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A Risk Assessment Tool for Predicting Fragility Fractures and Mortality in the Elderly

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ABSTRACT

Existing fracture risk assessment tools are not designed to predict fracture-associated consequences, possibly contributing to the current undermanagement of fragility fractures worldwide. We aimed to develop a risk assessment tool for predicting the conceptual risk of fragility fractures and its consequences. The study involved 8965 people aged ≥60 years from the Dubbo Osteoporosis Epidemiology Study and the Canadian Multicentre Osteoporosis Study. Incident fracture was identified from X-ray reports and questionnaires, and death was ascertained though contact with a family member or obituary review. We used a multistate model to quantify the effects of the predictors on the transition risks to an initial and subsequent incident fracture and mortality, accounting for their complex interrelationships, confounding effects, and death as a competing risk. There were 2364 initial fractures, 755 subsequent fractures, and 3300 deaths during a median follow-up of 13 years (interquartile range [IQR] 7–15). The prediction model included sex, age, bone mineral density, history of falls within 12 previous months, prior fracture after the age of 50 years, cardiovascular diseases, diabetes mellitus, chronic pulmonary diseases, hypertension, and cancer. The model accurately predicted fragility fractures up to 11 years of follow-up and post-fracture mortality up to 9 years, ranging from 7 years after hip fractures to 15 years after non-hip fractures. For example, a 70-year-old woman with a *T*-score of −1.5 and without other risk factors would have 10% chance of sustaining a fracture and an 8% risk of dying in 5 years. However, after an initial fracture, her risk of sustaining another fracture or dying doubles to 33%, ranging from 26% after a distal to 42% post hip fracture. A robust statistical technique was used to develop a prediction model for individualization of progression to fracture and its consequences, facilitating informed decision making about risk and thus treatment for individuals with different risk profiles. © 2020 American Society for Bone and Mineral Research.

KEY WORDS: FRAGILITY FRACTURE; MORTALITY; MULTISTATE PREDICTION MODEL; OSTEOPOROSIS; SUBSEQUENT FRACTURE

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Additional Supporting Information may be found in the online version of this article.

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Introduction

Fragility fractures impose a significant public health problem globally as they are highly prevalent[1,2] and are associated with significant morbidity and mortality[3–6] and substantial economic burden.[7] From the age of 50 years, approximately 16% and 32% of women in the United States will experience a hip or clinical vertebral fracture, respectively, compared with a 9% lifetime risk of developing breast cancer and 3% risk of developing endometrial cancer.[1,2] Both hospitalization burden and population facility-related hospital costs for fragility fractures are significantly greater than those for myocardial infarction, stroke, and breast cancer in American postmenopausal women.[7] The 1-year excess mortality after hip, femur, or pelvis fracture is also higher than the excess mortality for up to 5 years after the diagnosis of breast cancer in women and prostate cancer in men.[4,8] In addition to mortality, survivors after an initial fracture also have an increased risk of subsequent fracture,[5] increased dependence, and reduced quality of life.[6] It is thus critical to identify individualized risk of both fragility fracture and its related consequences to be able to make meaningful decisions about appropriate interventions to prevent not only the first fracture but also the deleterious consequences triggered by the first fracture.

Several fracture risk assessment tools have been developed to predict the risk of an initial fragility fracture, assisting clinical decision making and improving quality of health care.[9–11] Nevertheless, no risk assessment tool has been specifically designed to predict the risk of post-fracture consequences, such as subsequent fracture or mortality, though the conceptual risk of both fragility fracture and fracture-related complications is more informative than the risk of an initial fracture alone. The perceived risk of both fracture and its consequences is crucial for informed decision making and individualized health care planning, potentially contributing to global efforts to address the undermanagement of fragility fractures.[12,13]

Several studies have attempted to assess the risk of both fragility fracture and either post-fracture mortality[14] or immobilization[15] among postmenopausal women. However, the predictors were solely derived from the literature[14] or selected from separate regression models,[15] failing to account for the complex interrelationship between these correlated outcome events and thus possibly resulting in biased estimates.[16] To develop an assessment tool capable of predicting the risk of specific fractures and their related outcomes, the study should be of a large enough size and long enough to observe sufficient post-fracture consequences. Ideally, it should also be a representative sample of a whole population. The statistical methods should be comprehensive and robust to account for the interrelationships between fracture and its consequences and to objectively select the most optimal prediction model.

Multistate disease progression models were originally designed to simultaneously model a series of correlated outcome events during a stochastic process in a single framework, with robust accounting for their correlated nature.[16] Importantly, the multistate models are also able to take into account the competing of death and thus allow for unbiased estimates of each correlated outcomes separately.[17] The multistate model has been shown to be superior to the traditional Cox proportional models when examining the risk of correlated time-to-event outcomes.[18]

We thus aimed to develop a risk assessment tool to quantify the probabilities of both an initial fragility fracture and its related outcomes of subsequent fracture and mortality using a multistate model. The model was then further refined for specific types of initial fracture, broadly categorized as hip, vertebral, non-hip non-vertebral proximal, and distal fractures.

Materials and Methods

Study population

The study involved two similar prospective population-based cohort studies: the Dubbo Osteoporosis Epidemiology Study (DOES) and the Canadian Multicentre Osteoporosis Study (CaMos), for which the protocols and procedures have been described in detail elsewhere.[19,20] Briefly, for the DOES, through the electoral roll and via media campaign, all men and women 60 + years old as of 1989, living in Dubbo city (a regional city of 32,000 predominantly white people in New South Wales, Australia) were invited to participate in the study. The age and sex distribution of the Dubbo city population was known to closely resemble the Australian population.[19] Similarly, the CaMos is a national population-based prospective cohort study with an age-, sex-, and region-specific random sampling of the Canadian population surrounding nine urban centers from coast to coast. Between 1995 and 1997, community-dwelling participants were invited to participate in the study if they lived within a 50-km radius of one of the following nine Canadian cities: St. John's, Halifax, Quebec City, Kingston, Toronto, Hamilton, Saskatoon, Calgary, and Vancouver. The DOES study involved approximately 60% of the Dubbo population,[19] whereas the CaMos represented 40% of the Canadian population in 1995.[20] The current analysis included 6197 women (2016 from the DOES and 4181 from the CaMos) and 2768 men (1198 and 1570 from the DOES and the CaMos, respectively) aged 60 years or older at study entry (Fig. 1).

Anthropometric data, lifestyle factors, history of falls (ie, self-reported falls during the previous 12 months), prior fracture (any fracture after the age of 50 years before recruitment), comorbidities, and areal bone mineral density (BMD) were collected biennially for the DOES or 5 yearly for the CaMos. BMD was measured at the femoral neck by dual-energy X-ray absorptiometry. BMD *T*-scores at the femoral neck collected in the CaMos and the DOES cohort were derived using the published reference standards for Canadians[21] and Australians,[22,23] respectively. Additionally, the physical activity index calculated as minutes/week in the DOES cohort was dichotomized using tertiles[24] to match the regular physical activity variable in the CaMos cohort. Self-reported comorbidities at the time of interview were cardiovascular diseases (CVD; including heart failure, myocardial infarction, or stroke), cancer (excluding skin cancer), Paget's disease of bone, rheumatoid arthritis, osteoarthritis, thyroid, liver or kidney disease, hypertension, neuromuscular diseases, diabetes mellitus (DM), venous thromboembolism, and chronic obstructive pulmonary diseases (COPD).

