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Original Research

Higher cystatin C, but not creatinine, predicts frailty risk in individuals with normal kidney function

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ABSTRACT

Objective: This study investigates the associations of creatinine and cystatin C with frailty risk in individuals with normal kidney function, using data from the Health and Retirement Study (HRS) and the China Health and Retirement Longitudinal Study (CHARLS).

Methods: We used CKD-EPI to estimate glomerular filtration rate based on serum creatinine ($eGFR_{scr}$) and cystatin C ($eGFR_{cysc}$), respectively, and an eGFR ≥60 was considered "normal kidney function". Frailty was assessed using a frailty index derived from clinical and functional measures. Cox proportional hazards models were used to evaluate the associations of creatinine and cystatin C with incident frailty, adjusting for demographic, lifestyle, and clinical covariates.

Results: Creatinine levels showed no significant association with frailty risk in individuals with normal kidney function across both cohorts. In contrast, cystatin C levels were consistently and significantly associated with an increased risk of frailty in individuals with normal $eGFR_{scr}$. For each 1-unit increase in cystatin C, the adjusted hazard ratios (HRs) were 2.05 (95% CI: 1.30–3.22) in HRS and 2.12 (95% CI: 1.60–2.82) in CHARLS. Quartile analyses revealed a dose-response relationship, with the highest quartile of cystatin C associated with significantly higher frailty risk compared to the lowest quartile (HRS: HR = 1.34, 95% CI: 1.02–1.76; CHARLS: HR = 1.70, 95% CI: 1.40–2.07).

Conclusions: Higher cystatin C levels, but not creatinine levels, were significantly associated with an increased risk of frailty among individuals with normal kidney function, suggesting that cystatin C may be a useful biomarker for early identification of frailty risk.

1. Introduction

Frailty, a multidimensional syndrome characterized by decreased physiological reserve and increased vulnerability to adverse health outcomes, has emerged as a critical public health concern in aging populations worldwide [1]. It is associated with a higher risk of falls, hospitalization, disability, and mortality, posing significant challenges to healthcare systems and caregivers alike [2,3]. As populations age globally, the prevalence of frailty is expected to rise, underscoring the urgent need for early identification and intervention strategies to mitigate its impact [4].

Kidney function has been increasingly recognized as a key factor in frailty pathophysiology. Traditionally, kidney function is assessed using an estimated glomerular filtration rate (eGFR), which is calculated based on serum creatinine [5]. However, creatinine is influenced by factors such as muscle mass, diet, and physical activity, which may limit its accuracy in certain populations, particularly older adults [6]. For instance, individuals with low muscle mass, a common feature of aging and frailty, may have deceptively low creatinine levels, leading to an overestimation of kidney function [7]. This limitation has prompted the exploration of alternative biomarkers, such as cystatin C, which is less affected by muscle mass and has been proposed as a more reliable indicator of kidney function in aging populations [8].

Unlike creatinine, cystatin C levels are not significantly influenced by muscle mass, making it a potentially superior biomarker for kidney function in older adults [9]. Beyond its role in kidney function assessment, cystatin C has been implicated in systemic processes such as inflammation, oxidative stress, and metabolic dysregulation, all of

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which are closely linked to frailty [10]. Elevated cystatin C has been associated with adverse outcomes, including cardiovascular disease, cognitive decline, and mortality, even in individuals with normal eGFR based on creatinine ($eGFR_{scr}$) [11–13]. These findings suggest that cystatin C may capture subclinical physiological changes that are not reflected by creatinine levels alone.

The concept of "eGFR-normal populations" refers to individuals whose kidney function, as estimated by eGFR, falls within the normal range [14]. This group is of particular interest because traditional kidney function assessments may overlook subtle physiological changes that predispose individuals to frailty. For instance, individuals with normal $eGFR_{scr}$ may still exhibit elevated cystatin C levels, indicating underlying subclinical processes such as inflammation or early kidney dysfunction. Conversely, individuals with normal eGFR based on cystatin C ($eGFR_{cysc}$) may have creatinine levels that reflect variations in muscle mass rather than true kidney dysfunction. These discrepancies highlight the need to explore the independent and combined roles of creatinine and cystatin C in frailty risk assessment.

Frailty itself is a complex syndrome with multifactorial etiology, encompassing physical, cognitive, and social dimensions. Given that cystatin C is associated with these processes, it may serve as a more sensitive biomarker for frailty risk compared to creatinine. However, few studies have directly compared the predictive value of creatinine and cystatin C for frailty in eGFR-normal populations. This study aims to investigate the association between creatinine or cystatin C levels and frailty risk among individuals with normal kidney function.

2. Methods

This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (**Table S1**) [15].

2.1. Study population

This study utilized data from two large, nationally representative cohorts: the Health and Retirement Study (HRS, wave 13–15, 2016–2020 year) in the United States and the China Health and Retirement Longitudinal Study (CHARLS, wave 1–3, 2011–2015 year). The HRS cohort includes adults aged 50 years and older, with biennial follow-ups since 1992, while the CHARLS cohort comprises Chinese adults aged 45 years and older, with follow-ups every two to three years since 2011 [16,17]. For this analysis, participants were included if they had baseline measurements of creatinine, and cystatin C, as well as follow-up data on frailty status. Individuals with missing data on key variables, an eGFR below 60 mL/min/1.73 m^2, or pre-existing frailty at baseline were excluded. After applying these criteria, 4538/3907 participants from the HRS cohort and 5862/5031 participants from the CHARLS cohort were included in the final analysis (Fig. 1).

