ABSTRACT

Title of Thesis: RISK PREDICTION MODELS FOR HIP FRACTURE--
PARAMETRIC VERSUS COX REGRESSION

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Hip fracture is a public health burden due to high morbidity, mortality and cost. Risk prediction models can aid clinical decision-making by identifying individuals at risk.

Objective: To build risk prediction model for incident hip fracture using Weibull regression and compare this with Cox regression model.

Method: The Study of Osteoporosis prospectively collected risk factors were used to build a risk prediction model for first hip fracture using Threshold regression with Wiener process. Similar predictors were fitted using Cox regression for comparison.

Results: There were 632 first hip fractures. Age, bone density, maternal and personal prior fractures were significant risk factors for hip fracture. Weibull had better goodness of fit, higher D-statistic and R^2 values than the exponential. Models did not differ in c-index and ten-fold cross validation showed similar areas under the ROC curves.

Conclusion: Parametric and Cox models were comparable. External validation of the prediction model is required.

RISK PREDICTION MODEL FOR HIP FRACTURE-- PARAMETRIC VERSUS COX
REGRESSION

by

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Chapter 1: Introduction

The most common cause of fractures is osteoporosis. The Office of Surgeon General Report estimated that 1.5 million Americans suffer a fracture due to osteoporosis annually.[1] A study by Burge et al. in 2007 has projected that by 2025, due to increase in lifetime risk of fracture as people live longer and the aging population grows, there will be more than 3 million fractures incurring $25.3 billion in costs.[2]

Osteoporosis or "porous bones" is a systemic bone disease in which there is structural degradation of the bone and a low bone mass, resulting in brittle bones that are prone to low trauma or fragility fracture.[3] A fragility fracture results from forces which would not normally produce a fracture such as falling from standing height or a vertebral compression fracture.[4] Osteoporosis is diagnosed either by the presence of a fragility fracture or by the World Health Organization's bone density criteria—when the bone mineral density (BMD) measured at the hip, spine or wrist is 2.5 standard deviations below the mean in young adult women.[5] Although BMD (known also as the T-score) measured by dual-energy X-ray absorptiometry (DXA) is of modest predictive value it remains the current diagnosis and treatment evaluation criteria. Other bone components that determine fracture, such as the rate of bone loss and bone quality are not well characterized.[4]

The National Osteoporosis Foundation (NOF) estimates that 10 million Americans have osteoporosis, of which 80% are women and 20% are men.[6] Rates are higher for women than for men because postmenopausal estrogen deficiency is an important etiology of osteoporosis in women.[7] Additionally, rates of osteoporosis vary by

race being highest in whites. Cumming et al. reported age-adjusted incidence rates in the U.S. to be 6.2 per 1,000 among white females, 3.8 per 1,000 among Asian females, 2.4 per 1,000 among black females and 2.2 per 1,000 among Hispanic females.[8] In all demographic groups, osteoporosis rate increases with age.

The most common sites of osteoporotic fractures are the hip (43%), the spine (43%) and the wrist (13%).[9] In addition to the economic burden of osteoporosis, hip fracture has serious consequences that include pain, need for surgery and loss of independent living. It is estimated that up to 50% of hip fracture patients experience reduced mobility and some do not return to pre-fracture functional level and require home-care.[10, 11] Furthermore, there is a high mortality rate of up to 36% within the first year after an incident hip fracture.[12] Our study focuses on hip fracture as it is the most severe consequence of osteoporosis in terms of public health burden.

Osteoporosis is a chronic progressive disease and with the aging population on the rise the incidence of osteoporosis will increase. Even though the causes of osteoporosis and hip fracture are well characterized and there are opportunities for prevention and intervention, osteoporosis remains under-diagnosed and inadequately treated in the U.S.[13, 14] Possible reasons include the existence of different recommendations for testing and initiating treatment, confusion in interpreting test results and fragmentation of health care.[15] Increasingly, risk prediction models which take into account important clinical factors are used to provide a systematic approach in identifying individuals at risk of osteoporosis. Such a model will supplement and facilitate clinical decision-making as to

whether to provide lifestyle advice, to measure BMD or to initiate treatment according to

risks of osteoporosis.

1.1. The Cox Proportional Hazards Model

Established four decades ago, the Cox Proportional Hazards (PH) regression is a

standard method for analyzing survival and time-to-event data.[16] The Cox regression is a

semi-parametric method as it makes no distributional assumption on the baseline hazard

rate (the non-parametric component) and accommodates covariates in a multiplicative

linear regression form (the parametric component) as shown in the equation below:

$$h(t|\mathbf{Z}) = h_0(t)exp(\beta'\mathbf{Z})$$

Equation 1. Hazard rate

where $h(t|\mathbf{Z})$ represents the hazard rate of an individual at time, t, with risk vector, $\mathbf{Z}$,

$h_0(t)$ is the baseline hazard and

β' a parameter vector.

With proven applications in diverse fields, it is easy to use and presents results in

an easily interpretable form, the hazard ratio (HR):

$$HR = \frac{h(t|\mathbf{Z})}{h(t|\mathbf{Z}_*)} = \frac{h_0(t)\exp(\sum_{k=1}^{p}\beta_k Z_k)}{h_0(t)\exp(\sum_{k=1}^{p}\beta_k Z_k^*)} = \exp\left[\sum_{k=1}^{p}\beta_k(Z_k - Z_k^*)\right]$$

Equation 2. Hazard ratio

However, the Cox regression relies heavily on the PH assumption that factors

have a constant effect on risk or hazard over time. This assumption when violated,

especially in the presence of long follow-up, leads to incorrect inference and misleading

conclusions. Current methods to handle non-proportional hazards assumption include

either using the modified Cox model which "stratify" on the predictors not satisfying the

PH assumption or using the extended Cox model for time-dependent variables to analyze a time-independent predictor not satisfying the PH assumption.[17] These methods are, however, not without limitations. In the stratified Cox model, the effect of the stratified predictor cannot be studied as the hazard ratio for this predictor is no longer obtainable. In the extended Cox model, the hazard ratios for the predictor not satisfying the PH assumption can be obtained at time points before and after a change in risk. This method may produce a complex model if the hazard ratios for the predictor not satisfying the PH assumption change at more than one time point or if there are several predictors in the model that do not satisfy the PH assumption.

1.2. Parametric Regression Models

Parametric survival models make more efficient use of information, give more precise estimates and can be more powerful than semi-parametric method if the distributional form of the hazard function is known. However, when a parametric model is incorrectly specified it may produce consistent estimates of the wrong magnitude. Parametric models are characterized by the distribution of the baseline hazard function. This paper focuses on the exponential, the Weibull and the threshold regression models.

1.2.1. The Exponential Model

The exponential model has a constant hazard, λ, and the following proportional hazards parameterization:

$$h(t|\mathbf{Z}) = h_0(t)exp(\beta'\mathbf{Z}) = \lambda exp(\beta'\mathbf{Z})$$

Equation 3. Hazard rate with exponential baseline hazard

The survival function decreases linearly while the cumulative hazard function increases linearly with time.

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1.2.2. The Weibull Model

The Weibull has a monotonic increasing or decreasing hazard with the following proportional hazards parameterization:

$$h(t|\mathbf{Z}) = h_0(t)exp(\beta'\mathbf{Z}) = \lambda\alpha t^{\alpha-1}exp(\beta'\mathbf{Z})$$

Equation 4. Hazard rate with Weibull baseline hazard

where λ and α are the scale and the shape parameters respectively. When $\alpha = 1$, the hazard shape is flat giving rise to the exponential hazard function which is thus a special case of Weibull. When $\alpha > 1$, the hazard is increasing and when $\alpha < 1$, the hazard is decreasing.

