# Incremental Prognostic Value of Ankle-Brachial Index in High Atherosclerosis Risk Patients: Prediction model assessment on ABILITIES Study

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## Abstract

# Background

Previous studies have demonstrated association between ankle–brachial index (ABI) and cardiovascular disease (CVD), and confirmed patients with high atherosclerotic risk (AR) had worse prognosis. But after controlling traditional risks, the prognostic value of ABI with all-cause mortality and CVD-cause mortality remains unclarified, especially lack of prediction model assessment.

# Methods

2988 valid participants were separated into 0-0.40, 0.41–0.89, 0.90–0.99, and 1.00-1.40 four ABI subgroups, and followed up by six year. Factors related to all-cause mortality and CVD-cause mortality were observed by multivariate Cox regression analysis, log-rank test and nomogram. Restricted cubic splines (RCS) were used to explore relationship with ABI and mortality. Incremental discrimination was evaluated by net reclassification index (NRI), integrated discrimination improvement (IDI), and decision curve analysis (DCA).

# Results

RCS and Kaplan–Meier survival curve all manifested abnormal ABI levels increased mortality. Compare with normal value, among 0-0.40 and 0.41–0.89 subgroup, adjusted HR of all-cause mortality was 2.12, 95% CI (1.63–3.17), and 2.06, 95% CI (1.35–2.90), respectively. HR of CVD-cuase mortality was 2.39, 95% CI (2.41–3.09), and 2.29, 95% CI (1.83–2.87), respectively. RCS presented reverse J-shaped relationship with ABI and mortality. Nomogram indicated ABI as a strong risk, occupied the second weight. Adding ABI to traditional AR model, NRI, IDI, and DCA was 0.11, 0.12, and 0.18, respectively.

# Conclusion

Combining ABI with traditional AR can improve all-cause mortality and CVD mortality prediction. Routine ABI evaluation and intensive intervention were pressing needed, especially in high AR patients.

## Introduction

Atherosclerosis risk (AR) including age, gender, body mass index (BMI), cigarette smoking, blood pressure, total cholesterol (TC), LDL-cholesterol (LDL-C) and diabetes mellitus (DM)[1]. Previously, Framingham cohortstudy and other study has confered patients with high AR had worse prognosis[2,3,4]. However, AR was mostly used to predict CVD risk of general population[5], detection CVD mortality and all-cause mortality had proven difficult[6,7]. Particularly, it was tending to over-estimate risk in low risk populations

and under-estimate in high risk populations[8,9]. Meanwhile, several studies have shown abnormal ABI was also an indicator of general atherosclerosis and independently associated with CVD mortality in prospective studies [6,10,11]. Some researches also reported predictive value of adding ABI compared to classical risk factors alone in northern European and American populations[12,13,14]. But, there are few study about incremental prognostic value of ABI on prediction model, and most date from western countries, especially lack of China multi-center prospective cohort study. Therefore, this research was aimed at combining ABI with traditional AR model whether can improve prediction of all-cause and CVD mortality in high AR patients.

In this study, we evaluated abnormal ABI performance using a modified risk-prediction model with AR and conventional Framingham Risk Scores, and examining how its performs with all-cause mortality and CVD mortality. Previous, most prediction models adopted hazard ratios (HR) and receiver-operator characteristics curves (ROC) to assess performance of risk prediction[15,16]. Recently, the net reclassification index (NRI) and integrated discrimination improvement (IDI) have been described as more responsive to assess new risk prediction systems [17,18]. The evaluation of a new risk variable more accurately stratifies into higher-risk categories by reclassification is perhaps the most important statistic to consider when evaluating its use[19]. Since improved risk prediction by this method would not simply represent a tradeoff between sensitivity and specificity, but could actually improve overall predictive ability, or area under ROC[20]. Meanwhile, sensitivity, specificity, and ROC only measure the diagnostic accuracy of predictive model, fail to consider the clinical utility of specific model[21]. In contrast, decision curve analysis (DCA) is a simple method to evaluate clinical prediction models and diagnostic tests[22]. Moreover, advantage of DCA is that it integrates the preferences of decision makers into the analysis. Currently, this concept meets the practical needs of clinical decision-making, and is widely used in clinical analysis[23]. In addition, the nomogram transforms the complex regression model into a simple and visual graph, which makes the prediction model more readable and valuable. And, this advantage makes the nomogram get more attention and application in clinical practice. Consequently, on theabove-mentioned reasons, this study adopted NRI, IDI, DCA and nomogram methods to assess new risk prediction model, including ABI as independent of AR.

# Methods

# Study Population

The ABILITIES study (Clinical Trials.gov Identifier: NCT03616418) was a multi-center prospective Cohort Study. The first cross-section<link rid="Sec8">a</link>l survey was conducted in 2011. The eligible participants were followed up from November 2011 to June 2018 (mean follow-up month was 68.71 ± 11.35). During the follow up time, 147 subjects had missing data and 126 had no compliance. The exclusion criteria were severe congestive heart failure. Severe congestive heart failure was defined that above or equal to cardiac functional classify 3 formulated by the New York Heart Association (NYHA). In our study, patients with ABI more than 1.40 were also excluded because these values may be falsely

elevated due to severe arterial calcification[24,25]. In the same reason, it has been reported severe renal insufficiency also can cause the increasing of ABI value and give rise to false-negative, so patients with estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73 $m^2$ were also excluded. Severe renal failure was defined as eGFR < 30 ml/min/1.73 $m^2$ (Fig. 1). Thus, the study sample actually comprised 2,988 valid participants (1980 male, 1008 female) whose age older than or equal to 35 years (mean age 60.2 ± 10.4 years) were followed up. A total of hospitalized subjects were consecutively enrolled from the cardiology or endocrinology departments of Beijing and Shanghai university affiliated hospitals. All subjects are under treatment because of cardiovascular diseases or endocrine diseases and ABI was measured. The inclusion criteria were with high AR patients. All participants gave written informed consent to this study, which was approved by the ethics committee of Tongji University. And this study was accordance with the TRIPOD statement[26].

### Cardiovascular Events Definitions

Hospitalized myocardial infarction was classified as definite or probable based on chest pain symptoms, cardiac enzyme levels, and electrocardiographic (ECG) findings, or angioplasty. Coronary heart disease (CHD) was determined to be present if there was (1) ECG evidence of a prior myocardial infarction, (2) prior coronary artery bypass surgery or angioplasty, (3) Coronary angiography show coronary heart disease, (4) have symptoms of angina and ECG revealed myocardial ischemia performance or laboratory tests showed cardiac enzymes increased and exclude other types of disease, (5) a self-reported history of a physician-diagnosed heart attack. CHD death was classified as “definite” based on chest pain symptoms, hospital records, and medical history.