The study protocols were approved by the Ethical Review Committee of Perking University (CHARLS: IRB00001052–11,015), and the National Institute on Aging and the Social Security Administration (HRS: HUM0061128), and the detailed ethical approval could be found on respective origin surveys. Meanwhile, written informed consent was also obtained from any participant.

2.2. Assessment of kidney function

Kidney function was assessed using $eGFR_{scr}$ and $eGFR_{cysc}$, respectively, which was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (**Table S2**) [8]. According to the guideline, participants were classified as having "normal kidney function" if their eGFR was ≥60 mL/min/1.73 m^2 based on either creatinine or cystatin C [14].

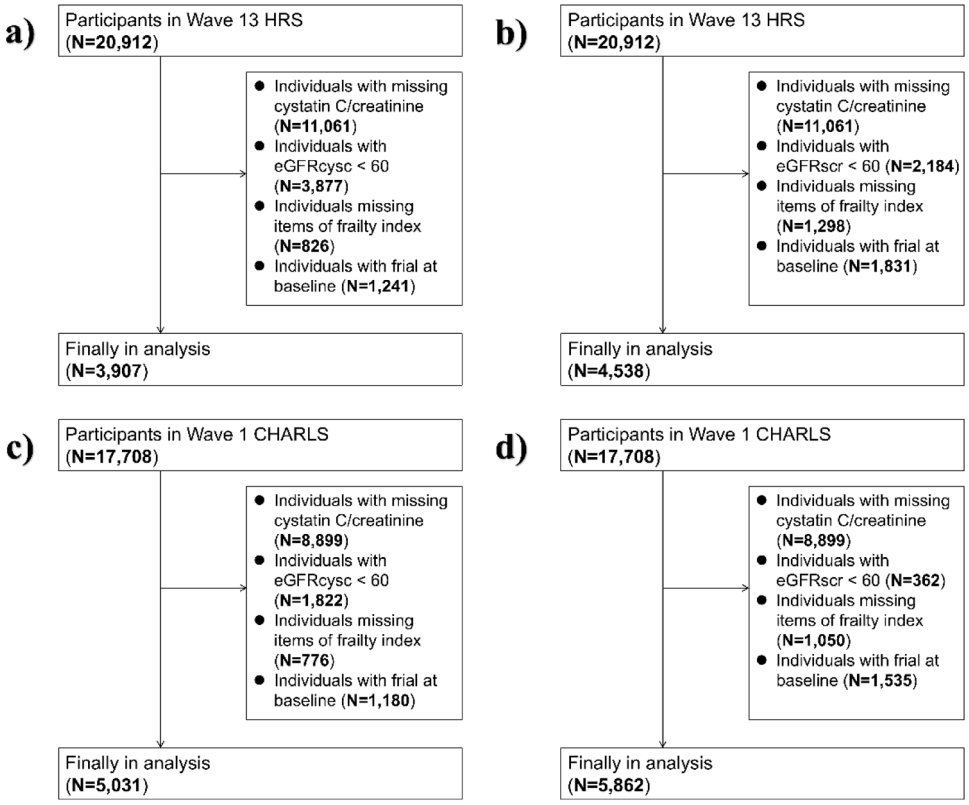

Fig. 1. Participants screening flowchart. (a) HRS: creatinine and risk of frailty among individuals with a normal $eGFR_{cysc}$; (b) HRS: cystatin C and risk of frailty among individuals with a normal $eGFR_{scr}$; (c) CHARLS: creatinine and risk of frailty among individuals with a normal $eGFR_{cysc}$; (d) CHARLS: cystatin C and risk of frailty among individuals with a normal $eGFR_{scr}$.

2.3. Ascertainment of incident frailty

The frailty status was assessed using a frailty index, which is calculated based on the accumulation of age-related health deficits [18]. Drawing on previous research [19,20], we selected several items that could be applied across two cohorts. After the screening, 30 items were identified in the HRS and CHARLS datasets to construct the frailty index [18]. These items included various chronic diseases, self-reported health status, functional limitations, depression, and cognition (**Table S3**). Participants with missing data >10% of frailty index items in the two cohorts were excluded from the analysis. Most items were dichotomized into 0 or 1, where 0 indicated no deficit and 1 indicated the presence of a deficit. Certain conditions, such as self-reported general vision, hearing, health status, and cognitive ability, were scored on a scale from 0 to 1, with higher values indicating greater severity of the deficit.

In our study, the frailty index was calculated by summing the number of existing deficits, dividing this total by 30, and multiplying the result by 100 [18]. As such, the frailty index is represented as a continuous variable ranging from 0 to 100. Participants were categorized into non-frail (frailty index $\leq$ 25) and frail (frailty index > 25), [21,22] based on established frailty index thresholds.