Fracture assessment

Incident fractures were continuously ascertained from 1989 until July 2018 for the DOES by review of X-ray reports from all three radiological services for the entire Dubbo area, or between 1995 and 2013 for the CaMos by annual posted self-reported questionnaire and verified from medical records or from telephone interview. Fractures in the CaMos were radiologically confirmed in approximately 78% of cases.[25] Only minimal trauma

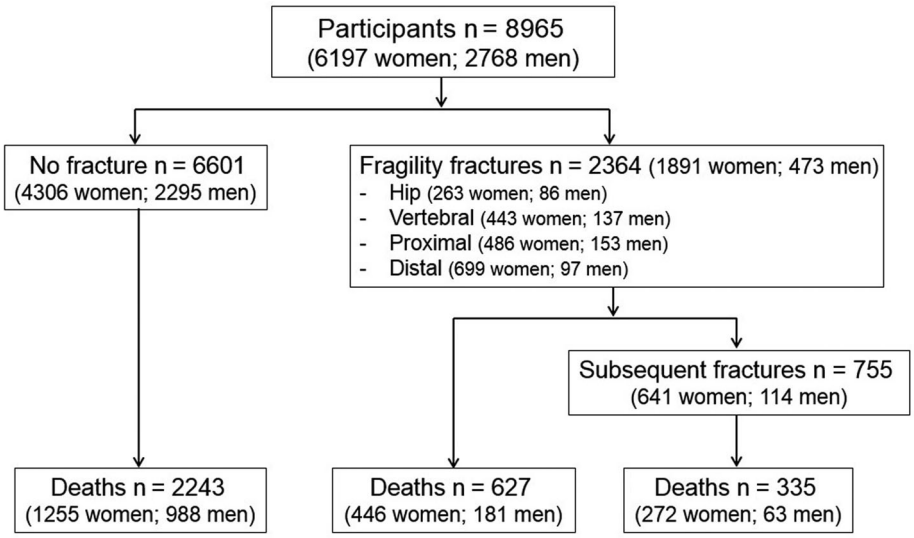

Fig 1 Flowchart of recruitment and follow-up. Non-hip non-vertebral proximal fractures include clavicle, rib, humerus, elbow, pelvis, and upper leg fracture; non-hip non-vertebral distal fractures include forearm, lower leg, knee, ankle, hand, and foot fracture.

fractures involving trauma less than or equivalent to fall from standing height were included. Potential pathological fractures (from Paget's disease or metastatic cancer) or fractures of the skull, face, finger, and toe were excluded from the analysis. The first fracture event after recruitment was the initial fracture, while the next separate fracture event occurring after the first fracture was the subsequent fracture. Due to low fracture numbers, all further fracture incidents were not included as separate states. If an individual had sustained more than one fracture during one event, the fracture event was classified by the skeletal site of the more serious fracture. Initial fractures were broadly classified into hip, clinical vertebral, non-hip non-vertebral proximal (ie, clavicle, rib, humerus, elbow, pelvis, upper leg), and distal fractures (forearm, lower leg, knee, ankle, hand, foot).[26]

Mortality ascertainment

Mortality incidence was ascertained through contact with a member of the participant's family or a contact person (if the annual questionnaire was not returned) for the CaMos or obituary review with verification from the New South Wales Births, Deaths and Marriages registry for the DOES.

Statistical analysis

The incidence rate for fracture and mortality was estimated for 1000 and 100 person-years of follow-up, respectively, assuming a Poisson distribution. We used a multistate model[18] to quantify the effects of predictors on occurrence of initial fracture, subsequent fracture and mortality, and the focused information criterion approach[27] to search for the most optimal prediction model.

We used a progressive multistate model with time as a continuous variable using the exact time of event occurrence to model the longitudinal course of transition to and after a fragility fracture (Supplemental Fig. S1). The recruitment date and self-reported date of fractures and death were used to estimate the time interval from the study entry to the outcome events of interest (ie, the time on study). Previous studies have shown that time-on-study analyses making adjustment for age at entry provided similar results to those using age as the primary time scale in many scenarios similar to ours.[28,29] The model included four states: (i) state 1 (individuals alive and free of incident fracture) for all participants; (ii) state 2 (initial fracture) for those who sustained a fragility fracture during the study follow-up; (iii) state 3 (subsequent fracture) for those who had a second fracture; and (iv) state 4 (death) for those who died during the follow-up period. The model provides estimated probabilities that an individual with a specific risk profile, characterized by the presence or absence of one or more predictors from the optimal prediction model, would move from one state to another state (denoted as $q_{i\text{-}j}$) during a given time. For instance, `q1_2` is the probability of sustaining an initial fracture during a particular time line (ie, moving from no fracture state [state 1] to fracture state [state 2]) or `q2-4` the probability a person with a fracture would die (moving from fracture state [state 2] to all-cause death [state 4]). As a result, the model is able to quantify the individualized risk of both fragility fractures and mortality for an individual who is fracture free (state 1) or who already has a fracture (state 2), and the risk of death after a subsequent fracture (state 3). The multistate model was fitted using the maximum likelihood method with the R '*msm*' package under an assumption that the intensities are constant or piecewise constant for time-dependent variants and the time scale variable enters the likelihood through the differences between successive times.[30]

The potential predictors, including baseline demographics (sex, age, history of falls, prior fracture), lifestyle factors (smoking, physical activity, alcohol assumption), and specific comorbidities were systematically examined together to search for the optimal prediction model. Age was used as a time-variant covariate (ie, age at baseline for all transitions from state 1, age at an initial fracture for those from state 2, and age at a subsequent fracture from state 3) to minimize an immortal bias since participants who lived longer were more likely to experience a fragility

fracture. Other predictors were considered fixed using their status at recruitment under an assumption of little change over follow-up time intervals.[18,31] Our study did not incorporate treatment for osteoporosis into the prediction model because making inferences on the effects of treatment from observational data is subject to potential biases and confounding effects.[32] The analysis approach would require using a subgroup of untreated participants who would have the same chance of getting treated as those people who were on treatment,[33] which would impair the representativeness of the overall study population, making development of a prediction model not possible. There were no missing data for the outcomes of interest (ie, initial and subsequent incident fracture, death), but several potential predictors had missing data (ie, self-reported comorbidities [1% to 2%] and BMD [10.7%]). We performed multivariate imputation by chained equations (MICE) algorithm[34] using the predictive mean matching and logistic regression method to impute the most plausible values of missing data for continuous and binary variables, respectively. Every variable has its own imputation equation. We also carried out a sensitivity analysis including only participants with available data for all potential predictors to assess the robustness of our findings.

The model comparison used the focused information criterion (FIC) approach that was originally designed to search for the "best" model most suitable for each outcome under consideration, making it particularly robust for simultaneously modeling multiple correlated outcomes.[27] Thus different models might be better for different outcomes. The model selection process started with a "wide" model having the highest predictive accuracy as it included all potential predictors collected for the study regardless of their statistical significance.[27] The "narrow" model (ie, the most parsimonious prediction model with the established evidence of good prediction accuracy) included sex, age, BMD, history of falls, and prior fracture. The narrow model includes the risk factors in one of the existing fracture risk assessment tools (ie, the Garvan fracture risk calculator) that has been shown to be accurate for fracture prediction.[35,36] The potential predictive sub-models were then created by adding each potential predictor to the narrow model.[27,37] We calculated the adjusted mean residual squared error (MRSE) that quantifies the difference in predictive accuracy between the sub-model and the full model and the FIC that quantifies the predictive accuracy difference adjusted for number of predictors in the sub-models for each individual sub-model. The optimal prediction model is ideally the sub-model with the smallest MRSE and FIC, resulting in a model with fewest predictors and the best predictive accuracy compared with the full model with all potential predictors. If the ranking of MRSE is not consistent with FIC, the optimal model should be selected, taking other factors such as a compromise between the more complex model with higher predictive accuracy and the simpler but less accurate model into account.[38] The MRSE and FIC were calculated using the R '*fic*' package.[38]

To maximize the predictive accuracy, we used the weighted average of all MRSEs, averaging the individual MRSEs for each specific outcome of interest (initial fracture, subsequent fracture, and mortality) to search for a single prediction model with the smallest average MRSE combining all outcomes of interest in the one model.[38] As the predictive performance was our primary goal, the predictors of one specific outcome might not be statistically associated with another outcome after taking into account the inevitable correlations between these outcomes.[37,39] Data management and analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), and R statistical environment (R Foundation, Vienna, Austria; https://www.rproject.org) on a Windows platform (Microsoft Corp., Redmond, WA, USA).