### Assessment of New-onset Cardiovascular Events and Identification of Death from All-Causes and CVD

Cardiovascular events are composed of cardiac including non-fatal myocardial infarction, unstable angina, and coronary revascularization procedures during follow-up time. Exclusion criteria were stale angina ( >6 months), revascularization procedure for CAD ( >6 months) and myocardial infarction( >6 months).

In this study, the cardiovascular death was only cardiac event death. Medical records and death certificates of all patients who had an event were obtained and validated by cardiologist or endocrinologist. Death was confirmed from hospital records or by contact with participants and their families. All materials were reviewed independently by five senior physicians of the cohort study to confirm the cause of death.

### Measurement of Ankle and Arm Blood Pressures

Qualified ultrasonographers measured ankle and brachial systolic blood pressures. Doppler ultrasound (Nicolet Vascular, Elite 100R, USA) was used to measure systolic blood pressure (SBP) in the bilateral brachial, tibial and dorsal pedal arteries. The occluding cuffs (55*12.5cm) were applied just above the malleoli to measure ankle pressure. ABI was measured after participants had rested supine for 5 min. The value was calculated as the average of the two ankle systolic measurements divided by the average of

the first two brachial readings. The lower ABI of the two legs was used as predictor of future cardiovascular events.

A questionnaire was designed to collect information about general characteristics, diagnosis, medical history and relation factors, medical treatment and biochemical examination in all participants. And yet, besides history and duration of hypertension, cardiovascular heart disease, chronic renal disease, stroke, dyslipidemia and smoking, other potential possible risk factors are also recorded in this questionnaire, it is including age, gender and BMI.

### Framingham Risk Score and High Atherosclerosis Risk

The Framingham risk score (FRS) was calculated based on coronary risk factors, including age, gender, total cholesterol, LDL-C, hypertension and smoking status according to the National Cholesterol Education Program-Adult Treatment Panel III algorithm[1]. The calculated total scores were used to estimate the 10-year coronary heart disease risk in participants without previous CVD, and Framingham risk > 20% was identified as high for 10-year coronary heart disease risk[27]. When FRS more than 20% or among 10% and 20% was considered high AR[27].

### Statistical Analysis

All analyses were performed using the R statistical package (version 3.6.2) (http://www.r-project.org) [28]. Continuous variables are expressed as the mean±SD, and categorical variables as percentage. Continuous and categorical variable differences comparison was made by Independent samples ANOVA (analysis of variance) and the Chi-square test, as appropriate. Kruskal-Wallis test for non-normally distributed continuous variables. A p-value <0.05 was considered statistically significant. Due to skewed distribution, TC, TG, HDL-C, LDL-C, BUN, Cr, SUA were logarithm-transformed (log) in analyses. Crude deaths from all-cause and CVD were examined by ABI stratification. Cumulative event rates were estimated with Kaplan-Meier survival curves, and probability values were calculated with the log-rank test. Cox proportional hazard analyses were performed to test the association of the ABI and deaths from all-causes or CVD. And model was adjusted for potential confounders, including age, gender, duration of hypertension, smoking status, dyslipidemia history, chronic renal insufficiency history, diabetes mellitus (DM) history, percutaneous coronary stent implantation (PCI) history, coronary artery by pass grafting (CABG) history, PAD history, myocardial infarction (MI) history, ischemic stroke history, hypertension, ABI, FRS, eGFR, SUA, center, year of screening examination. Potential confounding variables with P□0.10 were adjusted for multivariate analysis. Restricted cubic splines with knots were used to further explore the shape the relationship with ABI value and HR of all-cause mortality and CVD mortality. Knots were at the 5th, 95th, and quartile of ABI distribution. Missing values were handled byK-means clustering imputation. All data P values were 2-tailed, and less than 0.05 were considered significant. A nomogram was formulated based on the results of multivariate Cox regression analysis. The predictive performance of nomogram was measured by concordance index (C-index) and calibration with 2000 bootstrap samples to decrease the overfit bias. Determination of net reclassification

improvement (NRI) and integrated discrimination improvement (IDI) for both models provided estimates of adding ABI value to AR model. Decision curve analysis (DCA) for classic model and model with addition of ABI value.

# Results

### Baseline characteristics

A total of 2,988 eligible participants with available baseline data were enrolled in this cohort. Through careful calculation, the missing participants did not significantly affect the major results. Our research demonstrated that all subjects were under treatment for secondary prevention. The PAD prevalence in these patients was 27.2%. The average ABI was 1.10 ± 0.12 (mean ± SD). Table 1 presented the baseline characteristics of our subjects. According to the degreeof lower extremity arterial st-enosis, from normal to borderline, moderate, and severe stenosis. ABI value was subdivided into four subgroups including 1.0-1.40, 090-0.99, 0.41–0.90, and 0-0.40. Among all variables examined, our research revealed moderate and severe stenosis subgroups had hypertension, had chronic renal insufficiency, high FRS risk stratification, higher proportion of male subjects, old enough, had MI history and PCI history, smoking state and suffered from ischemic stroke. Of note, there was no significant statistical difference on dyslipidemia, level of Cr, DBP, and CABG history. Meanwhile, in contrast with the reference group, participants were more likely to be treated with ARB.

### All-cuase Mortality, CVD Mortality, and Survival Analysis of ABI Subgroups

As Table 2 represented, among 0-0.40, 0.41–0.89, 0.90–0.99, and 1.00-1.4 four subgroups, all-cause mortality were 50%, 38.1%, 23.7%, and 22.4%, respectively. CVD mortality were 33.6%, 20.2%, 13.5%, and 9.1%, respectively. After multivariable adjusted, Cox regression models revealed that compared with 1.0-1.40 subgroup, among 0-0.40, 0.41–0.90, and 0.91-1.0 subgroups, HR of all-cause mortality were 2.12, 95% CI (2.39–2.98), 2.06, 95%CI (1.35–2.90), and 1.86, 95%CI (1.54–2.89), respectively. And HR of CVD-cause mortality were 2.39, 95%CI (2.41–3.09), 2.29, 95%CI (1.83–2.87), and 2.02, 95%CI (1.73–2.81), respectively. The Kaplan–Meier curves illustrated the survival rate decreasing with lower levels after 6 years follow-up, ($P < 0.001$; Fig. 2). In Fig. 3, below the horizontal dotted line represents null risk. This figure indicated after multivariable adjusted, cubic spline models with nodes presented reverse J-shaped with ABI value whether all-cause mortality or CVD mortality.From the Fig. 3, there was a significant increasing tendency in all-cause mortality and CVD mortality with lower andhigher levels after 6 yearsfollow-up. ($P < 0.001$).