1.2.3. The Threshold Regression Model

The Threshold regression (TR) is a parametric method that serves as a useful alternative to the Cox regression for analyzing time-to-event data when the PH assumption is violated.[18] Known as the first hitting time (FHT) model, TR provides more information about the underlying disease than the Cox model.[19] It treats the unobservable initial health status as a stochastic process that degrades over time to the threshold event or FHT. The stochastic process can be of different distributional forms. If it is a Poisson process, the FHT follows a gamma distribution; a Bernoulli process has a negative binomial distribution as FHT; and a Wiener diffusion process has inverse Gaussian as the FHT.[20] The bivariate Wiener TR model has been used in the analysis of an AIDS clinical trial to investigate the effect of CD4 cell count ratio in response to antiretroviral drug treatment[21] while the TR mixture model has been used in a clinical trial to evaluate the efficacy of Velcade[R] in multiple myeloma.[22] Additionally, the TR with a Wiener

diffusion process has been used in the Nurses' Health Study to examine the effect of smoking and lung cancer.[23]

A common stochastic process in the TR model is the Wiener process with a positive initial value, mean and variance parameters. When applied to osteoporotic fracture, the unobservable bone deterioration is modeled by a Wiener process with time to an incident fracture as the first hitting time of the threshold. The first hitting time of the Wiener process has an inverse Gaussian distribution with the following probability density function:

$$f(t|\mu, \sigma^2, y_0) = \frac{y_0}{\sqrt{2\pi\sigma^2 t^3}} \exp\left[-\frac{(y_0 + \mu t)^2}{2\sigma^2 t}\right]$$

Equation 5. Inverse Gaussian probability density function

where parameters μ is the drift of the Wiener process (i.e. the mean change in the level of the sample path per unit time; FHT approaches the threshold if $\mu < 0$), y_0 the initial value of the process is positive and σ^2 the variance per unit time of the process is set to 1. The TR with Wiener process can be implemented using the stthreg package available in Stata.[24]

Covariates, $\mathbf{Z}$, enter the model through the log link and the identity link functions respectively as shown in the following two equations:

$$\ln(y_0) = \gamma_0 + \gamma_1 Z_1 + \cdots + \gamma_k Z_k = \mathbf{Z}'\boldsymbol{\gamma}$$

$$\mu = \beta_0 + \beta_1 Z_1 + \cdots + \beta_k Z_k = \mathbf{Z}'\boldsymbol{\beta}$$

where $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}$ are vectors of regression coefficients for $\ln(y_0)$ and μ respectively.

Most studies that have examined risk factors for hip fractures have used Cox regression with or without checking for the violation of the PH assumption.[25-28] TR model

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is available to the parametric survival models. The current objectives of the study are to build risk prediction model for the first hip fracture using parametric regression and to compare this with a similarly built Cox regression model. The resulting parametric prediction model can then be used to develop a risk assessment tool to aid physicians in the management of osteoporotic hip fractures over time.

Chapter 2: Methods

2.1. Study Population

The training data set was from the Study of Osteoporotic Fractures (SOF). The SOF is an ongoing multicenter observational study that evaluated risk factors for osteoporosis prospectively in 9,704 white women who were at least 65 years old. Age-eligible women from community-based listings were recruited by mailings between September 1986 and October 1988 from four metropolitan areas in the United States to clinic centers in Baltimore, Maryland; Portland, Oregon; Minneapolis, Minnesota; and the Monongahela Valley, Pennsylvania.[25] Standardized interviews and clinical examinations were conducted approximately every 2 years; data collected include anthropometric measures, vital status, DXA, cognitive and physical functions, falls, vision, lifestyle characteristics, family and medical histories, and other risk factors for fractures. Additionally, between 1997 and 1998, 662 African American women were recruited to this original cohort. Follow-up rates of participants exceeded 98% as efforts were made every quarter to ascertain fractures, falls or change in address by postcard or phone. The event of interest was time to first hip fracture. Hip fractures were confirmed by review of radiographs.[25, 26]

Our analysis excluded 662 African-Americans recruited at year 10 of the SOF study because their risk of fracture is low (2.5 times lower than white women). In addition, a shorter follow-up due to late recruitment may result in a smaller number of women with incident hip fractures. Other exclusion criteria were women unable to walk without assistance, women with bilateral hip replacements, and women who reported hip

fracture prior to enrollment as the focus in this study was incident hip fracture and prospectively collected risk factors.

2.2. Predictors

Risk factors for first hip fractures are well-characterized.[29-39] A literature review was conducted and factors used in other risk assessment tools were also examined (Table 1). Four of these seven tools did not utilize bone density. While BMD T-score was optional in the Fracture Index developed using SOF data, both the WHO FRAX and the Garvan Normogram offered optional BMD T-score or femoral neck BMD measured by different DXA machines. Both femoral neck and total hip BMD were included in our list of potential predictors as a result of their predictive value for hip fractures.[49]

Twenty-four potential predictors of hip fracture measured at baseline visit or at visit 2 were considered as variables in the TR model: age, body mass index (BMI), weight change since age 25 years old, parental history of fracture, previous fracture at age less than 50 years, total hip and femoral neck BMD, fall and faint histories, comorbidities like rheumatoid arthritis, Parkinson's disease, diabetes, stroke and hyperthyroidism, walk for exercise, use of medications like hormone replacement therapy, long-acting benzodiazepine (sleep medication) and glucocorticoids (steroids), use of supplements such as vitamin D and calcium, consumption of alcohol, caffeine and tobacco smoking.

2.3. Statistical Analysis and Model Development

Comparisons of baseline characteristics of women with and without hip fractures were made using two-sample independent t-test for normally distributed continuous variables with equal variances, Wilcoxon rank-sum test for non-normally distributed continuous variables and chi-squared test for categorical variables. Univariate analyses

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for first hip fracture were performed with and without adjustment for age. Clinically relevant covariates that showed association with hip fracture after adjustment for age in univariate analyses (p < 0.2) were included into the pool of predictors for consideration in the multivariate TR model for first hip fracture. The TR predictive model was built using the method of purposeful selection of covariates.[50] A complete case analysis was performed using STATA version 11.2 and version 13.0 for somersd package (StataCorp, College Station, Texas).

2.4. Model Comparison

The important factors identified from the TR model were used to fit an exponential, Weibull and Cox regression models. Models were compared in terms of predicted baseline for survival, hazard and cumulative hazard functions; for goodness of fit using Cox-Snell residual plots; and for discrimination using R^2 statistic, D-statistic, Harrell's c index of concordance and area under the Receiver Operating Characteristics (ROC) curves at 5 and 10 years.

2.5. Model Validation

To avoid over-fitting and optimism in model performance, the final model for first hip fracture was internally validated using ten-fold cross validation technique. The discriminative ability of the models was compared using area under the ROC curves at 5 and 10 years.

Chapter 3: Results

3.1. Participant characteristics

Among the 9,704 women who participated in the study, 632 women had a first hip fracture. Over a mean follow-up of 8.8 years (standard deviation 6.5) the incidence rate of first hip fracture was 7.4 per 1000 person-years.

Baseline characteristics of women without hip fracture and women with first hip fracture were compared (Table 2). Women with a first hip fracture compared to those without a hip fracture were older (75.9 vs. 73.4 years, $p < 0.05$), had significantly lower body weight (63.4kg vs. 66.5kg, $p < 0.05$) and BMI (25.3kg/m^2 vs. 26.2 kg/m^2, $p < 0.05$), were shorter (158.3cm vs. 159.2cm, $p < 0.05$) and, gained less weight since age 25 (8.4kg vs. 10.9kg, $p < 0.05$). However, the mean weight and height at age 25 years old, and current waist-hip ratio did not differ significantly in these two groups of women. Significantly more women with a first hip fracture had a maternal history of fracture than those without a hip fracture (44.8% vs. 36.4%, $p < 0.05$). A higher percentage of women with a first hip fracture than women without hip fracture had a medical history of Parkinson's disease (1.6% vs. 0.5%, $p < 0.05$) or cataract (37.6% vs. 30.4%, $p < 0.05$). Significantly more women without hip fracture than those with a first hip fracture were current users of oral estrogen (14.2% vs. 10.2%, $p < 0.05$). The two groups of women were similar in their duration of estrogen use and proportion taking sleep medication. Significantly more women with first hip fracture than those without a hip fracture were currently taking calcium (48.5% vs. 42.3%, $p < 0.05$) and vitamin D supplements (49.8% vs. 44.5%, $p < 0.05$); had ever fallen during the past year (33.6% vs. 29.3%, $p < 0.05$). More women without a hip fracture compared to those with a first hip fracture drank

alcohol in the past year (70.4% vs. 63.7%, $p < 0.05$). The two groups of women did not differ significantly in terms of caffeine intake, tobacco use, walk for exercise or had ever fainted in past 12 months. Women with a first hip fracture compared to those without hip fracture had significantly lower total hip (0.672 g/cm^2 vs. 0.763g/cm^2, $p < 0.05$) and femoral neck bone density measurements (0.584 g/cm^2 vs. 0.653 g/cm^2, $p < 0.05$).

