80	1.29–2.50
FN T-score	−0.5 SD	3.19	2.09–4.86
Posterior probability	0.61		
Model II			
Age	+5	1.92	1.38–2.68
Smoking	Yes	6.47	1.96–21.37
FN T-score	−0.5 SD	2.62	1.80–3.81
Posterior probability	0.16		
Model III			
Sex	Male	6.63	2.24–19.62
Age	+5	1.74	1.25–2.44
BMI	+1 kg/m^2	1.11	0.96–1.28
FN T-score	−0.5 SD	3.5	2.22–5.5
Posterior probability	0.07		

Model I: Predictors are sex, age, femoral neck T-score.
Model II: Predictors are age, smoking, and femoral neck T-score.
Model III: Predictors are sex, age, body mass index, and femoral neck T-score.
The posterior probability suggests that Model I was the most parsimonious model for predicting vertebral fracture risk in this sample of participants.
FN, femoral neck; BMI, body mass index.

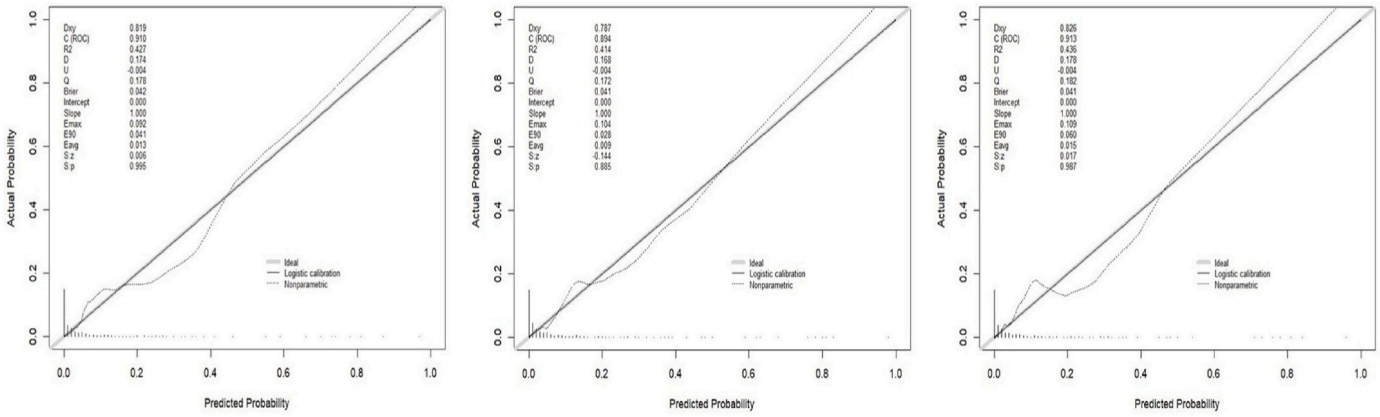

Fig. 1. Analysis of calibration of model I, II, and III.