### Reclassificationof Model with and without ABI for All-cause Mortality and CVD-cause Mortality

In table 3, after adding ABI to AR,for all-cause mortality and CVD-cause mortality, the NRI was 11%, 95% CI (0.09–0.19) and 12%, 95% CI (0.10–0.21), respectively. Meanwhile, for all-cause mortality and CVD-cause mortality, IDI was all 18%, 95% CI (0.07–0.23) and 95% CI (0.08–0.23), respectively.

### Nomogram to Predict All-cause Mortality and CVD-cause Mortality

Nomogram was derived from Cox proportional hazard model. It assessed risk factors that might predict all-cause mortality and CVD mortality. To estimate mortality probability, first obtain and add point values foreach variable (i.e. age, ABI, BMI, TC and so on ) by connecting vertical line intercepts to the horizontal “score” bar. Theaccumulated “total score” bar then aligns with the probability axis of model. From figures 4 A and B, nomogram also demonstrated mortality of risk factors included gender, age, SBP, stroke, DM, MI history, PCI history, smoking state, CABG history, glucose, BMI, LDL-C, and ABI value. Of noted, among these risk factors, age, ABI value, BMI, LDL-C, glucose, and SBP occupied major probability weight. Especially, when ABI value was from 0.0 to 1.4, match score calculated among all-cause mortality and CVD-cause mortality was from zero to 70 and from zero to 60, respectively.

### DCA Plot of Classic AR Model and Model with ABI to Predict All-cause Mortality and All-cause Mortality

DCA was clinical benefit of model plotting the net benefit versus threshold probabilities. The grey line assumed that allpatients with mortality, whereas the black line assumes none with mortality. The blue dotted line was the clinical benefit of AR model, and red dotted line was the clinical benefit of adding ABI value to AR model. DCA plot demonstrateda significant positive benefit at predicting all-cause mortality and CVD-cause mortality, at a threshold probability of 18% where the red line diverges from the blue line.

## Discussion

Since the profile of risk related all-cause mortality and CVD mortality had quite disparity in the geographical population, ABILITIES study selected Peking and Shanghai patients, to represent AR demographic characteristics of North and South China. Recent studies have demonstrated low ABI value was not only associated with CVD, independent of traditional AR[12, 29], but also had been examined as a tool to improve the risk prediction prospectively[30]. However, the increment of prognostic value whether has statistical difference remains controversial, especially in high AR patients, owing to its complex inter relationships with other established all-cause and cardiovascular risks, such as coronary heart disease, stroke, diabetes, hypertension, and dyslipidemia. In this multi-center cohort study, according to ABI levels, after further adjusting potential confounders, revealed combining ABI with conventional AR substantially improved prediction of all-cause and CVD mortality, suggesting ABI could serve as a marker into cardiovascular risk stratification model.

Previous researches had indicated cut-off point of ABI affected prognostic result, and presently, most studies used values according to stenosis levels of lower extremity arteries. In the same way, our research also chose the value from normal to borderline, moderate, and severe stenosis, namely ABI was divided into 1.0-1.40, 090-0.99, 0.41–0.90, and 0-0.40, four subgroups. Among severe stenosis, moderat, and borderline subgroup, the six-year study showed all-cause mortality was 50%, 38.1%, 23.7%, respectively, and CVD mortality was 33.3%, 20.2%, 13.5%, respectively. Even normal group, all-cause mortality and CVD mortality still reached 22.4% and 9.9%. In addition, compare with normal value, among 0-0.40 and 0.41–

0.90 subgroup, the HR of all-cause mortality and CVD mortality was 2.12, 2.06, respectively, and 2.38, 2.27, respectively. Due to participants with high AR, in contrast with the Strong Heart Study reported, 10-year CVD mortality in man and woman was 18.7% and 4.4%[31], the result of our study increased more obviously. Meanwhile, Gerry Fowkes et al. in a meta-analysis of 20 studies have demonstrated a non-linear relation between HR of all-cause mortality and ABI value[12]. Similarly, adopting multivariable adjusted cubic spline models, our research further confirmed this relationship presented reverse J type, whether all-cause mortality or CVD mortality. Moreover, restricted cubic splines and Kaplan–Meier survival estimation all presented abnormal levels increased mortality and illustrated ABI as a powerful independent risk factor, the predictive ability similar to Framingham risk.

Furthermore, when adding ABI to Framingham risks, Yeboah J et al. found AUC was raised from 0.646 to 0.655 in men and from 0.605 to 0.658 in women[27]. But, the study was limited by the absence of important covariates such as time and BMI. Our research applying time-dependence ROC also revealed AUC of all-cause mortality and CVD mortality was 0.689 and 0.712, respectively. Due to high AR as clinical indicators, were not dichotomous variables, but multi-category variables, NRI and IDI may be better choices, while AUC was more complex and difficult to predict the prognosis. Thus, although the outcome of ROC was unsatisfied, when incorporating AR and ABI, the research manifested NRI and IDI for all-cause mortality and CVD mortality were from 12% to18%. And result implied remain effect of NRI and IDI may compensate for poor performance of C-index. As calculation of NRI and IDI were closely related to threshold, if grade division too narrow, then would get more precisely, but had lost significance of clinical practice. Therefore, according to Framingham ten-year risk categories, from 10–20% and more than 20% were selected as cut-off pointfor mortality in this study[12]. Similarly, considering clinical feasibility, compared with FRS, the figure of DCA also revealed adding ABI to AR model improved 18% incremental prognostic value. These findings all demonstrated the strong association between abnormal ABI value and clinical prognosis.

Meanwhile, when using nomogram methods to assess new risk prediction model, indicated besides ABI, age, SBP, TC, LDL-C, BMI, ischemic stroke, DM, MI, PAD and smoking were strongly associated with all-cause mortality and CVD mortality. Among these risks, age, ABI, SBP, BMI, TC, LDL-C, and glucose occupied major position. Particularly, ABI account for the second weight. When ABI value was from 0.0 to1.4, match score calculated with all-cause mortality and CVD-cause mortality was from zero to 70 and from zero to 60, respectively. In addition, due to our study enrolled high AR patients, although baseline characteristics indicated no significant statistical difference on hyperlipidemia, nomogram still revealed TC and LDL-C were strong hazard factor with mortality.