3.2. Predictors identified by TR model

The TR model identified nine significant covariates as shown in Table 3. For every one year increase in age, baseline health decreased by 3% ($p < 0.05$) while controlling for the other covariates. For every standard deviation (-10.2 kg) decrease in weight since age 25 years, baseline health decreased by 6% ($p < 0.05$). For every standard deviation (+0.141 g/day) increase in daily caffeine consumption, baseline health decreased by 3% ($p < 0.05$). A white woman with rheumatoid arthritis compared to another white woman without arthritis had a lower baseline health by 13.7% ($p < 0.05$). A white woman who had fallen at least once in the past 12 months compared to another white woman without a fall history had a lower baseline health by 10.3%. A white woman taking glucocorticoid in the past 12 months compared to another white woman not taking glucocorticoid had a lower baseline health by 22.1% ($p < 0.05$).

For every standard deviation decrease in femoral neck bone density (-0.11 g/cm^2) the mean rate of decline in bone health was 11.7% per year ($p < 0.05$). A white woman with a history of fracture before age 50 had a mean rate of bone loss of 5.2% per year. A white woman with a mother's history of fracture had a mean rate of bone loss of 6.1% per year ($p < 0.05$).

3.3. Kaplan-Meier plots

The Kaplan-Meier survival function plot is as shown in Figure 1. The plot showed a linear decline in survival function over time. Graphical plots of Kaplan-Meier survival functions for binary predictors such as maternal fracture, falls in the past 12 months, medical history of rheumatoid arthritis and glucocorticoid intake in the past 12 months showed similar linear decline as depicted in Figure 2.

3.4. Comparison of Exponential, Weibull and Cox models

A table comparing the exponential, Weibull and Cox models fitted with the predictors obtained using the TR model is as shown in Table 4. Hazard ratios for predictors in the exponential, Weibull and Cox were very similar up to the first decimal place. Additionally, the shape parameter in the Weibull model was 1.2181 which was greater than one—the special case when the hazard function is exponential.

3.5. Comparison of post-estimation plots

For each model post-estimation plots for baseline survival, cumulative hazard and hazard functions were obtained for comparison as illustrated in Figures 3, 4 and 5 respectively. The estimated baseline Cox survival plot was a decreasing parabola that resembled Weibull survival function than the decreasing straight line plot of the exponential survival function. The estimated cumulative hazard for Cox model increased in a curvilinear manner that resembled the shape of the Weibull cumulative hazard than the increasing linear plot of the exponential cumulative hazard. The estimated hazard function for Cox was very different from those of Weibull and the exponential hazard plots.

3.6. Post-estimation goodness of fit

A plot of estimated Nelson-Aalen cumulative hazard against Cox-Snell residuals should produce a 45° straight line through the origin for a model of good fit. As illustrated in Figure 6, Cox-Snell residuals plot for the exponential model deviated away from the reference line more than the Weibull model and the Cox model.

3.7. Checking the Proportional Hazards (PH) Assumption for the Cox model

A global test and separate tests on each predictor in the model for PH violation were performed. Results in Table 5 verified that p-values for both global (p = 0.7426) and separate tests were all greater than 0.05. Hence there was no evidence of violation in PH assumption. Additionally, comparison of Kaplan-Meier observed survival curves with Cox predicted curves for the same binary variables were made (Figure 7). Except for yes response to glucocorticoid use, the observed Kaplan-Meier plots for maternal fracture, falls in the past 12 months and rheumatoid arthritis were very close to the predicted Cox curves suggesting that the PH assumption was less likely to be violated.

3.8. Comparison of models for measures of discrimination

Discrimination is ability of the model to usefully identify individuals at risk as diseased and those not at risk as non-diseased. R^2 statistic, a measure of the variation explained by survival models, was calculated for each model (Table 6).[51] The Cox model explained 48.51% of the variation while the Weibull model accounted for 47.92% and the exponential 46.01%. Royston and Sauerbrei's *D* statistic which measures prognostic separation of survival curves with adjustment for optimism was highest for the Cox model (1.639), followed by Weibull (1.610), and then the exponential model (1.535).[52] The three models, however, did not differ for Harrell's *c*-index, which is the probability

that subject pairs are concordant for predictions and outcomes with or without

censoring.[53] This was moderately high at 0.7729. A comparison of the area under the

ROC curves using the method described by Pepe *et al.* at 5 and 10 years for Cox versus

exponential and Cox versus Weibull (Table 7) further confirmed that the models did not

differ in discriminative ability.[54]

3.9. Internal cross validation

Internal validation is a measure of how well a model is able to predict the

outcome for new observations that were not used in developing the model. Ten-fold cross

validation which uses the entire data set for development and validation is a useful

method for internal validation. This method was implemented by randomly dividing the

data into 10 mutually exclusive subsets of equal size containing approximately the same

number of events as illustrated in Table 8. Each subset was set aside in turn while the

remaining 9 subsets were used for model development. A measure of prediction error can

be estimated from the corresponding subset of observations set aside for use in predicting

the outcome. The whole process was repeated until all 10 subsets had been used for

prediction. Areas under the ROC curves at years 5 and 10 obtained using ten-fold cross

validation for Weibull and exponential models were very similar (Table 9).

Chapter 4: Discussion

4.1. Risk factors for first hip fracture

The TR model identified nine risk factors for first hip fracture from the SOF data. Factors that lowered the initial state of health included age, weight loss since age 25 years, a history of falls in the past 12 months, presence of rheumatoid arthritis, increased daily consumption of caffeine and glucocorticoid intake. Additionally, the TR model revealed that femoral neck bone density, a previous fracture before age 50 years and maternal fracture were important in reducing health status and time to a hip fracture. While femoral neck bone density and previous fracture before age 50 served as surrogates for underlying bone loss, the risk factor maternal fracture implied genetic factors or heritable traits such as low BMI and low bone mass associated with small body build and bone size may play a role in osteoporosis.[55] In contrast, only four of these factors (age, weight loss since age 25 years, a previous fracture before age 50 years and maternal fracture) were significantly associated with increased risk of hip fracture (with HR >1) when fitted into the Cox, the exponential and the Weibull models.

Age, history of maternal fracture, change in weight since age 25 years, current caffeine intake, prior fracture at age <50 years were risk factors identified in other studies.[25, 26, 40] In this study the important modifiable risk factors identified were history of falls, increased caffeine consumption and glucocorticoid intake and weight loss since age 25 years. Hence prevention strategies for individuals at risk of osteoporosis include prevention of falls, reduction in daily caffeine intake and glucocorticoid use as well as good dietary habits and exercise to maintain bone mass, muscle strength, body posture and balance.

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The inclusion of fall history as a risk factor in the TR model is an improvement over the FRAX tool, making it similar to the Garvan normogram which quantifies fall history. In a previous study, history of falls was identified as an important risk factor for hip fracture that became insignificant after adjusting for inability to rise from chair, spending less than 4 hours on one's feet per day and self-rated poor health status.[26] Our data set did not contain these adjustment variables. Additionally, there is greater awareness that increased risk of falls is not only a better and easier parameter to measure but also encompasses both frailty and sarcopenia (concepts that include weight loss, lack of physical activity, reduced walking speed and muscle strength) which are difficult and time-consuming to assess.[56]

4.2. Comparison of models

Our results demonstrated that although the Kaplan Meier survival plot showed a linear decline over time, and suggested an exponential parametric model might be appropriate, it was good to confirm the magnitude of the shape parameter in the Weibull model which turned out to be slightly greater than 1. Compared to the Cox model, the exponential model differed more than the Weibull model in magnitudes of hazard ratios, baseline survival, hazard and cumulative hazard plots, extent in Cox-Snell residuals goodness of fit, D-statistic and R^2 but not Harrell's c-index. The exponential is a special case of Weibull which in turn is a special case of Cox. In this study both the Weibull and the exponential models were comparable to the Cox model as reflected by the areas under the ROC curves for the internal validation by ten-fold cross validation technique.

Some of the strengths of this study are the data had large numbers of events with comprehensive risk factors that were prospectively collected over a long follow-up

period. Our study showed that the Weibull model was comparable with the Cox model. It provided a good fit with more precise estimates when the prior hazard distribution is known.

