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A Novel Risk Score to the Prediction of 10-year Risk for Coronary Artery Disease Among the Elderly in Beijing Based on Competing Risk Model

Long Liu, MD, Zhe Tang, BA, Xia Li, MD, PhD, Yanxia Luo, MD, PhD, Jin Guo, MD, PhD, Haibin Li, MD, Xiangtong Liu, MD, PhD, Lixin Tao, MD, PhD, Wei Wang, PhD, Aoshuang Yan, MD, PhD, and Xiuhua Guo, MD, PhD

Abstract: The study aimed to construct a risk prediction model for coronary artery disease (CAD) based on competing risk model among the elderly in Beijing and develop a user-friendly CAD risk score tool.

We used competing risk model to evaluate the risk of developing a first CAD event. On the basis of the risk factors that were included in the competing risk model, we constructed the CAD risk prediction model with Cox proportional hazard model. Time-dependent receiver operating characteristic (ROC) curve and time-dependent area under the ROC curve (AUC) were used to evaluate the discrimination ability of the both methods. Calibration plots were applied to assess the calibration ability and adjusted for the competing risk of non-CAD death. Net reclassification index (NRI) and integrated discrimination improvement (IDI) were applied to quantify the improvement contributed by the new risk factors. Internal validation of predictive accuracy was performed using 1000 times of bootstrap re-sampling.

Of the 1775 participants without CAD at baseline, 473 incident cases of CAD were documented for a 20-year follow-up. Time-dependent AUCs for men and women at $t = 10$ years were 0.841 [95% confidence interval (95% CI): 0.806–0.877], 0.804 (95% CI: 0.768–0.839) in Fine and Gray model, 0.784 (95% CI: 0.738–0.830), 0.733 (95% CI: 0.692–0.775) in Cox proportional hazard model. The competing risk model was significantly superior to Cox proportional hazard model on discrimination and calibration. The cut-off values of the risk score that marked the difference between low-risk and high-risk patients were 34 points for men and 30 points for women, which have good sensitivity and specificity.

A sex-specific multivariable risk factor algorithm-based competing risk model has been developed on the basis of an elderly Chinese cohort, which could be applied to predict an individual's risk and provide a useful guide to identify the groups at a high risk for CAD among the Chinese adults over 55 years old.

(*Medicine* 95(11):e2997)

Abbreviations: AUC = area under the ROC curve, BLSA = Beijing Longitudinal Study on Aging, BMI = body mass index, CAD = coronary artery disease, CHD = coronary heart disease, CI = confidence interval, CKD = chronic kidney disease, CVDs = cardiovascular diseases, ECG = electrocardiogram, FHS = Framingham Heart Study, FRS = Framingham Risk Score, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, IDI = integrated discrimination improvement, LDL-C = low-density lipoprotein cholesterol, MONICA = monitoring cardiovascular disease, NRI = net reclassification index, ROC = receiver operating characteristic, SBP = systolic blood pressure, SD = standard deviation, TC = total cholesterol.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death for both men and women worldwide. An estimated 17.5 million people died from CVDs in 2012, which accounts for 31% of all global deaths.[1] In the last 30 years, the rapid development of economy and medical science in China has led to a drastic improvement in public health infrastructure; however, cardiovascular relevant morbidity and mortality in Chinese population still rose quickly, an estimated 290-million Chinese adults have CVDs in 2013.[2] Coronary artery disease (CAD) including stable and unstable angina, myocardial infarction, and coronary death is the largest contributor to the CVDs death, which is also called coronary heart disease (CHD).[3] CAD is the second leading cause of death in China, representing 22% of cardiovascular deaths in urban areas and 13% in rural areas for Chinese population.[4,5]

As it is well known, age is the main risk factor for certain diseases such as cancer, CAD, and neurodegeneration.[6] Beijing entered an aging society in 1990, and the general population of Beijing had reached 12.3 million by the end of 2008, with the number of population aged over 60, over 65, and over 80 years being 2.18, 1.62, and 0.29 million, respectively, making up 17.7%, 13.2%, and 2.4% of the general population.[7] Although

many epidemiologic studies had built the risk prediction model for CAD, for example, Framingham Heart Study (FHS), the Score project, CMCS cohort study, the Suita study, the Globorisk study,[8–12] there was no risk prediction model of CAD for the elderly, especially in China. Many other studies have found CAD-related risk factors, such as age, blood pressure, and etc., which can provide us reference to build the risk prediction model of CAD.[11–16] In addition, a few CAD risk prediction models included marital status; however, some studies confirmed that marital status was an important CAD risk prediction factor.[17,18]

From the methodology point of view, most studies on CAD risk assessment are based on Logistic regression models, Weibull, or Cox proportional hazard models.[11,12,19–21] However, in certain situations, applying the commonly used survival analysis methods may not be appropriated. In time-to-event analysis, the occurrence of the interested event is often precluded by another event, that is, competing event, and the usual survival analysis methods for the assessment of covariates in such data would lead to incorrect and biased results.[22–24] To overcome these problems, Fine and Gray competing risk model is available in the presence of competing events.[25] The competing risk model not only takes into account the events of interest but also considers competing events, when exist competing events, the cumulative incidence function is estimated by all type of events.[26] Competing risks methodology is being increasingly applied to risk prediction of diseases.[27] In this study, the interested outcome event was CAD events, and death from non-CAD events were considered as competing events.