In conclusion, this research supported as a non-invasive, objective, easy and reproducible method, ABI was an ideal tool for predicting all-cuase mortality and CVD Mortality. Adding ABI to traditional risk model, especially in high AR individuals, was likely to compensate deficiencies of conventional prediction model. And, in clinical practice, more intensive management and aggressive treatment of vascular risk factors should be encouraged in high AR individuals, especially combined with abnormal ABI patients.

# Conclusion

Among high AR patients, the PAD prevalence was 27.2%. In ABI 0-0.40, 0.41–0.89, 0.90–0.99, and 1.00-1.4 subgroups, all-cause mortality were 50%, 38.1%, 23.7%, and 22.4%, respectively. CVD mortality were 33.6%, 20.2%, 13.5%, and 9.1%, respectively. RCS with nodes and Kaplan–Meier survival curve all manifested abnormal ABI levels increased mortality. After multivariable adjusted, compared with 1.0-1.40 subgroup, among 0-0.40, 0.41–0.90, and 0.91-1.0 subgroups, HR of all-cause mortality were 2.12, 95% CI (2.39–2.98), 2.06, 95% CI (1.35–2.90), and 1.86, 95% CI (1.54–2.89), respectively. HR of CVD-cause mortality were 2.39, 95% CI (2.41–3.09), 2.29, 95% CI (1.83–2.87), and 2.02, 95% CI (1.73–2.81), respectively. RCS presented reverse J-shaped relationship with ABI levels and all-cause mortality as well as CVD-cause mortality. Nomogram indicated ABI, age, SBP, TC, LDL-C, DM, MI, and smoking were strongly associated with all-cause mortality and CVD-cause mortality. And, ABI as a strong risk, occupied the second weight. Adding ABI to traditional AR model, NRI, IDI, and DCA for all-cause mortality was 0.11, 95% CI (0.10–0.19), 0.12, 95% CI (0.07–0.23), and 0.12, 95% CI (0.08–0.23) respectively. For CVD-cause mortality was 0.12, 95% CI (0.10–0.21), 0.18, 95% CI (0.07–0.25 ), and 0.12, 95% CI (0.07–0.23), respectively.

# Study Limitations And Strengths

Firstly, in order to have a study population as homogenous as possible, this research adopted HAR patients. Therefore, results cannot be extended to the entire population. Secondly, due to follow-up population were contacted by annual phone interview, the results maybe have information bias. In addition, some participants have inferior compliance, thus withdrawal bias maybe lie in this research. Finally, in comparison with western countries prospective study, the follow-up times of this study are not long. Hence, date from this research was not comprehensive, additional studies are also needed.

The strengths of our study included its prospective design and applied various reliable methods to assess ABI prediction model. Secondly, this research was multi-central register cohort study focused on high AR. In addition, compared with other China researches, this cohort study had longer follow-up time and larger sample size.

# Abbreviations

ABI: ankle–brachial index; CVD: cardiovascular disease; HAR: high atherosclerotic risk; RCS: restricted cubic splines; NRI: net reclassification index; IDI: integrated discrimination improvement; DCA: decision curve analysis; BMI: body mass index; TC: total cholesterol; LDL-C: LDL-cholesterol; DM: diabetes mellitus; HR: hazard ratios; ROC: receiver-operator characteristics curves; FRS: Framingham risk score;  PAD: Peripheral arterial disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; PCI: percutaneous coronary stent implantation; CABG: coronary artery by pass grafting; MI: myocardial infarction; Cr: serum creatinine; SUA: serum uric acid;

# Declarations

### Ethics approval and consent to participate

Approved by the ethics committee of Tongji University (NCT03616418).

### Conflict of interest

The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

### Consent to Publish

The Author confirms: that the work described has not been published before; that it is not under consideration for publication elsewhere; that its publication has been approved by all co-authors.

### Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.


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### Contributors

Yan Cang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yan Cang, Acquisition of data: Yan Cang, Jue Li, Jingyi Ju, Shaojie Xu,Yawei Xu. Analysis and interpretation of data: Yan Cang. Drafting of the manuscript: Yan Cang, Critical revision of the manuscript for important intellectual con-tent: Yan Cang Statistical analysis: Yan Cang. Study supervision: Yan Cang, Jue Li