Results

The study involved 8965 individuals aged 60 years or older with an average age of 70 years who were followed up to a total of 108,005 person-years for incident fractures and mortality (Fig. 1). Women and men sustained initial and subsequent fractures at similar ages (age at an initial fracture was 78 $\pm$ 7.6 years for women and 78 $\pm$ 7.6 years for men, and subsequent fracture was at 80 $\pm$ 7.1 years for women and 81 $\pm$ 7.2 years for men) (Table 1). There were 1351 individuals (18.7% of women and 7.0% of men) found to meet BMD criteria for osteoporosis (*T*-score < −2.5) at the study entry. Approximately two-thirds of the study population had at least one reported disease at the study entry with the most common comorbidities being hypertension (41.1%), CVD (20.7%), COPD (10.1%), or diabetes mellitus (9.8%).

Incidence rate of fracture and mortality:

During a median follow-up of 13 years (interquartile range [IQR] 7–15), 1891 women and 473 men sustained an incident initial fracture, yielding incidence rates of 29.9/1000 person-years (95% confidence interval [CI] 28.6–31.3) and 16.0/1000 person-years (14.6–17.5), respectively. Non-hip non-vertebral distal fractures were the most common fracture group in women (10.5 fractures/1000 person-years), while non-hip non-vertebral proximal fractures (5.3 fractures/1000 person-years) were the most common initial fracture group in men.

During the follow-up, a third of women with incident fractures and a quarter of men with incident fractures sustained another fracture (Table 2). The incidence rate of subsequent fracture was 66/1000 person-years (95% CI 61.1–71.3) and 50.6/1000 person-years (42.1–60.8), in women and men, respectively. There was a total of 3300 deaths during the follow-up (mortality rates 3.2/100 person-years [95% CI 3.0–3.3] in women and 4.3/100 person-years (4.1–4.6) in men). Regardless of specific comorbidities, these elderly women and men who had sustained either an initial fracture at hip, clinical vertebrae or a proximal site, or a subsequent fracture had a greater associated mortality risk than those who remained fracture-free (Supplemental Fig. S2). Additionally, women with DM and men with COPD or CVD had the highest mortality rates, irrespective of their fracture status.

The model for predicting fragility fractures and mortality

Our analysis searched for a single prediction model capable of accurately predicting all correlated outcomes of interest simultaneously, accounting for not only their complex interrelationships and possible confounding effects but death as a competing risk as well. The optimal prediction model included sex, age, BMD, history of falls, prior fracture, and comorbidities including CVD, DM, COPD, hypertension, and cancer (Table 3). This model had the smallest average RMSE and FIC, indicating its accuracy in simultaneously predicting the occurrence of an initial fracture, subsequent fracture, and mortality closest to the full model with all potential predictors. Sex and age were important predictors

Table 1 Baseline Characteristics by Events of Interest

	No fracture		Only initial fracture		Initial and subsequent fracture		
Baseline characteristics	Alive	Dead	Alive	Dead	Alive	Dead	Total
Women	***n* = 3051**	***n* = 1255**	***n* = 804**	***n* = 446**	***n* = 369**	***n* = 272**	***n* = 6197**
Age (years), mean ± SD							
At entry	**68.8 ± 6.3**	**73.4 ± 7.6**	**69.0 ± 6.0**	**74.3 ± 7.6**	**69.3 ± 6.1**	**72.4 ± 7.1**	70.3 ± 7.0
At an initial fracture			**76.4 ± 6.9**	**80.9 ± 7.9**	**74.8 ± 6.9**	**78.5 ± 7.5**	77.5 ± 7.6
At a subsequent fracture					**79.1 ± 6.8**	**82.3 ± 7.1**	80.4 ± 7.1
At death		**81.5 ± 7.8**[a]		**85.3 ± 7.5**[a]		**86.4 ± 6.8**[a]	83.1 ± 7.8
BMI (kg/m^2), mean ± SD	27.0 ± 4.97	26.8 ± 4.48	**27.1 ± 4.82**	**26.3 ± 4.20**	26.3 ± 4.49	26.0 ± 3.68	27.0 ± 4.98
Femoral neck BMD *T*-score, mean ± SD	**−1.43 ± 0.97**	**−1.71 ± 1.08**	**−1.65 ± 0.90**	**−2.05 ± 0.98**	**−1.96 ± 0.80**	**−2.33 ± 0.95**	−1.63 (1.00)
History of falls, *n* (%)	**384 (12.6%)**	**248 (19.8%)**	**134 (16.7%)**	**119 (26.7%)**	**73 (19.8%)**	**84 (30.9%)**	1042 (16.8%)
Prior fracture, *n* (%)	722 (23.7%)	306 (24.4%)	238 (29.6%)	145 (32.5%)	140 (37.9%)	87 (32.0%)	1638 (26.4%)
Alcohol assumption, *n* (%)	**1461 (47.9%)**	**450 (35.9%)**	**421 (52.4%)**	**179 (40.1%)**	**191 (51.8%)**	**108 (39.7%)**	2810 (45.3%)
Current smoking, *n* (%)	**411 (13.5%)**	**266 (21.2%)**	**115 (14.3%)**	**90 (20.2%)**	**53 (14.4%)**	**75 (27.6%)**	1010 (16.3%)
Regular physical activity, *n* (%)	**1816 (59.5%)**	**606 (48.3%)**	**467 (58.1%)**	**223 (50.0%)**	233 (63.1%)	160 (58.8%)	3505 (56.6%)
Comorbidities, *n* (%)							
Hypertension	**1185 (38.8%)**	**648 (51.6%)**	**315 (39.2%)**	**218 (48.9%)**	**136 (36.9%)**	**137 (50.4%)**	2639 (42.6%)
Cardiovascular diseases[b]	**356 (11.7%)**	**344 (27.4%)**	**106 (13.2%)**	**116 (26.0%)**	**79 (21.4%)**	**85 (31.3%)**	1086 (17.5%)
Chronic obstructive pulmonary diseases	**267 (8.8%)**	**160 (12.8%)**	**71 (8.8%)**	**60 (13.5%)**	36 (9.8%)	39 (14.3%)	633 (10.2%)
Diabetes mellitus	**226 (7.4%)**	**195 (15.5%)**	53 (6.6%)	39 (8.7%)	**15 (4.1%)**	**25 (9.2%)**	553 (8.9%)
Cancer	223 (7.3%)	103 (8.2%)	71 (8.8%)	46 (10.3%)	36 (9.8%)	31 (11.4%)	510 (8.2%)
Rheumatoid arthritis	156 (5.1%)	77 (6.1%)	58 (7.2%)	36 (8.1%)	27 (7.3%)	30 (11.0%)	384 (6.2%)
Neuromuscular diseases	100 (3.3%)	52 (4.1%)	35 (4.4%)	29 (6.5%)	26 (7.1%)	27 (9.9%)	269 (4.3%)
Men	***n* = 1307**	***n* = 988**	***n* = 178**	***n* = 181**	***n* = 51**	***n* = 63**	***n* = 2768**
Age (years), mean ± SD							
At entry	**68.5 ± 6.0**	**72.4 ± 6.9**	**68.5 ± 5.8**	**72.8 ± 6.9**	69.8 ± 5.5	71.2 ± 5.8	70.3 ± 6.6
At an initial fracture			**75.9 ± 7.1**	**79.8 ± 7.7**	76.5 ± 7.2	77.8 ± 7.8	77.7 ± 7.6
At a subsequent fracture					80.9 ± 6.6	80.9 ± 7.7	80.9 ± 7.2
At death		**80.7 ± 7.5**[a]		**83.6 ± 6.9**[a]		**83.3 ± 7.1**[a]	81.2 ± 7.5
BMI (kg/m^2), mean ± SD	27.2 ± 3.86	27.1 ± 3.33	27.4 ± 3.54	26.7 ± 2.95	26.5 ± 3.76	26.8 ± 3.09	27.1 ± 3.96
Femoral neck BMD *T*-score, mean ± SD	**−0.95 ± 0.97**	**−1.08 ± 1.17**	**−1.13 ± 0.97**	**−1.52 ± 1.04**	**−1.50 ± 0.91**	**−1.98 ± 1.17**	−1.08 (1.07)
History of falls, *n* (%)	**145 (11.1%)**	**162 (16.4%)**	36 (20.2%)	36 (19.9%)	14 (27.5%)	21 (33.3%)	414 (15.0%)
Prior fracture, *n* (%)	**257 (19.7%)**	**160 (16.2%)**	34 (19.1%)	36 (19.9%)	15 (29.4%)	12 (19.1%)	514 (18.6%)
Alcohol assumption, *n* (%)	**841 (64.4%)**	**579 (58.6%)**	**126 (70.8%)**	**111 (61.3%)**	35 (68.6%)	38 (60.3%)	1730 (62.5%)
Current smoking, *n* (%)	**289 (22.1%)**	**397 (40.2%)**	**51 (28.7%)**	**84 (46.4%)**	**16 (31.4%)**	**32 (50.8%)**	869 (31.4%)
Regular physical activity, *n* (%)	782 (59.8%)	602 (60.9%)	106 (59.6%)	118 (65.2%)	32 (62.8%)	40 (63.5%)	1680 (60.7%)
Comorbidities, *n* (%)							
Hypertension	**440 (33.7%)**	**421 (42.6%)**	58 (32.6%)	74 (40.9%)	23 (45.1%)	27 (42.9%)	1043 (37.7%)
Cardiovascular diseases[b]	**261 (20.0%)**	**357 (36.1%)**	**35 (19.7%)**	**76 (42.0%)**	15 (29.4%)	25 (39.7%)	769 (27.8%)
Diabetes mellitus	149 (11.4%)	135 (13.7%)	17 (9.6%)	13 (7.2%)	7 (13.7%)	5 (7.9%)	326 (11.8%)
Chronic obstructive pulmonary diseases	**88 (6.7%)**	**117 (11.8%)**	21 (11.8%)	22 (12.2%)	9 (17.7%)	13 (20.6%)	270 (9.8%)