2.4. Covariates

Covariates were selected based on their potential associations with kidney function, frailty, or both. These included demographic factors (age, gender, education level, and marital status), lifestyle factors (smoking and alcohol consumption), and clinical factors (body mass index [BMI], hypertension [defined as systolic blood pressure $\geq$ 140 mmHg and diastolic blood pressure $\geq$ 90 mmHg or self-reported history of hypertension [23]], diabetes [defined as fasting plasma glucose $\geq$7.0 mmol/L, glycated hemoglobin $\geq$6.5%, self-reported physician diagnosis [24]], and history of heart disease [defined as self-reported physician diagnosis [25]). In the HRS cohort, covariates were obtained from self-reported questionnaires and clinical measurements, while in the CHARLS cohort, they were derived from standardized interviews and physical examinations. Given the relatively low rates of missing data (**Table S4**), single imputation was employed to address missing values, with continuous variables imputed using the median and categorical variables imputed using the most frequent category [26].

2.5. Statistical analysis

The baseline characteristics of participants were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables.

Person-time was calculated from the date of baseline examination until CKD diagnosis, loss to follow-up, or the end of follow-up, whichever came first. Event rates were reported per 1000 person-years of follow-up. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) for incident frailty were estimated using Cox proportional hazards models, with creatinine and cystatin C analyzed both as continuous variables, including 1-unit and standard deviation (SD), and by quartiles. Three models were constructed: Model 1 was unadjusted, Model 2 adjusted for age and gender, and Model 3 further adjusted for education, marital status, lifestyle factors, and clinical covariates. To compare the predictive performance of creatinine and cystatin C for frailty, receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated [27]. Possible nonlinear relationships between creatinine, cystatin C, and frailty risk were examined by a Cox regression model with restricted cubic spline with three knots at the 10th, 50th, and 90th percentiles [28].

Subgroup analyses were conducted to explore potential effect modifications by key demographic and clinical factors, including age (<65 vs. $\geq$65 years), gender (male vs. female), BMI (<24 vs. $\geq$24 kg/m^2), and the presence of comorbidities such as hypertension, diabetes, and heart disease. Interaction terms between these factors and the biomarkers (creatinine and cystatin C) were included in the Cox models to test for statistical significance.

Sensitivity analyses were performed to evaluate the robustness of the findings. First, using complete-case data, i.e., excluding participants with missing covariate data. Second, alternative thresholds for defining incident frailty were tested, such as using 20 or 30 instead of 25 to classify frailty events. Finally, excluding participants with borderline eGFR values (e.g., 60–65 mL/min/1.73 m^2) to ensure that the observed associations were not driven by individuals with marginal kidney function.

All analyses were conducted separately in the HRS and CHARLS cohorts. The objective was to examine whether the association between kidney biomarkers and incident frailty was reproducible across two distinct population-based settings, rather than to directly compare effect estimates between countries or to generate a pooled cross-cohort estimate. Accordingly, covariates were modeled and adjusted within each cohort according to the available data. Statistical significance was defined as a two-sided $P < 0.05$. Statistical analyses were performed using R software (version 4.2.0) and Stata (version 17.0).

3. Results

3.1. Characteristics of including participants

The baseline characteristics of the study participants are summarized in Table 1. Among individuals with normal eGFR$_{cysc}$, the mean age was 64.3 $\pm$ 8.2 years in the HRS cohort and 56.5 $\pm$ 8.5 years in the CHARLS cohort. In comparison, participants with normal eGFR$_{scr}$ were slightly older in both cohorts, with mean ages of 65.2 $\pm$ 8.8 years in HRS and 58.1 $\pm$ 9.4 years in CHARLS. The gender distribution differed markedly between the cohorts: in HRS, 43.6% of participants with normal eGFR$_{cysc}$ were male, compared to 70.0% in CHARLS. The prevalence of current smokers was higher in CHARLS (29.4% in normal eGFR$_{cysc}$ and 30.7% in normal eGFR$_{scr}$) compared to HRS (10.0% and 10.4%, respectively), while alcohol consumption was more common in CHARLS, with 33.4% of participants in the normal eGFR$_{cysc}$ group being current drinkers, compared to 19.6% in HRS. The mean BMI was higher in HRS (28.0 $\pm$ 5.3 kg/m^2 in normal eGFR$_{cysc}$ and 28.3 $\pm$ 5.5 kg/m^2 in normal eGFR$_{scr}$) compared to CHARLS (23.9 $\pm$ 14.1 kg/m^2 and 24.2 $\pm$ 34.9 kg/m^2, respectively). Inflammatory markers, such as C-reaction protein, were higher in HRS (3.5 $\pm$ 6.9 mg/L in normal eGFR$_{cysc}$) compared to CHARLS (2.2 $\pm$ 5.3 mg/L in normal eGFR$_{cysc}$).

Regarding kidney function, mean serum creatinine levels were consistent across cohorts and groups (approximately 0.8 $\pm$ 0.2 mg/dL), while cystatin C levels were slightly higher in the eGFR$_{scr}$ groups. The baseline frailty index was similar across groups, ranging from 12.2 $\pm$ 6.2 in HRS (normal eGFR$_{cysc}$) to 12.8 $\pm$ 6.3 in HRS (normal eGFR$_{scr}$), and increased during follow-up in all groups. Exposure quartiles for creatinine and cystatin C were evenly distributed across all groups, with approximately 25% of participants in each quartile.

3.2. Association of creatinine/cystatin C and risk of frailty

During the follow-up period, frailty events occurred in 490 of 3907 participants in the HRS cohort with normal eGFR$_{cysc}$ (incidence: 75.02 per 1000 person-years, 95% CI: 71.24–78.80) and in 659 of 4538 participants with normal eGFR$_{scr}$ (incidence: 37.00 per 1000 person-years, 95% CI: 34.17–39.82). In the CHARLS cohort, 823 of 5031 participants with normal eGFR$_{cysc}$ developed frailty (incidence: 41.10 per 1000 person-years, 95% CI: 38.29–43.91), while 1055 of 5862 participants with normal eGFR$_{scr}$ experienced frailty (incidence: 45.22 per 1000 person-years, 95% CI: 42.50–47.95) (**Table S5**).

