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The prognostic significance of stress hyperglycemia ratio in evaluating all-cause and cardiovascular mortality risk among individuals across stages 0–3 of cardiovascular–kidney–metabolic syndrome: evidence from two cohort studies

Mo-Yao Tan[1†], Yu-Jun Zhang[2†], Si-Xuan Zhu[3], Shan Wu[3], Ping Zhang[1] and Ming Gao[1*]

Abstract

Background The American Heart Association (AHA) proposed the concept of cardiovascular–kidney–metabolic (CKM) syndrome, underscoring the interconnectedness of cardiovascular, renal, and metabolic diseases. The stress hyperglycemia ratio (SHR) represents an innovative indicator that quantifies blood glucose fluctuations in patients experiencing acute or subacute stress, correlating with detrimental clinical effects. Nevertheless, the prognostic significance of SHR within individuals diagnosed with CKM syndrome in stages 0 to 3, particularly with respect to all-cause or cardiovascular disease (CVD) mortality risks, has not been fully understood yet.

Methods The current study analyzed data from 9647 participants with CKM syndrome, covering stages 0 to 3, based on the NHANES (National Health and Nutrition Examination Survey) collected from 2007 to 2018. In this study, the primary exposure variable was the SHR, computed as fasting plasma glucose divided by (1.59 * HbA1c – 2.59). The main endpoints of study were all-cause mortality as well as CVD mortality, with death registration data sourced through December 31, 2019. The CHARLS database (China Health and Retirement Longitudinal Study) was utilized as validation to enhance the reliability of the findings.

Results This study included 9647 NHANES participants, who were followed for a median duration of 6.80 years. During this period, 630 all-cause mortality cases and 135 CVD-related deaths in total were recorded. After full adjustment for covariates, our results displayed a robust positive association of SHR with all-cause mortality (Hazard ratio [HR] = 1.09, 95% Confidence interval [CI] 1.04–1.13). However, the SHR exhibited no significant relationship with

[†]Mo-Yao Tan and Yu-Jun Zhang have contributed equally to the article.

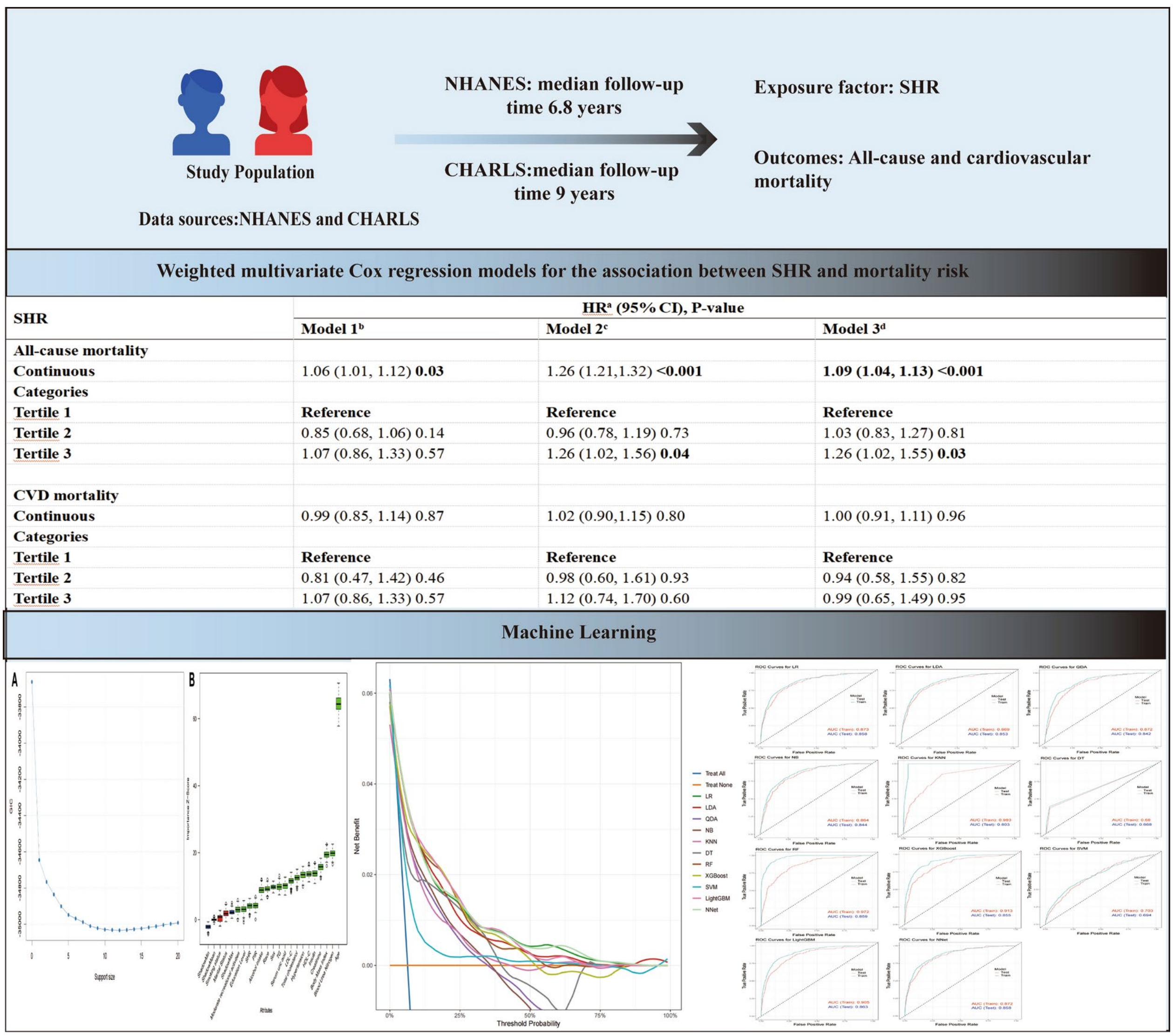
*Correspondence:
Ming Gao
18224409355@163.com

Full list of author information is available at the end of the article

CVD mortality (HR = 1.00, 95% CI 0.91–1.11). The mediation analysis results suggested that the relationship between SHR and all-cause mortality risk is partially mediated by RDW, albumin, and RAR. Specifically, the mediating effects were − 17.0% (95% CI − 46.7%, − 8.7%), − 10.1% (95% CI − 23.9%, − 4.7%), and − 23.3% (95% CI − 49.0%, − 13.0%), respectively. Additionally, analyses of the CHARLS database indicated a significant positive correlation between SHR and all-cause mortality among individuals diagnosed with CKM across stages 0–3 during the follow-up period from 2011 to 2020.

Conclusions An increased SHR value is positively associated with an elevated likelihood of all-cause mortality within individuals diagnosed with CKM syndrome across stages 0–3, yet it shows no significant association with CVD mortality. SHR is an important tool for predicting long-term adverse outcomes in this population.

Graphical abstract



Research insights summary Cardiovascular–kidney–metabolic (CKM) syndrome emphasizes the interconnectedness of cardiovascular, kidney, and metabolic diseases. The stress hyperglycemia ratio (SHR) is a novel marker reflecting stress-induced glucose fluctuations, but its prognostic value in individuals with CKM syndrome (stages 0–3) remains uncertain. This study explores the association between SHR and all-cause and cardiovascular disease (CVD) mortality in this population. Our findings indicate that SHR is significantly associated with an increased risk of all-cause mortality (HR = 1.09, 95% CI 1.04–1.13), but not with CVD mortality (HR = 1.00, 95% CI: 0.91–1.11). Mediation analysis results suggested that the relationship between SHR and all-cause mortality risk is partially mediated by RDW, albumin, and RAR. Specifically, the mediating effects were − 17.0% (95% CI − 46.7%, − 8.7%), − 10.1% (95% CI − 23.9%, − 4.7%), and − 23.3% (95% CI − 49.0%, − 13.0%), respectively. Validation using the CHARLS database supports these findings. These results suggest that SHR could serve as a prognostic biomarker for long-term mortality risk in CKM patients, offering potential clinical utility in risk stratification and management.

Keywords Cardiovascular–kidney–metabolic syndrome, Stress hyperglycemia ratio, All-cause and cardiovascular

Introduction

As of 2021, the worldwide incidence of cardiovascular diseases (CVD) had surged to 523 million cases, double that of 1990, positioning CVD as the foremost cause of death globally [1]. All-cause mortality denotes the proportion of deaths from all causes within a certain timeframe relative to the average population of that group during the same period [2]. For instance, in 2022, global deaths attributed to CVD reached 19.8 million, further emphasizing the urgency of addressing all-cause mortality [3].

Many research has demonstrated the complex and close interrelationship among CVD, chronic kidney disease (CKD), and metabolic diseases [4–6]. In its presidential advisory published in October of 2023, the American Heart Association (AHA) portrayed the cardiovascular-kidney-metabolic (CKM) syndrome as a systemic condition triggered by the pathophysiological interactions among cardiovascular disorders, CKD, and metabolic risk factors [7]. The interaction of these three factors significantly elevates the occurrence of adverse CVD outcomes and multi-organ dysfunction [7]. Data from 2015 to 2020 indicates that over a quarter of U.S. residents may have CKM syndrome, with healthcare expenditures for related diseases accounting for over 75% of total healthcare costs [8, 9]. As academic attention to CKM continues to grow, the staging framework for CKM has become more clearly defined, ranging from stage 0 (absence of risk factors) to stage 4 (confirmed CVD) [7]. The AHA emphasizes that preclinical prediction is crucial for individuals and suggests that research on the CKM syndrome population across stages 0–3 should prioritize preventing CVD-related events [10]. Given the disproportionate clinical burden of CKM about CVD, preventing and treating these three conditions as a whole will help prevent the rapid progression of CKM stages 0–3 [11].