(Continues)

Table 1. Continued

Baseline characteristics	No fracture		Only initial fracture		Initial and subsequent fracture		Total
	Alive	Dead	Alive	Dead	Alive	Dead	
Cancer	**68 (5.2%)**	**91 (9.2%)**	11 (6.2%)	12 (6.6%)	5 (9.8%)	5 (7.9%)	192 (6.9%)
Rheumatoid arthritis	48 (3.7%)	41 (4.2%)	11 (6.2%)	6 (3.3%)	3 (5.9%)	3 (4.8%)	112 (4.1%)
Neuromuscular disease	**35 (2.7%)**	**51 (5.2%)**	5 (2.8%)	9 (5.0%)	3 (5.9%)	3 (4.8%)	106 (3.8%)

Boldface indicates statistically significant difference ($p < 0.05$) between participants remaining alive and those dying during the study period, using Student's *t* test or chi-square test for continuous and categorical variables, respectively.

BMI = body mass index; BMD = bone mineral density.

[a]Statistically significant difference in age at death between fracture-free participants, those with only initial fracture, and those with subsequent fracture using analysis of variance test.

[b]Cardiovascular diseases include myocardial infarction, heart failure, or stroke.

for both fragility fracture and mortality. By contrast, low BMD, history of falls, and prior fracture were predominantly related to fracture risk and comorbidities (CVD, DM, COPD, hypertension, and cancer) related to mortality risk. After an initial fragility fracture, sex, history of falls, presence of CVD, and COPD were no longer independent predictors of a subsequent fracture. Being female, a history of falls, and presence of CVD or COPD were associated with about 12%, 7%, 22%, and 16%, respectively, increased risks for subsequent fracture, though these associations did not reach statistical significance, probably due to small number of subsequent fractures. This model was nevertheless found to be able to predict the risk of subsequent fracture accurately (Fig. 2).

The sensitivity analysis was conducted for 7808 participants (~87% of the primary analysis population) who had available data for all potential covariates of interest. Participants in the sensitivity analysis appeared to be about 1 year older at fractures and death than those in the primary analysis. The differences in baseline characteristics between alive and dead participants by the fracture status in the sensitivity analysis were similar to those in the primary analysis, although some did not reach statistical significance, probably due to the smaller study population (Supplemental Table S1). There was no difference in the incidences of fractures or mortality between the two analyses. Most importantly, in both analyses, the model with age, BMD *T*-score, history of falls, prior fracture, and specific comorbidities (CVD, hypertension, diabetes mellitus, pulmonary diseases, and cancer) had the smallest average RMSE and FIC, suggesting it is the optimal prediction model.

Fig. 2 assesses to what extent the model accurately predicted the occurrence of these events of interest by comparing the observed numbers of individuals in each state of interest (ie, alive and free of fracture, initial fracture, subsequent fracture, and death) with their expected events estimated from the model during the 15-year period of time. An observed event within 5% of the expected events is considered acceptably accurate.[30] Overall, the observed numbers of individuals in each state were very close to their estimated numbers up to about 11 years of follow-up for a fracture and 9 years for mortality, indicating the high accuracy of the model for predicting both fractures and mortality. The finding that the model somewhat underestimated the long-term mortality risk beyond 9 years of follow-up warranted further assessment to explore the extent of predictive accuracy for predicting mortality in different groups of participants (ie, fracture-free individuals, those with specific types of fragility initial fracture, or those with any subsequent fracture). The model was found to be able to predict mortality risk accurately for fracture-free individuals (Supplemental Fig. S3) or those who had sustained a non-hip fracture (Supplemental Fig. S4) up to 15 years of follow-up. However, the model only predicted mortality risk most accurately up to about 7 years after a hip fracture (Supplemental Fig. S4).