In both cohorts, among individuals with normal eGFR$_{cysc}$, creatinine levels showed no significant association with risk of incident frailty, whether assessed per 1-unit increase, per 1-SD increase, or by quartile

Table 1
Characteristics of including participants.

Characteristic	HRS (Normal $eGFR_{cysc}$) N = 3,907[1]	HRS (Normal $eGFR_{scr}$) N = 4,538[1]	CHARLS (Normal $eGFR_{cysc}$) N = 5,031[1]	CHARLS (Normal $eGFR_{scr}$) N = 5,862[1]
Age, year	64.3 ± 8.2	65.2 ± 8.8	56.5 ± 8.5	58.1 ± 9.4
Gender				
Male	1705 (43.6%)	1924 (42.4%)	3523 (70.0%)	2898 (49.4%)
Female	2202 (56.4%)	2614 (57.6%)	1508 (30.0%)	2964 (50.6%)
Marriage				
Married	2698 (69.1%)	3066 (67.6%)	2419 (48.1%)	5250 (89.6%)
Other	1209 (30.9%)	1472 (32.4%)	2612 (51.9%)	612 (10.4%)
Education				
Less than middle school education	418 (10.7%)	496 (10.9%)	4448 (88.4%)	5212 (88.9%)
High school and vocational training	2145 (54.9%)	2530 (55.8%)	515 (10.2%)	570 (9.7%)
Higher education	1344 (34.4%)	1512 (33.3%)	68 (1.4%)	80 (1.4%)
Drinking				
Never drinker	3142 (80.4%)	3727 (82.1%)	3021 (60.0%)	3508 (59.8%)
Past drinker	-	-	329 (6.5%)	427 (7.3%)
Current drinker	765 (19.6%)	811 (17.9%)	1681 (33.4%)	1927 (32.9%)
Smoking				
Never smoker	1904 (48.7%)	2173 (47.9%)	3179 (63.2%)	3620 (61.8%)
Past smoker	1612 (41.3%)	1891 (41.7%)	373 (7.4%)	445 (7.6%)
Current smoker	391 (10.0%)	474 (10.4%)	1479 (29.4%)	1797 (30.7%)
Body mass index, kg/m^2	28.0 ± 5.3	28.3 ± 5.5	23.9 ± 14.1	24.2 ± 34.9
Heart disease				
None	3401 (87.0%)	3920 (86.4%)	4619 (91.8%)	5361 (91.5%)
Yes	506 (13.0%)	618 (13.6%)	412 (8.2%)	501 (8.5%)
Diabetes				
None	3248 (83.1%)	3739 (82.4%)	4380 (87.1%)	5118 (87.3%)
Yes	659 (16.9%)	799 (17.6%)	651 (12.9%)	744 (12.7%)
Hypertension				
None	2150 (55.0%)	2382 (52.5%)	3063 (60.9%)	3452 (58.9%)
Yes	1757 (45.0%)	2156 (47.5%)	1968 (39.1%)	2410 (41.1%)
Total cholesterol, mg/dl	194.0 ± 40.5	194.9 ± 40.2	193.2 ± 38.0	192.7 ± 38.2
HDL, mg/dl	60.1 ± 20.2	59.3 ± 19.9	50.9 ± 15.0	51.3 ± 15.2
LDL, mg/dl	108.1 ± 34.0	107.3 ± 34.2	116.3 ± 34.4	116.2 ± 34.6
Triglyceride, mg/dl	142.8 ± 93.4	143.8 ± 91.8	134.4 ± 110.4	131.1 ± 105.5
CRP, mg/l	3.5 ± 6.9	3.7 ± 7.5	2.2 ± 5.3	2.4 ± 6.0
Serum urea, mg/dl	15.7 ± 4.2	15.9 ± 4.3	15.4 ± 4.2	15.6 ± 4.3
Serum creatinine, mg/dl	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
Cystatin C, mg/l	0.9 ± 0.1	1.0 ± 0.2	0.9 ± 0.2	1.0 ± 0.2
$eGFR_{cysc}/eGFR_{scr}$, mL/min/1.73 m^2	82.9 ± 14.7	83.8 ± 12.7	86.3 ± 16.3	94.5 ± 13.3
Frailty index (baseline)	12.2 ± 6.2	12.8 ± 6.3	12.3 ± 5.6	12.5 ± 5.6
Frailty index (follow-up)	15.1 ± 9.1	15.9 ± 9.4	16.7 ± 10.0	17.3 ± 10.5
Exposure				
Quartile 1	910 (23.3%)	1059 (23.3%)	1233 (24.5%)	1450 (24.7%)
Quartile 2	1029 (26.3%)	1147 (25.3%)	1196 (23.8%)	1475 (25.2%)
Quartile 3	983 (25.2%)	1165 (25.7%)	1239 (24.6%)	1451 (24.8%)
Quartile 4	985 (25.2%)	1167 (25.7%)	1363 (27.1%)	1486 (25.3%)

Note: HRS, Health and Retirement Study; CHARLS, China Health and Retirement Longitudinal Study; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C reaction protein; eGFR, estimate glomerular filtration rate.
[1] Data was presented as Mean ± SD or *n* (%).

groups (**Table S5** and Fig. 2).