The aims of present study were to construct a CAD risk prediction model with relevant risk factors on the basis of competing risk model among the elderly population in Beijing and develop an efficient CAD risk score tool.

METHODS

Study Design and Population

Participants were selected from the BLSA (Beijing Longitudinal Study on Aging) community-based cohort study from 1992 to 2012, hosted by Xuanwu Hospital in Beijing, China. To ensure the representativeness of the older adults in Beijing, a 3-stage stratification random clustering procedure was determined, which was described in details elsewhere.[28,29] In the present study, participants with a history of angina pectoris and acute myocardial infarction at baseline were excluded. There were 326 participants who were excluded in this study. The included participants in final analysis were 886 men and 889 women between 55 and 96 years without CAD events at baseline. By the end of follow-up (2012), there were 473 participants who developed CAD events, 693 died from non-CAD events. Multiple imputation (MI) method was applied to impute the missing information on biochemical measurements. This research was approved by ethic committees of Xuanwu Hospital Capital Medical University and written informed consent was given to each participant.

Measurement of CAD Risk Factors

The procedures of CAD risk factors measurement had been reported elsewhere.[16,30] Factors such as age, smoking, and marital status used in this study were assessed by the questionnaires with a high degree of reliability and accuracy. Age was used as a continuous variable. Cigarette smoking was ascertained by self-report. Marital status was grouped into 2 levels: have a spouse or mate-less. The average of the blood

pressure measurements was recorded after blood pressure was measured twice on the left arm of the seated participants with a mercury sphygmomanometer and an appropriately sized cuff. The ratio of weight to height squared was used to calculate body mass index (BMI). Weight and height were determined by the standardized anthropometric measurements during routine examinations. Participants in our study were divided into 2 BMI groups: normal (<24 kg/m^2), overweight or obesity (≥24 kg/m^2). Biochemical measures of total cholesterol (TC, mg/dL) and high-density lipoprotein cholesterol (HDL-C, mg/dL) levels were determined with standardized enzymatic methods.[11] Diabetes was defined as fasting blood glucose ≥7.0 mmol/L or postprandial blood glucose ≥11.1 mmol/L or use insulin or oral hypoglycemic medications.

Clinical Outcomes

In the present study, the eight waves of investigations were conducted in 1992, 1994, 1997, 2000, 2004, 2007, 2009, and 2012, respectively. The surveys were conducted face-to-face in the respondents' homes or interviewed by telephone. All interviewers had got standardized training before the study started. CAD events were defined as angina pectoris, acute myocardial infarction, and coronary deaths in this study. Information about first diagnosis of participants' CAD events during follow-up was obtained with the aid of in-hospital medical records, physical examination reports, death medical certificates, and communication during the interview. To ensure diagnostic validity, all suspected CAD events were reviewed by a panel of 3 experienced investigators including 2 cardiologists who evaluated all medical records. In addition, we also carried out a systematic search for fatal cases through death medical

TABLE 1. Characteristics of Participants for Men and Women at Baseline

Characteristics	Men (n = 886)	Women (n = 889)	T/χ²/Z	P
Age, mean (SD), yrs	70.22 (8.35)	69.70 (8.70)	1.28	0.202
TC (mg/dL), n (%)			−5.95	<0.001
<200	729 (82.28)	625 (70.30)		
200–239	118 (13.32)	192 (21.60)		
≥240	39 (4.40)	72 (8.10)		
HDL-C (mg/dL), n (%)			−1.99	0.047
<35	73 (8.24)	63 (7.09)		
35–59	516 (58.24)	489 (55.01)		
≥60	297 (33.52)	337 (37.91)		
Smoking, n (%)	438 (49.44)	160 (18.00)	196.32	<0.001
Diabetes, n (%)	70 (7.90)	64 (7.20)	0.31	0.576
Marital status (mate-less), n (%)	316 (35.67)	334 (37.57)	0.69	0.405
BMI (kg/m²), n (%)			30.82	<0.001
Normal	565 (63.77)	451 (50.73)		
Overweight/Obesity	321 (36.23)	438 (49.27)		
Blood pressure, n (%)			−2.49	0.013
Normal	378 (42.66)	333 (37.46)		
Stage-1 hypertension	265 (29.91)	278 (31.27)		
Stage-2 hypertension	151 (17.04)	157 (17.66)		
Stage-3 hypertension	92 (10.38)	121 (13.61)		
Incident CAD events, n (%)	207 (23.36)	266 (29.92)		

BMI = body mass index, CAD = coronary artery disease, HDL-C = high-density lipoprotein, SD = standard deviation, TC = total cholesterol.