Stress-induced hyperglycemia is marked by a significant elevation in blood glucose (BG) concentrations resulting from physiological or pathological stress [12]. This phenomenon is typically linked to regulating hormone secretion, immune responses, and nervous system activity [13]. In light of these observations, researchers have introduced stress-induced hyperglycemia ratio (SHR). This index directly quantifies the degree of blood glucose fluctuation as well as the physiological reaction to stress [14]. SHR is calculated by dividing the BG level at admission by glycated hemoglobin (HbA1c) [15]. Numerous research has shown that SHR is closely linked to a range of diseases [16–20]. For example, SHR has been shown to predict disease prognosis in various contexts, including hospital-acquired pulmonary infections, the prognosis of coronary artery disease, and the extent of thrombus formation [16–18]. SHR is also significantly correlated with a heightened likelihood of hemorrhagic transformation among individuals suffering from acute ischemic stroke [19].

Furthermore, SHR can serve as a valuable indicator for predicting risk of all-cause mortality among individuals diagnosed with acute myocardial infarction (MI) or heart failure (HF) [20]. The above evidence highlights the clinical potential of SHR. Given the complex interactions between CKD, CVD, and metabolic syndrome, exploring the correlation of SHR with all-cause mortality and CVD mortality within the context of CKM syndrome holds significant promise. A study conducted by Gregory et al. revealed a U-shaped correlation of BG control with all-cause mortality, emphasizing the critical need to maintain BG within a specific range to reduce adverse outcomes [21]. Similarly, a study conducted by Yang et al. observed a U-shaped association of SHR with cardiovascular adverse events among individuals diagnosed with acute coronary syndrome, while another study demonstrated a J-shaped correlation of critical illness with SHR [22, 23].

Given the pivotal influence of CKM syndrome on the progression of CVD, the risk of such diseases increases as CKM progresses [24]. All-cause mortality, an important indicator of overall health risks, reflects the combined impact of various factors, including CVD and metabolic abnormalities [25]. Therefore, studying the correlation of SHR with all-cause as well as CVD mortality across various CKM stages (i.e., from stage 0 to 3) is crucial. The current study uses data from the NHANES database (National Health and Nutrition Examination Survey) (2007–2018) to examine the association of SHR with mortality within the American population. To strengthen the robustness of our findings, a sensitivity analysis was performed utilizing data from the CHARLS database (China Health and Retirement Longitudinal Study) for further validation.

Methods

Study population

NHANES is a cross-sectional survey that has been carried out since the 1960s to evaluate the nutritional as well as health status of the non-institutionalized American population, providing critical information for public health research and policy. This survey applied a sophisticated multistage probability sampling design to ensure the selection of nationally representative samples regularly. Conducted under the auspices of the Centers for Disease Control and Prevention, the results of the survey release comprehensive datasets biennially. All study protocols must be approved by the Ethics Review Board of the National Center for Health Statistics (NCHS), and informed consent is required from every participant prior to their inclusion in the survey [26].

We included data from six consecutive cycles spanning 2007 to 2018, covering 59,842 participants. First, we excluded subjects under the age of 20 years (n = 25,072). Next, we excluded participants with incomplete or missing data related to CKM (n = 18,707) and SHR (n = 701), as well as participants in CKM stage 4 (n = 1920). We then excluded individuals with missing demographic data: marital status (n = 6), education level (n = 12), poverty-to-income ratio (PIR) (n = 1271), and body mass index (BMI) (n = 110); missing lifestyle data: alcohol consumption (n = 1318) and smoking status (n = 9); missing biochemical data: serum uric acid (n = 135), low-density lipoprotein cholesterol (LDL-C) (n = 171), triglycerides (n = 102), high-density lipoprotein cholesterol (HDL-C) (n = 1), and fasting insulin (n = 109); missing disease data: diabetes (n = 111); and those with a weight less than or equal to zero (n = 435). Finally, after excluding participants with missing survival status data, 9647 participants remained for analysis (Fig. 1).

Definition of SHR

The SHR served as the primary exposure factor in this study, providing a quantitative measure of BG fluctuations among individuals experiencing acute or subacute stress conditions. SHR represents the extent of BG variation experienced by patients during stressful situations

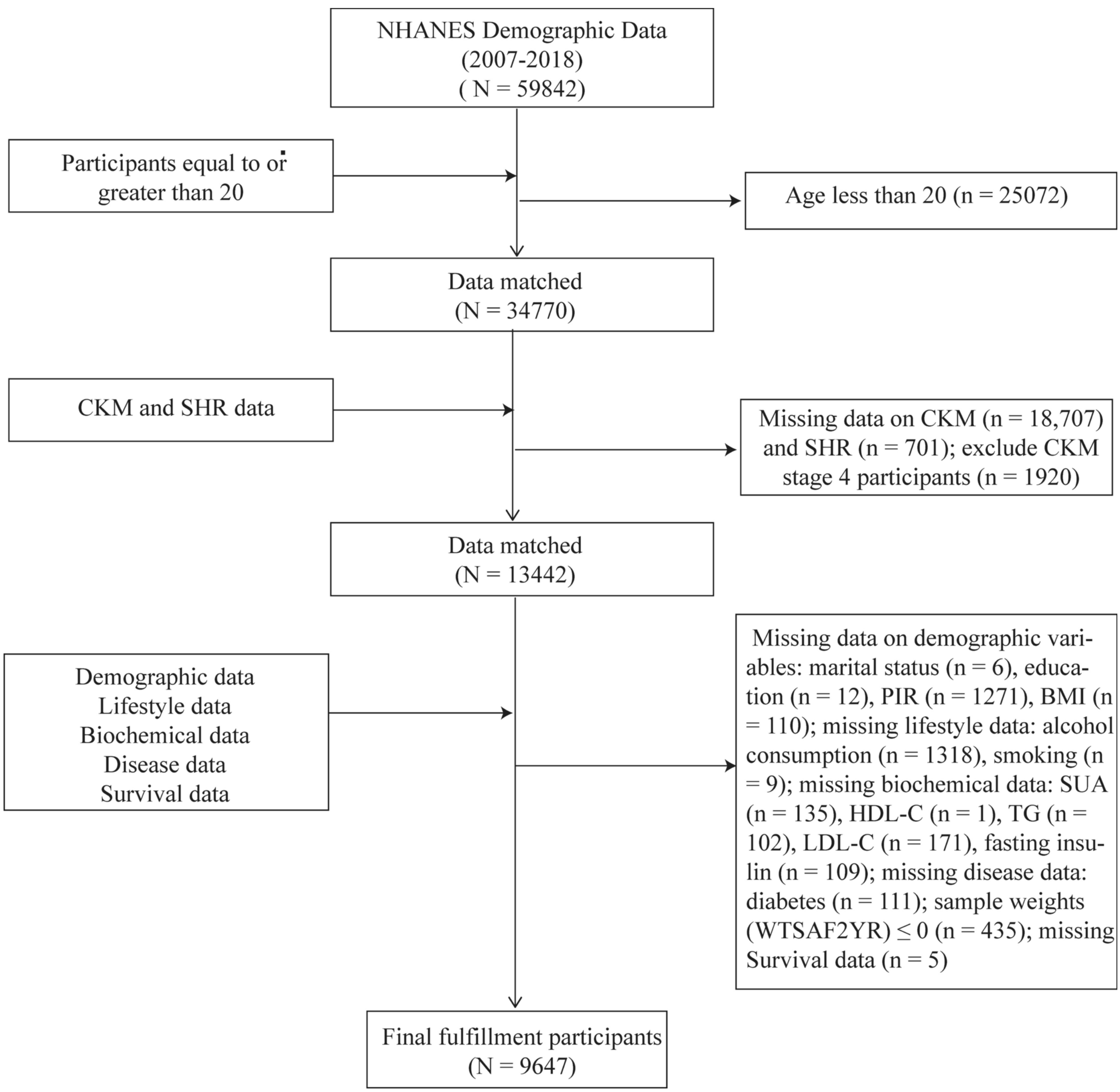


Fig. 1 Flow chart of the study participant selection process

while hospitalized, as well as the effectiveness of controlling these fluctuations. The SHR was determined according to the equation: SHR = FPG/(1.59 × HbA1c—2.59), where FPG denotes fasting plasma glucose level (measured in mg/dL), and HbA1c refers to glycated hemoglobin (expressed as a percentage, %) [27]. In addition to analyzing SHR as a continuous variable, subjects were also categorized into three groups (T1, T2, and T3) based on SHR values using the tertile method, with T1 designated as the reference group for comparative analyses against T2 and T3. This stratified approach allows for a granular evaluation of the associations of SHR with other variables or health-related outcomes.