In contrast, among individuals with a normal $eGFR_{scr}$, cystatin C levels were consistently and significantly associated with an increased risk of frailty in both cohorts. For each 1-unit increase in cystatin C, the HRs were 5.62 (95% CI: 3.94–8.02) in the HRS cohort and 2.99 (95% CI: 2.35–3.81) in the CHARLS cohort in unadjusted models. These associations remained robust after adjusting for age, gender, and other covariates (HRS: HR = 2.05, 95% CI: 1.30–3.22; CHARLS: HR = 2.12, 95% CI: 1.60–2.82). Per SD increase in cystatin C, the HRs also remained significant across all models in both cohorts. Quartile analyses revealed a clear dose-response relationship, with individuals in the highest quartile (Q4) of cystatin C having a significantly higher risk of frailty compared to the lowest quartile (Q1). For example, in fully adjusted models, the HRs for Q4 versus Q1 were 1.34 (95% CI: 1.02–1.76) in the HRS cohort and 1.70 (95% CI: 1.40–2.07) in the CHARLS cohort (Table S5 and Fig. 2).

The restricted cubic spline analysis demonstrated no significant nonlinear association between creatinine levels and risk of frailty among individuals with a normal $eGFR_{cysc}$, either in the HRS cohort or the CHARLS cohort (Fig. 3). The AUC for creatinine in predicting frailty was 0.52 (95% CI: 0.49–0.55) in HRS cohort, and 0.56 (95% CI: 0.54–0.58) in CHARLS cohort (Fig. 4). In contrast, the results revealed a significant and nonlinear association between cystatin C levels and risk of frailty among individuals with a normal $eGFR_{scr}$ in the HRS cohort (Fig. 3). The CHARLS cohort further confirmed that the risk of frailty increased progressively with higher cystatin C levels, which was consistent with the findings in the HRS cohort. The AUC for cystatin C in predicting frailty was 0.63 (95% CI: 0.60–0.65) in HRS cohort, and 0.57 (95% CI: 0.56–0.59) in CHARLS cohort (Fig. 4).

3.3. Subgroup analysis

The associations between creatinine, cystatin C, and frailty risk were generally consistent across most subgroups, with some variations observed based on demographic and clinical factors. In both the younger group and the older group, higher cystatin C was observed to be associated with an increased risk of frailty (Q4 vs. Q1: CHARLS [<60 years]: HR = 1.74, 95% CI: 1.32–2.30; CHARLS [≥ 60 years]: HR = 1.41, 95% CI: 1.06–1.88; Q4 vs. Q1: HRS [<60 years]: HR = 1.11, 95% CI: 0.66–1.86; HRS [≥ 60 years]: HR = 1.57, 95% CI: 1.14–2.18;). In the gender subgroups, both cohorts observed significance of the highest versus the lowest tertile in the female population, whereas there was no significant, but still positive, association in men (Q4 vs. Q1: CHARLS [male]: HR = 1.41, 95% CI: 0.99–2.02; CHARLS [female]: HR = 1.76, 95% CI: 1.38–2.23; Q4 vs. Q1: HRS [male]: HR = 1.42, 95% CI: 0.91–2.21; HRS [female]: HR = 1.48, 95% CI: 1.06–2.06;). In addition, a positive but partially non-significant association of cystatin C with the risk of new-onset frailty was shown across body mass index and comorbidity populations. These results highlight the predictive value of

