ORIGINAL ARTICLE

Predictive value of creatinine/cystatin C ratio and physical activity for all-cause mortality risk in hypertensive patients: A cohort study based on NHANES data

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ABSTRACT

Physical activity (PA) is a cornerstone of hypertension management, but whether muscle mass influences its survival benefits remains unclear. The serum creatinine-to-cystatin C ratio (CCR) has been proposed as a surrogate marker of muscle mass, although it is also affected by renal function, nutritional status, and inflammation. This study examined the association between CCR and mortality in hypertensive adults and explored the role of PA intensity. This retrospective cohort study included 2,432 adults with essential hypertension from the National Health and Nutrition Examination Survey (NHANES). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Muscle mass was estimated using CCR, and PA was classified as inactive, moderate, or vigorous. All-cause mortality was obtained through linkage with the National Death Index. Covariates included age, sex, race/ethnicity, education, smoking status, body mass index (BMI), albumin, C-reactive protein (CRP), lipid profile, and estimated glomerular filtration rate (eGFR). Kaplan–Meier analyses and multivariable Cox regression models were used. Low CCR was associated with older age, female sex, higher CRP, and lower albumin levels. In multivariable analyses, low CCR independently predicted all-cause mortality and outperformed indicators such as BMI and lipid measures. Stratified analyses suggested a stronger association between low CCR and mortality among participants performing vigorous PA (HR 1.95) than among those with moderate PA (HR 1.20) or inactivity (HR 1.29), although the interaction between CCR and PA was not significant (*p*-interaction = .21). Exercise was associated with survival in those with higher CCR. CCR is an independent predictor of mortality in hypertensive adults and adds value beyond conventional markers. Low CCR may be associated with reduced survival benefits from vigorous PA, although this finding requires confirmation. Incorporating CCR into risk assessment may help identify patients who could benefit from muscle-preserving strategies and resistance training.
Keywords: sport medicine; hypertension; creatinine-to-cystatin c ratio (CCR); muscle mass; physical activity; all-cause mortality; sarcopenia; national health and nutrition examination survey (NHANES); risk stratification; nomogram; survival analysis.

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INTRODUCTION

Hypertension is a major risk factor for cardiovascular morbidity and premature mortality, highlighting the importance of its management worldwide (Mills et al., 2020). Regular PA is a foundational non-pharmacological approach to blood pressure regulation (Whelton et al., 2018) and cardiovascular risk mitigation, but its survival benefits may also be conditioned by skeletal muscle integrity, which is an important element of glucose homeostasis and systemic inflammation (Pedersen & Febbraio, 2012). Sarcopenia, a syndrome characterized by progressive loss of muscle mass and function, is especially prone to occur in patients with hypertension, driven by chronic inflammation, oxidative stress, and excessive activation of the renin-angiotensin-aldosterone system (RAAS) (Springer et al., 2017). This loss of muscle can reduce exercise capacity, making conventional measures such as BMI, which cannot differentiate lean mass from fat mass, less useful in the accurate classification of risks (Srikanthan & Karlamangla, 2014). Serum CCR may provide a more valid assessment of muscle reserve, as it is a biomarker combining muscle-derived creatinine and cystatin C (Tabara et al., 2020), where a lower CCR value may indicate muscle wasting and frailty (Chen et al., 2022). Though PA and muscle mass are correlated with longevity independently, it is not clear how muscle mass influences the survival advantage of PA among hypertensive patients (Liao et al., 2025). Using NHANES data, this study tested the relationship between CCR and all-cause mortality and further identified the interaction between muscle mass and PA with the aim of guiding muscle-centred exercise interventions to help manage hypertension.

MATERIALS AND METHODS

Data source and study population

The present study used NHANES data. NHANES is a program conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC). NHANES uses a stratified, multistage, complex probability sampling design to determine the health and nutrition of the non-institutionalized US civilian population. The research protocol was approved by the NCHS Research Ethics Review Board, and written informed consent was obtained from all participants. Adults with essential hypertension were selected for inclusion in the study if they had a mean systolic blood pressure ≥140 mmHg or ≥90 mmHg diastolic blood pressure measured in the Mobile Examination Center (MEC), or if they reported a physician diagnosis of hypertension with current use of antihypertensive medication.

Data cleaning

To ensure analytical rigor, an exclusion process was followed strictly. Individuals were excluded if they were: (1) below the age of 18 years or pregnant; (2) lacking laboratory data on serum creatinine or cystatin C needed to estimate the primary exposure; (3) lacking verifiable information on mortality status or duration of follow-up through probabilistic linkage with the NDI; or (4) lacking one of the main sociodemographic or clinical covariates: education, marital status, BMI, or smoking history. After applying these criteria, the final analytic cohort included 2,432 hypertensive adults, of whom 1,179 were men and 1,253 were women.

Variable definitions

The main exposure, serum CCR, was calculated using standardized laboratory values (serum creatinine [mg/dL]/cystatin C [mg/L]) and was used as a proxy indicator that primarily reflects skeletal muscle mass but is also influenced by renal function, nutritional status, and inflammatory state. The major outcome was all-cause mortality; survival status and follow-up time were determined by probabilistic linkage with NDI records. A detailed covariate list was taken into consideration to control potential confounding: sociodemographic variables (age, sex, race/ethnicity, education, marital status), lifestyle variables (smoking, alcohol

consumption), anthropometric variables (body mass index [BMI]), and biochemical variables (albumin, C-reactive protein [CRP], total cholesterol, high-density lipoprotein cholesterol [HDL-C], and estimated glomerular filtration rate [eGFR]). PA was assessed using structured questionnaires, whereby participants were classified into inactive, moderate-intensity, and vigorous-intensity groups according to self-reported frequency and duration.

Statistical analysis

The statistical tests were carried out with standard statistical software. Baseline characteristics were reported as mean ± standard deviation (SD) for continuous data and frequencies (expressed as percentages) for categorical data, with intergroup comparisons using Student's t-test or Mann–Whitney U test for continuous data and the chi-square test for categorical variables. Kaplan–Meier curves were used to visualize survival curves, and the log-rank test was used to compare them. Multivariable Cox proportional hazards regression models were used to estimate hazard ratios with 95% confidence intervals (CIs), especially the interaction between CCR levels and physical activity levels on mortality risk. A prognostic nomogram was then constructed using identified independent predictors, and its performance was assessed by discrimination using the area under the receiver operating characteristic curve (AUC), calibration plots to assess agreement between predicted and observed survival, and decision curve analysis (DCA) to measure net clinical benefit over a range of threshold probabilities. All statistical tests were two-sided, and statistical significance was set at $p < .05$.