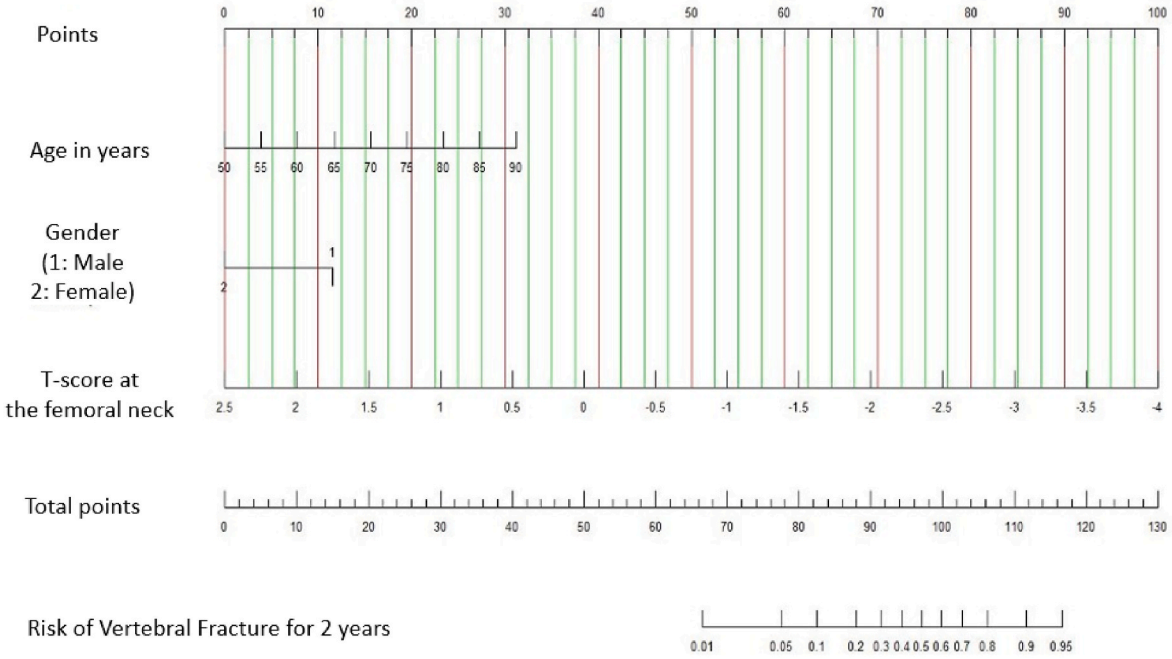

Fig. 2. Nomogram for predicting the individual risk of asymptomatic vertebral fracture. Usage instruction: Mark an individual's age on the "Age" axis and draw a vertical line to the "Point" axis to determine how many points toward the probability of vertebral fracture the individual receives for his/her age value. Repetition is required for each additional risk factor. Summarize the risk factor's salient features. Extending a vertical line from the final sum on the "Total points" axis to intersect with the "2-years Overall of Vertebral Fracture Probability" axis to determine the individual's likelihood of sustaining a vertebral fracture within the next two years. The 2-year risk of vertebral fracture for a 75-year-old woman with T-score of −2.0 is illustrated as following. The "Age in years" of 75 years old has 20 "Points"; woman at the "Sex" axis has 0 points; the T-score of −2.0 is approximately equivalent to 70 points. Consequently, the sum of the individual point values yields 90. Extending a vertical line from the 90-point mark on the "Total points" axis to intersect with the "2-years Overall of Vertebral Fracture Probability" axis, we can determine a probability of 0.25, equivalent to 25%.

findings are consistent with a previous multinational study, which also found a higher incidence of vertebral fractures in Asians than in Caucasians [11]. The current study's findings were also comparable to those in Brazil [12] which also used the Genant's semi-quantitative method. Notably, while the majority of studies showed a higher incidence of vertebral fracture in women than in men [11,12,27,28,32], our study found the opposite. We note that in Thailand vertebral fracture was also more common in men than women [13]. Several authors suggest that the higher fracture incidence in men are attributable to undetected microtrauma related to physical activity and heavy labor rather than osteoporosis, particularly among younger and/or male populations [13,33,34]. This perspective study's finding is consistent with our findings, as the study population comprises predominantly lower-to-middle income individuals of moderate age (mean age 60 years) in Vietnam, a nation transitioning from an agricultural to an industrial economy where manual labor remains prevalent. Conversely, among women, those in physically intensive jobs were observed to have a lower vertebral fracture rate than women in less physically active roles [33]. Regarding age, all published studies corroborate that the incidence of vertebral fractures increases with age [11,12,27,28,32], which is supported by our data. Population aging, which increases the risk of senescence-related maladies such as a decrease in BMD [3], is a plausible explanation for this trend. Age-related bone loss and structural deterioration to bone tissues and microarchitecture lead to bone fragility, thereby increasing the risk of fragility fractures [35].

In this study, grade 2 spinal fractures (according to Genant's criteria) accounted for the majority (59%) of fracture cases. Our findings contrast with those of previous studies in Brazil [12] and France [36] even

though both studies used the same methodology (Genant's criteria). The difference could be explained by our study's definition of fracture incidence which includes both new and increased severity fractures. According to our criteria, the study shows that nearly two-thirds of the fractures were caused by increased severity. Previous research has revealed that mild vertebral fractures were associated with an increased risk of further and more severe vertebral fractures [37,38].

All commonly used fracture risk calculators focus on any fracture, not just vertebral fracture [39]. The current study has developed a simple model capable of predicting asymptomatic vertebral fractures accurately. The model has a high posterior probability and a small number of variables including age, sex and T-score at the femoral neck. Age and sex have also been shown to be important predictors of BMD and bone fractures [40], and these factors are widely used in many models to predict bone fractures [41]. Importantly, we used the principles of Bayesian analysis to identify important variables and select this optimal vertebral fracture prediction model. The BMA method allows selection of an optimal model based on posterior probabilities [21]. The present prediction model demonstrates a better discriminatory performance than previous models [42–44], but is equivalent to a model recently developed for Asian population (AUC = 0.91; 95% CI: 0.86–0.96) [45]. Similarly, Brier score was low for incident vertebral fracture of model (0.042). However, the high AUC value observed in this study is likely to be driven by the non-vertebral fractures and few fractured cases, not necessarily an indicator of accurate prediction of new cases.