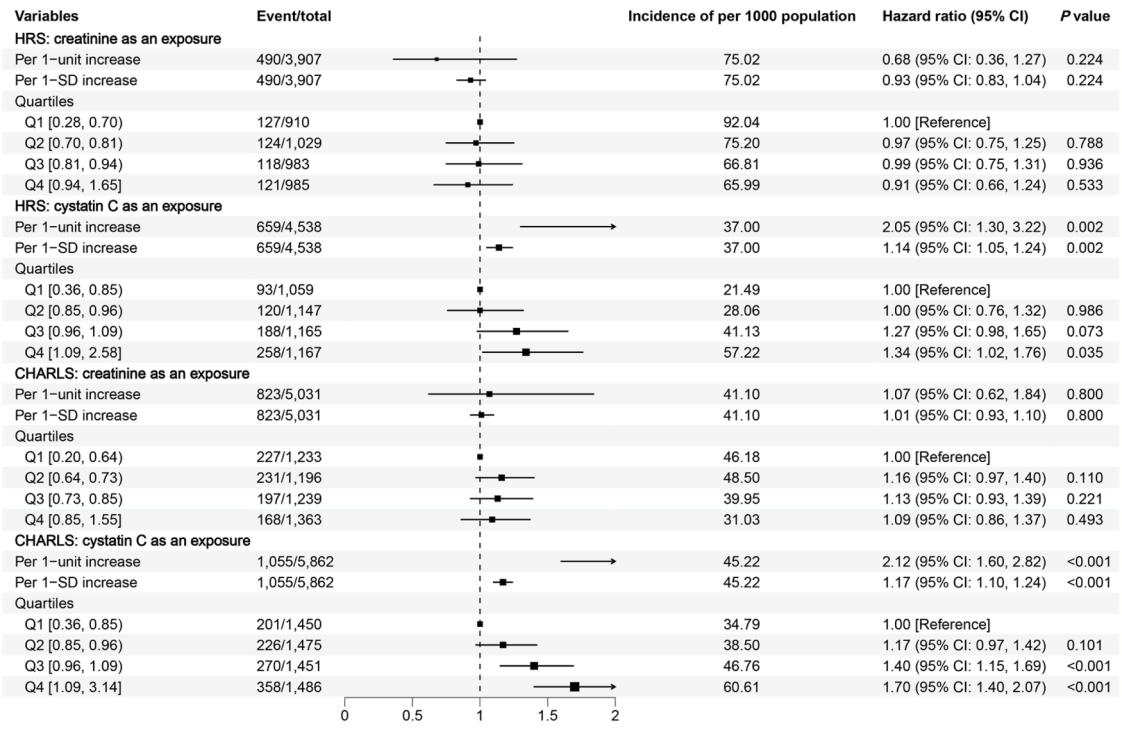

Fig. 2. Forest plot of creatinine/cystatin C and risk of frailty. Adjusted for age, gender, education level, marriage, drinking, smoking, body mass index, heart disease, hypertension, and diabetes. Q = quartile; SD = standard deviation; 95% CI = 95% confidence interval.

cystatin C for frailty risk, particularly in individuals with normal $eGFR_{scr}$, while creatinine showed no significant associations in $eGFR_{cysc}$-normal populations.

3.4. Sensitivity analysis

When restricting the analysis to participants with complete covariate data, the associations between cystatin C and frailty risk remained consistent. For Q4 versus Q1, the HR for cystatin C was 1.69 (95% CI: 1.36–2.11) in CHARLS, 1.31 (95% CI: 0.99–1.73) in HRS (approaching significance), while creatinine remained non-significant across quartiles (**Table S6-Table S9**). Using alternative thresholds for defining frailty (e.g., 20 or 30 instead of 25 as the cutoff for frailty classification) (**Table S10-Table S17**) or excluding participants with borderline eGFR values (**Table S18-Table S21**) did not change the direction of the outcome.

4. Discussion

This study examined the associations between creatinine and cystatin C levels and frailty risk in individuals with normal $eGFR_{cysc}$ and $eGFR_{scr}$ using data from the HRS and CHARLS cohorts. Cystatin C, but not creatinine, was associated with increased frailty risk in individuals with normal $eGFR_{scr}$. Subgroup analyses revealed consistent associations across age, sex, BMI, and comorbidity subgroups, with stronger effects in older adults (≥60 years) and females, suggesting heightened vulnerability to systemic changes reflected by cystatin C. Sensitivity analyses confirmed robustness, with consistent results across alternative frailty thresholds and exclusion of borderline eGFR values. These results highlight cystatin C's potential as a biomarker for frailty risk, particularly in populations where traditional kidney measures may miss subclinical changes.

Among individuals with normal $eGFR_{cysc}$, creatinine levels were not significantly associated with frailty risk, whether analyzed per unit increase, per SD increase, or by quartile groups. This lack of association persisted across all models and subgroups, suggesting the limited utility of creatinine as a frailty biomarker in this population. In contrast, cystatin C showed a robust and consistent association with frailty risk among individuals with normal $eGFR_{scr}$. Each 1-unit increase in cystatin C was associated with a significantly higher frailty risk in both cohorts, even after adjusting for age, gender, and other covariates. Quartile analyses revealed a dose-response relationship, with the highest quartile associated with markedly increased frailty risk compared to the lowest. Restricted cubic spline analysis suggested a potential threshold effect, particularly in the HRS cohort, where frailty risk rose sharply beyond the 75th percentile of cystatin C levels. These findings are consistent with evidence that cystatin C, less influenced by muscle mass, may better reflect systemic processes. Cystatin C also demonstrated superior predictive performance, with higher AUC values compared to creatinine, though modest, suggesting its potential as a more sensitive biomarker for frailty risk in eGFR-normal populations.

Additionally, cystatin C is associated with endothelial dysfunction and microvascular damage, increasingly recognized as contributors to frailty. Impaired endothelial function can lead to reduced tissue perfusion, oxidative stress, and mitochondrial dysfunction, accelerating the decline in physiological reserve [29,30]. Furthermore, cystatin C may capture subclinical kidney dysfunction not detected by creatinine-based eGFR measures [31]. Emerging evidence suggests that even mild reductions in kidney function can disrupt homeostatic mechanisms, including acid-base balance, erythropoiesis, and toxin clearance, thereby increasing frailty risk [32].