TABLE 2. Characteristics of Participants between with CAD Event and Without CAD Event for Men and Women at Baseline

Characteristics	Men (n = 886)				Women (n = 889)			
	Non-CAD Events	CAD Events	$T/\chi2/Z$	P	Non-CAD Events	CAD Events	$T/\chi^2/Z$	P
Age, mean (SD), yrs	70.08 (8.60)	70.68 (7.48)	−0.91	0.818	69.20 (8.91)	70.88 (8.10)	−2.65	0.996
TC (mg/dL), n (%)			−4.00	<0.001	450 (72.00)	175 (28.00)	−1.96	0.051
<200	578 (79.29)	151 (20.71)			127 (66.15)	65 (33.85)		
200−239	76 (64.41)	42 (35.59)			46 (63.89)	26 (36.11)		
≥240	25 (64.10)	14 (35.90)			623 (70.08)	266 (29.92)		
HDL-C (mg/dL), n (%)			2.82	0.005			3.06	0.002
<35	53 (72.60)	20 (27.40)			38 (60.32)	25 (39.68)		
35−59	381 (73.84)	135 (26.16)			330 (67.48)	159 (32.52)		
≥60	245 (82.49)	52 (17.51)			255 (75.67)	82 (24.33)		
Smoking, n (%)	301 (68.72)	137 (31.28)	30.31	<0.001	84 (52.50)	76 (47.50)	28.75	<0.001
Diabetes, n (%)	43 (61.43)	27 (38.57)	9.82	0.002	27 (42.190)	37 (57.81)	25.59	<0.001
Marital status (mate-less), n (%)	222 (70.25)	94 (29.75)	11.18	0.001	228 (68.26)	106 (31.74)	0.84	0.359
BMI (kg/m², n (%)								
Normal	459 (81.24)	106 (18.76)	18.45	<0.001	341 (75.61)	110 (24.39)	13.36	<0.001
Overweight/Obesity	220 (68.54)	101 (31.46)			282 (64.380)	156 (35.62)		
Blood pressure, n (%)			−3.53	<0.001			−4.00	<0.001
Normal	311 (82.28)	67 (17.72)			256 (76.88)	77 (23.12)		
Stage-1 hypertension	196 (73.96)	69 (26.04)			195 (70.14)	83 (29.86)		
Stage-2 hypertension	109 (72.19)	42 (27.81)			98 (62.42)	59 (37.58)		
Stage-3 hypertension	63 (68.48)	29 (31.52)			74 (61.160)	47 (38.84)		

BMI = body mass index, CAD = coronary artery disease, HDL-C = high-density lipoprotein, SD = standard deviation, TC = total cholesterol.

certificates, in-hospital medical records, and interviewed surviving household members. For the diagnosis of stable angina and unstable angina pectoris, it was mainly from the history of heart disease, clinical signs and symptoms, biochemical examination, and ECG (electrocardiogram) examination according to ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina and ACC/AHA guidelines for the management of patients with unstable angina, especially the ECG during angina pectoris attacking.[31,32] Acute myocardial infarction was diagnosed according to the criteria used for the MONICA (monitoring CVD) Project of the World Health Organization when the patients had at least 2 of the following 3 criteria: typical chest pain for myocardial ischemia, initial and serial conventional electrocardiographic changes in standard or precordial leads, and enzymatic evidence of myocardial necrosis.[33,34] The diagnostic criteria of coronary death included sudden coronary death with 24 hours after the occurrence of acute symptoms or CAD followed by coronary artery bypass or angioplasty from the MONICA project. The targeted outcome was CAD events, and death from non-CAD events consisted of competing events by the end of follow-up.

Statistical Analysis

Sex differences were examined using Pearson Chi-square tests or Wilcoxon rank-sum tests for categorical variables and *t* tests for continuous variables. Fine and Gray model was used to establish the parsimonious model for CAD risk prediction, which was adjusted for background information (age, marital status, and smoking), anthropometric indicators (blood pressure, BMI), and biochemical variables (TC, HDL-C, and diabetes). In addition, due to sex-specific effects of diabetes,

smoking and TC on the risk of CAD were found among the Chinese adults in the previous study,[11] the final sex-specific Fine and Gray model included eight risk factors for CAD: age, TC, HDL-C, blood pressure, smoking, diabetes, marital status, and BMI. On the basis of the risk factors that were included in the competing risk model, we constructed the CAD risk prediction models on the basis of Fine and Gray model and Cox proportional hazard model separately, which were implemented by the stcrreg and stcox commands in STATA, respectively.