Given that vertebral fracture is associated with increased risk of mortality, our findings have important public health implications for preventing osteoporosis in the general community. The incidence is comparable with other populations. Thus, the identification of asymptomatic cases is highly relevant. We have developed a predictive nomogram for evaluating the risk of vertebral fracture that anyone in the community can use. The model can be implemented easily in routine clinical practice because it uses only common risk factors such as age, sex, and BMD. The data reported here represents a contribution to the global epidemiology of vertebral fracture, and evidence for preventing vertebral fractures in Vietnam.

Our findings should be interpreted within the context of strengths and potential weaknesses. The study participants were drawn from the general population by a standardized sampling scheme, ensuring representativeness and external validity. We controlled for the study's internal validity by three independent readers of radiographs. However, the sample size was modest, and the estimates of incidence may be unstable. All participants were largely drawn from urban areas, and the finding may not be generalizable to rural populations, among whom lifestyle factors and living conditions differ from urban populations. Moreover, the lack of an external validation of our prediction model is a potential weakness.

5. Conclusions

Our population-based study suggests an annual incidence of new asymptomatic vertebral fracture of approximately 28/1000 person-years in Vietnamese people with an average age of 60, indicating osteoporosis should be considered a national health priority. The independent risk factors for asymptomatic vertebral fractures recorded in the present study were used to construct a prediction model. The model has an excellent predictive performance, indicating its great potential for clinical implication to identify individuals at risk of asymptomatic vertebral fractures who most benefit from a timely intervention.

CRediT author statement

Hoa T. Nguyen: Conceptualization, Methodology, Formal Analysis, Writing – Original draft. **Bao T. Nguyen**: Study Design, Data Collection, Diagnosis. **An V. Tran**: Study Design, Data Collection, Diagnosis. **Tan T. Nguyen**: Study Design, Data Collection, Diagnosis. **Long H. Ngo**: Study Design, Data Collection, Diagnosis. **Tam Vo**: Methodology, Formal Analysis, Interpretation, Writing – Review & editing. **Thi H. Nhung Thai**: Study Design, Data Collection. **Linh D. Mai**: Study Design, Data Collection, Diagnosis. **Thach S. Tran**: Study Design, Data Analysis, Interpretation, Writing – Review & editing. **Tuan V. Nguyen**: Conceptualization, Methodology, Formal Analysis, Writing – Review & editing. **Lan T. Ho-Pham**: Conceptualization, Methodology, Formal Analysis, Writing – Review and editing.

Conflicts of interest

The authors declare no competing interests.

Acknowledgments

This research is partly funded by the Foundation for Science and Technology Development of Ton Duc Thang University, Vietnam (FOSTECT, http://fostect.tdt.edu.vn), Grant number FOSTECT.2014.BR.09, and a grant from the Department of Science and Technology of Ho Chi Minh City, Vietnam. We are greatful to express our sincere gratitude to the Rectorate Board of Can Tho University of Medicine and Pharmacy and Hue University of Medicine and Pharmacy for creating favorable conditions for this study to be carried out and we also sincerely thank Ms Tran Thi Ngoc Trang and Fr Pham Ba Lam for coordinating the recruitment of participants. We also thank doctors and medical students of the Pham Ngoc Thach University of Medicine for the data collection and clinical measurements. Dr. Hoa T. Nguyen, Dr. Tuan V. Nguyen, and Dr. Lan T. Ho-Pham are guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Tuan V. Nguyen is supported by a fellowship from the Australian National Health and Medical Research Council (APP1195305). **ORCID** Hoa T. Nguyen: 0000-0002-6062-9228, Bao T. Nguyen: 0009-0001-4623-7033, An V. Tran: 0000-0002-6629-6954, Long H. Ngo: 0009-0002-7254-4464, Tan T. Nguyen: 0000-0001-7559-4550, Tam Vo: 0000-0003-4042-568X, Thi H. Nhung Thai: 0000-0001-6723-5304, Linh D. Mai: 0000-0002-5774-9931, Thach S. Tran: 0000-0002-6454-124X, Tuan V. Nguyen: 0000-0002-3246-6281, Lan T. Ho-Pham: 0000-0001-8382-5080.

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