Definition of CKM syndrome across stage 0–3

As detailed in previously published literature [28], CKM syndrome is classified into stages 0 through 4, as defined by the 2023 AHA Presidential Advisory on CKM Health. Stage 0 represents the absence of risk factors for CKM syndrome, characterized by individuals with normal BMI, waist circumference, BG, blood pressure (BP), lipid levels, kidney function, as well as no signs of CVD. For U.S. populations, BMI should be below 25 kg/m^2 for non-Asian individuals and below 23 kg/m^2 for Asian individuals. Waist circumference should be less than 88 cm for women and less than 102 cm for men in non-Asian populations, less than 80 cm for women, and less than 90 cm for men in Asian populations. Stage 1 includes individuals who have obesity or impaired glucose metabolism, characterized by excess or dysfunctional fat accumulation. Specifically, BMI should be ≥ 25 kg/m^2 for non-Asian populations while ≥ 23 kg/m^2 for Asian populations. Waist circumference should be ≥ 88 cm for the female population ≥ 102 cm for the male population in non-Asian populations ≥ 80 cm for the female population, and ≥ 90 cm for the male population in Asian populations. Prediabetes is characterized by an HbA1c level between 5.7% and 6.5% or a fasting BG level between 100 mg/dL and 126 mg/dL. Stage 2 encompasses subjects with moderate to high-risk CKD, defined by an eGFR of 30 to 60 mL/min/1.73 m^2 and/or a self-reported CKD, as well as those presenting with metabolic risk factors. Metabolic risk factors include elevated hypertension, diabetes, fasting serum triglycerides level greater than 135 mg/dL, or the presence of metabolic syndrome. Furthermore, a diagnosis of the metabolic syndrome is established when an individual exhibits at least three of the following criteria: increased waist circumference, reduced HDL-C levels under 40 mg/dL in males or 50 mg/dL in females, fasting triglycerides exceeding 150 mg/dL, elevated BP (Systolic BP ≥ 130 mmHg or diastolic BP ≥ 80 mmHg), or a prediabetic state. CKD is assessed using eGFR, with stages determined by the KDIGO criteria. Stage 3 involves individuals exhibiting subclinical CVD, defined by clinical indicators such as a higher CVD risk based on the Framingham risk score (female ≥ 21.5%, male ≥ 21.6%) or those with very advanced-stage CKD (i.e., eGFR < 30 mL/min/1.73 m^2). Finally, Stage 4 refers to individuals with clinical CVD, determined by self-reported CVD such as HF, coronary heart disease, or stroke.

Mortality data collection and analysis

We selected all-cause mortality and CVD mortality as the primary and secondary outcome measures, respectively, in patients with CKM (stages 0–3). The primary endpoint was all-cause mortality, with CVD mortality as the secondary endpoint. The follow-up period started at the time of the initial interview and concluded either at the time of death or on December 31, 2019, whichever came first, marking the cutoff for the mortality period. Mortality data were downloaded from publicly available files from NHANES, with the final data point set to December 31, 2019. These files were linked to the National Death Index (NDI) using a probabilistic matching algorithm to ensure accurate mortality tracking. The causes of death were categorized according to the ICD-10 (International Classification of Diseases, 10th edition), with potential underlying causes reclassified. All-cause mortality was regarded as death attributable to any cause, whereas CVD-related mortality included deaths attributed to heart disease (i.e., I00–I09, I11, I13, or I20–I51) or cerebrovascular disease (i.e., I60–I69).

Covariates

This study examines the impact of numerous covariates on the correlation of SHR with all-cause and CVD mortality within patients across CKM stages 0–3, based on prior research [29]. Continuous variables consist of age (years), BMI, creatinine, total cholesterol (TC), as well as LDL-C. Categorical variables include gender (male, female), race/ethnicity, education level, and marital status. Alcohol consumption is categorized into five groups: never, former, mild, moderate, or heavy, while smoking status is classified as never smoker, former smoker, or current smoker. The PIR is divided into low (PIR < 1.3), medium (1.3 ≤ PIR < 3.5), and high (PIR ≥ 3.5). Recreational physical activity is classified as either active or inactive, whereas "active" refers to participating in moderate or vigorous activity at least once a week, as per Yu et al. [30]. Hypertension is diagnosed according to any one of the following conditions: (1) systolic BP greater than 140 mmHg, (2) diastolic BP greater than 90 mmHg, (3) a self-reported prior diagnosis of hypertension, or (4) ongoing use of anti-hypertensive medications.

Statistical analysis

All statistical analyses accounted for the sampling weights inherent to the NHANES survey design, ensuring an accurate representation of the complex multistage sampling design. This approach guaranteed that findings could be generalizable to the non-institutionalized American population and prevented overestimation of statistical significance. As *per* NHANES guidelines, weight selection prioritizes representative variables for the small population subgroup, subsequently allocating the appropriate weights accordingly. Data for this study were sourced from the Mobile Examination Centers, including indicators such as fasting plasma glucose (FPG). Following the NHANES weight selection guidelines, the FPG data-related sub-weight variable (i.e., WTSAF2YR) was applied. For all selected cycles, the two-year weight for each cycle was divided by the total number of cycles (6) to compute the new weight. Weighted means accompanied by standard errors (SE) were presented for continuous variables, whereas counts with corresponding percentages for categorical variables. Group comparisons were conducted by Student's t-test and Chi-square test for continuous and categorical variables, respectively. To estimate the hazard ratios (HRs) with corresponding 95% confidence intervals (CI) for the relationship of the SHR index with all-cause and CVD mortality, multivariate Cox proportional hazards regression models were developed. Model 1 was unadjusted, Model 2 adjusted for age, race/ethnicity, and gender, and Model 3 further adjusted for age, race/ethnicity, gender, BMI, PIR, marital status, education level, smoking status, alcohol consumption, recreational physical activity, creatinine, TC, LDL-C, and hypertension. Furthermore, the SHR index was converted from a continuous variable into tertiles (T1, T2, T3) for subsequent analysis. The dose–response correlation of SHR index with mortality was analyzed by performing restricted cubic splines (RCS) analysis. In cases of nonlinear relationship, potential threshold effects were identified by systematically testing all possible inflection points and selecting the most probable values. A piecewise Cox proportional hazards regression model was then applied to investigate SHR index's correlation with all-cause mortality and CVD mortality, stratified by the identified inflection point. If a significant correlation of SHR with either all-cause mortality or CVD mortality was observed, further analyses would be conducted for the mortality outcome that showed a significant relationship.

The dataset was randomly partitioned into two separate subsets, i.e., a training set and a test set. The training set included 70% (N = 6753) of the total sample, while the test set constituted 30% (N = 2894). Complex high-dimensional data can significantly impact the performance of machine learning (ML) algorithms. Consequently, prior to constructing the ML model, we employed the Adaptive Best Subset Selection (ABESS) algorithm and the Boruta algorithm to identify key features. The objective of the ABESS algorithm is to identify a minimal set of predictor variables that yield the highest predictive accuracy in the constructed model [31]. The Boruta algorithm, on the other hand, is a robust feature selection technique rooted in random forest methodology, which evaluates the importance of the original features by comparing their importance scores with those of shadow features. This method aims to reduce the error of the random forest model and ultimately to select the optimal subset of features [32]. These two methods effectively mitigate the risk of losing key predictors and are now widely employed [33–36]. Upon completing variable selection, we further utilized the variance inflation factor (VIF) to assess multicollinearity among the variables, thereby refining the selection process. Variables with VIF values exceeding 10 indicated severe multicollinearity and were excluded from model construction. Subsequently, we developed eleven ML methods on the training set to predict all-cause mortality risk, including logistic regression (LR), quadratic discriminant analysis (QDA), linear discriminant analysis (LDA), Naive Bayes (NB), decision tree (DT), K-nearest neighbor (KNN), random forest (RF), extreme gradient boosting (XGBoost), support vector machines (SVM), light gradient boosting machine (LightGBM) as well as neural network (NNet). Each machine learning model underwent hyperparameter tuning and tenfold cross-validation to ensure optimal performance and reliability. To evaluate the predictive accuracy of the models, we employed the receiver operating characteristic (ROC) curve and computed the area under the curve (AUC), which is designed to compare the predictive capabilities of different ML models. We utilized the following metrics: AUC of the ROC, average precision score (APS), accuracy, recall, negative predictive value (NPV), positive predictive value (PPV), false negative rate (FNR), precision, false positive rate (FPR), and F1 score. Additionally, we applied decision curve analysis (DCA) to assess the clinical validity of the methods and utilized calibration curves to determine the accuracy of absolute risk predictions.

The red cell distribution width (RDW) to albumin ratio (RAR) is a novel integrative biomarker of inflammation and nutrition, which can be employed to assess immune status and response [37, 38]. Recent studies indicate that elevated RAR levels are associated with an increased risk of all-cause and cause-specific mortality in the general population [39]. Consequently, a four-way decomposition method was applied to assess the mediating effects of RDW, albumin, and RAR on the relationship between SHR and mortality.