RESULTS

Comparison of baseline characteristics

The final analytic cohort included 2,432 adults with hypertension, comprising 1,253 women and 1,179 men. Women were slightly older than men (68.1 ± 13.4 vs. 65.8 ± 14.3 years) and had lower weight and height, but a slightly higher BMI (29.6 ± 6.6 vs. 28.8 ± 5.4 kg/m²). Women also exhibited higher mean systolic blood pressure (149.1 ± 22.5 mmHg) and elevated lipid parameters, including total, high-density lipoprotein (HDL), and non-HDL cholesterol, whereas men had higher serum albumin, creatinine, and cystatin C levels. The CCR, a surrogate marker of skeletal muscle mass, was significantly lower in women (0.77 ± 0.18 vs. 0.99 ± 0.23), and the prevalence of low CCR was higher among women (26.1% vs. 23.7%), despite similar eGFR between sexes. Women had a longer follow-up duration (161 ± 71 months vs. 149 ± 76 months in men). Sociodemographic and lifestyle patterns also differed: men were more likely to be married or cohabiting (69.0%) and reported higher rates of smoking and physical activity (49.8% overall, with 22.1% engaging in vigorous activity), whereas women were more often widowed or divorced (53.4%), predominantly never-smokers (62.8%), and had a slightly higher rate of antihypertensive medication use (64.6% vs. 60.3% in men). These baseline differences indicate a female phenotype characterized by older age, dyslipidaemia, and lower muscle reserve, while men exhibited larger body size and higher levels of smoking and exercise, providing a heterogeneous basis for prognostic modelling.

Correlation between CCR and clinical characteristics

CCR-based stratification identified different clinical phenotypes. The low-CCR group was significantly older (mean age 69.8 vs. 64.2 years) and had smaller body size, but BMI was also higher, indicating a sarcopenic obesity phenotype. This population had a distinct hemodynamic and metabolic pattern with increased pulse pressure (greater systolic and reduced diastolic blood pressure), lower serum albumin, and increased inflammatory (CRP) and lipid markers (total cholesterol), although HDL levels were higher. Despite lower serum creatinine levels, eGFR was higher, possibly reflecting creatinine-based overestimation in the context of skeletal muscle loss.

Table 1. Baseline participant characteristics.

Characteristics	Female (n = 1253)	Male (n = 1179)
Age	68.06 ± 13.41	65.84 ± 14.26
Weight, kg	74.67 ± 18.68	85.90 ± 18.74
Height, cm	158.82 ± 7.22	172.51 ± 7.49
Body Mass Index	29.57 ± 6.57	28.82 ± 5.42
Systolic BP, mmHg	149.10 ± 22.53	143.18 ± 20.41
Diastolic BP, mmHg	70.00 ± 17.28	72.83 ± 18.38
Albumin, g/dL	4.19 ± 0.30	4.32 ± 0.33
CRP, mg/dL	0.66 ± 1.18	0.55 ± 1.19
Total Cholesterol, mg/dL	216.06 ± 40.09	200.57 ± 42.21
HDL Cholesterol, mg/dL	56.85 ± 16.66	46.59 ± 14.13
Non-HDL Cholesterol, mg/dL	159.25 ± 40.54	153.62 ± 43.49
Creatinine, mg/dL	0.86 ± 0.75	1.13 ± 0.86
Cystatin C, mg/L	1.11 ± 0.64	1.16 ± 0.69
CCR Ratio	0.77 ± 0.18	0.99 ± 0.23
GFR, mL/min/1.73m²	82.47 ± 24.61	81.86 ± 24.44
Overall Survival, months	161.00 ± 71.31	148.88 ± 75.79
Ethnicity		
Non-Hispanic White	679 (54.2%)	637 (54.0%)
Mexican American	235 (18.8%)	227 (19.3%)
Non-Hispanic Black	252 (20.1%)	254 (21.5%)
Other Race	24 (1.9%)	23 (2.0%)
Other Hispanic	63 (5.0%)	38 (3.2%)
Education level		
Less than 9th grade	126 (10.1%)	221 (18.7%)
9-11th grade	283 (22.6%)	297 (25.2%)
High school graduate/GED	327 (26.1%)	245 (20.8%)
Some college/AA	241 (19.2%)	207 (17.6%)
College graduate or above	271 (21.6%)	208 (17.6%)
Unknown	5 (0.4%)	1 (0.1%)
Marital status		
Married or living with partner	520 (41.5%)	814 (69.0%)
Widowed, divorced or separated	669 (53.4%)	325 (27.6%)
Never married	64 (5.1%)	40 (3.4%)
Hypertension medication		
No	444 (35.4%)	468 (39.7%)
Yes	809 (64.6%)	711 (60.3%)
Diabetes		
No	1031 (82.3%)	947 (80.3%)
Yes	221 (17.6%)	232 (19.7%)
Unknown	1 (0.1%)	0 (0.0%)
Low CCR		
No	926 (73.9%)	900 (76.3%)
Yes	327 (26.1%)	279 (23.7%)
Smoking status		
Never smoked	787 (62.8%)	404 (34.3%)
Former smoker	329 (26.3%)	579 (49.1%)
Current smoker	137 (10.9%)	196 (16.6%)
Exercise habits		
No exercise	754 (60.2%)	592 (50.2%)
Exercise	499 (39.8%)	587 (49.8%)
Exercise intensity		
Light	754 (60.2%)	592 (50.2%)
Moderate	324 (25.9%)	327 (27.7%)
Vigorous	175 (14.0%)	260 (22.1%)

Table 2. Association between CCR and clinical characteristics.