To evaluate the performance of prediction models, discrimination and calibration are the 2 essential aspects of evaluating predictive ability for prediction models.[35] In the present study, time-dependent receiver operating characteristic (ROC) curve and time-dependent area under the ROC curve (AUC) were used to evaluate the discriminative ability of competing risk model, which were implemented by the time ROC package of R.[36,37] The calibration plot was used to observe the outcome by decile of predictions, to compare the mean predicted probability with the mean observed outcome.[38] The more spread between the deciles, the better discriminating model. Internal validation techniques were advocated to evaluate the potential on overfitting and optimism for prediction model.[35] In this study, internal validation of predictive accuracy was performed using 1000 times of bootstrap re-sampling. The difference between the AUC estimated from using the original data and the AUC estimated from the bootstrap re-sample was considered as a measure of optimism. The bootstrap optimism-corrected AUC was computed by subtracting the optimism from the original AUC. Bootstrap-adjusted regression coefficients reflect better what can be expected when the model is tested or applied

TABLE 3. Comparison of Bootstrap-adjusted Regression Coefficients in Fine and Gray Model and Cox Proportional Hazard Model

Variable	Fine and Gray model		Cox Proportional Hazard Model	
	β*	P	β*	P
Men				
Age	0.03	0.001	0.07	<0.001
TC (mg/dL)				
<200	Reference			
200−239	0.45	0.017	0.41	0.028
≥240	0.84	<0.001	0.86	<0.001
Diabetes	0.57	0.007	0.46	0.032
Blood pressure				
Normal	Reference			
Stage-1 hypertension	0.42	0.016	0.55	0.003
Stage-2 hypertension	0.46	0.016	0.50	0.011
Stage-3 hypertension	0.72	0.001	0.99	<0.001
Smoking	0.78	<0.001	0.67	<0.001
HDL-C (mg/dL)				
<35	0.08	0.748	0.08	0.739
35−59	Reference			
≥60	−0.32	0.056	−0.26	0.122
BMI	0.59	<0.001	0.38	0.009
Marital status (mate-less)	0.47	0.001	0.42	0.004
Women				
Age	0.03	<0.001	0.06	<0.001
TC (mg/dL)				
<200	Reference			
200−239	0.43	0.002	0.43	0.003
≥240	0.47	0.012	0.48	0.016
Diabetes	0.99	<0.001	0.77	<0.001
Blood pressure				
Normal	Reference			
Stage-1 hypertension	0.17	0.262	0.21	0.199
Stage-2 hypertension	0.41	0.016	0.34	0.065
Stage-3 hypertension	0.54	0.006	0.69	<0.001
Smoking	0.83	<0.001	0.79	<0.001
HDL-C (mg/dL)				
<35	0.17	0.400	0.19	0.379
35−59	Reference			
≥60	−0.21	0.119	−0.26	0.065
BMI	0.38	0.004	0.28	0.030
Marital status (mate-less)	0.25	0.050	0.23	0.087

BMI = body mass index, HDL-C = high-density lipoprotein, TC = total cholesterol.
* Estimated regression coefficient.

FIGURE 1. Time-dependent ROC curves for CAD risk prediction models at $t = 10$ years. CAD = coronary artery disease, ROC = receiver operating characteristic.

NRI and IDI are the 2 new metrics for the formal assessment of new risk factors, to supplement the improvement in the AUC, which were evaluated using the R package of survIDINRI.

All statistical tests were 2-sided with a Type 1 error of 0.05 and probability values of <0.05 were considered statistically significant. Competing risk analysis was performed by STATA (Version14.0; Stata Corp LP, College Station, TX). Prediction measures and risk reclassification analysis were implemented in R (Version 3.1.3; R Foundation for Statistical Computing, Vienna, Austria).

FIGURE 2. Time-dependent AUC curves for CAD risk prediction models. AUC = area under the ROC curve, CAD = coronary artery disease.

in new individuals from the same theoretical source population.[35] We emphasize that no external validation methods can be substituted by internal validation.