To rigorously evaluate the robustness of our findings, we performed a range of comprehensive sensitivity analyses. The specific steps are as follows: (1) First, we considered the potential influences of medication usage, dietary habits, and stress levels on the results. Accordingly, we further adjusted for antihyperglycemic medications, energy intake, the Healthy Eating Index 2015 (HEI-2015) [40] and the Patient Health Questionnaire-9 (PHQ-9) score [41] as outlined in Model 3 to assess the robustness of our findings. (2) Secondly, we used the CHARLS database, with 2011 as the baseline and a 9-year follow-up (until 2020), to examine the influence of SHR on all-cause mortality within CKM stages 0–3 population (CVD mortality was not analyzed because of the unavailability of relevant data within the CHARLS database). We validated the analysis using three models: Model 1 had no adjustments for covariates. In Model 2, adjustments were applied to the age, gender, as well as education level. In Model 3, we further adjusted for smoking status, alcohol consumption, creatinine, blood urea nitrogen, HDL-C, LDL-C, TC, hypertension, and residence. (3) Thirdly, we conducted stratified analyses to explore potential modification effects based on age (≤65/ > 65), sex (female/male), drinking status (never drinker/current drinker/former drinker), smoking status (non-smoker/current smoker/former smoker), moderate recreational activity (inactive/active), hypertension status (no/yes), and CKM stages (0–3). The interactions between these stratified covariates and mortality were estimated using the likelihood ratio test.

A statistically significant result was determined when the *P*-value fell below 0.05. All analyses in the present study were carried out using R software (version 4.1.2).

Results

Baseline characteristics

Table 1 presents an overview of the baseline characteristics of the included subjects, both overall and grouped by SHR index tertiles. Finally, 9647 participants in total were included, with a mean age of 45.54 ± 0.30 years. The mean SHR index among included participants was 16.79 ± 0.05, with the SHR index ranges for tertiles 1–3 being 1.95–15.67, 15.68–17.30, and 17.31–38.05, respectively. Among the participants, 4984 were female (51.38%), and 4,663 were male (48.62%). Significant statistical differences across the SHR index tertiles were observed for various factors, including age, insulin, blood urea nitrogen, HbA1c, creatinine, serum uric acid, triglycerides, TC, LDL-C, HDL-C, and BMI ($p < 0.05$). Participants in the highest SHR tertile showed significant differences in various health indicators when compared to those in the lowest SHR tertile. Participants of the highest SHR tertile were older and had lower levels of LDL-C, HDL-C, HbA1c, and TC. In contrast, they exhibited higher BMI, serum uric acid, creatinine, blood urea nitrogen, TG, as well as insulin levels. Furthermore, apart from health indicators, participants in the highest SHR tertile also displayed distinct socioeconomic characteristics, including a higher proportion with low PIR values, as well as a greater proportion being White and former drinkers.

Association of SHR index with all-cause and CVD mortality

To explore the independent relationship of SHR index with all-cause and CVD mortality risks, we constructed three Cox regression models (Table 2). In Model 1, without adjustment for any covariates, a significant positive correlation was identified between the SHR index and the all-cause mortality risk (HR 1.06, 95% CI 1.01–1.12). The above positive correlation was further confirmed in Model 2 (HR 1.26, 95% CI 1.21–1.32). After full adjustment in Model 3, the positive correlation of the SHR index with the risk of all-cause mortality remained significant (HR 1.09, 95% CI 1.04–1.13). Additionally, similar trends were observed when subjects were grouped according to the three tertiles of the SHR index. In Model 3, compared with individuals within the lowest tertile of the SHR index, those within the highest tertile exhibited a significantly elevated risk of all-cause mortality (HR 1.26, 95% CI 1.02–1.55). However, no significant correlation was found of SHR index with the risk of CVD death across any of the models ($p > 0.05$).

RCS and threshold effect analysis

To validate the correlation of the SHR index with both all-cause and CVD mortality, we conducted RCS analysis and threshold analysis. Our results suggested a U-shaped association of the SHR index with both outcomes (Fig. 2). Additionally, we employed two segmented Cox regression models to investigate the correlation of baseline SHR index with mortality. The threshold for all-cause mortality was established at 17.93, while the threshold for CVD mortality was determined to be 14.02 (Table 3). For SHR values ≥ 17.93, we found that each 1-unit increase in SHR index was related to a 16% higher risk of all-cause mortality (HR 1.16, 95% CI 1.11–1.22). However, for SHR values < 17.93, no significant association was found between SHR index and all-cause mortality risk. The overall linear regression analysis failed to reveal a significant link between the SHR index and CVD mortality (HR = 1.01, 95% CI 0.95–1.09, $p = 0.72$). Nevertheless, segmented linear regression analysis suggested a significant nonlinear correlation of the SHR index with CVD mortality. When the SHR index was below 14.02, a significant reduction in the CVD mortality risk was observed (HR = 0.77, 95% CI 0.66–0.89, $p = 0.001$); conversely, when the SHR index exceeded 14.02, the risk of CVD mortality significantly increased (HR = 1.07, 95% CI 1.01–1.15, $p = 0.04$). These findings suggest a threshold effect of SHR index on CVD mortality, with significant differences at different levels. Further likelihood ratio tests ($p = 0.002$) supported using

Table 1 Weighted baseline characteristics of participants

Characteristics	Stress-induced hyperglycemia				
	Total	**T1**	**T2**	**T3**	***P*-value**
	(1.95, 38.05)	**(1.95, 15.67)**	**(15.68, 17.30)**	**(17.31, 38.05)**	
Age (years)	45.54 (0.30)	46.90 (0.41)	45.60 (0.43)	44.39 (0.40)	< 0.001
Body mass index (kg/m^2)	28.88 (0.12)	28.42 (0.15)	28.66 (0.17)	29.47 (0.18)	< 0.001
Total cholesterol (mg/dl)	192.65 (0.66)	194.14 (1.04)	195.22 (0.94)	188.98 (0.97)	< 0.001
Blood urea nitrogen (mg/dl)	13.27 (0.08)	13.10 (0.11)	13.16 (0.10)	13.51 (0.12)	0.01
Serum uric acid (mg/dl)	5.45 (0.02)	5.26 (0.03)	5.39 (0.03)	5.65 (0.03)	< 0.001
Creatinine (mg/dl)	0.86 (0.00)	0.86 (0.01)	0.84 (0.00)	0.88 (0.01)	< 0.001
HDL-C (mg/dl)	54.56 (0.27)	56.52 (0.44)	55.27 (0.40)	52.30 (0.37)	< 0.001
LDL-C (mg/dl)	115.28 (0.49)	115.87 (0.81)	117.49 (0.83)	112.67 (0.83)	< 0.001
TG (mg/dl)	114.07 (1.05)	108.80 (1.78)	112.29 (1.63)	120.03 (1.61)	< 0.001
Insulin (uU/ml)	12.33 (0.19)	11.11 (0.32)	11.83 (0.24)	13.80 (0.30)	< 0.001
Fasting glucose (mg/dl)	104.68 (0.39)	94.82 (0.36)	101.85 (0.36)	115.35 (0.82)	< 0.001
HbA1c	5.56 (0.01)	5.75 (0.02)	5.53 (0.01)	5.45 (0.02)	< 0.001
SHR	16.79 (0.05)	14.53 (0.03)	16.44 (0.01)	18.94 (0.04)	< 0.001
Sex, n (%)					< 0.001
Male	4663 (48.62)	1282 (37.92)	1508 (46.29)	1873 (59.49)	
Female	4984 (51.38)	1926 (62.08)	1703 (53.71)	1355 (40.51)	
Race, n (%)					< 0.001
Non-Hispanic White	4138 (68.30)	1152 (61.27)	1462 (70.29)	1524 (72.05)	
Non-Hispanic Black	1835 (10.46)	904 (18.02)	476 (7.71)	455 (7.02)	
Mexican American	1512 (8.44)	441 (7.43)	527 (8.93)	544 (8.78)	
Other Race	2162 (12.80)	711 (13.28)	746 (13.07)	705 (12.15)	
PIR, n (%)					0.09
High-income	2619 (37.65)	832 (35.49)	909 (39.03)	878 (38.08)	
Low-income	1977 (14.00)	665 (15.61)	632 (13.23)	680 (13.43)	
Middle-income	5051 (48.35)	1711 (48.90)	1670 (47.74)	1670 (48.49)	
Education level, n (%)					0.01
High school or less	4246 (36.31)	1477 (39.38)	1322 (34.26)	1447 (35.80)	
More than high school	5401 (63.69)	1731 (60.62)	1889 (65.74)	1781 (64.20)	
Marital status, n (%)					0.29
Married or living with partner	5855 (63.78)	1896 (62.31)	1966 (63.76)	1993 (64.99)	
Widowed/divorced/separated/ never married	3792 (36.22)	1312 (37.69)	1245 (36.24)	1235 (35.01)	
Smoking status, n (%)					< 0.001
Former	2242 (24.10)	685 (21.24)	739 (23.91)	818 (26.60)	
Never	5525 (57.18)	1855 (57.00)	1876 (58.15)	1794 (56.40)	
Now	1880 (18.72)	668 (21.76)	596 (17.94)	616 (17.00)	
Alcohol intake, n (%)					< 0.001
Never	1301 (10.31)	516 (12.93)	433 (9.63)	352 (8.85)	
Mild	3383 (37.81)	1126 (36.42)	1154 (39.08)	1103 (37.71)	
Moderate	1563 (18.37)	496 (18.17)	524 (17.96)	543 (18.92)	
Heavy	2066 (22.34)	576 (19.61)	674 (21.50)	816 (25.34)	
Former	1334 (11.17)	494 (12.87)	426 (11.83)	414 (9.18)	
Hypertension, n (%)					0.01
No	5967 (66.00)	1982 (67.39)	2066 (67.95)	1919 (63.01)	
Yes	3680 (34.00)	1226 (32.61)	1145 (32.05)	1309 (36.99)	
Moderate recreational activity, n (%)					0.76
Inactive	4750 (43.86)	1579 (44.35)	1548 (43.16)	1623 (44.12)	
Active	4897 (56.14)	1629 (55.65)	1663 (56.84)	1605 (55.88)	
CKM stage, n (%)					< 0.001
0	905 (11.48)	367 (14.37)	351 (13.98)	187 (6.73)	
1	2217 (25.82)	729 (25.03)	755 (25.78)	733 (26.54)	

