**Proposal for Biostatistics Workplace Project**

**Title:** Competing death in fracture risk assessment

**Context:** Death is considered a competing event to fragility fracture, as many elderly people die before they sustain a fracture. Traditional statistical models for predicting fracture risk take into account death as a competing risk, and they often yield underestimates of fracture risks. As a result, there is no agreement as the current fracture prediction models account for competing risk very differently1-3. While the Garvan1 and other fracture prediction models2 considered death as a right-censored event, the FRAX model3 is known to account for competing risk using the Fine and Gray approach though an algorithm that has never been published. Of note, the FRAX model has been shown to underestimate both osteoporotic and hip fractures, though the Garvan model slightly overestimates hip fracture in high-risk group4. The inappropriate handling of competing risk of death could contribute to the suboptimal predictive performance of current fracture prediction models2,4.

We propose to solve the problem by a multistate model. In this model, we consider 3 events: fracture, refracture, and death in a sequential manner. Thus, an individual can move from no fracture to fracture, no fracture to death, fracture to refracture but not death, fracture to death, etc. This multistate model simultaneously models the series of correlated events during a stochastic process in a single framework, with robust accounting for their correlated nature5. Importantly, the multistate model is also able to take into account the competing of death and thus allow for unbiased estimates of each correlated outcomes separately6. To the best of our knowledge, no studies to date have compared the predictive values of different approaches to account for competing death in fracture assessment, though accuracy prediction is the ultimate goal of any fracture risk calculator.

We hypothesize that the multistate regression model would account for competing death better, leading to a more accurate prediction of fracture.

**Specific aims:**

1. To develop fracture prediction models using different approaches to account for competing death
2. To compare the extent how accurate the models could predict fracture

**Approach:** The analysis will be conducted using data from the Dubbo Osteoporosis Epidemiology Study7 that recruited ~ 3,500 elderly people aged 60+ years old as of 1989, living in Dubbo City, Australia. They were followed biannually up until 31 July 2018 for fracture and mortality. The data are clean and ready for analysis. The study cohort will be randomly split into 60% for development in aim 1 and 40% for validation in aim 2. The following steps will be carried out:

1. *Development:* we will use three different statistical approaches to account for competing death: (i) treating competing death as a right-censored event, (ii) the Fine and Gray sub-distribution approach, and (iii) the multistate Cox-Markov approach. The same set of fracture predictors, namely gender, age, bone mineral density, history of falls and prior fracture1 will be used in these models to estimate the risk of any osteoporotic fracture and hip fracture.
2. *Validation:* Both discrimination and calibration ability will be examined to compare the predictive performance of these three models. We use the Harrell’s C index to assess the discrimination power, and compare the predicted fracture risk with the observed risk by centiles of the predicted fracture risk to assess the calibration power.

**Innovation and novelty**: The appropriate approach to account for competing death in fracture risk assessment has never been determined, possibly resulting in the suboptimal fracture prediction2,4 and current global under-management of osteoporotic fractures8. The project will provide better methodological background to develop a fracture risk assessment tool with much better predictive power. Given the increasing importance of osteoporotic fractures that affect one in two women and one in three men aged 60+, the project thus has important impact on public health policy as it would contributes to better identify patients at risk of fracture who will most benefit from timely treatment.

**Supervisors:**

Prof Tuan Van Nguyen

Osteoporosis and Bone biology division, Garvan Institute of Medical Research

Email: [t.nguyen@garvan.org.au](mailto:t.nguyen@garvan.org.au); Phone: (61-2) 9295 8277

**Timeline:**

* September- October 2021: Data analysis and interpretation
* November 2021: The project portfolio preparation

**References:**

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