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Review article

Individualized fracture risk assessment: State-of-the-art and room for improvement

Tuan V. Nguyen [a, b, c, *]

[a] Bone Biology Division, Garvan Institute of Medical Research, Sydney, Australia
[b] St Vincent's Clinical School, UNSW Sydney, Australia
[c] School of Biomedical Engineering, University of Technology, Sydney (UTS), Sydney, Australia

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ABSTRACT

Fragility fracture is a serious clinical event, because it is associated with increased risk of mortality and reduced quality of life. The risk of fracture is determined by multiple risk factors, and their effects may be interactional. Over the past 10 years, a number of predictive models (e.g., FRAX, Garvan Fracture Risk Calculator, and Qfracture) have been developed for individualized assessment of fracture risk. These models use different risk profiles to estimate the probability of fracture over 5- and 10-year period. The ability of these models to discriminate between those individuals who will and will not have a fracture (i.e., area under the receiver operating characteristic curve [AUC]) is generally acceptable-to-good (AUC, 0.6 to 0.8), and is highly variable between populations. The calibration of existing models is poor, particularly in Asian populations. There is a strong need for the development and validation of new prediction models based on Asian data for Asian populations. We propose approaches to improve the accuracy of existing predictive models by incorporating new markers such as genetic factors, bone turnover markers, trabecular bone score, and time-variant factors. New and more refined models for individualized fracture risk assessment will help identify those most likely to sustain a fracture, those most likely to benefit from treatment, and encouraging them to modify their risk profile to decrease risk.

1. Why fracture risk assessment?

At the individual level, fragility fracture is a serious clinical problem, because it is associated with increased risk of recurrent fractures, reduced mobility and quality of life, and increased risk of mortality. An initial fracture, at any skeletal site, is a signal for further fractures, and the relative risk ranges between 1.4 and 4.9 [1], depending on the site of initial fracture. For instance, a woman with a hip fracture is associated with a 2.8- and 4.9-fold increase in subsequent fracture in women and men, respectively [1]. The time from an initial fracture to a subsequent fracture is also shorter than the time from no fracture to an initial fracture. The importance of fragility fracture also lies in the fact that individuals with a fracture tend to have reduced life expectancy, and the risk is greater in men than in women [2]. The relative risk of mortality in men with fracture (1.8 fold) is substantially greater than that in women (1.4 fold) [3]. The increased mortality risk was also observed in younger individuals with fracture [4]. Moreover, up to 24% women and 38% men will die within the first 3 months after experiencing a hip fracture [5]. Those who survive a fracture usually develop one or more of chronic pain, increased dependence, and reduce quality of life [6].

At the population level, fragility fracture remains a significant public health burden, because it is highly prevalent in the general population and can incur a substantial healthcare cost. The lifetime risk of fracture is approximately 50% in women and ~30% in men aged 50 years [7]. It is little known that in women, the remaining lifetime risk of hip fracture is equivalent to or higher than the risk of invasive breast cancer [7], and in men, the risk of hip and clinical vertebral fractures (17%) is comparable to the risk prostate cancer [8]. Taken together, recent data clearly suggest that fragility 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.

There are high quality data suggesting that treating individuals at high risk of fracture or individuals with an initial fracture reduces

* Osteoporosis and Bone Biology Division, Garvan Institute of Medical Research, 384 Victoria St, Darlinghurst, NSW 2010, Australia.
E-mail address: t.nguyen@garvan.org.au.
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the risk of subsequent fracture [9]. The magnitude of risk reduction typically ranges between 30% and 60% [10]. More importantly, there are high quality evidence that treatment of individuals with a fracture could reduce the risk of postfracture mortality. For instance, a large randomized controlled trial (RCT) showed that zoledronic acid treatment reduced the risk of post–hip-fracture mortality by 28%, when given within 3 months post hip surgery [11]. More recent studies have also suggested that individuals on oral bisphosphonates have lower risk of mortality [12]. Despite these evidence [12,13], 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 [14]. Thus, osteoporosis is an undertreated disease, and the undertreatment status could partly be responsible for excess mortality associated with fracture [2].

2. Risk factors for fracture: not just low BMD!

The risk of fracture is influenced by multiple risk factors, but the most robust risk factors are low bone mineral density (BMD) [15]. Each standard deviation lower in BMD is typically associated with a 2-fold increase in fracture risk [16]. The magnitude of association between BMD and fracture is equivalent to or greater than the association between serum cholesterol and cardiovascular disease [17]. Thus, measurement of BMD is considered the gold standard for the diagnosis of osteoporosis in elderly men and postmenopausal women. In 1994 the World Health Organization (WHO) expert panel proposed an operational definition of osteoporosis, by which a postmenopausal woman is considered to have osteoporosis if the woman's femoral neck BMD is decreased by at least 2.5 standard deviations as compared to mean value in young adults [18]. The operational criteria of osteoporosis for women were subsequently adopted for men [19]. Although the WHO criteria were criticized as a flawed approach [20], they have been widely used in clinical practice.