Table 1 (continued)

Characteristics	Stress-induced hyperglycemia				
	Total	**T1**	**T2**	**T3**	***P*-value**
	(1.95, 38.05)	**(1.95, 15.67)**	**(15.68, 17.30)**	**(17.31, 38.05)**	
2	5894 (58.93)	1906 (56.63)	1918 (56.95)	2070 (62.67)	
3	631 (3.77)	206 (3.97)	187 (3.29)	238 (4.06)	

All values are presented as number (n) and proportion (%) for categorical variables, assessed via weighted chi-square tests, or mean (standard error) for continuous variables, assessed via weighted Student's t-tests

T1, Tertile 1; T2, Tertile 2; T3, Tertile 3; PIR: Ratio of family income to poverty; CKM: Cardiovascular-Kidney-Metabolic; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglyceride; HbA1c: Hemoglobin A1c; SHR, stress-induced hyperglycemia

Table 2 Weighted multivariate Cox regression models for the association between SHR and mortality risk

SHR	HR[a] (95% CI), P-value		
	Model 1[b]	**Model 2[c]**	**Model 3[d]**
All-cause mortality			
Continuous	1.06 (1.01, 1.12) **0.03**	1.26 (1.21,1.32) < **0.001**	**1.09 (1.04, 1.13) < 0.001**
Categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	0.85 (0.68, 1.06) 0.14	0.96 (0.78, 1.19) 0.73	1.03 (0.83, 1.27) 0.81
Tertile 3	1.07 (0.86, 1.33) 0.57	1.26 (1.02, 1.56) **0.04**	1.26 (1.02, 1.55) **0.03**
CVD mortality			
Continuous	0.99 (0.85, 1.14) 0.87	1.02 (0.90,1.15) 0.80	1.00 (0.91, 1.11) 0.96
Categories			
Tertile 1	Reference	Reference	Reference
Tertile 2	0.81 (0.47, 1.42) 0.46	0.98 (0.60, 1.61) 0.93	0.94 (0.58, 1.55) 0.82
Tertile 3	1.07 (0.86, 1.33) 0.57	1.12 (0.74, 1.70) 0.60	0.99 (0.65, 1.49) 0.95

In sensitivity analysis, SHR is transformed from a continuous variable to a categorical variable (Tertiles); HR[a]: effect size; Model 1[b]: no covariates were adjusted; Model 2[c]: adjusted for sex, age, race, marital status and education level; Model 3[d]: adjusted for age, race, gender, BMI, PIR, education level, marital status, smoking status, alcohol consumption, recreational physical activity, creatinine, LDL-C, total cholesterol, and hypertension; The bolded p-values represent statistical significance

SHR, stress-induced hyperglycemia; CVD, cardiovascular diseases; 95% CI, 95% confidence interval; HR, hazard ratio

the segmented model, indicating a nonlinear association of the SHR index with CVD mortality.

Variable selection for the model

We employed the ABESS and Boruta algorithms for feature selection of all covariates. In the ABESS algorithm (Fig. 3A), the model achieved the minimum generalized information criterion value when predicting all-cause mortality risk in the validation set using only 12 variables [42]. According to the Boruta algorithm (Fig. 3B), variables identified in the green Area, including SHR, were confirmed as essential factors in the model. Through an intersection analysis of the results from both the ABESS and Boruta algorithms, we identified 11 common feature variables selected by both methods: age, race/ethnicity, PIR, education level, BMI, alcohol intake, moderate recreational activity, blood urea nitrogen, SHR, creatinine, as well as TC. These variables were ultimately used to construct the model. We confirmed the absence of multicollinearity among these predictor variables by examining the VIF (Table S1).

Development and validation of predictive models

Figure 4 displays the ROC curves for various machine learning models, with the following AUC values in the test set: LR 0.858, LDA 0.853, QDA 0.842, NB 0.844, KNN 0.803, DT 0.668, RF 0.860, XGBoost 0.858, SVM 0.694, LightGBM 0.863, and NNet 0.858. Figure S1 presents the confusion matrices for these ten models based on the test set. For a comprehensive evaluation, we compared the performance metrics of these models, as shown in Table S2. AUC is a crucial criterion for selecting the most efficient machine learning methods; thus, the LightGBM model is deemed optimal. The LightGBM model demonstrated an average precision of 0.987, accuracy of 0.940, precision of 0.946, and an F1 score of 0.969. DCA further indicated that the LightGBM model offered substantial net benefit and exhibited strong clinical validity (Fig. 5).

Mediation analyses

The results of mediation analysis revealed that the correlation of SHR with all-cause mortality risk was partially mediated by RDW, albumin, and RAR. Specifically, the mediating effects were − 17.0% (95% CI − 46.7%, − 8.7%), − 10.1% (95% CI − 23.9%, − 4.7%), and − 23.3% (95% CI − 49.0%, − 13.0%), respectively (Table 4).

Sensitivity analyses

We performed a range of sensitivity tests to validate the robustness of our results. Firstly, after further adjustment for antihyperglycemic medications, energy intake, HEI-2015, PHQ-9 score, the results of the Cox regression analysis (Table S3) indicated a significant positive association between the SHR index with all-cause mortality (HR = 1.10, 95CI% 1.05–1.15). Secondly, using the CHARLS database with the CKM stages 0 to 3 population in 2011 as the baseline and following up until 2020,

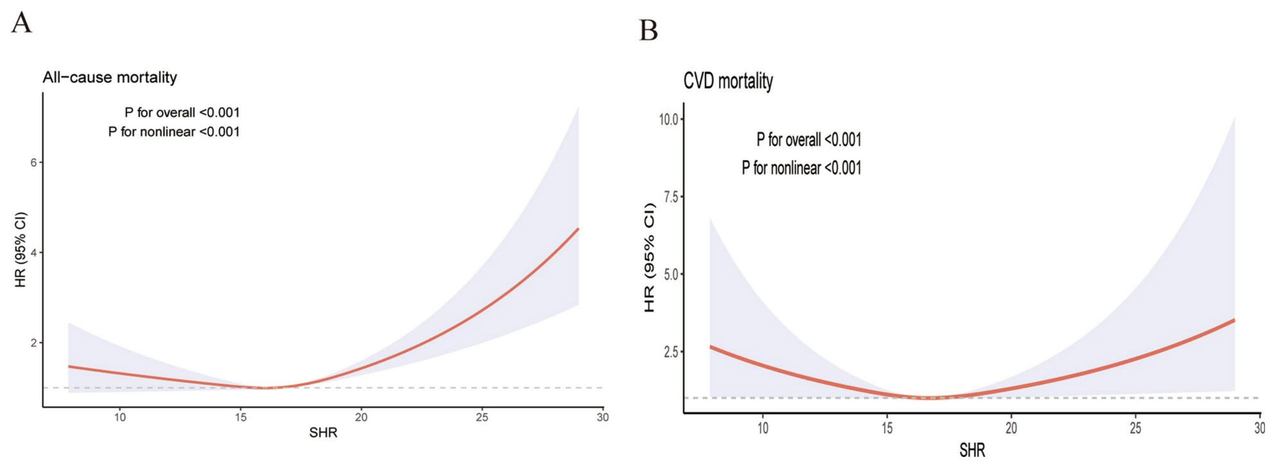


Fig. 2 Restricted cubic spline analysis of the SHR index and its association with mortality. (**A**) All-cause mortality. (**B**) Cardiovascular mortality

Table 3 Threshold effect analysis of SHR on all-cause and CVD mortality using a two-piecewise linear regression model

Mortality risk	Mortality	Adjust β (95% CI) *P*-value
All-cause mortality		
Total	630	
Fitting by linear regression model		1.06 (1.03, 1.10) < 0.001
Fitting by two-piecewise linear regression model		
Inflection point		17.93
< 17.93	454	0.97 (0.92, 1.02) 0.20
> 17.93	176	1.16 (1.11, 1.22) < 0.001
Log likelihood ratio test		< 0.001
Cardiovascular mortality		
Total	135	1.01 (0.95–1.09) 0.72
Fitting by linear regression model		
Fitting by two-piecewise linear regression model		
Inflection point		14.02
< 14.02	99	0.77 (0.66, 0.89) 0.001
> 14.02	36	1.074 (1.01–1.15) 0.04
Log likelihood ratio test		0.002