Implementation in clinical practice

The model estimates transition risks to fragility fractures and mortality within a given timeline for an individual with specific risk profiles. Each specific risk profile is characterized by a particular value of age and BMD *T*-score and whether one of the other predictors (ie, history of falls, prior fracture, and comorbidities, such as CVD, DM, COPD, hypertension, and cancer) were present. For simplicity, we illustrate how the model is used to predict the 5-year risks to initial and subsequent fracture and mortality for a

Table 2 Numbers of participants in each state during the study follow up by genders and specific types of initial fracture

From initial or transition state	Final states until the end of follow up			
Women	***Alive and fracture-free***	***Initial fracture***	***Subsequent fracture***	***Death***
From fracture-free state (*n* = 6197)	3051 (49.2%)	1891 (30.5%)	NA	1255 (20.3%)
		Alive and only initial fracture	***Subsequent fracture***	***Death***
From initial fracture state				
Specific types of initial fracture:				
• Hip (*n* = 263)		94 (35.7%)	75 (28.5%)	94 (35.7%)
• Vertebrae (*n* = 443)		154 (34.8%)	173 (39.1%)	116 (26.2%)
• NHNV proximal (*n* = 522)		236 (45.2%)	176 (33.7%)	110 (21.1%)
• NHNV distal (*n* = 633)		320 (48.3%)	217 (32.7%)	126 (19.0%)
Total initial fractures (n = 1891):		804 (42.5%)	641 (33.9%)	446 (23.6%)
			Alive and subsequent fracture	***Death***
From subsequent fracture state (*n* = 641)			369 (57.6%)	272 (42.4%)
Men	***Alive and fracture free***	***Initial fracture***	***Subsequent fracture***	***Death***
From fracture-free state (*n* = 2768)	1307 (47.2%)	473 (17.1%)	NA	988 (35.7%)
		Alive and only initial fracture	***Subsequent fracture***	***Death***
From initial fracture state				
Specific types of initial fracture:				
• Hip (*n* = 86)		25 (29.1%)	19 (22.1%)	42 (48.8%)
• Vertebrae (*n* = 137)		49 (35.8%)	36 (26.2%)	52 (38.0%)
• NHNV proximal (*n* = 158)		59 (37.3%)	38 (24.1%)	61 (38.6%)
• NHNV distal (*n* = 92)		45 (48.9%)	21 (22.8%)	26 (28.3%)
***Total initial fractures (n = 473)*:**		178 (37.6%)	114 (24.1%)	181 (38.3%)
			Alive and subsequent fracture	***Death***
From subsequent fracture state (*n* = 114)			51 (44.7%)	63 (55.3%)

NA = non-applicable; NHNV = non-hip non-vertebrae.

Non-hip non-vertebral proximal fractures include clavicle, rib, humerus, elbow, pelvis, and upper leg fracture; non-hip non-vertebral distal fractures include forearm, lower leg, knee, ankle, hand, and foot fracture.

Data are frequency (probability) of individuals in each state. For instance, among 6197 women who had entered the study, 3051 (49.2%) remained alive and fracture-free, 1891 (30.5%) sustained an initial fracture, and 1255 (20.3%) died during the study follow-up. Among 1891 women with an initial fracture (including 263 women with hip, 443 with clinical vertebral, 522 with non-hip non-vertebral proximal, and 633 with distal fractures), 804 (42.5%) had neither subsequent fracture nor death, 641 (33.9%) developed another fracture, and 446 (23.6%) died. Once sustaining a hip fracture (*n* = 263), 94 (35.7%) remained alive and had no subsequent fracture, 75 (28.5%) experienced a subsequent fracture, and 94 (35.7%) died. Similarly, among 443 women with the first clinical vertebral fracture, 173 (39.1%) sustained a subsequent fracture and 116 (26.2%) died. Finally, 272 women with a subsequent fracture (42.4%) died during the follow-up period.

70-year-old woman with a low-risk profile (Fig. 3) and with two arbitrarily selected risk profiles (Supplemental Fig. S5). Fig. 3 illustrates how the risks for fragility fractures and mortality are estimated for a 70-year-old woman with BMD *T*-score of −1.5 and no other risk factors (ie, no history of falls, no prior fracture, and no comorbidities [CVD, DM, hypertension, COPD or cancer]) when she is fracture free or already has a fracture. For instance, a 70-year-old fracture-free woman with a low-risk profile would have a 9.8% chance of sustaining a fragility fracture. If such a woman sustains a fracture, the chance of having another fracture or dying within 5 years are increased up to 33% (16.7% for subsequent fracture and 16.1% for post-initial fracture death). Although the risk of subsequent fractures did not differ substantially among specific initial fractures, their specific post-fracture mortality did. Indeed, the 5-year mortality risk after a hip fracture was 27% compared with 10% after a non-hip non-vertebral distal fracture. The high competing risk of death associated with hip fracture would partly explain the similarity in subsequent fracture risk among specific initial fractures. Finally, a 70-year-old low-risk woman who sustained a subsequent fracture would have 27.1% chance of dying within 5 years after this subsequent fracture. Clearly this mortality risk would vary by fracture type, but these estimates were beyond the scope of the data.

Supplemental Fig. S5 illustrates different risks of transition to fractures and mortality for a 70-year-old woman with two different risk profiles: (*A*) BMD *T*-score = −2.5 and (*B*) BMD *T*-score = −2.5 and COPD. As expected, a woman with BMD *T*-score of −2.5 and no other risk factors would have greater risk of both initial and subsequent fractures, but her mortality risk differed little from the low-risk woman (Supplemental Fig. S5*A*). Indeed, the probability of having a fracture in 5 years increased from 10% for the low-risk woman to 14% for an osteoporotic woman, whereas the chance she would have another fracture increased from 17% to 22%. By contrast, the presence of low bone mineral density and COPD would increase both fracture and mortality risk (Supplemental Fig. S5*B*). Compared with a low-risk woman, a

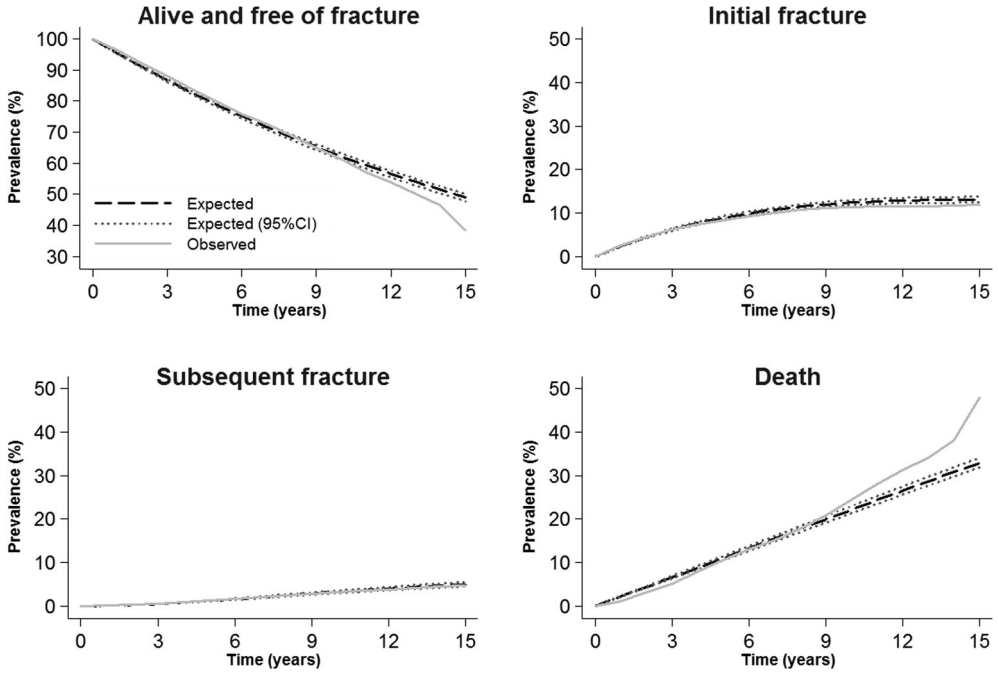

Fig 2 Assessment of model's accuracy for predicting fragility fractures and mortality.

70-year-old woman with BMD *T*-score of −2.5 and COPD would have a 3% absolute higher risk of mortality if fracture free, but up to 5% and 9% absolute higher mortality risk after an initial and subsequent fracture, respectively. Her risk of fragility fracture was also 6% to 7% greater than a similarly aged woman with a low-risk profile. Interestingly, the transition risks were also modified by severity of initial fracture. The more severe the initial fracture, the less the risk profiles added to the risk of subsequent fracture and the more they added to post-fracture mortality risk (Fig. 3; Supplemental Fig. S5).

