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Original Article

Fracture Risk Assessment: From Population to Individual

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Abstract

Fracture caused by osteoporosis remains a major public health burden on contemporary populations because fracture is associated with a substantial increase in the risk of mortality. Early identification of high-risk individuals for prevention is a priority in osteoporosis research. Over the past decade, few risk prediction models, including the Garvan Fracture Risk Calculator (Garvan) and FRAX®, have been developed to provide absolute (individualized) risk of fracture. Recent validation studies suggested that the area under the receiver operating characteristic curve in fracture discrimination ranged from 0.61 to 0.83 for FRAX® and from 0.63 to 0.88 for Garvan, with hip fractures having a better discrimination than fragility fractures as a group. Although the prognostic performance of Garvan and FRAX® for fracture prediction is not perfect and there is room for further improvement, these predictive models can aid patients and doctors communicate about fracture risk in the medium term and to make rational decisions. However, the application of these predictive models in making decisions for an individual should take into account the individual's perception of the importance of fracture relative to other diseases.

Key Words: Garvan Fracture Risk Calculator; fracture; FRAX®; osteoporosis; risk assessment.

"All models are wrong, but some are useful."
George E.P. Box (1919–2013)

Introduction

Osteoporosis and its consequence of fracture remain a major burden on contemporary populations. From the age of 50, 1 out of 2 women and approximately 1 out of 3 men will sustain a fracture during their remaining lifetime *(1)*. In women, the remaining lifetime risk of hip fracture is equivalent to or higher than the risk of invasive breast cancer *(1,2)*, and in men, the risk of hip and clinical vertebral fractures (17%) is comparable to the risk of prostate cancer *(2,3)*. More importantly, fracture is associated with an increased risk of mortality, and the risk is greater in men than in women. Indeed, numerous studies, including our own, have consistently shown that the relative risk of death in men with fracture (1.8-fold) is significantly greater than that in women (1.4-fold) *(4–6)*. The increased mortality risk was also observed in younger individuals with fracture *(3)*. Moreover, up to 24% of women and 38% of men will die within the first 3 mo after experiencing a hip fracture *(7,8)*. Those who survive a fracture usually develop 1 or more of chronic pain, increased dependence, and reduce quality of life *(9–11)*. Taken together, recent data clearly underline that osteoporotic fracture is a common and serious skeletal disorder that is expected to increase in magnitude over the next few decades as populations are rapidly aging.

It is the association between fracture and premature mortality that is of great concern. There are, however, high-quality data suggesting that treatment of individuals with fracture could reduce mortality risk. Indeed, a large randomized controlled trial has shown that zoledronic acid treatment reduces the risk of post-hip-fracture mortality by 28%, when given within 3 mo post hip surgery *(12)*. Interestingly, only a small part of the benefit of reducing death post fracture was attributable to preventing refracture. More recent studies *(13–15)* have also suggested that individuals on oral bisphosphonates have a lower risk of mortality. Despite these

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pieces of evidence (14,15), less than 30% of women and less than 10% of men who have already had an osteoporotic fracture receive treatment to reduce their risk of subsequent fractures (16). Thus, osteoporosis is an undertreated disease, and the undertreatment status could partly be responsible for the excess mortality associated with fracture (11).

One way to improve treatment uptake is by identifying high-risk individuals for closer observation and, possibly, for selecting individuals for an appropriate treatment option. The identification of individuals at high risk of osteoporotic fracture remains a significant challenge; the susceptibility to fracture is highly variable among individuals within a population as well as between populations. This high variability in fracture risk is expected, because fracture itself is associated with multiple factors, some of which may be causal. Therefore, any single risk factor is unlikely to be helpful for risk stratification; a more logical and better approach is to tailor the risk of fracture for an individual based on the individual's risk profile.

A risk profile must consider multiple risk factors by taking into account the magnitude of association between a risk factor and a fracture. Research during the past 3 decades or so have identified several risk factors for fracture, including advancing age, low bone mineral density (BMD), a personal history of fracture, fall, low body mass index, and, more interestingly, genetic factors (17). Advancing age is clearly a major risk factor of fracture, as the incidence of fracture increases exponentially with advancing age in both men and women (18–21). Recent data have shown that the 10-yr probability of fracture at the forearm, humerus, spine, or hip increases between the ages of 45 and 85 by as much as 8-fold for women and 5-fold for men (22).