Apart from low BMD, a personal history of fracture is also an important risk factor for fracture [21]. The relative risk of fracture associated with a prior fracture ranged between 1.5 and 9.5 fold depending on age at assessment, number of prior fractures and the site of the incident fracture. Even a pre-existing asymptomatic vertebral fracture increases the risk of a second vertebral fracture and nonvertebral fracture by at least 4 fold [22]. On average, the risk of subsequent fracture among those with a prior fracture at any site is 2.2 times that of people without a prior fragility fracture [21].

It is, therefore, logical that the assessment of fracture risk has traditionally been based on the measurement BMD and a personal history of fracture. Furthermore, treatment initiation is indicated for individuals with low BMD (i.e., osteoporosis) and/or with a pre-existing low trauma fracture. This strategy appears to be logical and evidence-based because results from randomized clinical trials show that treating these patients (e.g., with osteoporosis and/or a prior fracture) did reduce their fracture risk.

Although low BMD is the most robust risk factor for fracture, it does not account for most fracture cases. Indeed, among those aged 50 years and older, more than 50% of women and up to 70% of men who sustained a fracture had not had osteoporosis [23] as defined by bone density criteria alone. Among individuals aged 60 years or older with low BMD (high risk group) 60% of women and 70% of men did not sustain an osteoporotic fracture within a 13-year follow-up. In other words, more than half of individuals with low BMD are “resistant to fracture.”

Further studies have shown that apart from low BMD and prior fracture, other factors such as advancing age, being woman, family history of fracture, excessive bone loss, low body weight, falls, and smoking behavior were also associated with fracture risk [24]. Indeed, at any given level of BMD, fracture risk varies widely in relation to the burden of other risk factors. Thus, for any one individual, the likelihood of fracture depends on a combination of these and other risk factors. This means that 2 individuals, both with “osteoporosis,” can have different risks of fracture because they have different non-BMD risk profile. Similarly, an osteoporotic individual can have the same risk of fracture as a nonosteoporotic individual due to the difference in constellation of risk factors between the 2 individuals. The multifactorial nature of fracture implies that the assessment of fracture risk should ideally take into account the full profile of risk factors of an individual.

A challenging issue is how to synthesize information from multiple risk factors for predicting fracture risk for an individual. It is commonly believed that clinical experience or clinical intuition could predict clinical outcome fairly accurately. Indeed, since the Hippocrates' time, doctors have been valued for their ability to predict their patients' outcome. However, in the presence of multiple risk factors, clinician's assessment can be problematic because they are unable to weigh information in a reproducible and objective manner. Statistical prognostic models have been shown to out-perform clinical judgment [25], because these models can objectively incorporate data from many risk factors and produce reproducible risk estimates.

3. Individualized assessment of fracture risk

In the past, the assessment of risk was based on a grouping approach [26]. In the risk grouping approach, a continuously distributed risk factor is usually categorized into distinct groups, and the estimate of risk is therefore applicable to a group of individuals rather than to an individual. For instance, the stratification of BMD measurement into osteoporosis vs. Nonosteoporosis based on T-score splits 2 men with T-scores of −2.45 and −2.50 into 2 distinct groups despite the trivial difference, and despite the possibility that the 2 men may have comparable risk of fracture if other risk factors are considered. Moreover, because of the broad categories, such a stratification approach classifies a 80-year-old man with T-score of −2.5 and a 70-year-old man with T-score of −3.0 into a single group, despite the 2 men have very different risk profiles! The risk grouping approach is conceptually simple and sometimes useful in clinical practice, its predictive value is poorer than the individualized approach due to the arbitrariness of any numerical cutoff value [27].

A better approach of risk assessment should recognize that each individual is unique. The uniqueness can be defined in terms of an individual's measured profile. For instance, instead of categorizing BMD into distinct groups, the individualized approach would consider BMD in its full measurement range. This is more logical since the relationship between BMD and fracture risk is continuous, there is no threshold value for BMD that accurately separates those who will from those who will not sustain a fracture. Thus, 2 individuals with a BMD T-score of −2.5 and −2.6 should have different risks of fracture, and of course, their risks are modified by other risk factors. This implies that by considering risk factors in their continuous scale the estimated risk can be better tailored to an individual.

A number of models for fracture risk assessment have been developed based on the idea of individualized approach (Table 1). The most common models include FRAX [28], Garvan Fracture Risk Calculator [29,30], and Qfracture [31]. 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, sex, femoral neck BMD, prior fracture, and history of fall. The risk factors included in the Garvan model were identified by the Bayesian Model Averaging approach