Variable	Low CCR	High CCR	*p*-value
Age	69.80 ± 12.64	64.18 ± 14.47	<.001
Weight (kg)	77.30 ± 19.71	82.93 ± 18.94	<.001
Height (cm)	161.59 ± 9.15	169.33 ± 9.39	<.001
BMI	29.57 ± 6.50	28.84 ± 5.54	.003
SBP (mmHg)	148.94 ± 21.63	143.53 ± 21.50	<.001
DBP (mmHg)	68.92 ± 18.52	73.82 ± 16.85	<.001
Albumin (g/dL)	4.23 ± 0.33	4.27 ± 0.32	<.001
CRP (mg/dL)	0.71 ± 1.40	0.51 ± 0.91	<.001
TC (mg/dL)	210.25 ± 42.09	206.85 ± 41.54	.045
HDL (mg/dL)	53.18 ± 16.48	50.57 ± 16.04	<.001
Non-HDL (mg/dL)	157.11 ± 42.11	155.93 ± 42.07	.488
Creatinine (mg/dL)	0.80 ± 0.38	1.19 ± 1.05	<.001
Cystatin C (mg/L)	1.15 ± 0.49	1.11 ± 0.80	.192
eGFR (mL/min/1.73m²)	87.77 ± 23.24	76.58 ± 24.51	<.001
Follow-up time (months)	147.97 ± 74.94	162.27 ± 71.86	<.001
Gender			**<.001**
Female	883 (72.6%)	370 (30.4%)	
Male	333 (27.4%)	846 (69.6%)	
Ethnicity			**<.001**
Non-Hispanic White	697 (57.3%)	619 (50.9%)	
Mexican American	286 (23.5%)	176 (14.5%)	
Non-Hispanic Black	146 (12.0%)	360 (29.6%)	
Other Race	22 (1.8%)	25 (2.1%)	
Other Hispanic	65 (5.3%)	36 (3.0%)	
Education level			**<.001**
Less than 9th grade	128 (10.5%)	219 (18.0%)	
9-11th grade	332 (27.3%)	248 (20.4%)	
High school graduate/GED	301 (24.8%)	271 (22.3%)	
Some college/AA	219 (18.0%)	229 (18.8%)	
College graduate or above	233 (19.2%)	246 (20.2%)	
Unknown	3 (0.2%)	3 (0.2%)	
Marital status			**<.001**
Married/Living with partner	574 (47.2%)	760 (62.5%)	
Widowed/Divorced/Separated	566 (46.5%)	428 (35.2%)	
Never married	76 (6.2%)	28 (2.3%)	
Hypertension medication			**.402**
No	446 (36.7%)	466 (38.3%)	
Yes	770 (63.3%)	750 (61.7%)	
Diabetes			**.598**
No	987 (81.2%)	991 (81.5%)	
Yes	228 (18.8%)	225 (18.5%)	
Unknown	1 (0.1%)	0 (0.0%)	
Low CCR indicator			**<.001**
No	610 (50.2%)	1216 (100.0%)	
Yes	606 (49.8%)	0 (0.0%)	
Smoking status			**<.001**
Never	661 (54.4%)	530 (43.6%)	
Former	391 (32.2%)	517 (42.5%)	
Current	164 (13.5%)	169 (13.9%)	
Exercise habit			**<.001**
No	761 (62.6%)	585 (48.1%)	
Yes	455 (37.4%)	631 (51.9%)	
Exercise intensity			**<.001**
Light	761 (62.6%)	585 (48.1%)	
Moderate	300 (24.7%)	351 (28.9%)	
Vigorous	155 (12.7%)	280 (23.0%)	
Age binary			**<.001**
Low Age	490 (40.3%)	705 (58.0%)	
High Age	726 (59.7%)	511 (42.0%)	

The low-CCR group was predominantly female (around two-thirds) and included more non-Hispanic Whites or Mexican Americans, lower education levels, and higher rates of widowhood or divorce. The lifestyle features reflected a sedentary profile, with a higher percentage of never-smokers and a much lower percentage of moderate and vigorous physical activity. By contrast, the high-CCR group was predominantly younger and male, with larger body size, higher socioeconomic status, and active lifestyles, including increased rates of smoking and exercise intensity. Such results imply that low CCR is an indicator of low muscle mass and also suggests the presence of a susceptible hypertensive subgroup in terms of aging, systemic inflammation, physical inactivity, and social disadvantage.

The CCR distribution was highly sexually dimorphic, with a much higher median value in males than in females (~1.0 vs. .8, $p < .001$), which is suggestive of greater physiological muscle reserve. In line with the pathophysiology of sarcopenic aging, an age-related reduction in CCR was noted ($p < .001$), whereas physical activity intensity exhibited a positive gradient against CCR ($p < .001$), indicating that vigorous physical exercise may have protective effects on muscle preservation. Smoking status was statistically significant but may not be clinically meaningful, whereas diabetes status was not significantly associated with CCR distribution. Correlation-based studies showed that CCR had negative correlations with systolic blood pressure (r = -.138, $p < .001$) and positive correlations with diastolic blood pressure (r = .140, $p < .001$), suggesting that muscle depletion is connected to the expansion of pulse pressure. There was a negative relationship between CCR and inflammatory markers (CRP) and a positive relationship with nutritional markers (albumin), indicating that systemic inflammation and malnutrition could be involved in muscle wasting. The strongest inverse relationship was observed with eGFR (r = −.329, $p < .001$), reflecting the mathematical dependence of CCR on serum creatinine levels. The stratification into low- versus high-CCR phenotypes further demonstrated the presence of a high-risk profile: the low-CCR group comprised mostly (72.6%) elderly women with a sarcopenic-obese anthropometric appearance (lower weight and height and slightly higher BMI), lower socioeconomic attainment, and inactive lifestyles. Together, these results suggest that CCR is not only a proxy biomarker of muscle mass but a complex biomarker that expresses the interactions between aging, inflammatory burden, and physical frailty in hypertensive patients.

Survival analysis and Cox regression

In this hypertensive cohort, univariate Cox regression analysis showed that several continuous variables were significantly associated with all-cause mortality: each additional year of age increased the hazard by approximately 9% (HR = 1.09, 95% CI 1.08-1.09, $p < .001$); BMI was inversely associated with risk, with a 4% reduction per unit increase (HR = 0.96, 95% CI 0.95-0.97, $p < .001$); systolic blood pressure (SBP) increased risk by about 1% per mmHg (HR = 1.01, 95% CI 1.01-1.01, $p < .001$); higher serum albumin was protective (HR = 0.53, 95% CI 0.45-0.62, $p < .001$), whereas elevated CRP indicated increased risk (HR = 1.05, 95% CI 1.02-1.08, $p < .001$). Higher eGFR modestly reduced mortality (HR = 0.98, 95% CI 0.98-0.98, $p < .001$). Among categorical variables, men had a 17% higher risk than women (HR = 1.17, 95% CI 1.06-1.30, $p = .002$), and widowed or divorced individuals had a 33% higher risk (HR = 1.33, 95% CI 1.20-1.47, $p < .001$). Diabetes, smoking, and low CCR were each important risk factors, and regular physical activity was associated with a 35% reduction in mortality risk (HR = 0.65, 95% CI 0.58-0.72, $p = .001$). After multivariable adjustment, age, BMI, SBP, albumin, HDL cholesterol, CCR, eGFR, male sex, smoking, diabetes, and physical inactivity were independent predictors. It is important to note that CCR had a hazard ratio of 0.13 (95% CI 0.09-0.18), and a lower creatinine-to-cystatin C ratio, indicating lower muscle mass, was a powerful independent risk factor. These findings were confirmed by Kaplan–Meier survival curves: participants aged 69 or older with low BMI, high SBP, albumin of less than 4.30 g/dL, low CCR, and low eGFR had significantly worse survival outcomes, and smokers and individuals with diabetes showed poorer outcomes compared with those who exercised regularly. Taken together, these results indicate that CCR is not a simple reflection

of skeletal muscle mass but rather a composite marker influenced by age, nutritional status, and renal function, such that people with low CCR are older, frailer, and more susceptible to death.