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# Tables

**Table 1 Comparison of baseline characteristics according ABI in patients with high atherosclerosis risk.**

| ABI level<br>Variable | 0-0.40<br>N=77 | 0.41-0.89<br>N=731 | 0.90-0.99<br>N=416 | 1.00-1.40<br>N=1764 | P value |
|---|---|---|---|---|---|
| age, years | 71.7±9.5 | 68.0±10.8 | 65.4±11.4 | 63.8±10.7 | <0.001 |
| Male gender, N (%) | 469 (49.3%) | 251 (47.8%) | 543 (51.4%) | 717 (59.8%) | <0.001 |
| Smoking, N (%) | 405 (42.6%) | 189 (36.0%) | 375 (35.5%) | 490 (40.8%) | 0.003 |
| Smoking duration (years) | 15.3±20.2 | 11.6±17.9 | 11.0±16.7 | 12.0±16.3 | <0.001 |
| BMI, $kg/m^2$ | 23.9±3.7 | 24.2±3.9 | 24.2±3.7 | 24.9±3.4 | <0.001 |
| Hypertension, N (%) | 760 (79.9%) | 375 (71.4%) | 714 (67.6%) | 869 (72.4%) | <0.001 |
| Hypertension duration (years) | 12.2±1.24 | 9.4±1.16 | 8.7±1.14 | 9.0±1.08 | <0.001 |
| Diabetes , N (%) | 468 (49.2%) | 208 (39.6%) | 379 (35.9%) | 402 (33.5%) | <0.001 |
| Myocardial infarction History, N (%) | 201 (21.1%) | 70 (13.3%) | 117 (11.1%) | 109 (10.4%) | <0.001 |
| Ischemic Stroke History, N (%) | 432 (45.4%) | 169 (32.2%) | 294 (27.8%) | 324 (27.0%) | <0.001 |
| Dyslipidemia , N (%) | 349 (46.1%) | 190 (41.9%) | 353 (40.3%) | 427 (42.5%) | 0.122 |
| chronic renal insufficiency History, N (%) | 115 (12.5%) | 52 (10.2%) | 96 (9.4%) | 94 (8.1%) | 0.008 |
| CABG History, N (%) | 30 (3.2%) | 19 (3.6%) | 27 (2.6%) | 31 (2.6%) | 0.561 |
| PCI History, N (%) | 99 (10.4%) | 93 (10.2%) | 78 (8.8%) | 63 (13.0%) | 0.012 |
| PAD History, N (%) | 64 (6.7%) | 15 (2.9%) | 30 (2.8%) | 22 (1.8%) | <0.001 |
| SBP, mmHg | 143.3±24.7 | 141.3±23.2 | 138.5±22.0 | 138.3±21.9 | <0.001 |
| DBP, mmHg | 80.8±12.9 | 80.6±12.3 | 80.5±12.1 | 81.1±12.4 | 0.660 |
| TC, mmol/L | 4.7±0.12 | 4.7±0.12 | 4.6±0.12 | 4.6±0.11 | 0.102 |
| TG, mmol/L | 1.7±0.14 | 1.7±0.11 | 1.6±0.11 | 1.7±0.11 | 0.081 |
| HDL-c, mmol/L | 1.2±0.40 | 1.2±0.32 | 1.2±0.26 | 1.2±0.17 | 0.205 |
| LDL-c, mmol/L | 2.8±0.90 | 2.8±0.8 | 2.7±0.90 | 2.7±0.90 | 0.131 |
| CRE（mmol/L） | 107.4±7.73 | 102.2±10.46 | 95.4±6.62 | 100.7±10.57 | 0.116 |
| SUA | 340.9±12.67 | 314.5±11.75 | 315.1±11.89 | 315.6±10.86 | <0.001 |
| Blood glucose | 6.7±0.29 | 6.6±0.32 | 6.4±0.28 | 6.4±0.27 | 0.017 |
| Statin therapy, N (%) | 362 (38.1%) | 210 (40.0%) | 370 (35.1%) | 434 (36.3%) | 0.221 |
| ARB, N (%) | 89 (9.4%) | 51 (9.7%) | 98 (9.3%) | 104 (8.7%) | 0.908 |
| ACEI, N (%) | 505 (53.2%) | 255 (48.6%) | 443(42.0%) | 560 (46.9%) | <0.001 |
| Antiplatelet agents, N (%) | 664 (69.91%) | 331(63.05%) | 637 (60.42%) | 799 (66.92%) | <0.001 |
| Calcium antagonist, N (%) | 409 (43.12%) | 193 (36.85%) | 370 (35.04%) | 425 (35.67%) | 0.001 |
| Diuretics, N (%) | 348(36.6%) | 138 (26.3%) | 268 (25.4%) | 274 (22.9%) | <0.001 |
| FRS† | 362 (45.94%) | 193 (43.96%) | 320 (40.97%) | 305 (30.68%) | <0.001 |
| FRS†† | 345(43.78%) | 157 (35.76%) | 192(24.37%) | 214(21.51%) | <0.001 |

systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI (body mass index), Total cholesterol (TC), Triglycerides (TG), Fasting plasma glucose (FPG), high density lipoprotein (HDL-c), low density lipoprotein (LDL-c) , serum creatinine (Cr), serum uric acid (SUA), diabetes mellitus (DM), myocardial infarction (MI), Body mass index (BMI), cardiovascular disease (CVD), Peripheral arterial disease (PAD), ankle-brachial index (ABI), percutaneouscoronary angioplasty (PTCA), coronary artery bypass grafting (CABG), Hazard risk (HR), Framingham Risk Score (FRS), FRS† Analysis participants with Framingham risk score 10%-20%, FRS ††Analysis participants with Framingham risk score > 20%

**Table 2 Adjusted Hazards Risks for All-Cause Mortality and CVD Mortality By Cox Regression Models According to Ankle - Brachial Index.**

| | ABI | | | | P for difference |
|---|---|---|---|---|---|
| ristic ABI level<br>mber | 0-0.40 | 0.41-0.89 | 0.90-0.99 | 1.00-1.40 | |
| | 77 | 731 | 416 | 1764 | |
| *mortality* | 973 | 789 | 672 | 613 | |
| of deaths | 220(35.9%) | 238(24.5%) | 154(22.9%) | 151(19.1%) | |
| ableadjustment | | | | | |
| | 2.20(1.73-3.17) | 2.13(1.45-3.09) | 1.94(1.23-2.92) | 1 | 0.001 |
| 2 | 2.17(1.70-3.09) | 2.10(1.21-3.12) | 1.90(1.19-2.98) | 1 | 0.001 |
| 3 | 2.12(1.63-3.17) | 2.06(1.35-2.90) | 1.86(1.54-2.89) | 1 | 0.001 |
| *lity* | | | | | |
| of deaths(n,%) | 171(21.70%) | 58(13.21%) | 90(11.42%) | 86(8.65%) | 0.001 |
| abledjustment | | | | | |
| | 2.53(2.45-3.12) | 2.42(1.91-2.93) | 2.37(1.76-2.97) | 1 | 0.001 |
| 2 | 2.39(2.41-3.09) | 2.29(1.83-2.87) | 2.02(1.73-2.81) | 1 | 0.001 |
| 3 | 2.38(2.37-2.98) | 2.27(1.79-2.82) | 1.99(1.66-2.77) | 1 | 0.001 |

Iodel 1 was adjusted for age and gender, eGFR (estimated glomerular filtration rate), FRS(Framingham risk score)

Model 2 was adjusted for model 1 covariates and a history of heart failure, a history of CABG history, a history of PTCA history, a history of PAD history, a history of diabetes, a history of renal insufficiency, a history of smoking duration years , a history of hypertension duration years and a history of stroke

Model 3 was adjusted for model 2 covariates central effect, year of screening examination

**Table 3 Reclassification of Model with and without ABI for All-cause Mortality and CVD-cause**

| Model without ABI | Model with ABI | | Total |
|---|---|---|---|
| Frequency(Row per cent) | FRS (10-20 percent ) | FRS ( >20 percent ) | |
| †Participants who experienced all-cause mortality | | | |
| FRS (10-20 per cent ) | 134 | 132 | 266 |
| FRS ( > 20 per cent ) | 89 | 274 | 363 |
| Total | 223 | 406 | 629 |
| †Participants who without experience all-cause mortality | | | |
| FRS (10-20 per cent ) | 1629 | 83 | 1884 |
| FRS ( > 20 per cent ) | 192 | 392 | 475 |
| Total | 1884 | 475 | 2359 |
| ††Participants who experienced CVD-cause mortality | | | |
| FRS (10-20 per cent ) | 140 | 88 | 228 |
| FRS ( > 20 per cent ) | 54 | 259 | 313 |
| Total | 194 | 347 | 541 |
| ††Participants who without experience CVD-cause mortality | | | |
| FRS(10-20per cent) | 1665 | 101 | 1766 |
| FRS ( > 20 per cent ) | 229 | 452 | 681 |
| Total | 1894 | 553 | 2447 |

Net Reclassification Improvement (NRI): (( 132-89 )/ 629+( 192-83 ))/ 2359= 0.11, 95% CI (0.10-0.19 ), P <0.001.