Limitations in this study include the use of baseline risk factors and the lack of generalizability as the predictive model was developed using data collected from white women at least 65 years old who were healthy volunteers living in a community setting. Additionally, external validation of the predictive model is required.

Future work could explore the use of data from prospective studies that included younger women (age 50 to 64 years old), men and older women ($\geq$ 65 years old) of other races, quantifying covariates such as dose and duration of glucocorticoid intake, and eventually bone turnover markers, when these become widely used and readily available.[57]

This study adds to the current literature on risk factors for first hip fracture using parametric models instead of the widely used Cox proportional hazards model. The TR model was useful in identifying surrogate markers such as BMD and previous fracture at age < 50 and genetic factor (maternal fracture) as underlying mechanisms for hip fracture. The predictive model built can be used as a risk assessment tool after external validation to assess and identify white women $\geq$ 65 years old at risk of osteoporosis for prevention and treatment. Modifiable risk factors identified were history of falls, intake of glucocorticoids and increased daily consumption of caffeine as well as weight loss since age 25 years.

Chapter 5: Conclusion

The TR model identified nine risk factors to first hip fracture providing insights into the underlying disease process. Predictive model built using the Weibull and Cox regression models were comparable but need to be externally validated.

Table 1. Overview of risk assessment tools for osteoporotic fractures.

Risk assessment tool	Population studied	Risk factors	BMD	Predictive outcome	Validation (AUC range)
WHO FRAX[29-36] http://www.shef.ac.uk/FRAX/tool.jsp	Men, women from Europe, N. America, Asia, Australia	Age, gender, height, weight, previous fracture, parental fracture, current smoking, glucocorticoids, rheumatoid arthritis, secondary osteoporosis, alcohol (>3units/d) --12 factors	Optional femoral neck BMD (GE lunar, Norland, Hologic, T-score, DMS/Medilink, Mindways QCT)	10 year risk of major osteoporotic and hip fracture	c-statistic = 0.621 using WHI data[40] Osteoporotic fracture (0.54-0.78); hip fracture (0.65-0.81)[38]
WHI hip fracture risk calculator[41] http://hipcalculator.fhcrc.org/	US postmenopausal women aged 50-79 years old	Self-rated general health, race, physical activity, current smoking, previous fracture after 55 y/o, parental history of fracture after 40 y/o, current corticosteroid use, diabetic control, age, weight, height --11 factors	No	5 year risk of hip fracture	NA
Fracture Index[42] http://www.permanente.net/homepage/kaiser/pdf/36608.pdf	SOF data: US healthy white postmenopausal women >65 years old	Age, previous fracture after 50 y/o, mother's history of hip fracture after 50 y/o, weight (≤ 125pds) , current smoke, use arms to stand up from chair --7 factors	Optional BMD total hip T-score	5 year hip fracture risk and 5 year vertebral fracture risk	ROC $_{AUC}$ 0.714 without BMD, 0.766 with BMD. Externally validated using EPIDOS data from France in postmenopausal women ≥75 years old

AUC: area under the curve, NA: not available, y/o: years old, ROC: Receiver Operating Characteristic curve, EPIDOS: European Patent Information and Document Service fracture study

Table 1. Overview of risk assessment tools for osteoporotic fractures (continued).

Risk assessment tool	Population studied	Risk factors	BMD	Predictive outcome	Validation (AUC range)
Garvan Normogram[43] http://garvan.org.au/promotions/bone-fracture-risk/calculator/ (Australia)	DOES data (Dubbo Osteoporosis Epidemiology Study) Men and women >60 years old	Sex, age, fracture since 50 y/o, falls over past 12mths --6 factors	Optional BMD T-score or femoral neck BMD (DXA Lunar or Hologic)	5- and 10-yr risks of hip fractures and any osteoporotic fractures	NA
FRAMO (Fracture and Mortality) Index[44] (Sweden)	Population-based prospective study in Sweden in 3 rural primary health care districts Women ≥70 years old	Age, weight (<132lb or 60kg), ability to rise from chair w/o using arms, any fracture after 40 y/o --4 factors	No	2-yr risk of hip fracture and overall mortality	NA
Qfracture[45, 46, 47] http://www.qfracture.org/ (UK)	Prospective open cohort study in England and Wales Men and women 30-85 years old	Age, sex, race, smoking, alcohol, diabetes, parental history of fracture, living in institution, previous fracture, history of falls, 10 disease conditions, taking anticonvulsants, antidepressants, steroid tablets, estrogen, BMI --25 factors/questions	No	Calculates 1 to 10-yr (user's choice) risk of hip fracture and incidence of osteoporotic fracture (hip, shoulder or spine fracture)	0.86-0.89[38]
ORAI[48] http://depts.washington.edu/osteoed/tools.php?type=orai	Canadian Multicenter Osteoporosis Study Women ≥ 45 years old	Age, weight, current estrogen use (yes/no) --3 factors	No	Any fracture	0.63 (0.55-0.71)[38]

AUC: area under the curve, NA: not available, y/o: years old, ROC: Receiver Operating Characteristic curve, ORAI: Osteoporosis Risk Assessment Instrument

Table 2. Baseline characteristics of women without hip fracture versus women with one hip fracture.

Characteristics	Women with no incident hip fracture (N = 9,072)			Women with one incident hip fracture (N = 632)			P-value
Age (years)	73.4	±	5.1	75.9	±	5.5	0.000
Anthropometric measures							
Weight (kg)	66.5	±	11.9	63.4	±	11.2	0.000
Weight at age 25 (kg)	56.2	±	6.8	55.9	±	6.8	0.307
Weight gain since age 25 (kg)	10.9	±	10.3	8.4	±	9.9	0.000
Height (cm)	159.2	±	5.8	158.3	±	6.0	0.000
Height at age 25 (cm)	162.6	±	5.7	162.6	±	5.8	0.789
BMI (kg/m^2)	26.2	±	4.4	25.3	±	4.2	0.000
Waist-hip ratio	0.831	±	0.070	0.835	±	0.073	0.217
Parental history (% Yes)							
Maternal fracture	36.4			44.8			0.000
Paternal fracture	23.8			26.7			0.199
Medical history (%Yes)							
Ever been told by doctor had arthritis	63.0			65.0			0.323
Ever been told by doctor had a stroke	3.0			3.2			0.807
Ever been told by a doctor had diabetes	6.9			8.4			0.163
Ever been told by a doctor had hyperthyroidism	9.4			9.4			0.999
Ever been told by a doctor had Parkinson's disease	0.5			1.6			0.001
Ever been told by a doctor had cataract	30.4			37.6			0.000
Medication history							
Current oral estrogen use (% Yes)	14.2			10.2			0.006
No. of years on oral estrogen	8.5	±	9.2	7.3	±	8.7	0.059
Current use of long acting benzodiazepine (% Yes)	9.1			10.2			0.362
Lifestyle							
Weekly calcium intake from food (g)	5.0	±	3.0	4.8	±	2.8	0.038
Currently taking calcium supplements (% Yes)	42.3			48.5			0.002
Currently taking vitamin D (% Yes)	44.5			49.8			0.010
No. of years taken vitamin D	11.2	±	12.5	10.3	±	11.7	0.151
Current daily caffeine intake (g)	0.16	±	0.14	0.17	±	0.14	0.063
Drink alcohol past 12 months (% Yes)	70.4			63.7			0.000
No. of drinks/week in past 30 days	1.78	±	3.75	1.85	±	4.02	0.108
Current smoker (% Yes)	10.0			10.3			0.787
Pack year smoked	27.0	±	23.8	27.2	±	25.3	0.849
Walk for exercise (% Yes)	50.3			49.1			0.560
No. of blocks walked per day for exercise	12.0	±	10.2	11.3	±	9.7	0.485
Ever fallen in past 12 months (% Yes)	29.3			33.6			0.024
No. of falls last year	0.49	±	1.55	0.52	±	0.99	0.036
Ever fainted in past 12 months (% Yes)	3.81			5.1			0.116
No. of times fainted last year	0.05	±	0.29	0.07	±	0.31	0.114

Table 2. Baseline characteristics of women without hip fracture versus women with one hip fracture *(continued).*

Characteristics	Women with no incident hip fracture (N = 9,072)			Women with one incident hip fracture (N = 632)			P-value
Bone density measurements							
Total hip BMD (g/cm^2)	0.763	±	0.130	0.672	±	0.111	0.0000
Femoral neck BMD (g/cm^2)	0.653	±	0.110	0.584	±	0.093	0.0000
Intertrochanteric BMD (g/cm^2)	0.891	±	0.159	0.783	±	0.137	0.0000
Trochanteric BMD (g/cm^2)	0.562	±	0.102	0.488	±	0.085	0.0000
Calcaneal BMD (g/cm^2)	0.431	±	0.110	0.360	±	0.090	0.0000

Table 3. Factors identified for first hip fracture using threshold regression model with Wiener diffusion process (N = 5,336, number of hip fractures = 361 hip fracture cases).