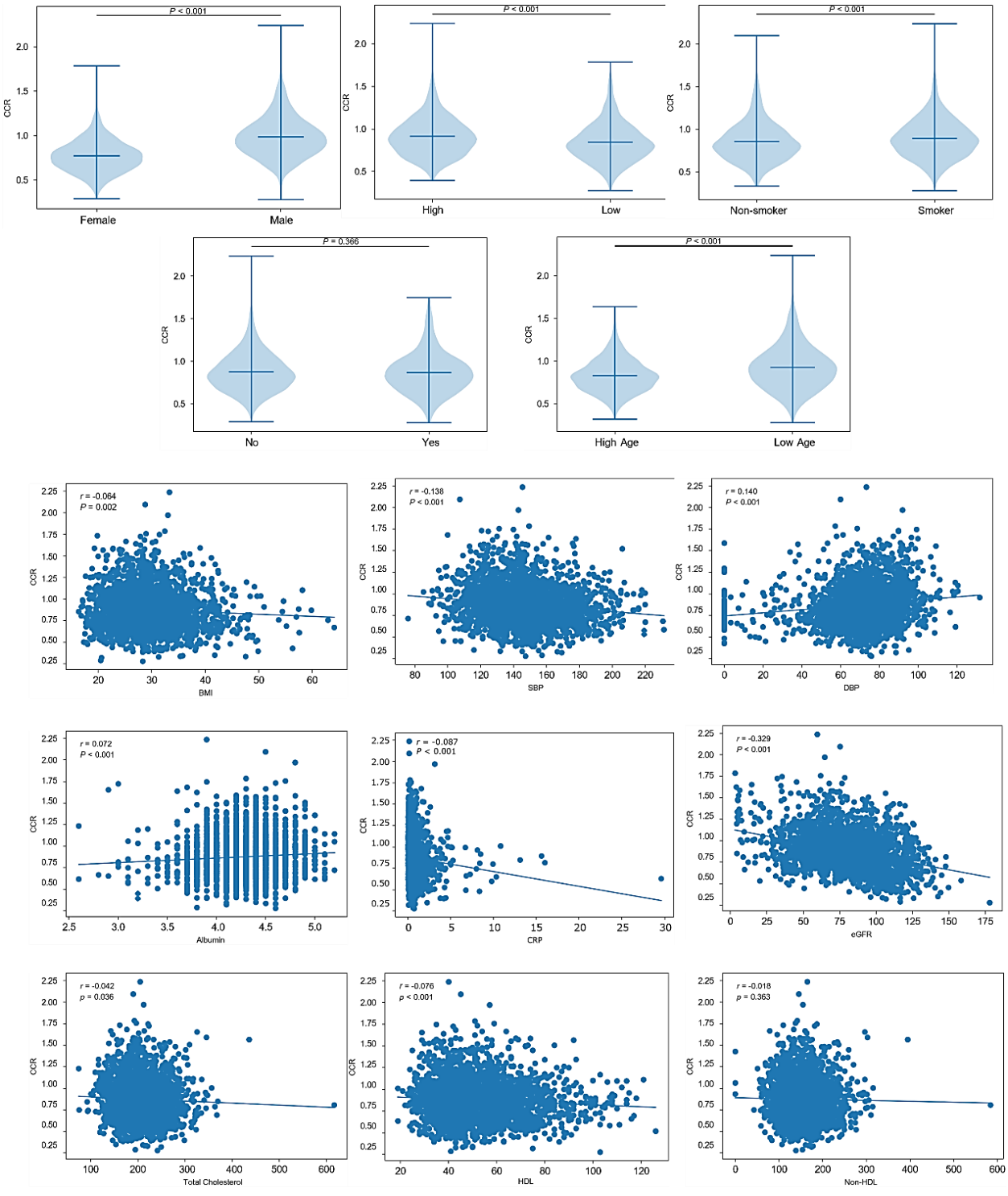

Figure 1. Stratified distribution and correlation analyses of CCR across baseline subject characteristics.

Table 3. Univariate Cox proportional hazards analysis of variables associated with all-cause mortality.

Numerical variable	**HR (95% CI)**	***p*-value**
Age	1.09 (1.08-1.09)	<.001
Weight (kg)	0.99 (0.98-0.99)	<.001
Height (cm)	0.99 (0.99-1.00)	.005
BMI	0.96 (0.95-0.97)	<.001
Systolic blood pressure (mmHg)	1.01 (1.01-1.01)	<.001
Albumin (g/dL)	0.53 (0.45-0.62)	<.001
CRP (mg/dL)	1.05 (1.02-1.08)	<.001
TC (mg/dL)	1.00 (1.00-1.00)	.023
HDL (mg/dL)	1.00 (1.00-1.01)	.124
Cystatin C (mg/L)	0.37 (0.3-0.46)	<.001
eGFR (mL/min/1.73m²)	0.98 (0.98-0.98)	<.001
Categorical variable		
Gender	1.17 (1.06-1.3)	.002
Ethnicity	0.69 (0.62-0.76)	<.001
Education level	0.96 (0.86-1.06)	.396
Marital status	1.33 (1.2-1.47)	<.001
Hypertension medication	1.31 (1.18-1.46)	<.001
Diabetes	1.51 (1.34-1.71)	<.001
Low CCR indicator	1.48 (1.33-1.65)	<.001
Smoking status	1.28 (1.16-1.42)	<.001
Exercise habit	0.65 (0.58-0.72)	<.001

Table 4. Multivariate Cox proportional hazards analysis of independent prognostic factors for all-cause mortality.