The findings of this study have important clinical implications. First, they highlight the limitations of creatinine as a biomarker for frailty risk assessment in eGFR-normal populations. Given its dependence on muscle mass and other non-renal factors, creatinine may fail to capture the subclinical physiological changes that predispose individuals to frailty. In contrast, cystatin C, as a biomarker less influenced by muscle mass, may provide a more accurate reflection of systemic processes associated with frailty, such as inflammation and metabolic dysregulation [33]. These findings support the integration of cystatin C into routine frailty risk assessment protocols, particularly in older adults and individuals with normal $eGFR_{scr}$. Second, the dose-response relationship

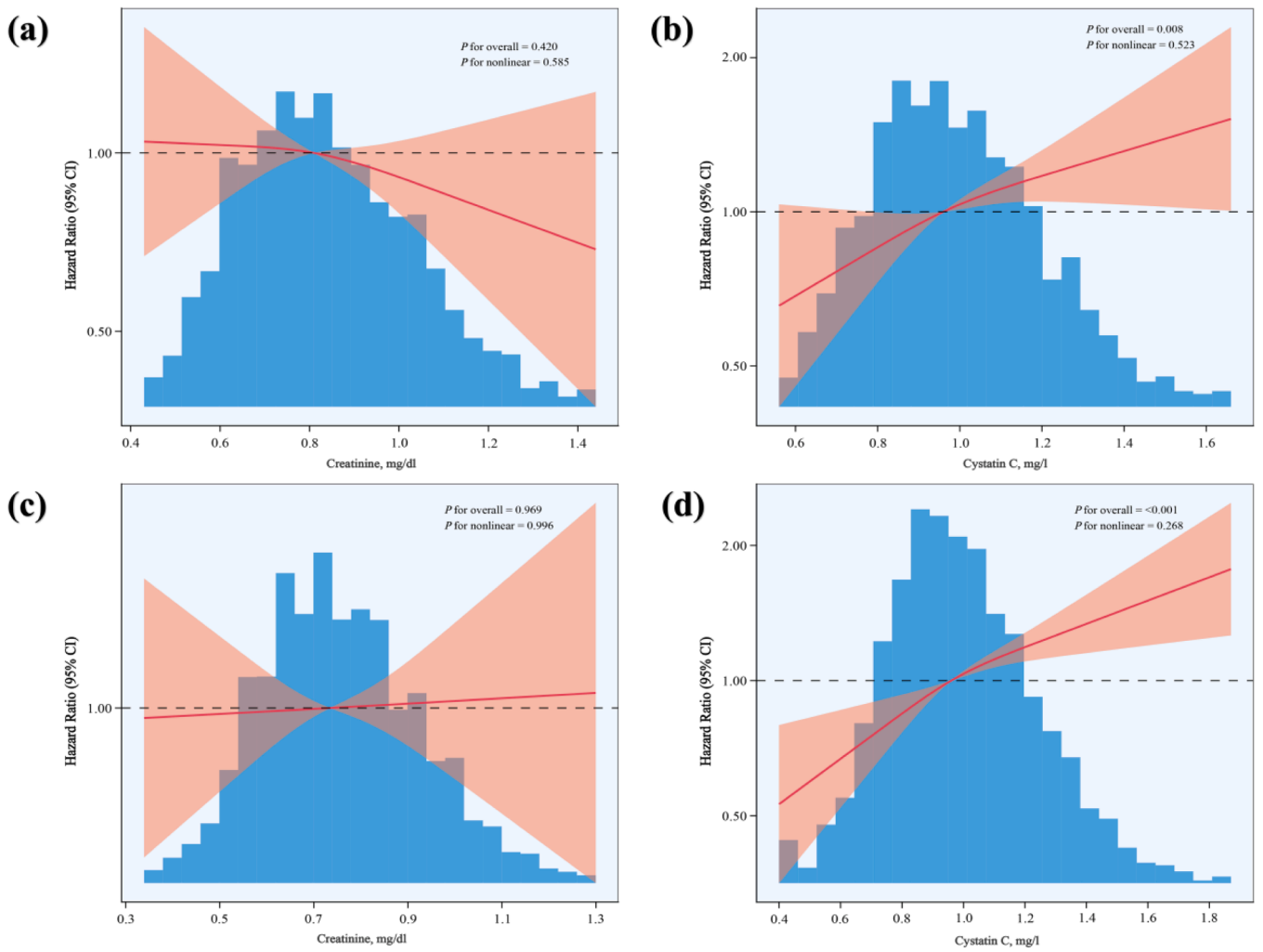

Fig. 3. Multivariable-adjusted restricted cubic spline plots. (a) HRS: creatinine and risk of frailty among individuals with a normal $eGFR_{cysc}$; (b) HRS: cystatin C and risk of frailty among individuals with a normal $eGFR_{scr}$; (c) CHARLS: creatinine and risk of frailty among individuals with a normal $eGFR_{cysc}$; (d) CHARLS: cystatin C and risk of frailty among individuals with a normal $eGFR_{scr}$.

and potential threshold effect observed for cystatin C suggest that elevated levels of this biomarker may serve as an early warning sign for frailty. Identifying individuals with high cystatin C levels could enable targeted interventions to prevent or delay the onset of frailty. For example, lifestyle modifications, nutritional support, and physical activity programs could be implemented in high-risk individuals to mitigate the systemic processes underlying frailty [34]. Finally, the findings underscore the need for a more nuanced approach to kidney function assessment in aging populations. Traditional measures of kidney function, such as eGFR based on creatinine, may overlook subclinical changes that are captured by cystatin C. Incorporating cystatin C into routine kidney function assessments could improve the identification of individuals at risk for frailty and other adverse outcomes, thereby enhancing clinical decision-making and personalized care.