NRI: ( 88-54 ) / 541+ (( 229-101 ) / 2447= 0.12 , 95% CI (0.10-0.21 ),P <0.001.

ntegrated Discrimination Improvement ( IDI): 0.18, 95% CI ( 0.07- 0.23 ),P <0.001.

IDI: 0.18, 95% CI ( 0.07- 0.25 ),P <0.001.

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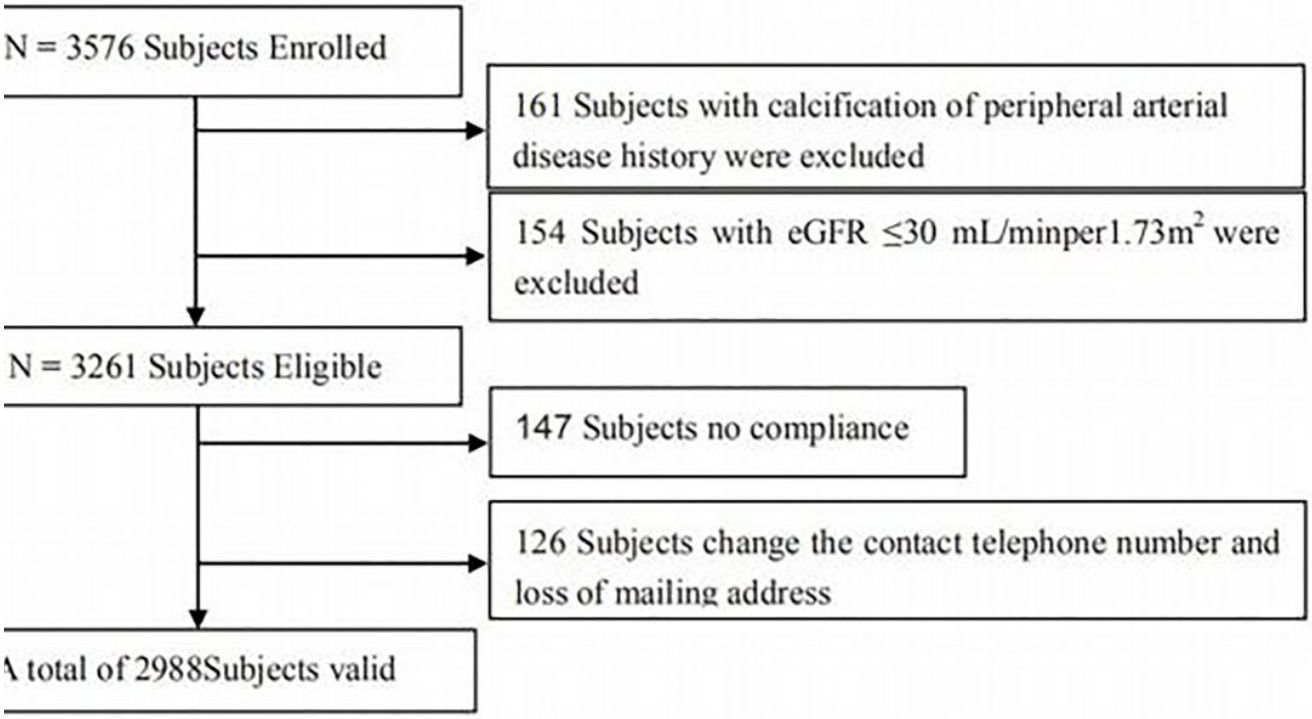
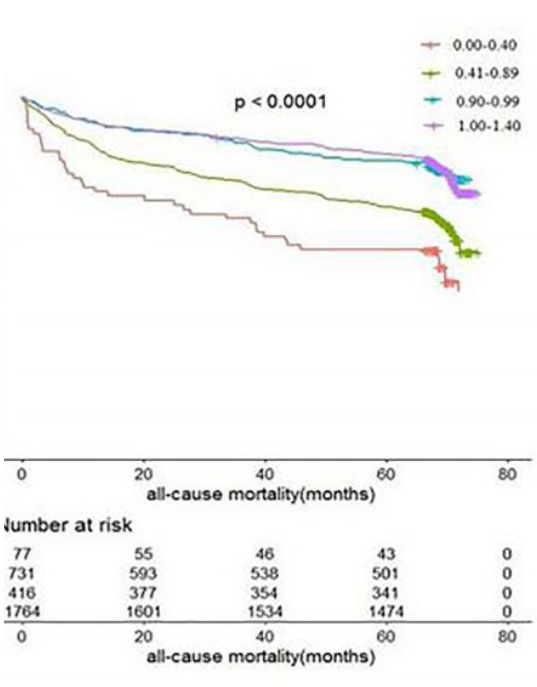
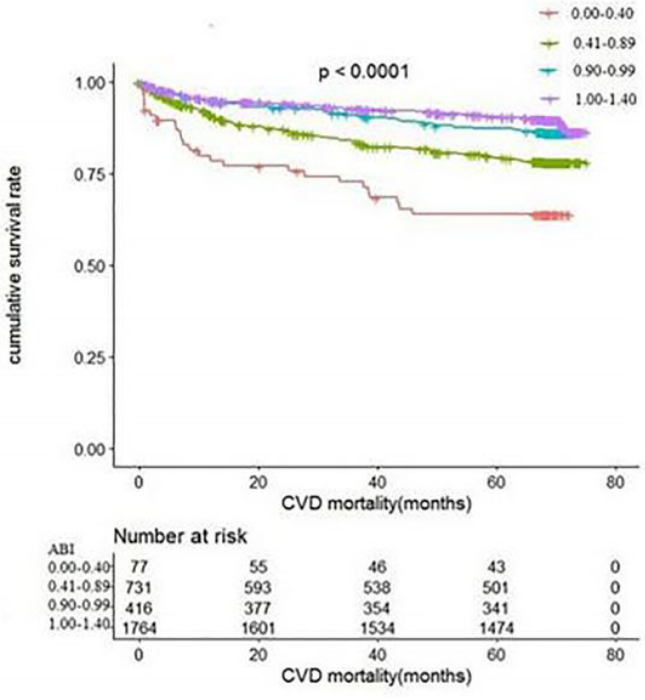
**1**