Variable	Coef. (lny0)	Std. Err.	P-value
Age (years)	-0.0304	0.0029	0.000
Weight loss since age 25 (-10.2 kg)*	-0.0625	0.0173	0.000
Told by doctor have rheumatoid arthritis (Y/N)	-0.1479	0.0338	0.000
Fall in past 12 months (Y/N)	-0.1091	0.0334	0.001
Daily caffeine intake (+0.141 g/day)*	-0.0300	0.0150	0.045
Taken steroid past 12 months (Y/N)	-0.2500	0.0685	0.000
Constant	3.4164	0.2178	0.000
	Coef. (mu)	**Std. Err.**	**P-value**
Femoral neck BMD (-0.11 g/cm^2)*	-0.1166	0.0124	0.000
Prior fracture before age 50 (Y/N)	-0.0519	0.0206	0.012
Mother's history of fracture (Y/N)	-0.0611	0.0200	0.002
Constant	0.4373	0.0178	0.000

* per standard deviation decrease or increase for continuous variable

BMD: bone mineral density

Y/N : Yes vs. No

Table 4. Comparison of Exponential, Weibull and Cox models for first hip fracture (N = 5,336, number of hip fractures = 361).

Variable	Exponential		Weibull		Cox	
	Haz. Ratio	P-value	Haz. Ratio	P-value	Haz. Ratio	P-value
Age (years)	1.0844	0.000	1.0923	0.000	1.0961	0.000
Femoral neck BMD (-0.11g/cm^2)	2.0401	0.000	2.0737	0.000	2.0833	0.000
Weight loss since age 25 (-10.17kg)	1.0580	0.373	1.0605	0.354	1.0618	0.344
Prior fracture before age 50 (Y/N)	1.3538	0.005	1.3876	0.003	1.3964	0.002
Mother's history of fracture (Y/N)	1.3350	0.007	1.3441	0.006	1.3504	0.005
Fall in past 12 months (Y/N)	1.1445	0.237	1.1418	0.246	1.1376	0.260
Told by doctor have arthritis (Y/N)	1.1952	0.113	1.1970	0.110	1.1976	0.109
Daily caffeine intake (+0.141g/day)	1.0830	0.122	1.0779	0.146	1.0768	0.151
Taken steroid past 12 months (Y/N)	1.1615	0.540	1.1909	0.475	1.1840	0.490
/ln_p			0.1973	0.000		
p, shape parameter			1.2181			
1/p			0.8210			

* per standard deviation decrease or increase for continuous variable

BMD: bone mineral density

Y/N: Yes vs. No

Table 5. Proportional Hazards Assumption tests for predictors in the Cox model.

PH test for risk factors in the Cox model	Chi2	P-value
Age (years)	0.02	0.8781
Femoral neck BMD (-0.11g/cm^2)*	1.63	0.2013
Weight loss since age 25 (-10.17kg)*	0.00	0.9708
Prior fracture before age 50 (Yes vs. No)	0.02	0.8906
Mother's history of fracture (Yes vs. No)	0.73	0.3921
Fall in past 12 months (Yes vs. No)	1.66	0.1977
Told by doctor have rheumatoid arthritis	0.25	0.6138
Daily caffeine intake (+0.141g/day)*	0.56	0.4543
Taken steroid past 12 months (Yes vs. No)	0.72	0.3963
Global test	**5.97**	**0.7426**

* per standard deviation decrease for continuous variable

Table 6. A comparison of Cox versus Exponential and Weibull models for measures of discrimination.

	Cox	95% CI	Exponential	95% CI	Weibull	95% CI
R^2	48.51	(42.30, 57.06)	46.01	(39.65, 54.34)	47.92	(41.50, 56.39)
D statistic	1.639	(1.550, 1.728)	1.535	(1.450, 1.620)	1.610	(1.523, 1.697)
Harrell's c	0.7729	(0.7488, 0.7970)	0.7729	(0.7487, 0.7970)	0.7729	(0.7488, 0.7971)

Table 7. A comparison of AUCs at 5 and 10 years: Cox versus exponential and Cox versus Weibull models for first hip fracture.

AUC comparison	Cox	95% CI	Exponential	95% CI	p-value	Weibull	95% CI	p-value	N=5336
Year 5	0.7883	(0.7540, 0.8226)	0.7886	(0.7544, 0.8229)	0.65	0.7885	(0.7543, 0.8228)	0.39	Ne=151
Year 10	0.7596	(0.7297, 0.7895)	0.7599	(0.7299, 0.7899)	0.56	0.7598	(0.7305, 0.7891)	0.35	Ne=254

AUC: area under the curve

CI: confidence interval

N: total sample size

Ne: no. of events (hip fractures)

Table 8. An illustration showing the random division of data into 10 mutually exclusive subsets of equal size for use in 10-fold cross validation.

First Hip Fracture	10 quantiles of uniform()								Total
	1	2	3	4	5	6	7	8	
no	505	506	509	509	510	515	514	504	5,082
yes	29	28	24	25	23	19	20	29	254
Total	534	534	533	534	533	534	534	533	5,336

First Hip Fracture	10 quantiles of uniform()		Total
	9	10	
no	500	510	5,082
yes	34	23	254
Total	534	533	5,336

Table 9. Ten-fold cross validation AUC results: Weibull and exponential models for first hip fracture.

Year	Exponential	95% CI	Weibull	95% CI	p-value
5	0.7804	(0.7453, 0.8156)	0.7795	(0.7442, 0.8148)	0.17
10	0.7542	(0.7239, 0.7844)	0.7544	(0.7242, 0.7846)	0.58