Adjusted for age, race, gender, BMI, PIR, education level, marital status, smoking status, alcohol consumption, recreational physical activity, creatinine, LDL-C, total cholesterol, and hypertension

we assessed the correlation of the SHR index with all-cause mortality, ultimately including 7525 participants. As presented in Table S4, the results of the cohort study demonstrated that in Models 1–3, the SHR index is positively correlated with all-cause mortality within the CKM stages 0–3 population (Model 1: HR = 1.05, 95% CI 1.02–1.07; Model 2: HR = 1.04, 95% CI 1.01–1.06; Model 3: HR = 1.04, 95% CI 1.01–1.06). Based on the threshold analysis and RCS regression results (Table S5 and Figure S2), a significant nonlinear correlation of SHR with all-cause mortality was observed. Specifically, when SHR value is below 15.69, the all-cause mortality risk decreases, with an adjusted β of 0.78 (95% CI 0.69–0.90) and a *p*-value less than 0.001. However, when SHR value exceeds 15.69, the all-cause mortality risk increases significantly, with an adjusted β of 1.05 (95% CI 1.02–1.07) and a *p*-value of < 0.001. The likelihood ratio test for the model indicated that overall *p*-value < 0.001, further confirming the significant nonlinear association of SHR with all-cause mortality (*p* for overall < 0.0001, *p* for nonlinear = 0.02). Next, subgroup analyses and interaction assessments were executed to systematically investigate the influences of different variables on the outcomes (Table S6), with stratification based on age, gender, moderate recreational activities, smoking status, hypertension, and CKM stages. Our analysis revealed that the positive association of SHR with all-cause mortality was consistently observed across all subgroups, suggesting the robustness of this correlation. Specifically, no significant interactions were found for age, gender, hypertension, or moderate recreational activities, indicating that these variables do not significantly affect the correlation of SHR with all-cause mortality (all interaction *p*-values > 0.05). Nevertheless, smoking status significantly influenced the strength of the correlation of SHR with all-cause mortality (interaction *p*-value < 0.05). Specifically, in contrast to former or never smokers, current smokers exhibited a significantly elevated all-cause mortality risk, with an HR of 1.18 (95% CI 1.06–1.31). The above evidence underscores the modulating role of smoking on the SHR–all–cause mortality relationship, with current smokers showing a stronger association.

Discussion

In the current study, we conducted a retrospective analysis of 9647 participants with CKM stages 0–3. The results indicated a U-shaped correlation of SHR index with all-cause mortality, with a threshold effect analysis

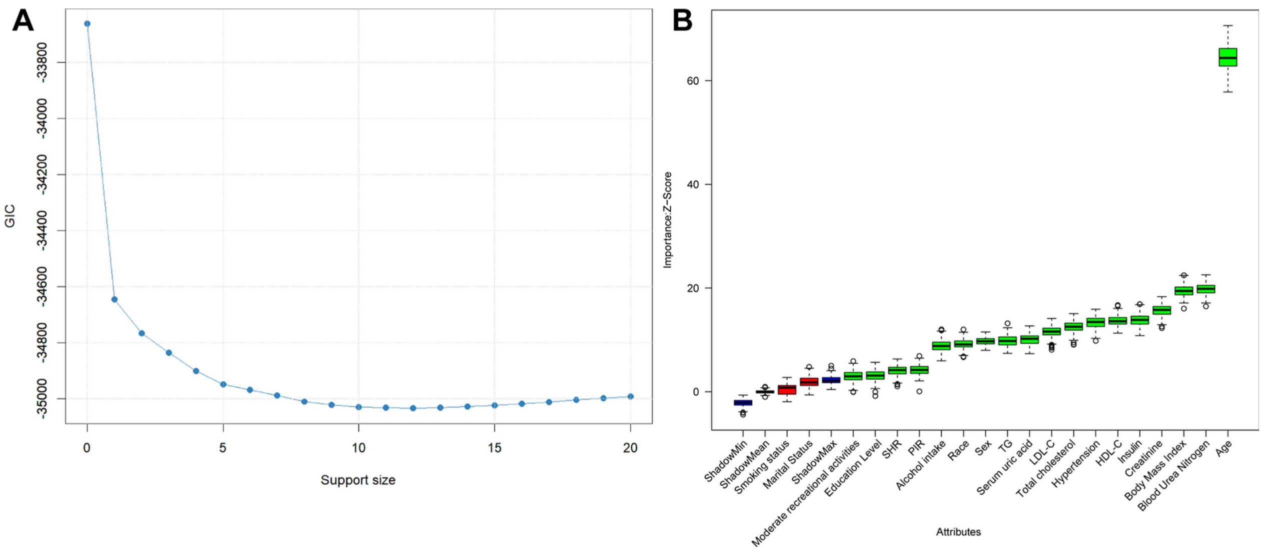


Fig. 3 ABESS algorithm (**A**) and Boruta algorithm (**B**) are employed during the variable selection phase. (**A**) The change in generalized information criterion (GIC) when selecting features using the ABESS algorithm. (**B**) The significance of potential mortality risk factors was assessed using the Boruta algorithm. The horizontal axis displays the names of the variables, while the vertical axis represents the Z-values for each variable. The box plots illustrate the Z-values during model calculations, with green boxes indicating important variables and red boxes denoting unimportant variables

identifying an inflection point at an SHR index of 17.93. This association was further validated using the CHARLS database in the CKM stage 0–3 population. To enhance predictive accuracy, we employed 10 machine learning algorithms to develop a predictive model incorporating the SHR index, with eight models achieving AUC values exceeding 0.80, indicating strong predictive performance. These findings provide new insights for clinical practice, suggesting that incorporating SHR into routine assessments offers a low-cost, accessible tool for evaluating patients with CKM stages 0–3 [7, 15]. Dynamic monitoring of SHR fluctuations enables physicians to better evaluate patients' metabolic health and tailor individualized treatment strategies, thereby improving the precision and effectiveness of disease management [43]. Regular SHR monitoring facilitates early detection of disease progression, supports clinical decision-making, and enables timely interventions to prevent deterioration, ultimately decreasing the likelihood of adverse outcomes as well as enhancing long-term survival rates [44].

SHR, as a potential prognostic index, has been validated in several studies for its relationship with all-cause mortality within populations with CKM stages 0 to 3, further supporting our viewpoint. For example, a study involving 1685 patients found that elevated SHR levels were significantly linked to the all-cause mortality risk at 30, 90, 180, and 365 days in critically ill atrial fibrillation patients [14]. Similarly, Liu et al. demonstrated that among critically ill patients with acute MI, high SHR levels were linked to 1-year and even long-term all-cause mortality. This finding was confirmed in both Chinese and American cohorts [45]. Other studies have highlighted that SHR is significantly correlated with in-hospital and ICU mortality in critically ill coronary heart disease patients, emphasizing its potential as a prognostic marker for ICU outcomes [15]. A retrospective analysis of 5564 cardiac ICU patients revealed a U-shaped correlation of SHR with short-term mortality, identifying a critical threshold of 0.95 that indicates poor prognosis [46]. Another study involving 8978 patients found that SHR was not only associated with short-term mortality but also exhibited a U-shaped association with long-term mortality, with a threshold of 0.96 for poor prognosis [47]. Moreover, Wang et al. showed that SHR could independently predict all-cause mortality within diabetic patients [48]. A longitudinal study with 15-year follow-up also found that SHR was significantly linked to all-cause mortality among community residents [49]. Lastly, Zhou et al. reported that SHR, regardless of low or high, was related to adverse outcomes during hospitalization in HF and type 2 diabetes patients without surgery, particularly in those with impaired renal function at admission, where the effects were more pronounced [50]. These findings further substantiate our results.

The mechanisms driving the heightened all-cause mortality risk associated with SHR and CKM stages are not yet fully understood. However, hormonal imbalances triggered by activation of the sympathetic-adrenal axis, as well as secondary insulin resistance (IR), may play a vital role in this pathophysiological process. During stress, activation of the sympathetic nervous system triggers increased release of adrenal hormones like cortisol and catecholamines, elevating glucagon levels and inhibiting insulin secretion [51]. This neuroendocrine