Numerical variable	**HR (95% CI)**	***p*-value**
Age	1.06 (1.05-1.07)	<.001
BMI	0.99 (0.98-1.00)	.013
Systolic blood pressure (mmHg)	1.00 (1.00-1.01)	.013
Albumin (g/dL)	0.62 (0.52-0.73)	<.001
HDL (mg/dL)	1.01 (1.00-1.01)	<.001
CCR Ratio	0.13 (0.09-0.18)	<.001
eGFR (mL/min/1.73m²)	0.98 (0.98-0.98)	<.001
Categorical variable		
Gender	2.25 (1.98-2.57)	<.001
Smoking status	1.36 (1.22-1.51)	<.001
Diabetes	1.39 (1.23-1.57)	<.001
Exercise habit	0.78 (0.70-0.87)	<.001

Subgroup analysis of exercise intensity and interaction

In this cohort, we examined the interaction between CCR and exercise on all-cause mortality. No significant interaction was observed between CCR status and exercise (*p*-interaction = .21), indicating that the adverse effect of low CCR on mortality was consistent regardless of exercise participation. Among non-exercisers, individuals with low CCR had a hazard ratio (HR) of 1.30 (95% CI 1.14-1.48) compared with those with high CCR, whereas among exercisers, the HR was 1.48 (95% CI 1.26-1.74). Stratification by exercise intensity revealed HRs for low versus high CCR of 1.29 (95% CI 1.13-1.47) for non-exercisers, 1.20 (95% CI 0.98-1.45, $p = .072$) for moderate-intensity exercisers, and 1.95 (95% CI 1.46-2.60, $p < .001$) for vigorous exercisers. Although the point estimates suggest a gradient of risk across exercise intensities, the lack of significant interaction ($p = .21$) precludes definitive conclusions about effect modification. Receiver operating characteristic (ROC) analysis showed that predictive performance was higher for selected variables: age (area under the curve or AUC = 0.835) had the highest predictive power, whereas systolic blood pressure, BMI, albumin, CCR, and eGFR had lower predictive value. Although CCR had a small AUC, it still had independent prognostic value when included in multivariable models. Forest plots and Kaplan–Meier curves repeatedly established that increased CCR correlated with improved survival regardless of exercise status

and that exercise resulted in relatively small benefits among individuals with low CCR, consistent with the possibility that muscle depletion may limit exercise benefits, though this interpretation is speculative given the non-significant interaction. The intensity-based analysis revealed the greatest risk in the vigorous exercise group, and the moderate-activity association was non-significant, potentially due to sample size constraints or selection bias. Overall, these results suggest that CCR, as a surrogate marker of muscle mass, has a close relationship with mortality in hypertensive patients, and its prognostic value remains consistent across different exercise behaviours. Although moderate exercise can have some overall health benefits, further studies with larger sample sizes are needed to clarify whether moderate exercise differentially affects survival in low-CCR individuals.

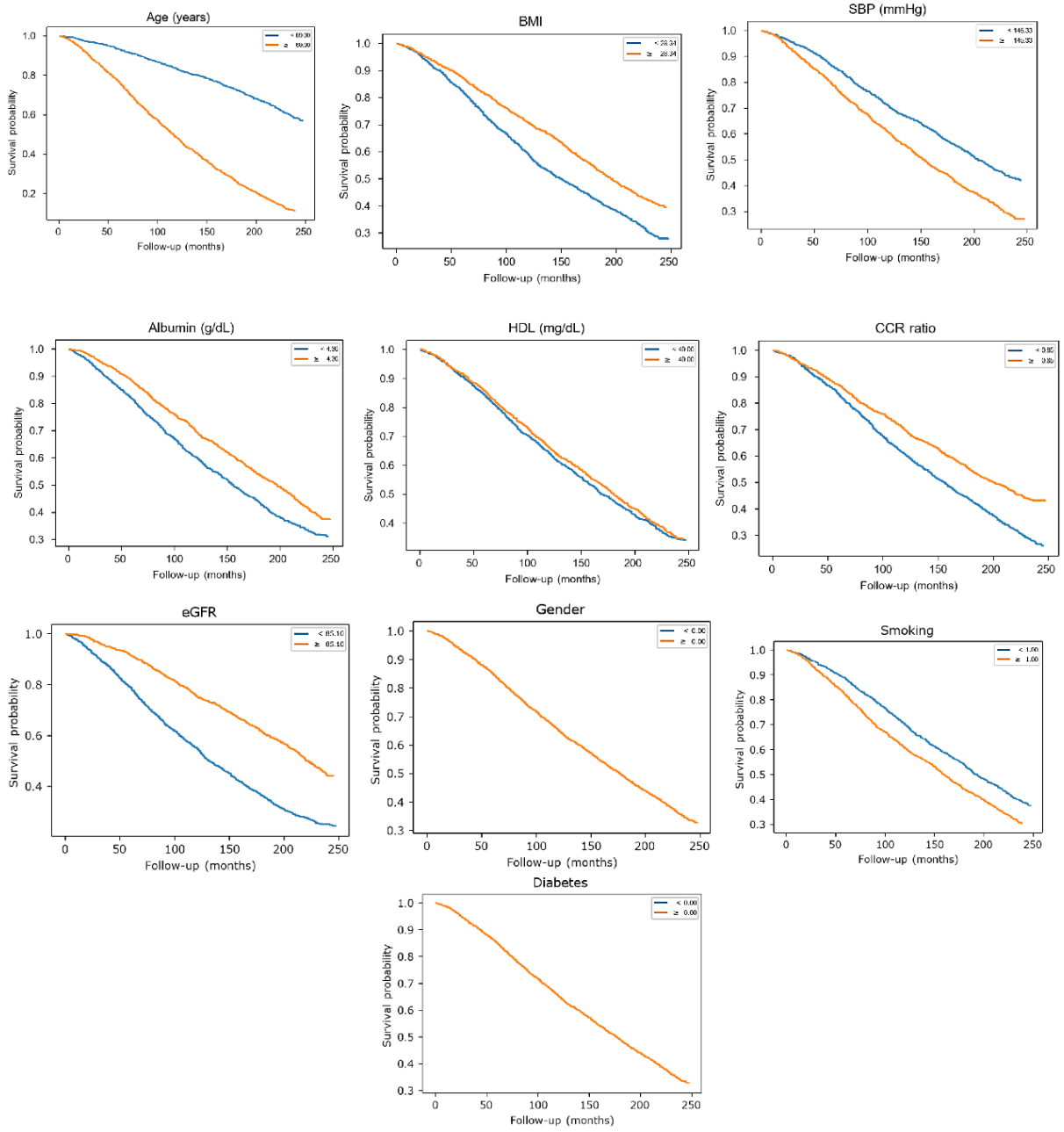

Figure 2. Kaplan-Meier survival analyses of significant predictive factors for survival outcome.

Table 5. Interaction analysis between CCR status and physical activity.