The standard method measuring the improvement from the new risk factor for prediction was to use the AUC, but it may not be sensitive enough to capture the incremental improvements from the new risk factor. Recently, some novel substitutes to AUC, such as integrated discrimination improvement (IDI) and net reclassification improvement (NRI), were proposed.[39] The
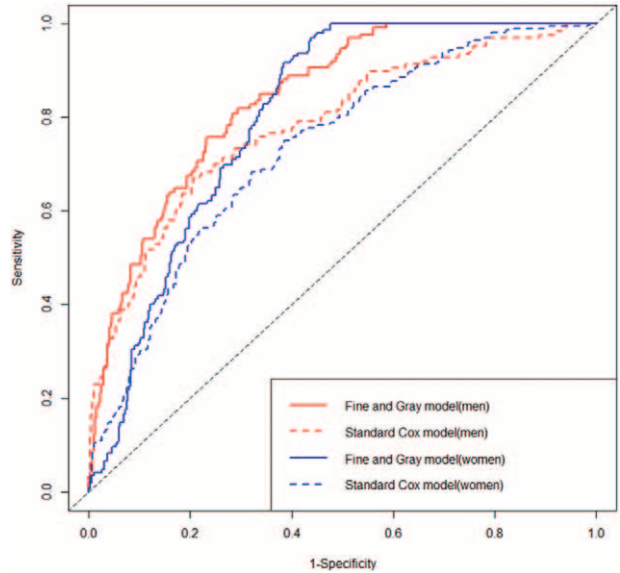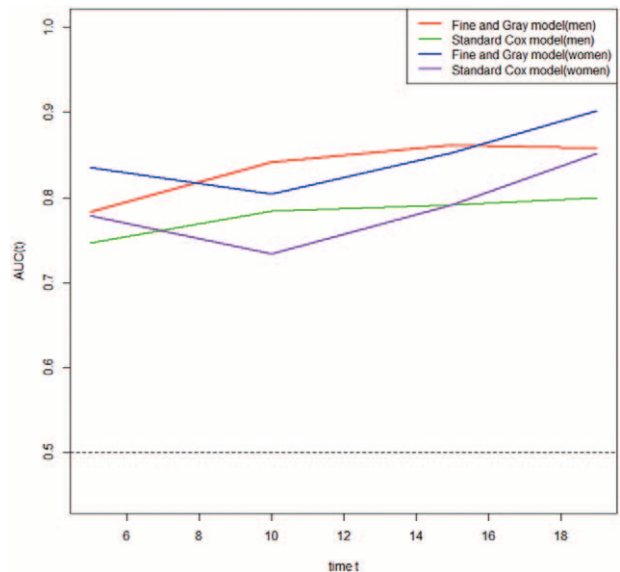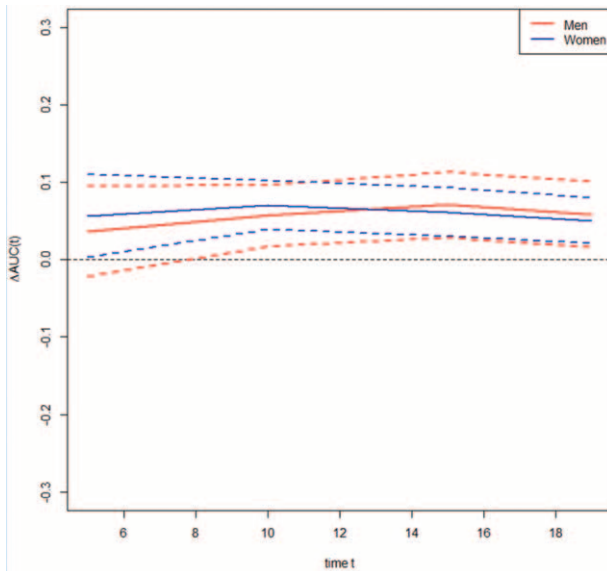
FIGURE 3. Time-dependent difference curves of AUC for CAD risk prediction models. AUC = area under the ROC curve, CAD = coronary artery disease.

RESULTS

Baseline Characteristics

We followed up 886 men and 889 women for a total of 17,008 person-years. During the follow-up, there were 473 participants who developed CAD events, 693 died from non-CAD events. The average age of women was 69.70 ± 8.70 years, and men were 70.22 ± 8.35 years at baseline. There were 207 (23.36%) men who developed CAD events, and 266 (29.92%) women who developed CAD events. There were sex differences in the prevalence of TC, HDL-C, blood pressure, smoking, and BMI ($P \leq 0.05$). The characteristics for men and women at baseline of this study are summarized in Table 1. HDL-C, smoking, diabetes, blood pressure, and BMI were found to have significant difference between participants with CAD event and without CAD event for men and women at baseline, respectively. TC and marital status were found to have significant difference between with CAD event and without CAD event only in men. Characteristics of the participants between with CAD event and without CAD event for men and women at baseline are provided in Table 2.

CAD Risk Prediction Models

The bootstrap-adjusted regression coefficients for Fine and Gray model and Cox proportional hazard model are presented in Table 3. Variables such as HDL-C (<35 mg/dL) for men, Stage-1 hypertension, and HDL-C (<35 mg/dL) for women in the competing risk model had no statistically significance, whereas the other variables had statistically significant relations to CAD event. There are less significant variables in Cox proportional hazard model than Fine and Gray model.

Discrimination, Calibration, and Reclassification

The Fine and Gray models performed better in terms of discrimination and calibration. Time-dependent AUC for men and women at $t = 10$-year were 0.841 (95% CI: 0.806−0.877),

0.804 (95% CI: 0.768−0.839) in Fine and Gray model, 0.784 (95% CI: 0.738−0.830), 0.733 (95% CI: 0.692−0.775) in Cox proportional hazard model (Figure 1). Time-dependent AUC values of the Fine and Gray model were better than Cox proportional hazard model for men and women (Figure 2). Time-dependent difference value of AUC was more than zero between Fine and Gray model and Cox proportional hazard model for men and women (Figure 3). The sex-specific calibration plots comparing predicted deciles of actual risk and predicted risk with both methods showed that the actual CAD risk in the BLSA cohort were similar to the predicted risk using Fine and Gray models (Figure 4). The paired difference of risk scores was used to evaluate the additional variable marital status. Figure 5 shows the empirical distribution function of the change in estimated risk score for participants who have events (thick solid line) and those who are event-free (thin solid line) for men and women. The difference between areas under 2 curves is IDI, and the distances between 2 black dots and between 2 gray dots are continuous NRI and median improvement, respectively. Estimations of IDI and NRI were 0.101 [95% confidence interval (95% CI): 0.041−0.156; $P < 0.0001$] and 0.306 (95% CI: 0.000−0.360; $P < 0.0001$) for men, 0.086 (95% CI: 0.037−0.128; $P < 0.0001$) and 0.290 (95% CI: 0.000−0.359; $P = 0.007$) for women, respectively. The median increment in the prediction model after including marital status was 0.108 (95% CI: 0.039−0.181; $P < 0.0001$) for men, and 0.085 (95% CI: 0.036−0.159; $P < 0.0001$) for women, respectively.