AUC: area under the curve

CI: confidence interval

FIGURES

Figure 1. Kaplan-Meier survival function for first hip fracture.
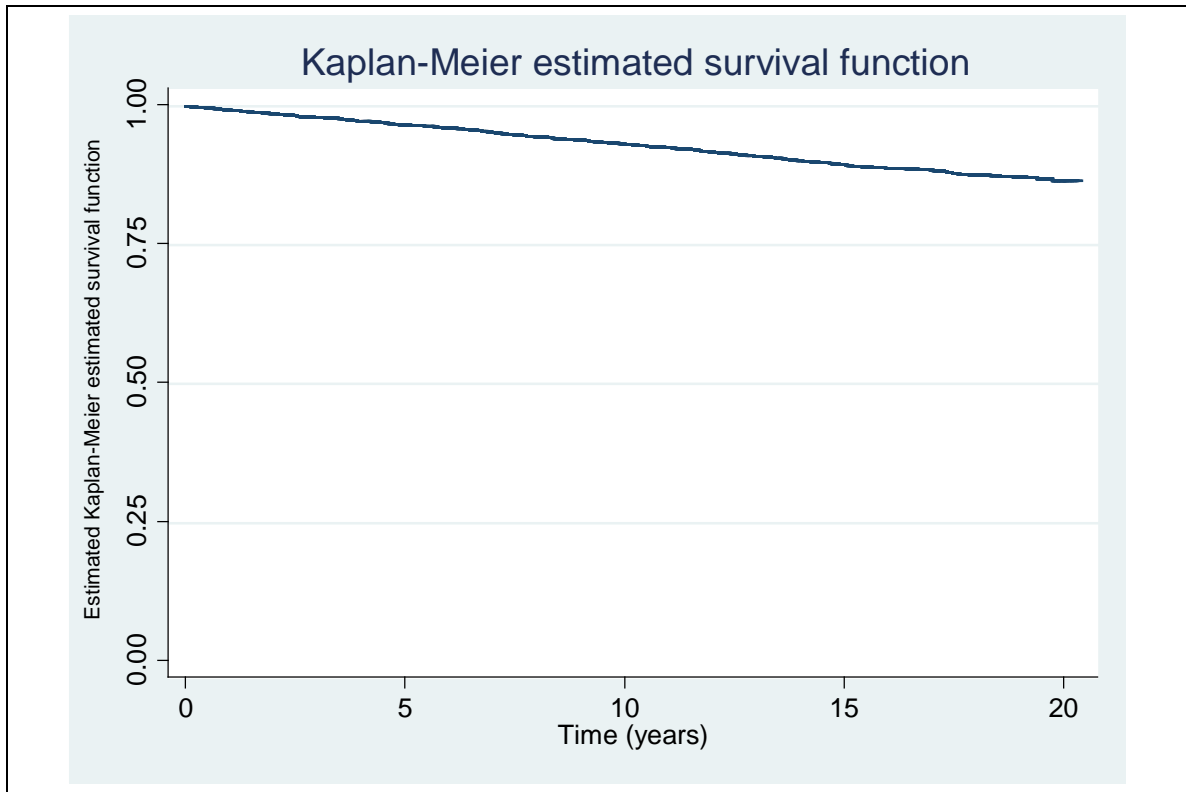
Figure 2. Kaplan-Meier survival function plots for categorical predictors—maternal fracture, history of falls in the past 12 months, presence or absence of rheumatoid arthritis and current intake of glucocorticoid (steroid).
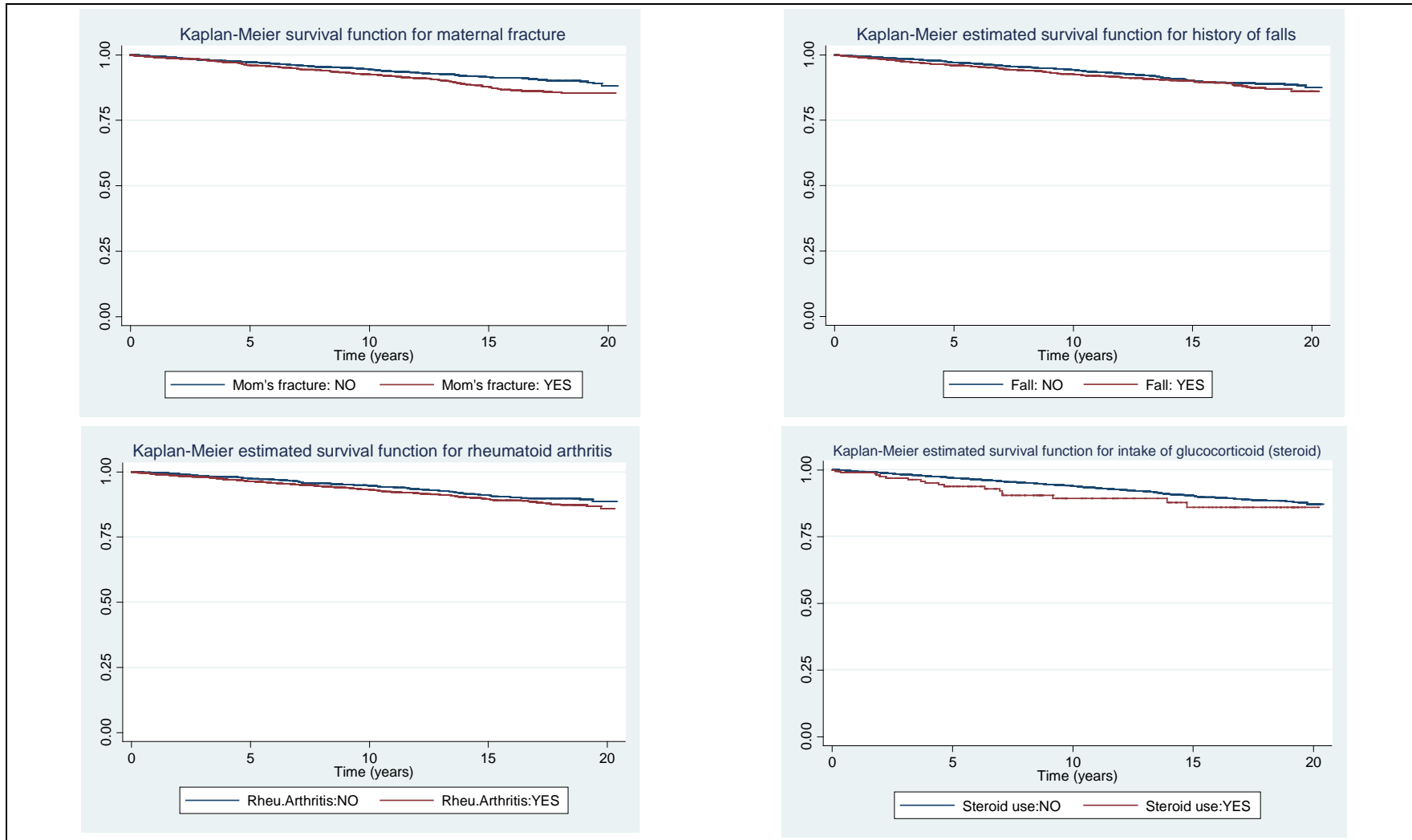