Exercise intensity	**HR (95% CI)**	***p*-value**
No exercise	1.29 (1.13 - 1.47)	<.001
Moderate intensity	1.2 (0.98 - 1.45)	.072
Vigorous intensity	1.95 (1.46 - 2.6)	<.001

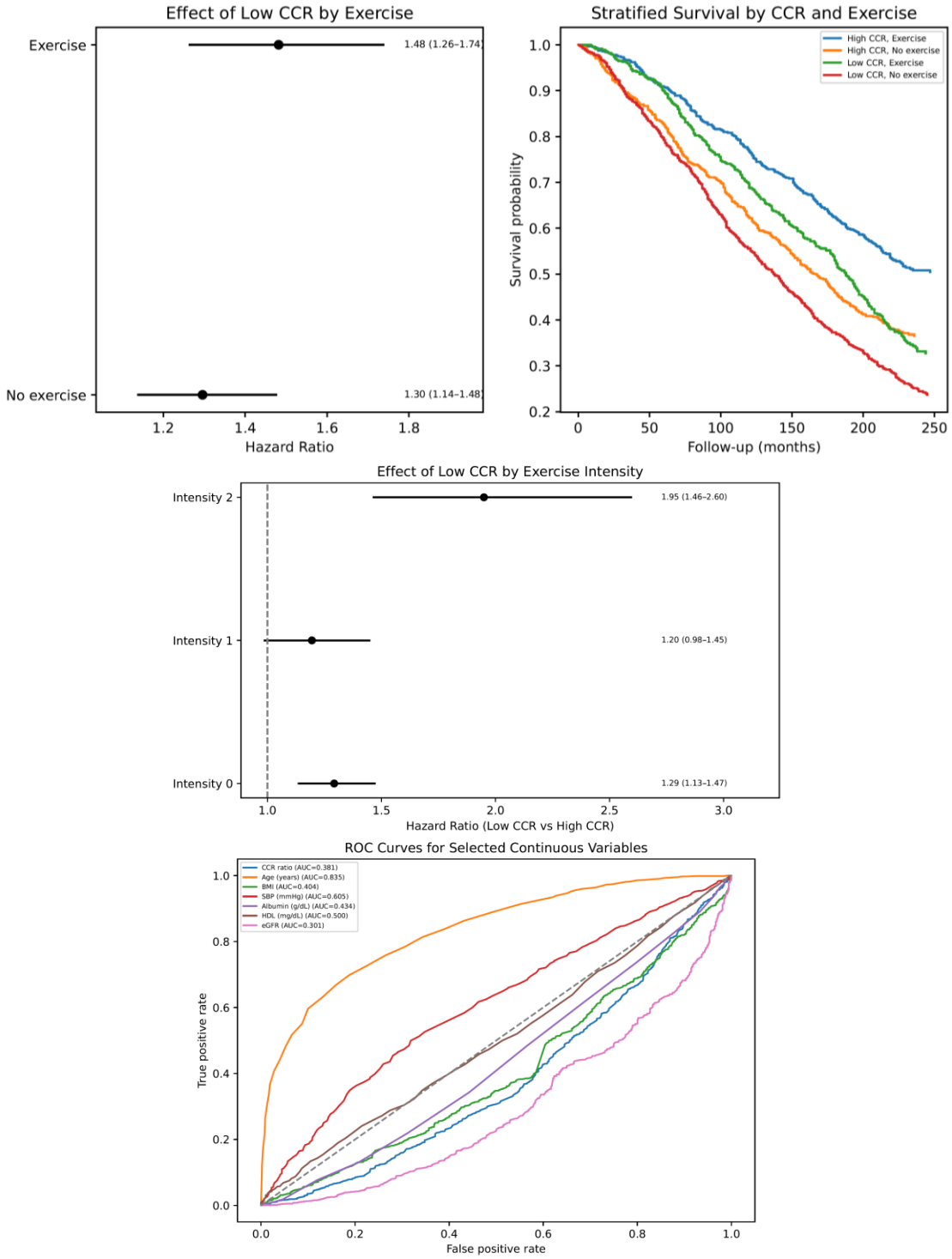

Figure 3. Interaction analysis of CCR and exercise, stratified survival curves, and ROC prediction curves.

Construction and validation of the prognostic nomogram

Specific risk scores were calculated using eleven predictors: age, BMI, SBP, albumin, HDL cholesterol, CCR, eGFR, sex, smoking, diabetes, and exercise in the nomogram. The highest range of points was exhibited by variables such as age, eGFR, and CCR, implying that age, poor kidney function, and muscle depletion had the greatest influence on mortality risk. The scale can predict 3-, 5-, and 10-year survival rates, with higher total scores indicating poorer predicted survival. Time-varying AUCs did not indicate any notable difference between the nomogram and a model based only on traditional cardiovascular risk factors (AUCs of 0.749 vs. 0.747 at 3 years, 0.753 vs. 0.744 at 5 years, and 0.789 vs. 0.785 at 10 years), suggesting limited additional prognostic information with the introduction of CCR and other variables. Calibration plots showed close agreement between predicted and observed survival at 3 and 5 years, as well as moderate deviation at 10 years. Decision curve analysis indicated that the nomogram had a larger net benefit than the basic model across various threshold probabilities (0.05-0.40) and was superior to treat-all and treat-none strategies, supporting its clinical utility. Risk stratification based on estimated 5-year risk showed a clear distinction between high- and low-risk groups, with significantly poorer survival in the former. A combined consideration of these results implies that inclusion of an indicator of muscle mass (CCR) into a multivariate nomogram may offer modest improvements in calibration and decision-analytic characteristics, though the incremental discriminative value appears limited relative to conventional risk-factor models.