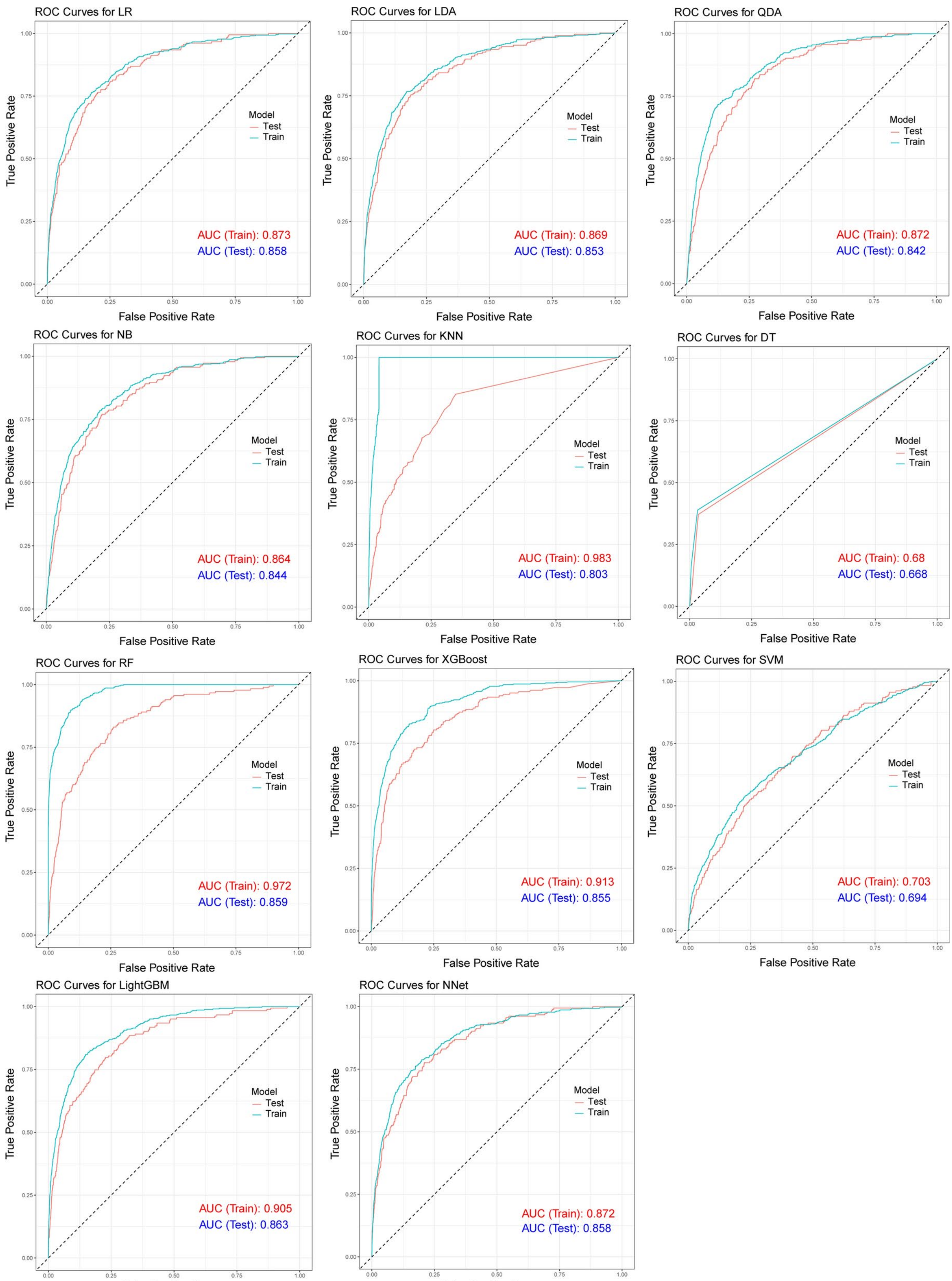


Fig. 4 The ROC of the ten machine learning models in train and test set

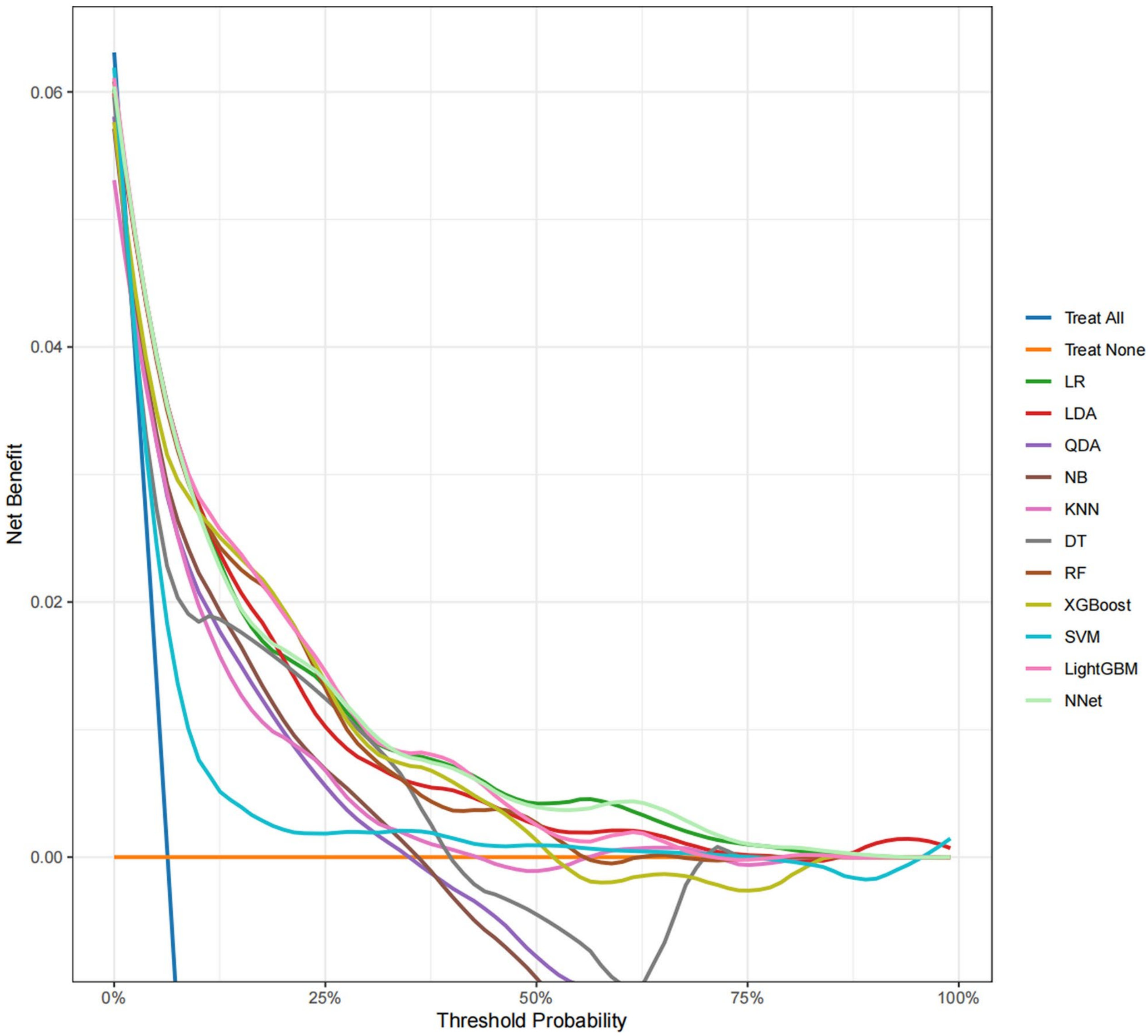


Fig. 5 DCA displaying net benefit across different risk thresholds, comparing the ten models

disruption induces acute hyperglycemia and exacerbates IR by impairing glucose transporter functions in myocardial and renal tubular cells [52]. In the early stages of CKM (stages 0–1), dysfunction in adipose tissue in obese or metabolically abnormal patients may further amplify this effect, accelerating the progression of metabolic syndrome [7]. IR also increases serum viscosity, creating a prothrombotic environment and enhancing the release of pro-inflammatory factors from adipocytes [53]. Together, these factors promote vascular atherosclerosis and dysfunction, significantly increasing the risk of CVD [27]. Hyperglycemia-induced uncoupling of the mitochondrial electron transport chain significantly increases the generation of reactive oxygen species (ROS), resulting in endothelial cell damage as well as mitochondrial dysfunction [54]. In CKM stages 2–3, patients often already suffer from hypertension, diabetes, or CKD [55]. The release of oxidative stress and inflammatory factors (such as IL-6 and TNF-α) exacerbates atherosclerosis, myocardial fibrosis, and glomerulosclerosis, increasing the risk of cardiovascular events (like HF and MI) as well as end-stage kidney disease, which elevates all-cause mortality [56]. Notably, although GLP-1 receptor and SGLT2 inhibitor agonists exert cardioprotective and nephroprotective effects by regulating sodium-glucose cotransport and glucagon secretion, stress-induced hyperglycemia may reduce their efficacy by downregulating drug transporter expression in target organs [57]. On the vascular biology level, the hyperglycemic environment significantly reduces the bioavailability of nitric oxide (NO) by inhibiting the phosphorylation of endothelial NO synthase (eNOS), promoting endothelial cell apoptosis and

Table 4 Mediation analyses for associations between SHR and all-cause mortality after excluding participants without RAR (n = 19) related data

Characteristics	Effect	Total effect	Natural direct effect	Natural indirect effect	Percentage mediated (%)
RDW(%)	OR (95% CI)	1.061 (1.026, 1.097)	1.071 (1.032, 1.106)	0.990 (0.985, 0.994)	− 17.0% (− 46.7%, − 8.7%)
	P value	< 0.001	< 0.001	< 0.001	0.002
Albumin (g/dL)	OR (95% CI)	1.070 (1.032, 1.108)	1.077 (1.039, 1.116)	0.993 (0.990, 0.996)	− 10.1% (− 23.9%, − 4.7%)
	P value	< 0.001	< 0.001	< 0.001	< 0.001
RAR	OR (95% CI)	1.069 (1.034, 1.105)	1.085 (1.050, 1.121)	0.985 (0.980, 0.990)	− 23.3% (− 49.0%, − 13.0%)
	P value	< 0.001	< 0.001	< 0.001	< 0.001

Adjusted for age, race, gender, BMI, PIR, education level, marital status, smoking status, alcohol consumption, recreational physical activity, creatinine, LDL-C, total cholesterol, and hypertension

resulting in microcirculatory dysfunction [58]. In CKM stage 3 (subclinical CVD or high-risk status), endothelial dysfunction accelerates coronary artery calcification (CAC) and left ventricular remodeling, further increasing the risk of CVD mortality [59]. Moreover, hyperglycemia suppresses the function of neutrophils and macrophages, increasing infection rates and further aggravating glucose metabolism disorders, creating a vicious cycle [60]. This mechanism is particularly significant in the CKM stage 2–3 population with concurrent CKD or diabetes, where infection-related complications (such as sepsis) are key contributors to increased all-cause mortality.