Figure 3. A comparison of estimated Cox versus exponential and Weibull baseline survival plots.
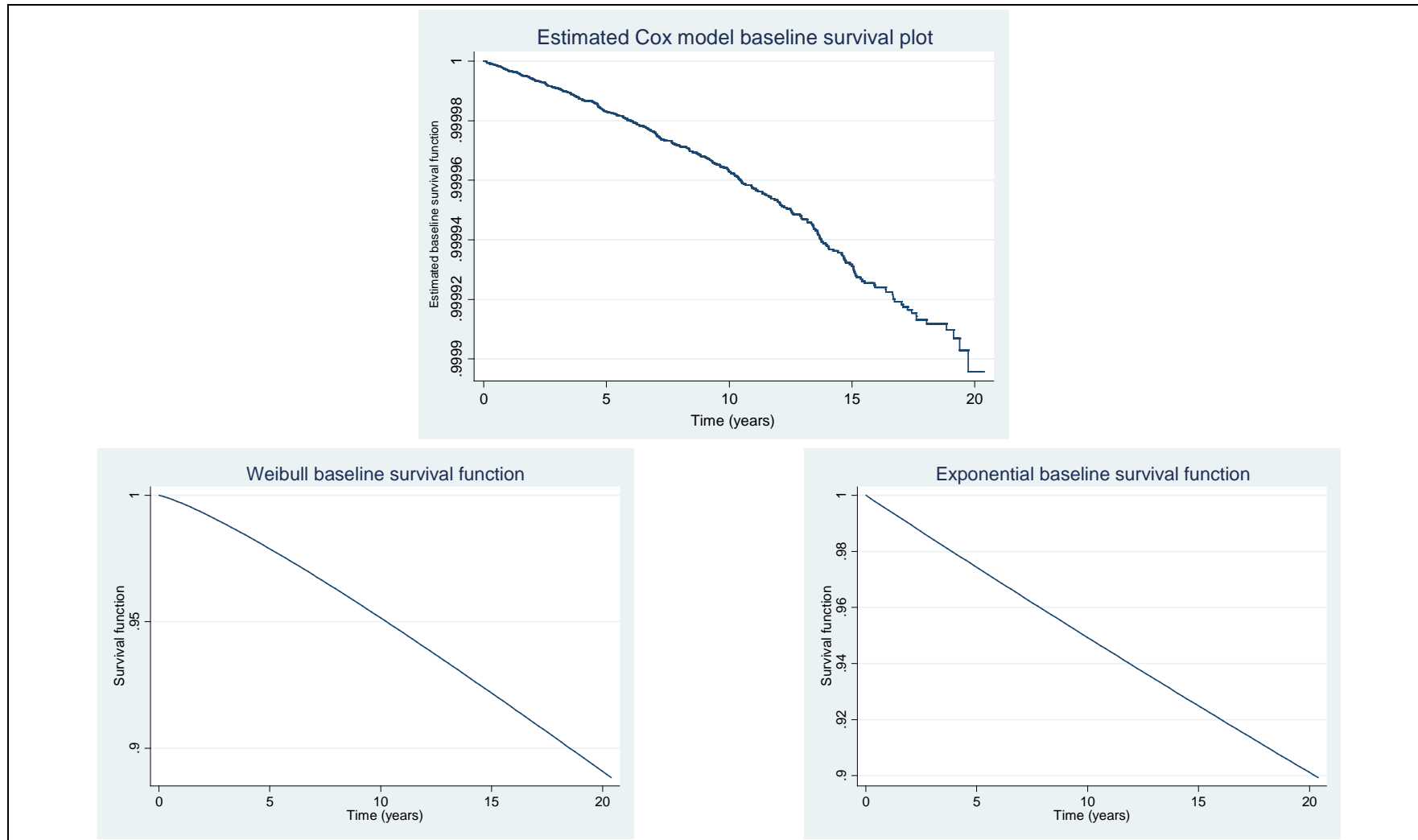
Figure 4. A comparison of estimated Cox versus exponential and Weibull cumulative hazard plots.
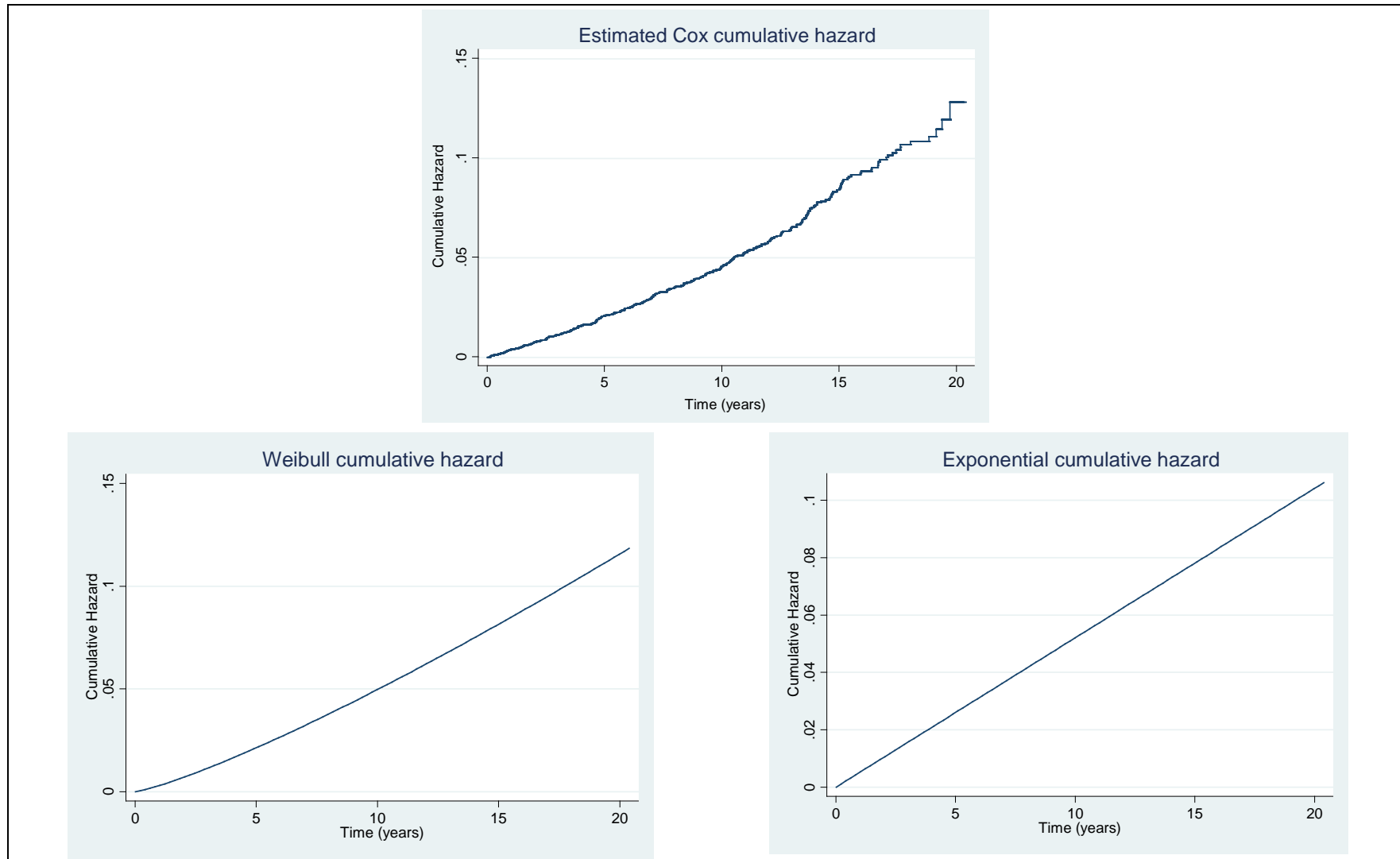
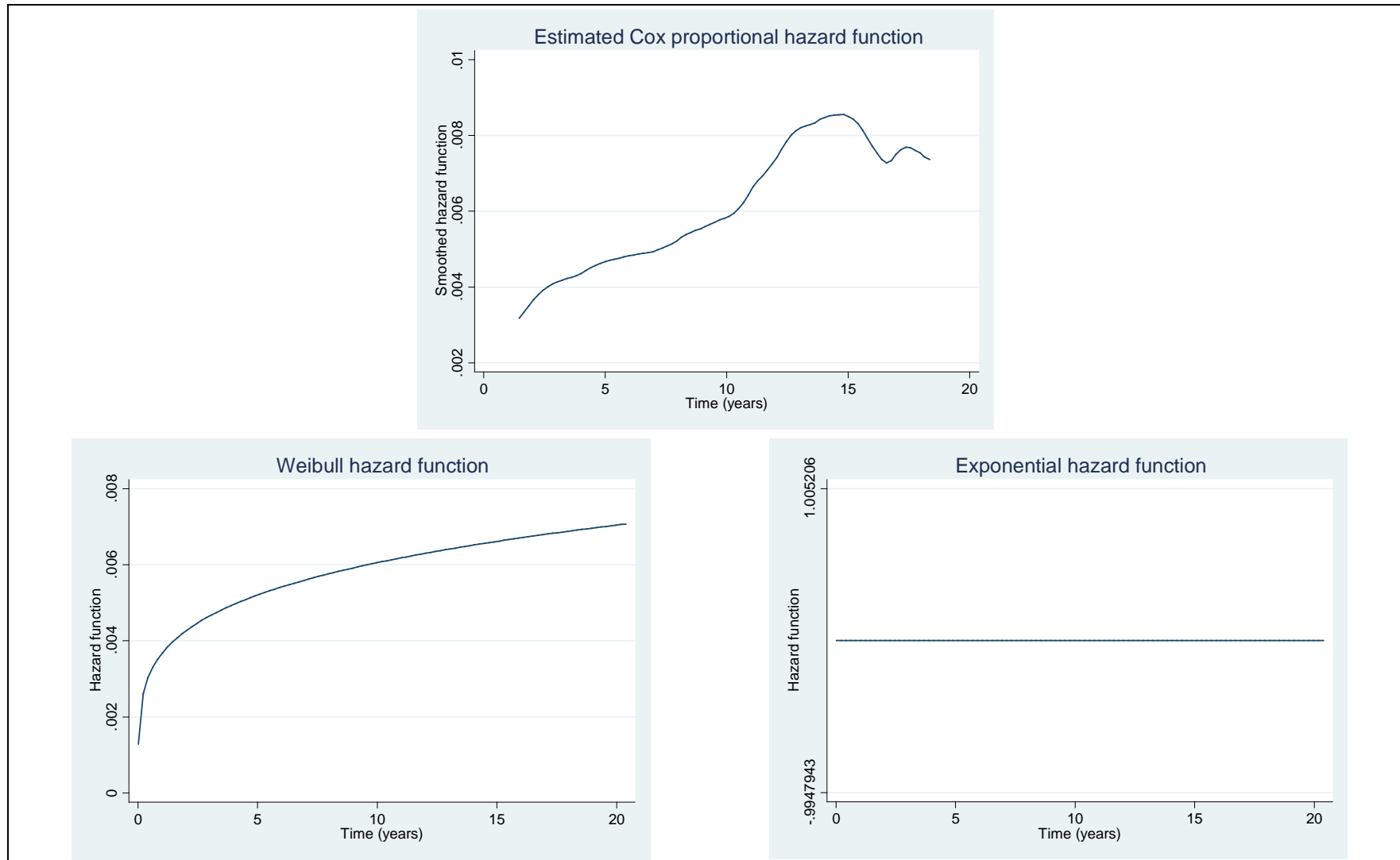**Figure 5.** A comparison of estimated Cox versus exponential and Weibull hazard plots.