Internal Validation

After internal validation by bootstrapping, the optimism-corrected AUCs of the Fine and Gray models for men and women at $t = 10$ years were 0.825 (95% CI: 0.792−0.858), 0.788 (95% CI: 0.743−0.833), the optimism-corrected AUC of Cox proportional hazard model for men and women at $t = 10$ years were 0.761 (95% CI: 0.716−0.806), 0.715 (95% CI: 0.676−0.754), suggesting that the models were all well-validated.

CAD Risk Score Tools

We developed a sex-specific simple risk score tool to estimate the CAD risk for each individual on the basis of Fine and Gray competing risk model (Table 4). The cut-off values of the risk score that marked the difference between low-risk and high-risk patients were 34 points for men and 30 points for women. Sensitivity and specificity of the cut-off values were calculated, which were 0.75, 0.72 for men, and 0.82, 0.68 for women, respectively. These cut-off points can be recommended as indicators for CAD preventive treatment among the elderly Chinese.

DISCUSSION

We constructed a sex-specific multivariable risk prediction model that could be applied to predict an individual's CAD risk and provide a useful guide to identify the groups at a high risk for CAD among over 55 years old. In terms of discrimination and calibration, the competing risk model was found significantly superior to Cox proportional hazard model. The present study also extends and expands the previous general CAD risk formulation by adding a new risk factor; the prediction model including marital status was superior to the model without it. A user-friendly risk score tool predicting 10-year probability of CAD was developed on the basis of the prediction model.
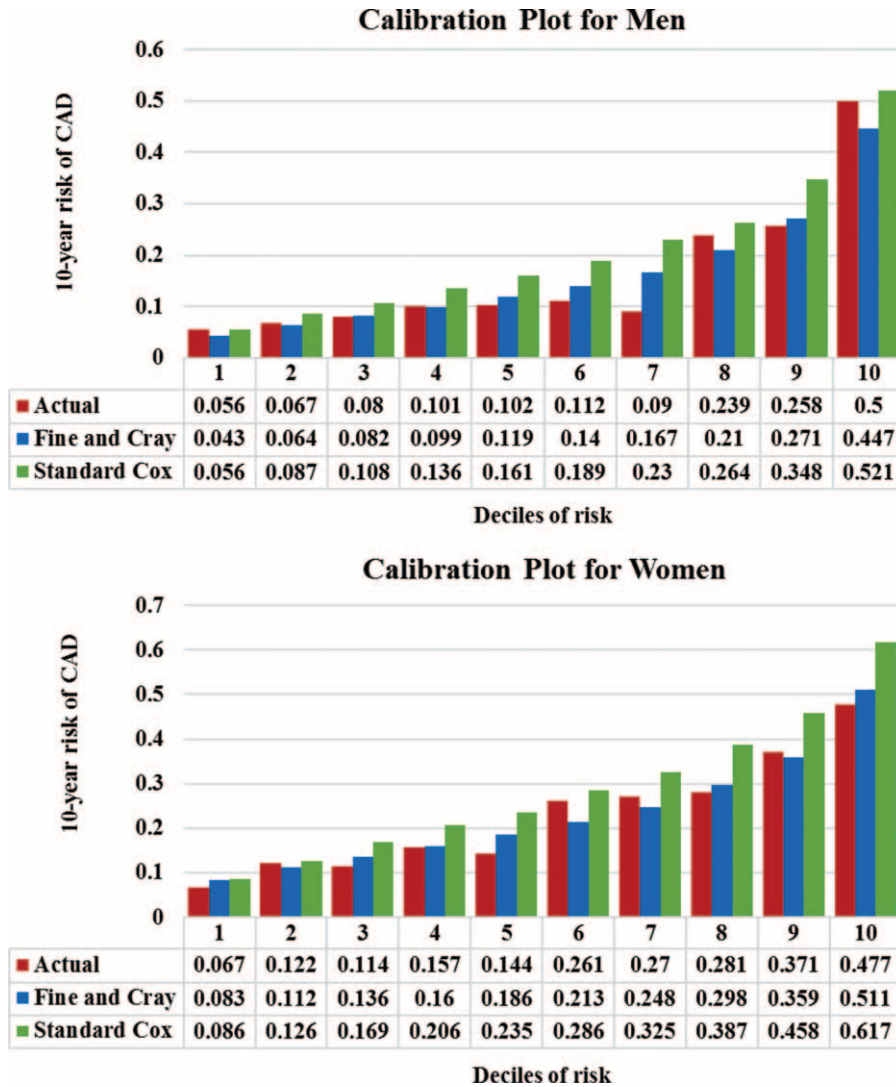
Calibration Plot for Men