N = 3576 Subjects Enrolled
161 Subjects with calcification of peripheral arterial disease history were excluded
154 Subjects with eGFR ≤30 mL/minper1.73m² were excluded
N = 3261 Subjects Eligible
147 Subjects no compliance
126 Subjects change the contact telephone number and loss of mailing address
A total of 2988Subjects valid

w chart

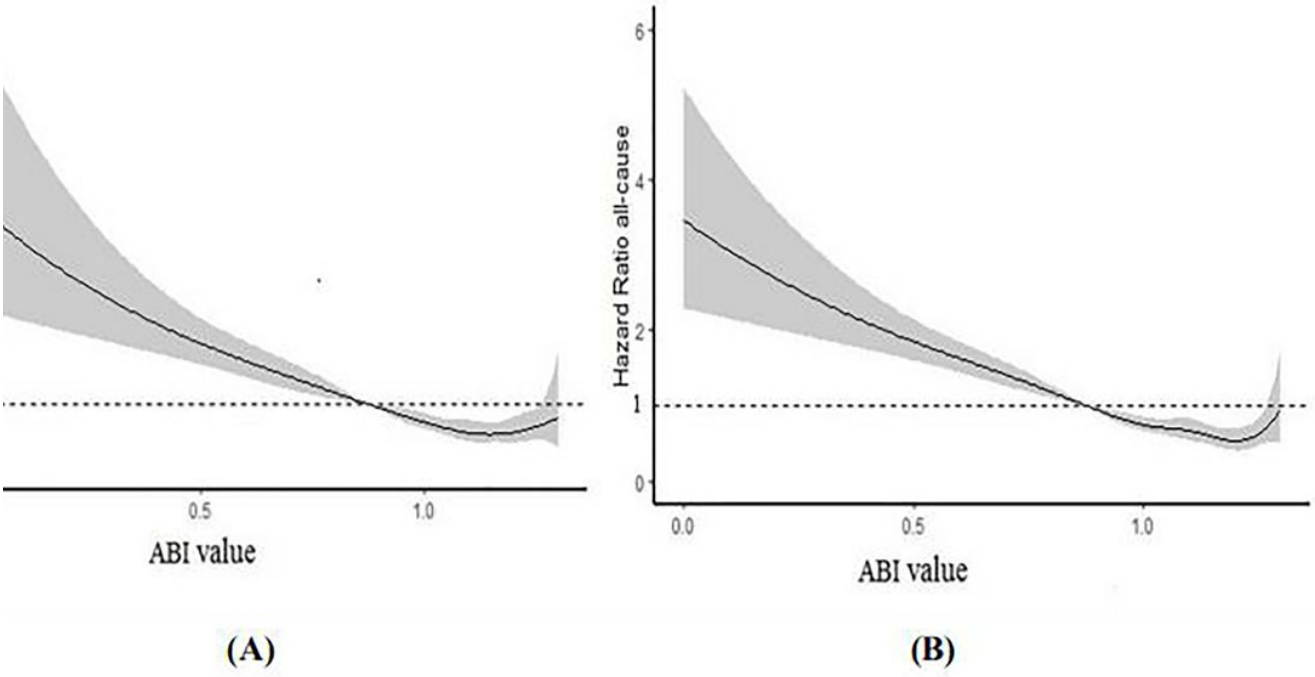

0.00-0.40
0.41-0.89
0.90-0.99
1.00-1.40
p < 0.0001
0
20
40
60
80
all-cause mortality(months)
Number at risk
77 55 46 43 0
731 593 538 501 0
416 377 354 341 0
1764 1601 1534 1474 0
0
20
40
60
80
all-cause mortality(months)

(A)