Nomogram for predicting all-cause mortality in hypertensive patients

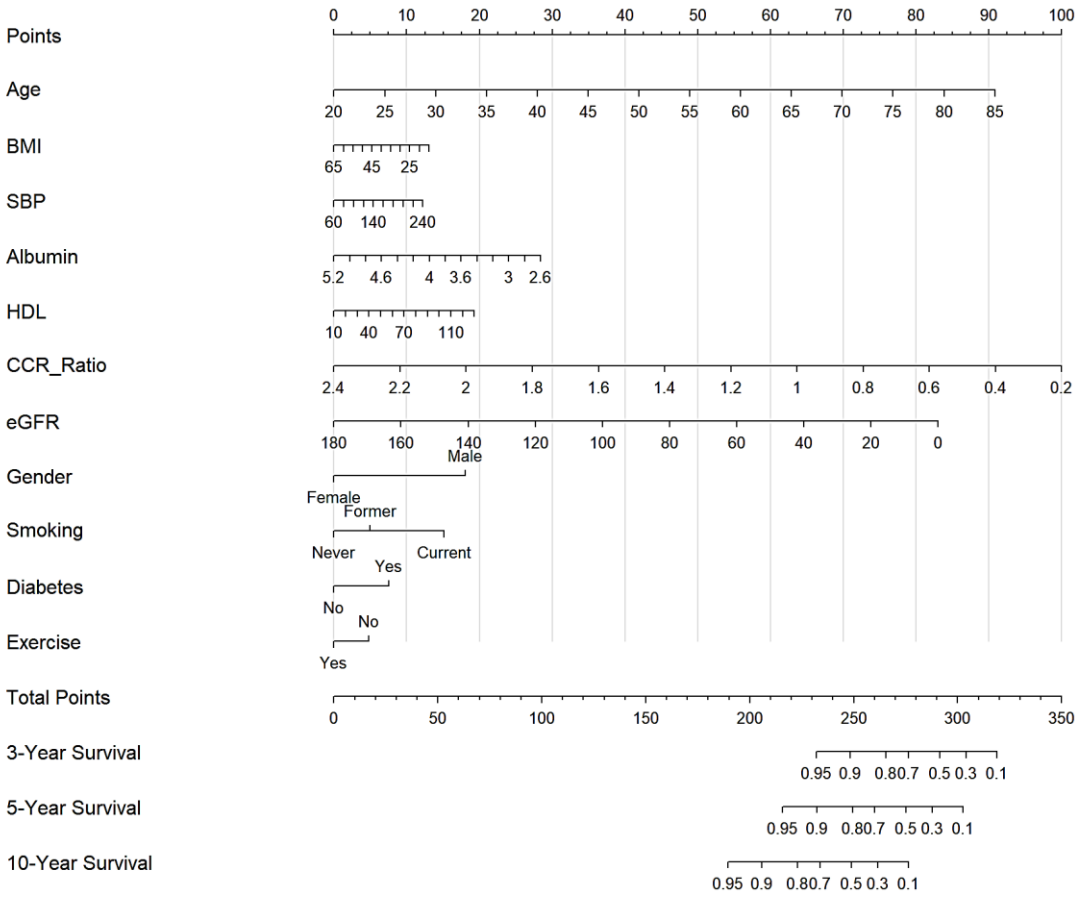

Figure 4. A prognostic nomogram to estimate long-term survival rates for patients with hypertension.

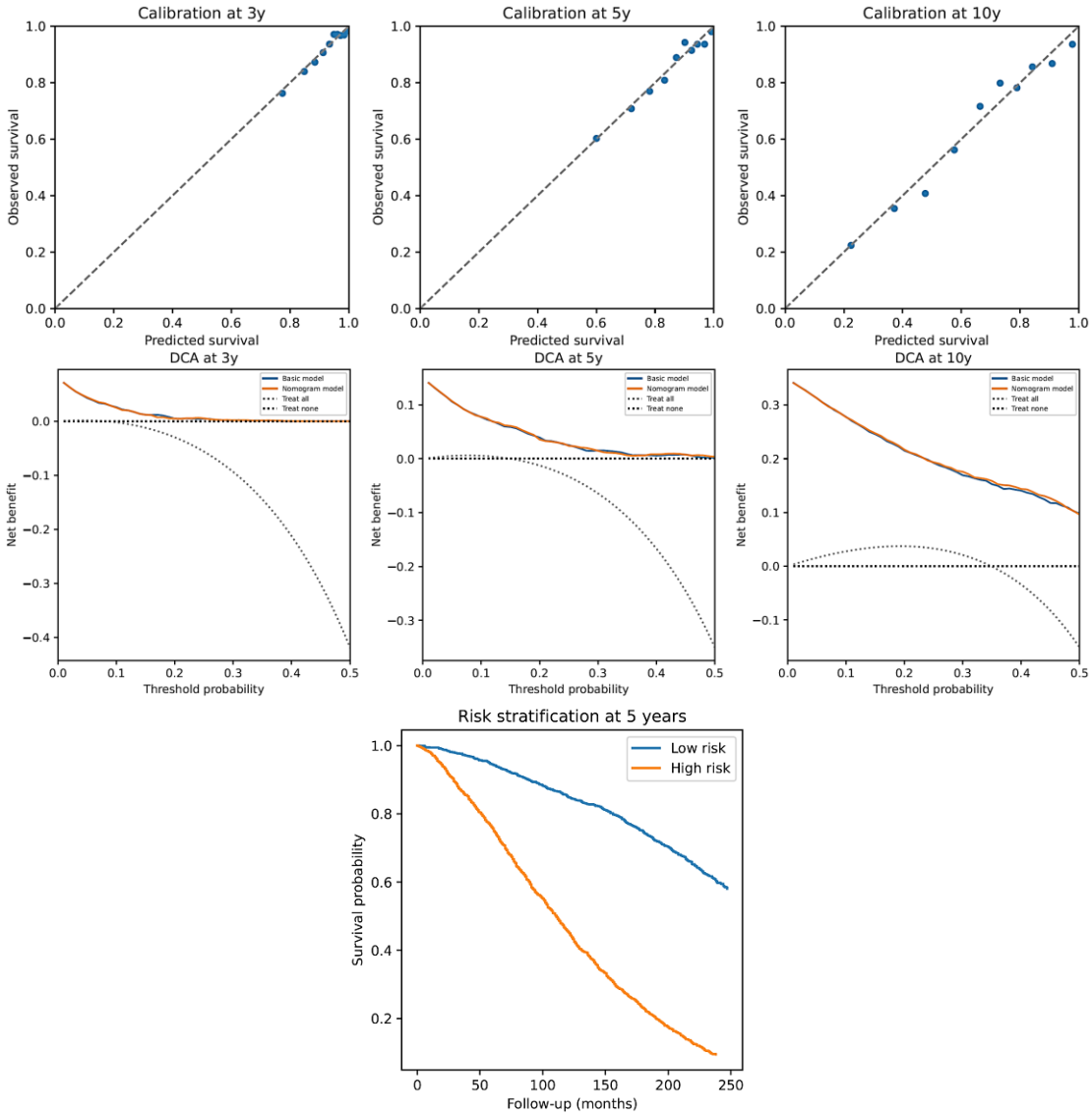

Figure 5. Calibration curves, decision curve analysis and risk-stratified survival curves for validating the prognostic nomogram.

DISCUSSION

Main findings

This is, to our knowledge, one of the larger studies examining the relationship between serum CCR and all-cause mortality in individuals with hypertension and one of the first to quantify the modifying influence of physical activity intensity using the nationally representative NHANES cohort (Osaka et al., 2018; Ren et al., 2025). In our analysis, lower CCR was identified as an independent predictor of mortality with a substantial effect size (Kirkman et al., 2021), though direct comparisons with BMI should consider their different biological meanings (Batsis & Villareal, 2018; Wannamethee & Atkins, 2015). Notably, we also found that the survival advantages of physical activity were not uniformly distributed, and poor skeletal muscle health may have reduced the potential benefit of vigorous exercise, implying that sufficient physiological muscle reserve is a major requirement for achieving the cardiovascular advantages of physical exercise (McPhee et al., 2016;

Reid & Fielding, 2012; Wolfe, 2006). Furthermore, the combined nomogram demonstrated modest incremental value beyond traditional risk factors, primarily through improved calibration and net benefit on decision curve analysis rather than substantial gains in discrimination (Pencina et al., 2008), supporting the incorporation of muscle-mass assessment into routine risk stratification of hypertensive patients (Sayer & Kirkwood, 2015).