Similar patterns were found for a man with different risk profiles (Supplemental Fig. S6). A 65-year-old man with a *T*-score of −1.5 and without other risk factors would have a 6% chance of sustaining a fragility fracture and 8% chance of dying in 5 years (Supplemental Fig. S6*A*). After an initial fracture, his chance of sustaining another fracture or dying is substantially increased to 13.5% and 19.1%, respectively. A similarly aged man with higher risk profile (ie, BMD *T*-score = −3.0 with prior fracture, CVD, and COPD but neither history of falls nor other comorbidities [DM, hypertension, and cancer]) would have

Table 3 Predictors for Transition Risks to Initial Fractures, Subsequent Fractures and Mortality

	From no fracture to		From initial fracture to		From subsequent fracture to
Predictors	Initial fracture	Death	Subsequent fracture	Death	Death
Sex (women versus men)	**1.50 (1.35–1.67)**	**0.60 (0.55–0.65)**	1.12 (0.91–1.37)	**0.53 (0.44–0.93)**	**0.55 (0.41–0.72)**
Age (+ 5 years)	**1.14 (1.11–1.18)**	**1.57 (1.53–1.62)**	**1.12 (1.07–1.19)**	**1.60 (1.51–1.70)**	**1.29 (1.19–1.41)**
Femoral neck BMD (−1 *T*-score)	**1.44 (1.37–1.50)**	1.02 (0.97–1.06)	**1.41 (1.30–1.55)**	1.06 (0.97–1.15)	**1.22 (1.08–1.38)**
History of falls within the previous 12 months	**1.26 (1.14–1.40)**	0.99 (0.89–1.10)	1.07 (0.90–1.26)	1.00 (0.83–1.21)	1.24 (0.98–1.57)
Prior fracture after the age of 50 years before recruitment	**1.37 (1.25–1.50)**	0.93 (0.83–1.03)	**1.19 (1.02–1.40)**	0.92 (0.77–1.10)	1.05 (0.51–2.83)
Cardiovascular diseases	**1.12 (1.01–1.24)**	**1.35 (1.23–1.48)**	1.22 (0.96–1.55)	**1.36 (1.14–1.62)**	1.22 (0.96–1.54)
Diabetes mellitus	0.90 (0.77–1.06)	**1.61 (1.43–1.81)**	1.05 (0.79–1.39)	**1.21 (1.03–1.42)**	1.15 (0.78–1.68)
Chronic obstructive pulmonary diseases	**1.23 (1.08–1.40)**	**1.39 (1.23–1.58)**	1.16 (0.93–1.43)	1.22 (0.96–1.54)	1.17 (0.87–1.58)
Hypertension	0.98 (0.90–1.06)	**1.17 (1.08–1.27)**	1.04 (0.90–1.21)	1.20 (0.90–1.59)	**1.29 (1.03–1.61)**
Cancer	1.14 (0.98–1.32)	**1.24 (1.07–1.42)**	1.00 (0.79–1.26)	1.00 (0.76–1.31)	1.08 (0.76–1.53)

Data presented as hazard ratios (95% confidence intervals). Boldface indicates statistical significance. Cardiovascular diseases include myocardial infarction, heart failure, or stroke.

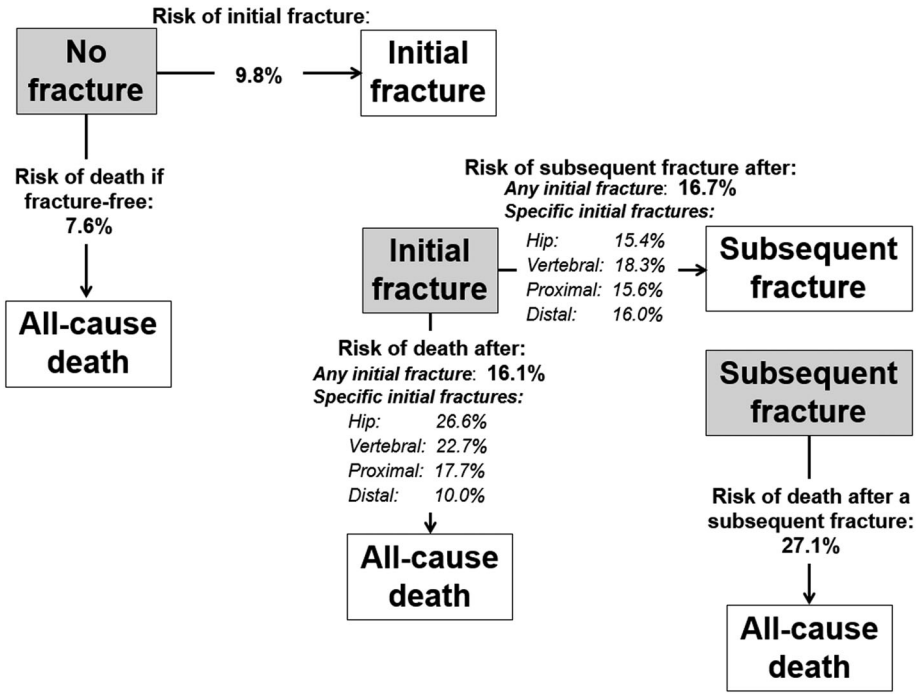

Fig 3 Predicted 5-year transition risks to fragility fractures and mortality for a 70-year-old woman with a low-risk profile (femoral neck BMD *T*-score = −1.5, no history of falls, no prior fracture, and no comorbidities). Shaded boxes indicate the timing when the estimated risks of future fractures or mortality are made. For instance, a 70-year-old fracture-free woman with a low-risk profile would have a 9.8% chance of sustaining a fragility fracture and 7.6% chance of dying in 5 years. After the initial fracture, her chance of having another fracture or dying within 5 years post initial fracture would increase to 16.7% and 16.1%, respectively. Finally, the same woman's risk of dying within 5 years after the subsequent fracture would increase to 27.1%. Non-hip non-vertebral proximal fractures include clavicle, rib, humerus, elbow, pelvis, and upper leg fracture; non-hip non-vertebral distal fractures include forearm, lower leg, knee, ankle, hand, and foot fracture.

higher chances of sustaining fragility fractures or dying (Supplemental Fig. S6*B*).

Discussion

Individualization of health care is crucial to allow tailoring of prevention and treatment in modern medicine. To our knowledge, this is the first risk assessment tool developed to predict the occurrence of not only an initial fracture but also of post-fracture outcomes, sufficiently accounting for their complex interrelationships. Of clinical importance also is the model's ability to predict the risk of post-fracture consequences for a patient with a particular risk profile who already has a fragility fracture. The optimal model both in terms of accuracy for prediction and for clinical applicability included sex, age, BMD *T*-score, history of falls, prior fracture, and comorbidities, namely CVD, DM, COPD, hypertension, and cancer. The model accurately predicted the occurrence of a fragility fracture and mortality, including the mortality up to 7 years post-hip fracture and 15 years after an initial non-hip fracture.

Prediction models are able to objectively incorporate data from multiple risk factors to estimate reproducible risk, making them superior to clinical judgment.[40] Despite many attempts to predict both fracture and its related outcomes, to date none has been comprehensive and able to account for the complex interrelationships between these correlated outcomes.[14,15] Failing to account for the correlated nature of fracture and its consequences would provide a biased estimation of risk.[18] By contrast, the multistate model used to develop our prediction model was specifically designed to quantify the effects of predictors related to progression of an illness to a series of correlated states, accounting for not only the interrelationships between these correlated outcomes but confounding effects and competing risk as well.[18] Death was examined together with other outcomes in a single regression framework, making it capable of accounting for the competing risk of other correlated outcomes. A direct head-to-head comparison between the multistate model and separate Cox regression models has indicated the superiority of the multistate model as the former but not the latter was able to yield new insights into breast cancer progression and associated pathways to cause-specific mortality.[41] The multistate model was also able to show the pathways of associations across the intermediate events between primary breast cancer and mortality, which are not directly visible with separate Cox regression models.[41] In addition to sex and age as important predictors for both fracture and mortality, BMD *T*-score, history of falls, and prior fracture were mainly focusing on prediction of the risk of initial and subsequent fractures and comorbidities for prediction of mortality, including post-fracture mortality.