Our study found a U-shaped relationship between SHR and all-cause mortality, consistent with previous research. For example, a study of 13,199 sepsis patients showed a U-shaped relationship between SHR and mortality, with higher SHR associated with an increased risk [61]. Another study indicated that SHR is an effective predictor of chronic kidney disease and also demonstrates a U-shaped relationship with all-cause mortality [62]. Research from the United States has shown that when SHR exceeds a certain threshold, particularly in populations over 65 years old and among women, both all-cause mortality and diabetes risk increase [29]. The physiological processes underlying the increased all-cause mortality associated with high SHR (above the threshold) may involve several factors: Firstly, severe stress (such as myocardial infarction or sepsis) activates the sympathetic nervous system and the HPA axis, leading to the release of large amounts of adrenaline and cortisol [51]. These hormones antagonize the action of insulin, causing a sharp increase in blood glucose levels [51]. Hyperglycemia exacerbates the release of inflammatory factors (such as IL-6 and TNF-α) and oxidative damage, impairing endothelial function and further triggering multi-organ failure, ultimately leading to increased all-cause mortality [56]. Additionally, acute hyperglycemia can directly damage myocardial cell mitochondrial function, worsen ischemia–reperfusion injury, and increase the risk of CVD death [63]. Secondly, acute hyperglycemia increases blood osmolarity, causing dehydration of red blood cells and reducing their deformability, which obstructs microcirculatory blood flow and increases the risk of thrombosis [64]. This exacerbates critical illnesses such as stroke and acute kidney injury caused by tissue ischemia, further contributing to increased all-cause mortality [65]. Moreover, the use of insulin to control acute hyperglycemia in clinical treatment may lead to hypoglycemia, and severe fluctuations in blood glucose levels are more likely to trigger arrhythmias and death than persistent hyperglycemia [66].

Our subgroup analysis found that the correlation of SHR with all-cause mortality risk was more pronounced among current smokers, a finding supported by related studies. Mexican research indicated that smokers with obesity, diabetes, or chronic kidney disease had a significantly increased risk of mortality, which may result from the cumulative effect of smoking on pre-existing comorbidities and vulnerabilities [67]. Additionally, a study involving 10,377 patients reported that smokers with higher coronary artery calcium scores had a four to nine times higher risk of mortality compared to their non-smoking peers [68]. Another study on patients with diabetes and HF also identified age, smoking, and hypertension as key contributors to mortality risk. Smoking may elevate mortality risk through multiple pathophysiological mechanisms [69]. First, tobacco toxins, such as carbon monoxide, can directly impair vascular endothelial cells, reduce NO bioavailability, and induce endothelial apoptosis [69]. Moreover, hyperglycemia can compromise endothelial barrier function by activating protein kinase C (PKC) and promoting reactive ROS production, thereby increasing thrombogenicity [70]. The worsening of endothelial dysfunction not only accelerates atherosclerotic plaque rupture but also heightens the likelihood of thrombotic events, including MI and stroke, significantly elevating mortality risk [71]. Second, tobacco smoke is rich in ROS as well as reactive nitrogen species (RNS), which could cause direct damage to lipid membranes, proteins, and DNA, compromising macrophage and neutrophil membrane integrity and impairing their function [72]. This weakens immune defenses, a phenomenon particularly pronounced in hyperglycemia, as diabetes impairs leukocyte chemotaxis and phagocytosis, delaying infection control [73]. Consequently, among smokers with elevated SHR, infection-related mortality (such as pneumonia and sepsis) is significantly increased

[74]. Finally, cadmium in tobacco may disrupt DNA methylation patterns, leading to aberrant anti-apoptotic gene expression and pancreatic β-cell apoptosis [75]. This mechanism may further deplete β-cell reserves, making it difficult for the body to maintain normal insulin secretion under stress conditions, resulting in poor glycemic control and a vicious cycle of metabolic deterioration. Furthermore, the depletion of β-cell reserves makes smokers more susceptible to ketoacidosis or hyperosmolar states during acute illness or physiological stress, markedly increasing mortality risk [76]. In summary, smoking may exacerbate the health risks associated with elevated SHR through multiple pathophysiological mechanisms, shedding light on the pathophysiological link between SHR and all-cause mortality.

Strength and limitation

The current study possesses a series of notable strengths. First, it focuses on the clinically relevant yet often overlooked group of individuals with CKM stages 0 to 3, and the SHR index, being simple and easily accessible, adds to its practical value. This article is the first to explore the potential of using the SHR index to assess mortality among patients across CKM stages 0–3, providing significant clinical value and innovation. Second, the data analyzed in the current study are obtained from the nationally representative NHANES survey, which employed an intricate multistage probability sampling method to select 9647 eligible participants with CKM stages 0–3. The large sample size ensures strong representativeness. Third, the current study investigates the correlation of the SHR index with both all-cause and CVD mortality among patients across CKM stages 0–3, advancing research in this field. Lastly, by utilizing the CHARLS database, our study further validates the association of the SHR index with all-cause mortality among the CKM 0–3 population, strengthening the robustness of the findings.

However, some limitations in the current study also need to be acknowledged. First, the sample was mainly from the United States. While sensitivity analyses included a Chinese cohort, the generalizability of the results might be limited by differences in racial background, living environment, dietary habits, and other factors. Therefore, future research should incorporate more cross-national and cross-cultural studies to validate the global applicability and broader relevance of our findings. Second, although we incorporated adjustments for multiple potential confounders in our analysis, other unmeasured or uncontrolled confounders may still exist. Third, the SHR index was measured only at baseline, and changes in the SHR index during the follow-up period were not assessed, leaving the potential impact of these changes on mortality risk unclear. Future studies should investigate how changes in the SHR index over time influence mortality risk. Finally, due to the lack of genomic data for the CKD stages 0–3 population, we were unable to conduct a Mendelian randomization analysis. Future research should focus on collecting relevant data to improve the accuracy of causal inferences.

Conclusions

Our research results indicate that the SHR index is not only economically efficient but also potentially clinically valuable in assessing the all-cause mortality risk among individuals across CKM stages 0–3. Therefore, we recommend monitoring the SHR index among individuals across CKM stages 0–3 as an effective tool for risk evaluation.

Abbreviations

CKM	Cardiovascular–kidney–metabolic
SHR	Stress hyperglycemia ratio
NHANES	National Health and Nutrition Examination Survey
CHARLS	China Health and Retirement Longitudinal Study
CVD	Cardiovascular disease
HbA1c	Glycated hemoglobin
CKD	Chronic kidney disease
AHA	American Heart Association
CDC	Centers for Disease Control and Prevention
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
BMI	Body mass index
NDI	National Death Index
NCHS	National Center for Health Statistics
FPG	Fasting plasma glucose
HR	Hazard ratio
CI	Confidence interval
RCS	Restricted cubic splines
ML	Machine learning
ABESS	Adaptive Best Subset Selection
VIF	Variance inflation factor
LR	Logistic regression
LDA	Linear discriminant analysis
QDA	Quadratic discriminant analysis
NB	Naive Bayes
KNN	K-nearest neighbor
DT	Decision tree
RF	Random forest
XGBoost	Extreme gradient boosting
SVM	Support vector machines
LightGBM	Light gradient boosting machine
ROC-AUC	Receiver operating characteristic area under the curve
AUC	Area under the curve
ROC	Receiver operating characteristic
APS	Average precision score
PPV	Positive predictive value
NPV	Negative predictive value
FPR	False positive rate
DCA	Decision curve analysis
RDW	Red cell distribution width
RAR	Red cell distribution width to albumin ratio
HEI-2015	Healthy Eating Index 2015
PHQ-9	Patient Health Questionnaire-9
IR	Insulin resistance
ROS	Oxygen species
NO	Nitric oxide
eNOS	Endothelial nitric oxide synthase
CAC	Coronary artery calcification
PKC	Protein kinase C
RNS	Reactive nitrogen species

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02689-6.

Additional file1 (DOC 4816 KB)

Author contributions

Mo-Yao Tan, Yu-Jun Zhang and Ming Gao conceived and designed the study. Mo-Yao Tan, Si-Xuan Zhu, Shan Wu and Ping Zhang conducted data collection, data analysis, and data interpretation. Mo-Yao Tan, Yu-Jun Zhang and Ming Gao contributed to literature checks and data visualization. Mo-Yao Tan, Yu-Jun Zhang and Ming Gao drafted the initial manuscript and all authors made critical revisions of the manuscript. Mo-Yao Tan, Yu-Jun Zhang and Ming Gao verified the underlying study data. All authors read the manuscript and approved the final draft. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

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Availability of data and materials

The datasets generated and analyzed during the current study are available in the CHARLS and NHANES website, available in http://charls.pku.edu.cn/en and https://www.cdc.gov/nchs/nhanes/index.htm, respectively.

Declarations

Ethics approval and consent to participate

The NHANES is approved by the National Center for Health Statistics Research Ethics Review Board, and all participants provide informed consent. The CHARLS is approved by the Biomedical Ethics Review Committee of Peking University, and all participants provide informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Cardiology, Chengdu Integrated TCM and Western Medicine Hospital, Chengdu, Sichuan, China
[2]Huankui Academy, Jiangxi Medical College, Nanchang University, Nanchang 330006, Jiangxi, China
[3]Clinical Medical School, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, China

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