Deciles of risk	1	2	3	4	5	6	7	8	9	10
Actual	0.056	0.067	0.08	0.101	0.102	0.112	0.09	0.239	0.258	0.5
Fine and Cray	0.043	0.064	0.082	0.099	0.119	0.14	0.167	0.21	0.271	0.447
Standard Cox	0.056	0.087	0.108	0.136	0.161	0.189	0.23	0.264	0.348	0.521

Calibration Plot for Women

Deciles of risk	1	2	3	4	5	6	7	8	9	10
Actual	0.067	0.122	0.114	0.157	0.144	0.261	0.27	0.281	0.371	0.477
Fine and Cray	0.083	0.112	0.136	0.16	0.186	0.213	0.248	0.298	0.359	0.511
Standard Cox	0.086	0.126	0.169	0.206	0.235	0.286	0.325	0.387	0.458	0.617

FIGURE 4. Calibration plots by decile for CAD risk prediction models, adjusted for the competing risk of non-CAD death. CAD = coronary artery disease.

Currently, the Framingham Risk Functions are the most widely used for clinical CAD guidelines; in addition, there are a number of other important risk functions.[40] Cross-sectional studies conducted in Kuwait adults provided a 10-year CAD risk based on the Framingham risk chart, which was built by Logistic regression model.[41] Among the studies, Framingham Risk Score (FRS) is used as a screening tool to estimate an individual's 10-year risk for developing hard CAD (myocardial infarction and CAD death). FRS is a sex-specific tool (a modified version of CAD risk prediction model from the FHS) that includes the individual's age, TC, systolic blood pressure (SBP), and other risk factors. Three risk categories are defined: low risk (<10%), moderate risk (10%–20%), and high risk (>20%).[42] However, cross-sectional studies could not reflect any changes over time that were to describe the relationship between diseases and other risk factors at a particular time. Among the cohort studies, CAD risk prediction model was conducted by Weibull or Cox proportional hazard models, and

clinical covariates, including age, gender, blood pressure, diabetes, smoking and BMI, have provided substantial predictive power for the risk of CAD.[43,44] QRISK2 CVD risk algorithm included ethnicity, age, sex, smoking status, SBP, HDL-C, BMI, and so on, which has improved the precision for identifying those with a high risk in a nationally representative population.[45] The finding of external validation for QRISK2 CVD risk score indicated that QRISK2 was more accurate for identifying the individuals who have a high risk of developing CVD in England than the NICE version of the Framingham equation.[46] Recently, a novel risk score to predict CVD (consisting of CAD and stroke) risk in national populations (Globorisk) was developed, including 50,129 participants when we construct Cox proportional hazards model. In the Globorisk study, the average age at baseline was 55 years (SD = 9) and one-third of eligible participants were women. The risk prediction model included smoking status, blood pressure, diabetes, and TC, and allowed the effects of gender and age on CVD to
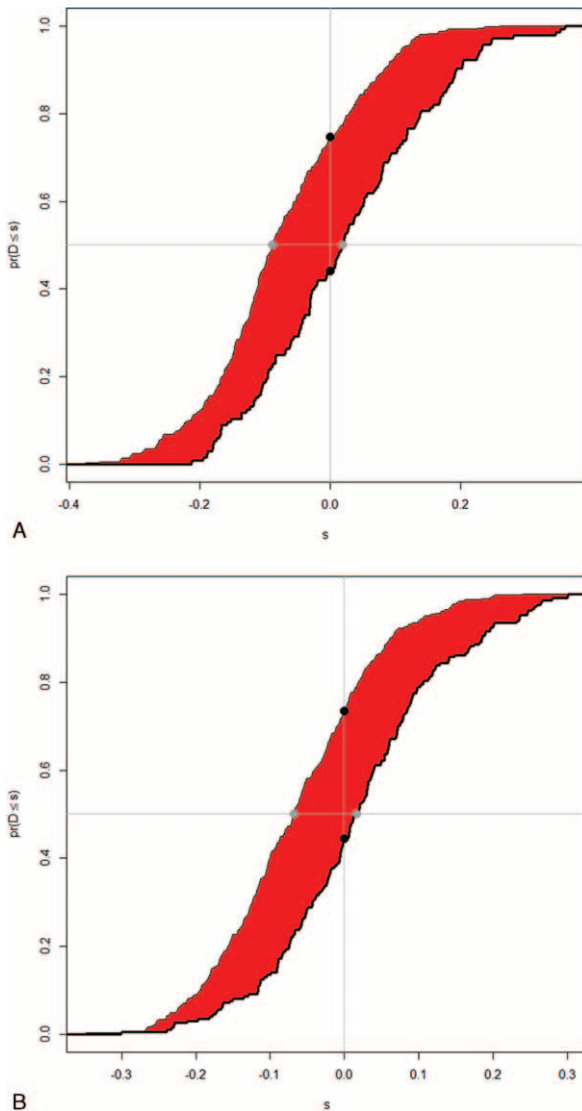
FIGURE 5. The assessment of additional variable marital status via the paired difference of risk scores for men (A) and women (B).