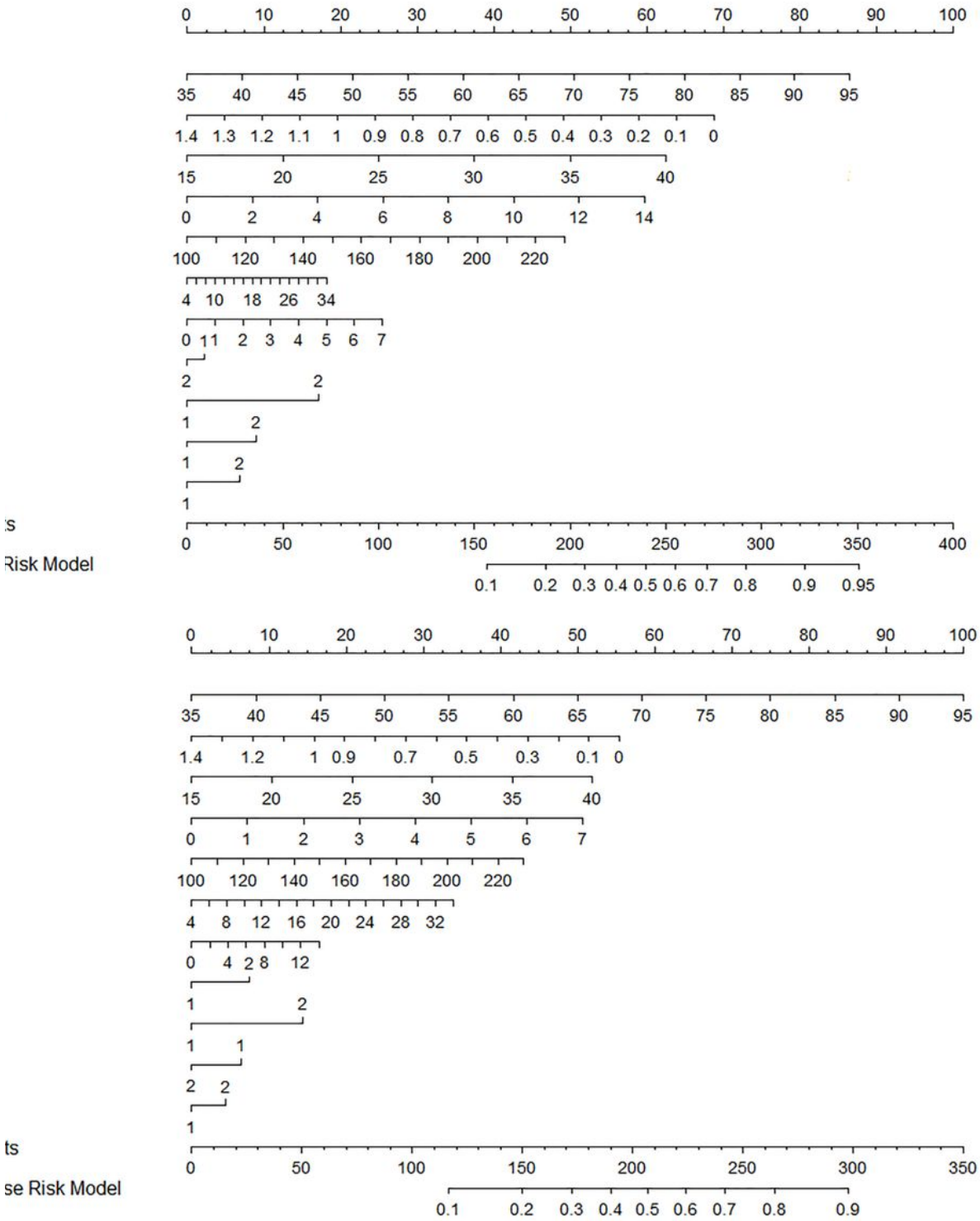

0.00-0.40
0.41-0.89
0.90-0.99
1.00-1.40
p < 0.0001
cumulative survival rate
1.00
0.75
0.50
0.25
0.00
0
20
40
60
80
CVD mortality(months)
Number at risk
ABI
0.00-0.40 77 55 46 43 0
0.41-0.89 731 593 538 501 0
0.90-0.99 416 377 354 341 0
1.00-1.40 1764 1601 1534 1474 0
0
20
40
60
80
CVD mortality(months)

(B)

ɹrse to death from for all-cause mortality (A) and cardiovascular disease (CVD) mortality (B)
g to ankle-brachial index (ABI) levels in the cohort study during 6-years follow-up.




able adjusted cubic spline models of the relationshipwith ankle-brachial index (ABI) levels and
atios (HR) for all-cause mortality (A) and cardiovascular disease (CVD) mortality (B).

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Risk Model

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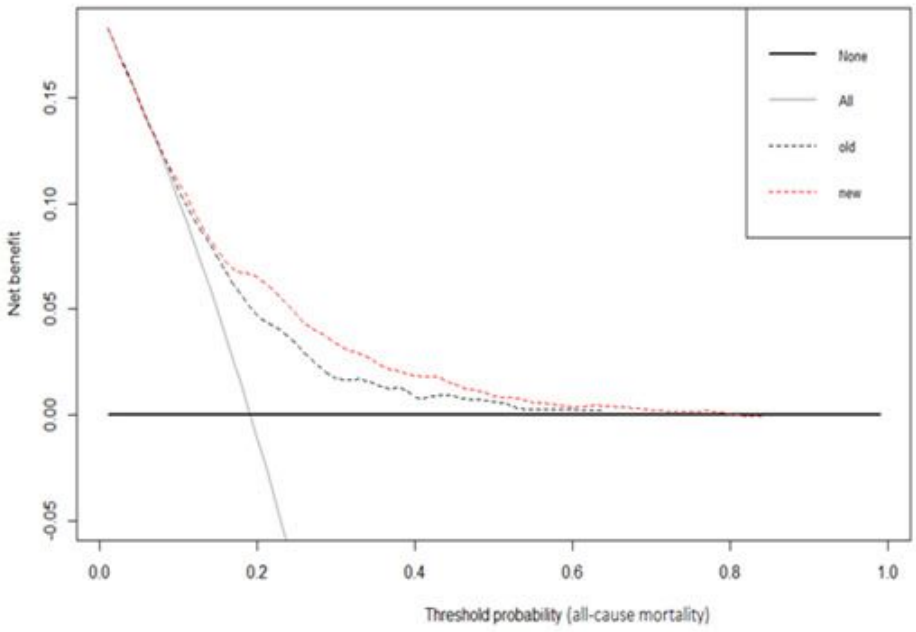
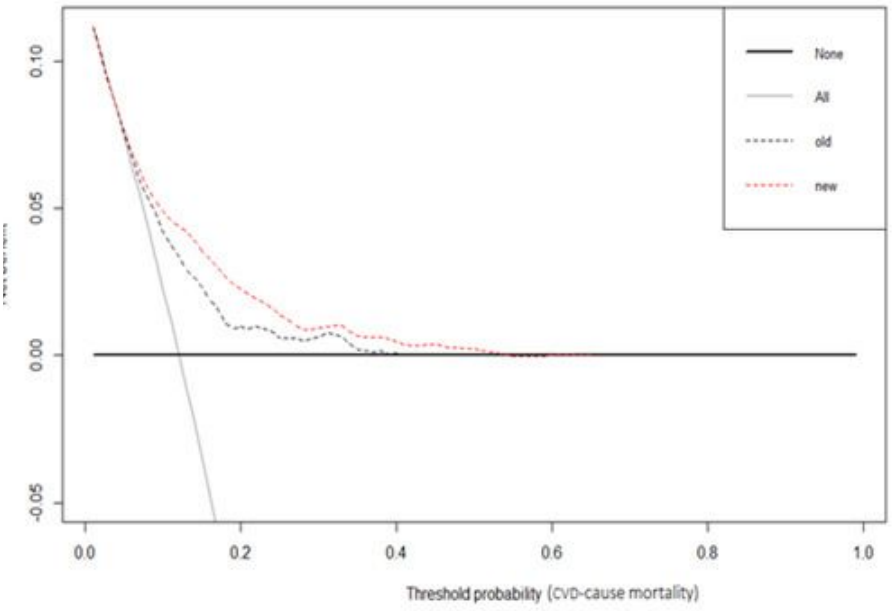
se Risk Model

able adjusted cubic spline models of the relationshipwith ankle-brachial index (ABI) levels and atios (HR) for all-cause mortality (Top) (A) and cardiovascular disease (CVD) mortality (B).




Curve Analysis (DCA) for Classic Atherosclerosis Risk Model (old) and Model with ABI (new)
t All-cause Mortality (A) and All-cause Mortality (B).