We found the prediction model developed in this study could accurately predict a fragility fracture and its related outcomes for women and men in the population aged 60+ years. A combination of sex, age, BMD, prior fracture, and history of falls has been

found to be able to accurately predict the occurrence of a fragility fracture[35] and hip fracture,[42] even in many external cohorts,[9–11] including the CaMos cohort.[36] Our model also suggests that sex, age, and several baseline comorbidities are able to predict mortality risk not only among fracture-free individuals but also after an initial or subsequent fracture. Cardiovascular diseases, COPD, DM, cancer, and hypertension have been long considered to be the leading causes of death in high-income countries[43] and independent predictors for mortality after hip fracture.[44] The prediction model was robust in predicting mortality risk accurately up to 15 years after a non-hip fracture and 7 years post-hip fracture. Regardless of its underestimation of the long-term mortality risk beyond 7 years post-hip fracture, the model remains clinically useful because a majority of deaths occur within 1 year post-hip fracture and certainly by 5 years.[3]

Our findings have important implications for clinical practice. Unlike the existing fracture risk assessment tools,[9–11] our prediction model is able to predict the conceptual risk of a fragility fracture and its related consequences, which should make informed decision making about the risk and potential value of treatment more convincing than just the estimated risk of an initial fracture alone. Importantly, the model is also able to predict the risk of subsequent fracture and mortality for a patient who already sustained a fragility fracture, making it possible to identify a fracture patient at particularly high risk in the fracture liaison service settings. Lack of information about the risk of fracture-related consequences may contribute to the current undermanagement of fragility fractures worldwide.[12,13] This prediction model with its capacity to provide an individualized estimate of risk of a fragility fracture and its consequences is expected to assist both doctors and patients to reach an informed clinical decision, ultimately improving appropriate and timely management of a fragility fracture and reducing its burden among older individuals. This is a critical step to increase treatment uptake and adherence for those who need it as the current worldwide undermanagement of fragility fractures is at least partly related to the fact that neither patients nor primary care practitioners are sufficiently informed about fragility fracture and its consequences.[45] Indeed, primary care practitioners usually consider osteoporosis far less important than other chronic diseases.[46]

No studies to date have examined whether the prospective use of a fracture risk assessment tool is associated with improved treatment uptake or adherence. However, prospective incorporation of a performance algorithm in clinical practice substantially increased the appropriate use of a vertebral fracture assessment (VFA) on lateral spine images,[47] which in turn significantly increased subsequent prescription of fracture prevention medication.[48] Compared with VFA-negative (ie, vertebral fractures were definitely not present), the VFA-positive (ie, vertebral fracture definitely present) and uncertain (ie, possible vertebral fractures) were associated with about threefold (odds ratio [OR] = 2.77; 95% CI 2.40–3.19) and 1.5-fold (OR = 1.43; 95% CI 1.07–1.92) increased odds of dispensing of subsequent fracture prevention medication, respectively.[48] The impact of VFA on subsequent use of fracture prevention medication became even more obvious for individuals with low to moderate estimated risk of fracture (10% to 20%) or without osteoporosis who otherwise might not be considered eligible for osteoporosis treatment.[48]

The results of the current study should be viewed in the context of its strengths and limitations. Its strengths include a large and homogenous study population and the rigorous analysis approach. Our study population included approximately 9000 participants from two very similar population-based prospective cohort studies in which the fracture risk assessment tool had been developed[42] and externally validated,[36] making the study population statistically homogenous for the analyses. Our large study population with a median of 13-year follow-up was robust to determine the long-term consequences after specific types of fracture. This model, to our knowledge, is the first prediction model able to quantify the risk of specific types of fragility fracture and their related long-term consequences, accounting for the complex intercorrelations that none of the existing fracture assessment tools have accommodated to date. Importantly, the multistate model is well recognized as a rigorous statistical method to develop a prediction model for the correlated ordered outcome events.[18]

Despite these strengths and regardless of large sample size with long follow-up, our study was not powered to examine the individual type of non-hip non-vertebral fractures. We thus grouped them as proximal and distal fractures.[26] Secondly, all covariates but age were considered fixed under an assumption that their status at fracture time was not substantially different from their recruitment status. That is a common practice used when applying multistate models,[18,31] and clinicians might find the prediction model with predictors reported when an individual has not experienced any outcome event more reasonable and far easier to be implemented in daily practice. Nevertheless, this assumption might not always be met for several comorbidities, possibly impacting the predictive accuracy for post-fracture mortality. Finally, the study population was predominantly white (~97%), so the findings may not be generalizable to other ethnicities.

Our project did not aim to validate the model's predictive performance against the existing fracture risk assessment tools. Instead, we plan to conduct an external validation to verify the robustness and generalization of the prediction model in other well-established cohorts. If the model is shown to be acceptably accurate, a web-based calculator will be developed to assist users to estimate the probabilities for an incident fragility fracture, subsequent fracture, and mortality for an individual with different risk profiles. Further studies are needed, if possible, to examine whether time-dependent predictors, including comorbidity status at the time of the intermediate outcome events, would improve the model's predictive performance.

In conclusion, we used a novel and robust statistical technique to develop a risk assessment tool capable of predicting the occurrence of fragility fracture and its consequences, sufficiently accounting for not only the complex interrelationships between these outcomes but also possible confounding effects. The model can inform decision-making about risk beyond the fracture itself and thus aid in individualized treatment decisions.

Disclosures

TT, DB, HMP, TvG, CB, DAH, RGJ, CSK, SMK, and JCP have no competing interests to declare. JDA has received research grants and/or personal fees from Amgen and Eli Lilly. JvdB has consulted for and/or received research funding from Amgen, MSD, and Eli Lilly. JAE has consulted for and/or received research funding from Amgen, Eli Lilly, Merck Sharp and Dohme, and Sanofi-Aventis. PG was advisory member for Amgen, has received speaker fees and/or research grants from Amgen, Pfizer, MSD, UCB, Abbott, Eli Lilly, BMS, Novartis, Roche, and Will Pharma. DG has consulted

for and received research funding from Amgen. LL has received research funding from Merck and Abbott Nutrition. TVN has received honoraria for consulting and symposia from Merck Sharp and Dohme, Roche, Servier, Sanofi-Aventis, and Novartis. JRC has consulted for and/or given educational talks for Merck Sharp and Dohme, Amgen, Actavis, and Sanofi-Aventis.

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Authors' roles: Study design: TT, DB, HMP, TVN, and JRC. Data analysis: TT, HMP, TVN, and JRC. Data interpretation: all authors. Drafting the manuscript: TT, TVN, and JRC. Revising the manuscript contents and approving the final version of the manuscript: all authors.