TABLE 4. The Sex-specific Risk Score Tool for CAD Based on Competing Risk Model Among the Elderly in Beijing

Risk Factor	Category	Points (Men)	Points (Women)
Age, yrs	55−59	17	18
	60−64	18	19
	65−69	20	21
	70−74	21	23
	≥75	24	25
Smoker	No	0	0
	Yes	8	8
Diabetes	No	0	0
	Yes	6	10
BMI	Normal	0	0
	Overweight/Obesity	6	4
Blood pressure	Normal	0	0
	Stage-1 hypertension	4	2
	Stage-2 hypertension	5	4
	Stage-3 hypertension	7	5
HDL-C (mg/dL)	<35	1	2
	35−59	0	0
	≥60	−3	−2
TC (mg/dL)	<200	0	0
	200−239	5	4
	≥240	8	5
Marital status	Have a spouse	0	0
	Mate-less	5	3

Men		Women	
Points Total	Estimated Risk	Points Total	Estimated Risk
≤20	0.037	≤20	0.075
21−25	0.061	21−25	0.116
26−30	0.095	26−30	0.184
31−35	0.149	31−35	0.278
36−40	0.236	36−40	0.394
41−45	0.345	41−45	0.572
46−50	0.514	46−50	0.765
>50	0.620	>50	0.821

BMI = body mass index, CAD = coronary artery disease, HDL-C = high-density lipoprotein, TC = total cholesterol.

vary between cohort and countries. A CVD risk model was developed, which could be applied in other countries by routinely available information after recalibration. In addition, Asian reports on a CAD prediction model are also available.[10,11,47] A study based on 268,315 Koreans between the ages of 30 and 74 years without CAD at baseline showed that age, blood pressure, smoking, diabetes, TC, and HDL-C predicted the CAD risk significantly. The optimal CAD model was created by adding HDL-C, LDL-C, and triglycerides to the basic CAD model, evaluating by the AUC and continuous NRI.[47] Another study composed of 5521 healthy Japanese, and during the follow-up, 213 cases of CAD events were observed. A multiple Cox proportional hazard model was used to construct the CAD risk prediction model by stepwise selection method. The Suita score including age, gender, diabetes, smoking, blood pressure, TC, LDL-C, HDL -C, chronic kidney disease (CKD) was more accurate for predicting CAD than the original FRS in

terms of the C-index and NRI.[10] Furthermore, in a study of 30,121 Chinese adults aged 35 to 64 years at baseline, Liu et al[11] constructed sex-specific risk prediction algorithms for 10-year risk of CAD, in which age, blood pressure, smoking, diabetes, TC, and HDL-C were included in the model. However, a prediction model specifically designed for CAD in Chinese elderly population has not been available, especially considering the competing risk. Our risk prediction model provided a feasible tool for identifying the high-risk individuals among the elderly in Beijing.

To our knowledge, this is the first CAD risk prediction model considering competing risks developed for an elderly population in China. Needs to be emphasized is that the current available general model evaluation method for CAD is not applicable for competing risk model. The merits of the CAD risk prediction model we created in this study include time-dependent ROC curves, time-dependent AUC, calibration plots,

NRI, and IDI, which adjusted for the competing risk of non-CAD death.

Limitations of the Study

First, we included only the convenient risk factors for CAD, but did not include psychosocial factors. Psychosocial factors as an important risk factor of CAD have been confirmed in some studies.[48–50] Two separate meta-analyses focused on depression and anxiety have found that depression is a significant and independent risk factor for the development of cardiac disease [hazard ratio (HR) = 1.60; 95% CI: 1.34–1.92],[49] and anxious persons are at a higher risk of suffering CAD (HR = 1.26; 95% CI: 1.15–1.38).[50] Second, external validation is the key process for prediction models that need to be generalized to different populations. A lack of an independent elderly population in China for external validation may not provide an accurate estimate for the model performance, due to that the internal validation used in this study might overoptimize the model-fitting measures. Third, the changes in the level of risk factors that were used to construct the competing risk model were not taken into account during the follow-up; only the data at baseline were used for building the risk prediction model. Four, due to the longitudinal nature of the cohort study, follow-up bias could not be avoided. A few values from biochemical measurements were missing, and thus MI method was applied to impute the missing biochemical information.

In summary, the simple points-based clinical models were constructed for predicting 10-year risk of developing CAD based on competing risk model among the elderly in Beijing. The user-friendly risk score tools could help identify the individuals who have a high risk of developing CAD and improve the strategies on prevention and treatment for the older adults in Beijing.

ACKNOWLEDGMENT

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