Low BMD is the most robust predictor of fracture risk. Each standard deviation difference in BMD is associated with about a 2-fold change in the risk of fracture (23,24). However, BMD alone cannot reliably predict an individual who is (or is not) going to sustain a fracture. It has been estimated that less than 40% of fracture cases occur in people with BMD in the osteoporotic range (25). Among women aged 60 yr or older with low BMD (high-risk group), only 40% sustained an osteoporotic fracture within 13 years of follow-up (25). On the other hand, among those who sustained a fracture, almost 60% had BMDs above the osteoporotic cut-point (T-score ≤–2.5). In other words, more than half of individuals with low BMD were "resistant to fracture." The situation in elderly men is similar: 70% of men with low BMD did not sustain a fracture; and among fracture cases, 77% occurred in those with nonosteoporotic BMD levels (25). This finding is consistent with the point raised by Geoffrey Rose in his influential essay (26), where he postulates that the majority of chronic disease cases arise from the mass of the population with risk around the average. Clearly, BMD alone cannot identify most individuals at high risk of fracture. A rethinking is needed for the majority of individuals whose BMD values are near the osteoporotic threshold.

A simple fact is that, at any age and level of BMD, fracture risk varies widely in relation to the burden of other risk factors, including prior fracture and falls. A prior fragility fracture signals a substantially elevated risk of future fracture (6,27–29). The elevated risk is 1.5- to 9.5-fold, depending on the age at assessment, the number of prior fractures, and the site of the incident fracture. Pooling the results from all studies (women and men) and for all fracture sites, the risk of subsequent fracture among those with a prior fracture at any site is 2.2 times more than the risk among those without a prior fragility fracture (29). Fall is also an important risk factor for fracture. Indeed, in the elderly population, falls are associated with hip fractures, Colles' fractures, pelvis fractures, and ankle fractures (30). Approximately 95% of hip fractures are results of falls (31). The prevalence of falls increases with advancing age (32) and is higher in women than in men (33). The gender-related difference in fall prevalence could partly explain the difference in fracture risk between men and women.

Thus, for any individual, the risk of fracture depends on a combination of factors (34). This means that 2 individuals, both with "osteoporosis," can have different risks of fracture because they have different risk profiles. Similarly, an osteoporotic individual can have the same risk of fracture as a nonosteoporotic individual because of the difference in constellation of risk factors between the 2 individuals. In other words, the assessment of fracture risk can and should be based on a multivariable model. The advantage of a statistical multivariable model is that it yields a more accurate and consistent prediction than human experts' prediction (35,36).

A number of statistical multivariable models have been developed for individualized fracture risk assessment. Among the models, the Garvan Fracture Risk Calculator (37,38), FRAX® (39), and QFracture (40) are widely used. FRAX® uses 12 risk factors, including femoral neck BMD, anthropometric factors, lifestyle factors, and comorbidities. The Garvan Fracture Risk Calculator (Garvan) uses 5 risk factors, namely, age, gender, femoral neck BMD, prior fracture, and history of fall. Garvan considers the frequency of prior fractures and the number of falls during the past 12 mo, not simply binary (yes/no) variables. Whereas Garvan provides 5- and 10-yr risks of total fracture and hip fracture, FRAX® provides a 10-yr risk of hip fracture and major osteoporotic fractures (Table 1).

Predictive Performance

The usefulness of a predictive model is usually quantified in terms of discrimination, calibration, and reclassification. Discrimination is the ability to separate individuals who will sustain a fracture along a continuum from those who will not. The primary metric of discrimination is the area under the receiver operating characteristic curve (AUC), which evaluates the compromise between sensitivity and specificity, and is thus a global estimate of prognostic accuracy (41).

Discrimination

Several independent studies have been carried out to examine the prognostic performance of Garvan (42,43),