Figure 6. A comparison of cumulative hazard of Cox-Snell residuals plot for Cox versus exponential and Weibull models.
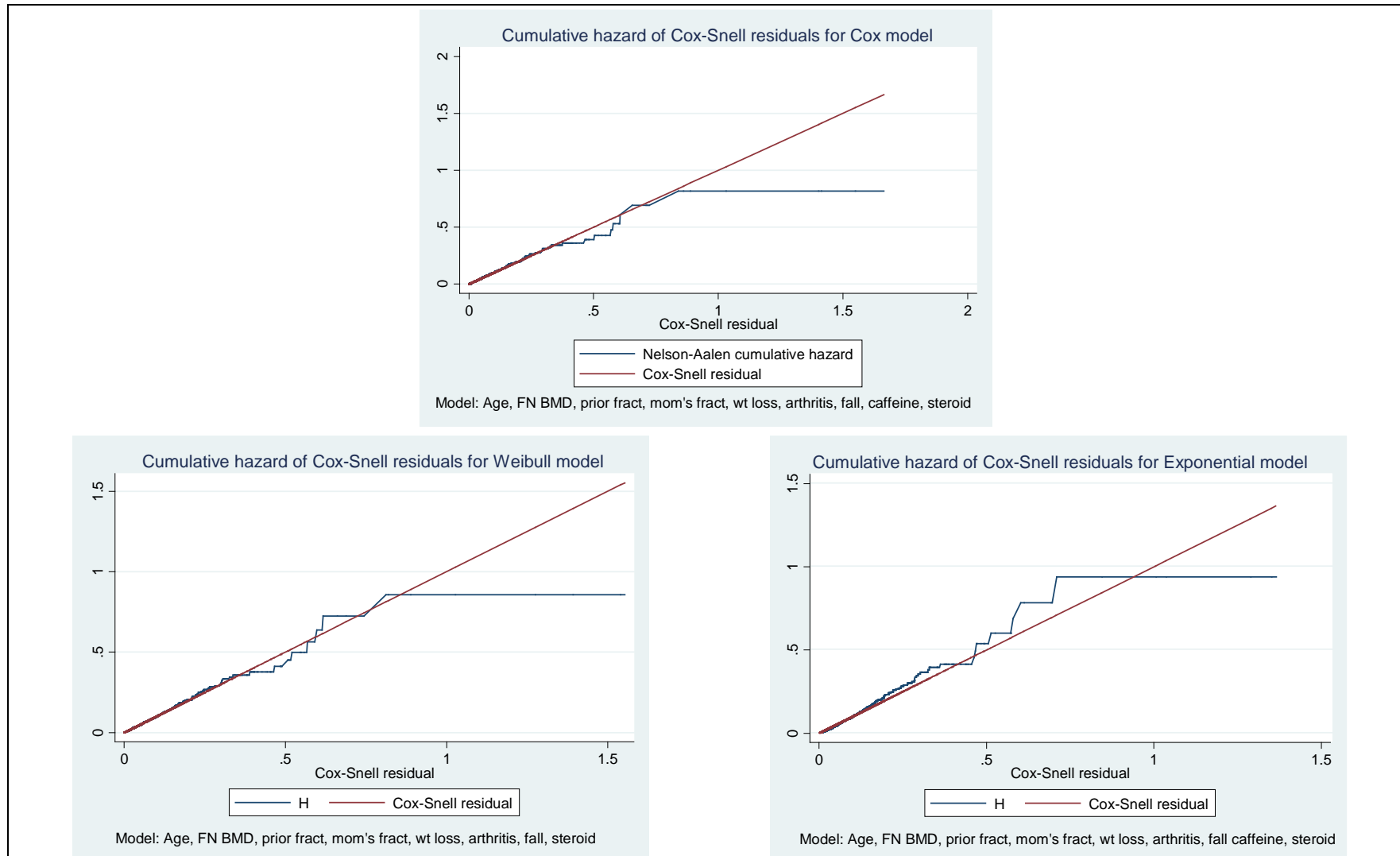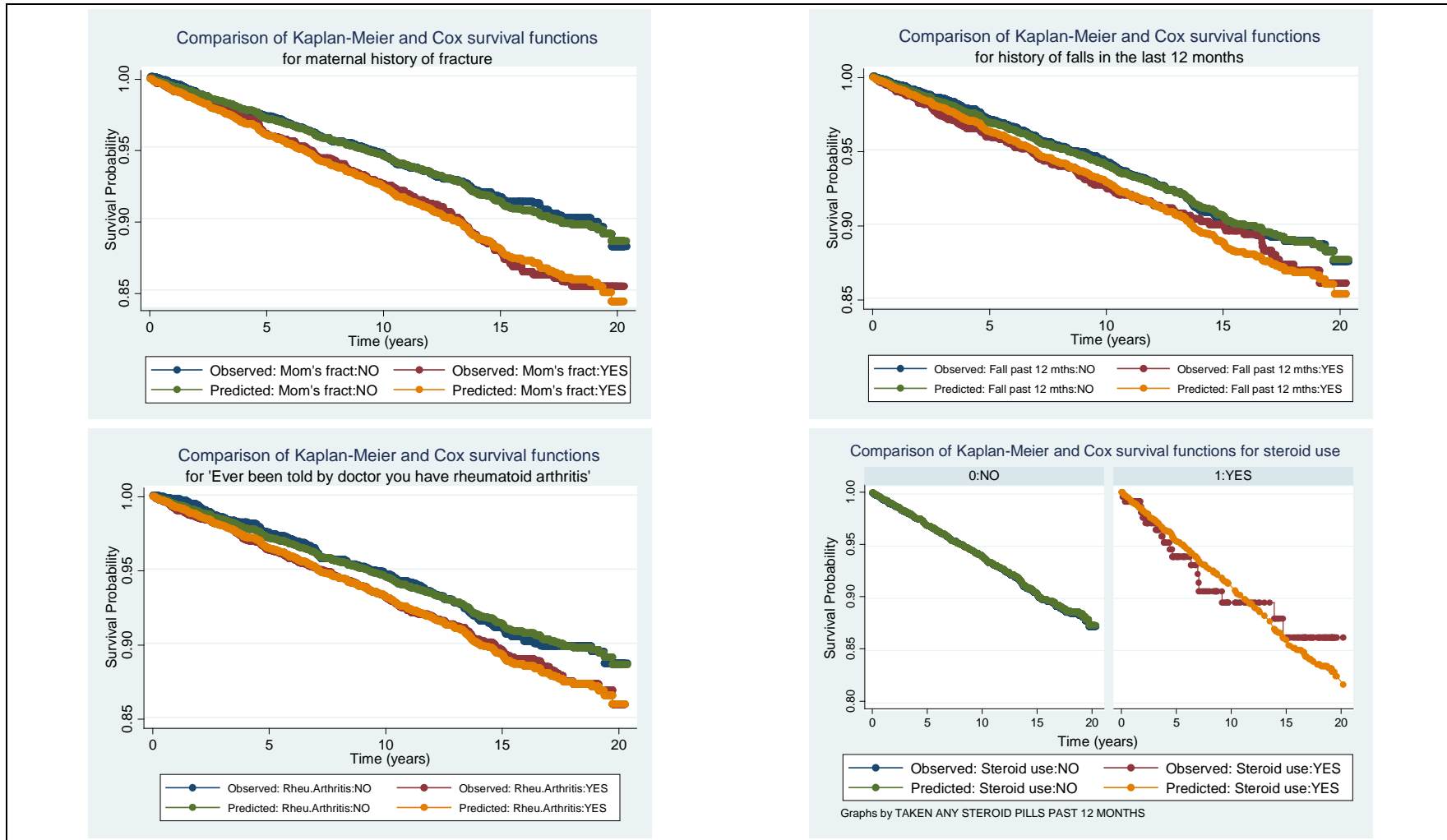
Figure 7. A comparison of Kaplan-Meier and Cox survival functions for binary predictors—maternal fracture, history of falls in the past 12 months, presence or absence of rheumatoid arthritis and current intake of glucocorticoid (steroid).

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