Effect modification of muscle mass on exercise benefits

The second important study finding is that there may be skeletal muscle mass-related effect heterogeneity in the universal survival benefits of vigorous physical exercise, a finding that contrasts with the widely held assumption. Our results suggest that among those with low CCR, indicating possible sarcopenic frailty, vigorous exercise was not clearly associated with survival benefit and may even have been associated with worse outcomes, possibly because it exceeded physiological capacity (Eijsvogels et al., 2016; Mons et al., 2014). The observation is in line with the recent phenomenon of the so-called physical activity paradox (Powers et al., 2020), according to which, under conditions of pathological muscle depletion, the ability of the musculoskeletal system to counteract exercise-induced oxidative stress and hemodynamic load is compromised, resulting in maladaptive instead of adaptive responses (Radak et al., 2008; Viña et al., 2000). This significant heterogeneity was likely masked by previous aggregate studies that did not take into consideration muscle mass (Bouchard et al., 2012; Pickering & Kiely, 2019). These exploratory findings suggest that CCR might serve as a potential safety indicator, pending validation in prospective studies (Franklin et al., 2020), to guide the prescription of high-intensity exercise and to support cautious approaches in potentially susceptible subpopulations (Fragala et al., 2019; Izquierdo et al., 2021).

Putative pathophysiological mechanisms

The pathophysiological interpretation of CCR is complex. While it partially reflects skeletal muscle anabolism, it is also mathematically dependent on serum creatinine and influenced by renal function, nutritional status, and systemic inflammatory load. Therefore, CCR should be understood as a composite biomarker of physiological reserve rather than a specific measure of muscle mass alone (Knight et al., 2004; Shlipak et al., 2013). High CCR may indicate adequate musculoskeletal reserve and a favourable anabolic environment. Skeletal muscle is a locomotor organ but also the largest endocrine organ in the body, which secretes protective myokines (e.g., IL-6, irisin) (Severinsen & Pedersen, 2020) that enhance insulin sensitivity and reduce endothelial dysfunction induced by hypertension (Boström et al., 2012). On the other hand, a low CCR indicates a maladaptive condition of loss of metabolic plasticity (Smith et al., 2018) and chronic low-grade inflammation, including inflammaging (Ferrucci & Fabbri, 2018; Visser et al., 2002), with stimulation of vascular stiffness and augmentation of oxidative stress (Piotrowicz et al., 2022; Simioni et al., 2018). Such a biological background may help explain the impaired exercise response observed in our study: in the context of sarcopenic depletion, intensive exercise may fail to trigger a hormetic compensatory response and could potentially impose hemodynamic strain and metabolic stress that surpass already impaired compensatory capacity, thereby nullifying the desired cardiovascular advantages (Ji et al., 2016).

Clinical implications, strengths, and limitations

These results may have potential implications for the management of hypertension, and it may be necessary to move away from a blood pressure-based model to a more holistic one that includes musculoskeletal assessment (Benetos et al., 2019; Richter et al., 2022). We suggest that serum CCR could be considered in routine risk stratification procedures to detect subclinical sarcopenia and frailty. Our findings support personalized exercise prescriptions, i.e., patients with intact CCR may achieve cardiovascular benefits from moderate-vigorous aerobic exercise (Bull et al., 2020), whereas patients with low CCR, particularly older or frail individuals, might consider muscle-preserving interventions, such as nutritional optimization and

resistance training, as a preparatory step before progressive increases in exercise intensity. These are hypothesis-generating suggestions rather than prescriptive recommendations (Bauer et al., 2013; Cadore & Izquierdo, 2015). This is one of the strategies that can be used to counter the risks of intense exercise among muscle-depleted patients. Moreover, CCR helps improve the assessment of renal function, particularly in individuals with increased muscle mass, where healthy individuals may be incorrectly classified as having renal impairment because of increased serum creatinine (Delanaye et al., 2017; Rule et al., 2004). The strengths of this study include the use of a nationally representative NHANES dataset (Ahluwalia et al., 2016), high statistical power and generalizability, and thorough adjustment for possible confounders of renal function and systemic inflammation. Limitations are that this is an observational cohort study and therefore does not allow causal inference (Sedgwick, 2015); there is the possibility of residual confounding by unmeasured variables; and the study used self-reported physical activity, which may introduce recall bias (Prince et al., 2008; Troiano, 2008). There is also a lack of longitudinal detailed dietary data that could be used to evaluate nutritional effects (Beasley et al., n.d.). Future prospective and interventional studies are warranted to determine whether interventions that improve CCR can enhance survival among hypertensive patients (Yoshimura et al., 2017).

CONCLUSION

This study suggests that serum CCR is a marker of skeletal muscle mass and skeletal muscle physiological reserve with prognostic ability beyond conventional indices for predicting long-term mortality in hypertensive patients (Tang et al., 2020). We suggest that low CCR, potentially reflecting sarcopenia, may serve as a predictor of unfavourable outcomes and challenge the assumption that exercise uniformly benefits all individuals regardless of muscle status, though this requires confirmation in interventional studies. Particularly, we demonstrate that the cardiovascular benefits of moderate-intensity exercise may be attenuated in individuals with insufficient muscle reserve, and vigorous exercise in this subgroup warrants careful consideration (O'Keefe et al., 2012). These findings emphasize the importance of skeletal muscle as a potential mechanistic effector and a key metabolic basis for buffering disease burden (Argilés et al., 2016). The nomogram developed in the current study may provide a useful instrument for individualized risk stratification.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. Contributions are specified according to the CRediT (Contributor Roles Taxonomy) as follows: Conceptualisation: Peng Zhang. Methodology: Zhujun Mao, Peng Zhang. Formal analysis: Zhujun Mao. Investigation: Jiahe Zhang. Data curation: Zhujun Mao. Writing – original draft: Zhujun Mao, Jiahe Zhang. Writing – review & editing: Peng Zhang. Supervision: Peng Zhang.

All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

AI USE DISCLOSURE

In accordance with current publishing ethics and transparency recommendations, artificial intelligence (AI) tools were used solely to assist with translation and language editing, with the aim of improving clarity and readability. No AI tools were used in the generation of scientific content, including the study design, data collection, analysis, interpretation of results, or the formulation of conclusions. The authors retain full responsibility for the content of the manuscript and confirm its originality, integrity, and accuracy.

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