Peer Review

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References

1. Cummings SR, Black DM, Rubin SM. Lifetime risks of hip, Colles', or vertebral fracture and coronary heart disease among white postmenopausal women. Arch Intern Med. 1989;149(11):2445–8.
2. Seidman H, Mushinski MH, Gelb SK, Silverberg E. Probabilities of eventually developing or dying of cancer—United States, 1985. CA Cancer J Clin. 1985;35(1):36–56.
3. Haentjens P, Magaziner J, Colon-Emeric CS, et al. Meta-analysis: excess mortality after hip fracture among older women and men. Ann Intern Med. 2010;152:380–90.
4. Tran T, Bliuc D, Hansen L, et al. Persistence of excess mortality following individual nonhip fractures: a relative survival analysis. J Clin Endocrinol Metab. 2018;103(9):3205–14.
5. Center JR, Bliuc D, Nguyen TV, Eisman JA. Risk of subsequent fracture after low-trauma fracture in men and women. JAMA. 2007;297(4):387–94.
6. Borhan S, Papaioannou A, Gajic-Veljanoski O, et al. Incident fragility fractures have a long-term negative impact on health-related quality of life of older people: the Canadian Multicentre Osteoporosis Study. J Bone Miner Res. 2019;34(5):838–48.
7. Singer A, Exuzides A, Spangler L, et al. Burden of illness for osteoporotic fractures compared with other serious diseases among postmenopausal women in the United States. Mayo Clin Proc. 2015;90(1):53–62.
8. Forjaz de Lacerda G, Howlader N, Mariotto AB. Differences in cancer survival with relative versus cause-specific approaches: an update using more accurate life tables. Cancer Epidem Biomar. 2019;28(9):1544–51.
9. Beaudoin C, Moore L, Gagne M, et al. Performance of predictive tools to identify individuals at risk of non-traumatic fracture: a systematic review, meta-analysis, and meta-regression. Osteoporos Int. 2019;30:721–40.
10. Bolland MJ, Jackson R, Gamble GD, Grey A. Discrepancies in predicted fracture risk in elderly people. BMJ. 2013;346:e8669.
11. Marques A, Ferreira RJ, Santos E, Loza E, Carmona L, da Silva JA. The accuracy of osteoporotic fracture risk prediction tools: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:1958–67.
12. Compston JE, McClung MR, Leslie WD. Osteoporosis. Lancet. 2019;393(10169):364–76.
13. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. J Bone Miner Res. 2014;29(9):1929–37.
14. Albertsson DM, Mellstrom D, Petersson C, Eggertsen R. Validation of a 4-item score predicting hip fracture and mortality risk among elderly women. Ann Fam Med. 2007;5:48–56.
15. Tanaka S, Yoshimura N, Kuroda T, Hosoi T, Saito M, Shiraki M. The fracture and immobilization score (FRISC) for risk assessment of osteoporotic fracture and immobilization in postmenopausal women—a joint analysis of the Nagano, Miyama, and Taiji cohorts. Bone. 2010;47:1064–70.
16. Andersen PK, Keiding N. Multistate models for event history analysis. Stat Methods Med Res. 2002;11:91–115.
17. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multistate models. Stat Med. 2007;26(11):2389–430.
18. Meira-Machado L, de Una-Alvarez J, Cadarso-Suarez C, Andersen PK. Multistate models for the analysis of time-to-event data. Stat Methods Med Res. 2009;18:195–222.
19. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). Osteoporos Int. 1994;4:277–82.
20. Kreiger N, Tenenhouse A, Joseph L, et al. Research notes: the Canadian Multicentre Osteoporosis Study (CaMos): background, rationale, methods. Can J Aging. 1999;18:376–87.
21. Tenenhouse A, Joseph L, Kreiger N, et al. Estimation of the prevalence of low bone density in Canadian women and men using a population-specific DXA reference standard: the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporos Int. 2000;11(10):897–904.
22. Henry MJ, Pasco JA, Pocock NA, et al. Reference ranges for bone densitometers adopted Australia-wide: Geelong Osteoporosis Study. Australas Radiol. 2004;48(4):473–5.
23. Henry MJ, Pasco JA, Korn S, Gibson JE, Kotowicz MA, Nicholson GC. Bone mineral density reference ranges for Australian men: Geelong Osteoporosis Study. Osteoporos Int. 2010;21(6):909–17.
24. Curcio F, Liguori I, Cellulare M, et al. Physical activity scale for the elderly (PASE) score is related to sarcopenia in noninstitutionalized older adults. J Geriatr Phys Ther. 2019;42(3):130–5.
25. Prior JC, Langsetmo L, Lentle BC, et al. Ten-year incident osteoporosis-related fractures in the population-based Canadian Multicentre Osteoporosis Study—comparing site and age-specific risks in women and men. Bone. 2015;71:237–43.
26. Tran T, Bliuc D, van Geel T, et al. Population-wide impact of non-hip non-vertebral fractures on mortality. J Bone Mine Res. 2017;32(9):1802–10.
27. Claeskens G, Hjort NL. The focused information criterion. J Am Stat Assoc. 2003;98:900–16.
28. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol. 1997;145(1):72–80.
29. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. Stat Med. 2007;26(6):1343–59.

30. Jackson CH. Multistate models for panel data: the msm package for R. J Stat Softw. 2011;38:1–28.
31. Ieva F, Jackson CH, Sharples LD. Multistate modelling of repeated hospitalisation and death in patients with heart failure: the use of large administrative databases in clinical epidemiology. Stat Methods Med Res. 2017;26:1350–72.
32. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. N Engl J Med. 2020;382(7):674–8.
33. Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. BMJ. 2013;347:f6409.
34. van Buuren S, Groothuis-Oudshoorn K. MICE: multivariate imputation by chained equations in R. J Stat Softw. 2011;45(3):1–67.
35. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of prognostic nomograms for individualizing 5-year and 10-year fracture risks. Osteoporos Int. 2008;19:1431–44.
36. Langsetmo L, Nguyen TV, Nguyen ND, et al. Independent external validation of nomograms for predicting risk of low-trauma fracture and hip fracture. CMAJ. 2011;183:E107–14.
37. Hjort NL, Claeskens G. Focused information criteria and model averaging for the Cox hazard regression model. J Am Stat Assoc. 2006; 101:1449–64.
38. Jackson G. FIC: Focused Information Criteria for Model Comparison. R package version 1.0.0. 2019. Available at: https://CRAN.R-project.org/package=fic.
39. Lo A, Chernoff H, Zheng T, Lo SH. Why significant variables aren't automatically good predictors. Proc Natl Acad Sci U S A. 2015;112 (45):13892–7.
40. Ross PL, Gerigk C, Gonen M, et al. Comparisons of nomograms and urologists' predictions in prostate cancer. Semin Urol Oncol. 2002; 20:82–8.
41. Eulenburg C, Schroeder J, Obi N, et al. A comprehensive multistate model analyzing associations of various risk factors with the course of breast cancer in a population-based cohort of breast cancer cases. Am J Epidemiol. 2016;183(4):325–34.
42. Nguyen ND, Frost SA, Center JR, Eisman JA, Nguyen TV. Development of a nomogram for individualizing hip fracture risk in men and women. Osteoporos Int. 2007;18:1109–17.
43. World Health Organization. Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000–2016. Geneva: World Health Organization; 2018.
44. Chang W, Lv H, Feng C, et al. Preventable risk factors of mortality after hip fracture surgery: systematic review and meta-analysis. Int J Surg. 2018;52:320–8.
45. Swart KMA, van Vilsteren M, van Hout W, et al. Factors related to intentional non-initiation of bisphosphonate treatment in patients with a high fracture risk in primary care: a qualitative study. BMC Fam Pract. 2018;19(1):141.
46. Merle B, Haesebaert J, Bedouet A, et al. Osteoporosis prevention: Where are the barriers to improvement in French general practitioners? A qualitative study. PloS One. 2019;14(7):e0219681.
47. Schousboe JT, Lix LM, Morin SN, et al. Vertebral fracture assessment increases use of pharmacologic therapy for fracture prevention in clinical practice. J Bone Miner Res. 2019;34(12):2205–12.
48. Schousboe J, McKiernan F, Fuehrer J, Binkley N. Use of a performance algorithm improves utilization of vertebral fracture assessment in clinical practice. Osteoporos Int. 2014;25(3):965–72.