Several limitations should be acknowledged. First, the observational design precludes causal inference, and residual confounding cannot be excluded despite multivariable adjustment. Second, the modest AUC values indicate that cystatin C has limited value as a standalone predictor and should complement, rather than replace, clinical and functional frailty assessments. Third, differences in frailty assessment between HRS and CHARLS may have introduced heterogeneity. In addition, the cohorts differed in age eligibility, calendar periods, ethnicity, sampling frameworks, healthcare settings, and lifestyle profiles. We therefore analyzed them separately and interpreted concordant results as evidence of external consistency rather than direct cross-cohort comparability. Unmeasured contextual and measurement differences may still have influenced the estimates. Fourth, BMI was the only harmonized body-size covariate and cannot distinguish adiposity from skeletal muscle mass. Direct measures of appendicular lean mass, muscle strength, physical performance, and validated sarcopenia status were unavailable or had substantial missingness across cohorts and survey waves. Thus, residual confounding by muscle mass or sarcopenia cannot be excluded, and we could not directly evaluate whether muscle-related factors explain the differential associations of creatinine and cystatin C with frailty. Similarly, harmonized subgroup analyses by muscle-related indicators were not feasible. Although excluding participants with borderline eGFR values (60–65 mL/min/1.73 m^2) did not materially change the findings, more detailed analyses across clinically relevant kidney-function ranges are needed. Finally, death may have competed with incident frailty, particularly among older participants. Because complete, harmonized information on death timing and ascertainment was unavailable in both datasets, Fine-Gray competing-risk analyses could not be performed. Accordingly, the Cox-model estimates should be interpreted as associations with incident frailty among participants who remained alive and under follow-up. Future studies with complete mortality data should apply competing-risk methods to confirm these findings.

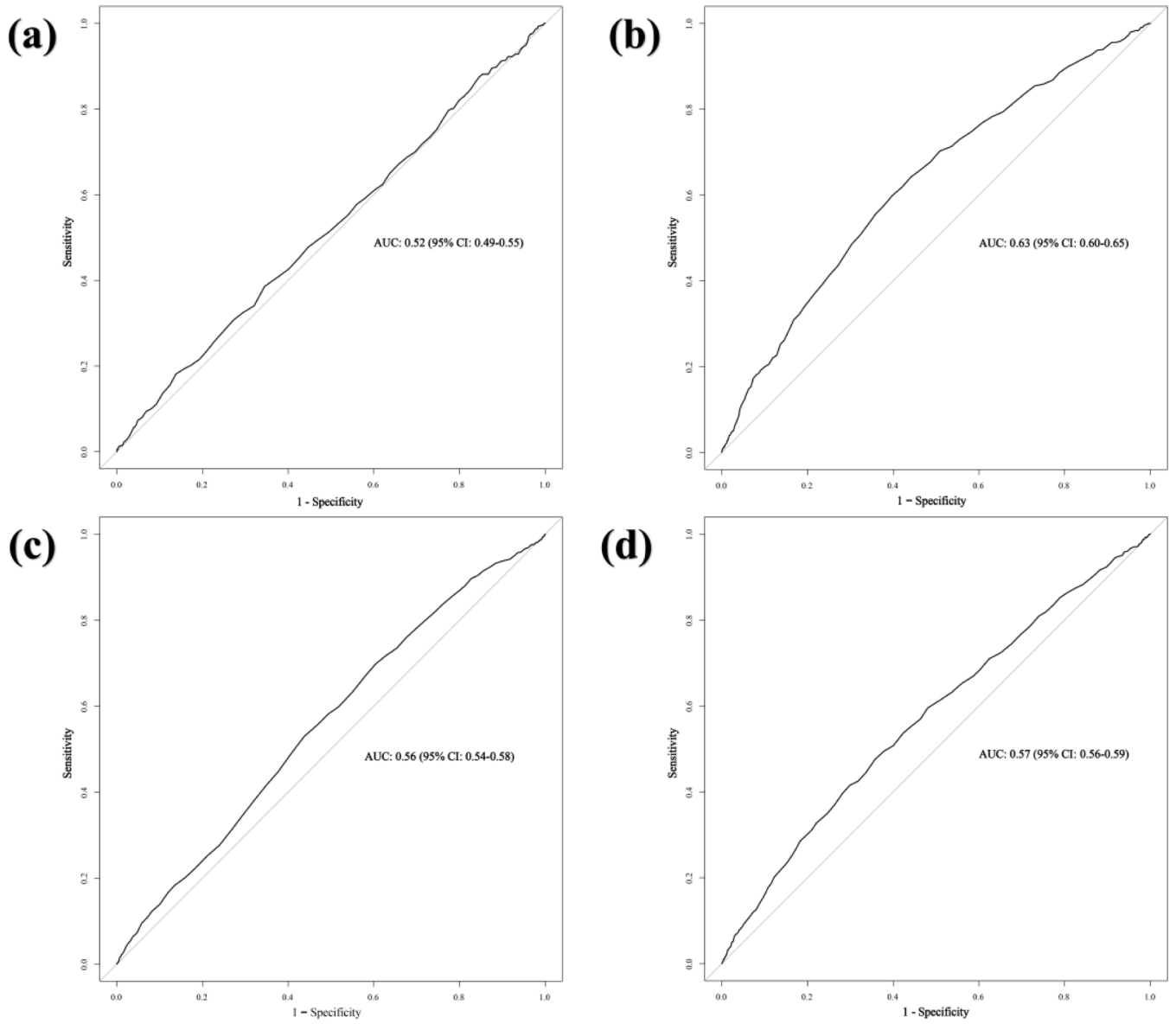

Fig. 4. Receiver operating characteristic analysis. (a) HRS: creatinine and risk of frailty among individuals with a normal $eGFR_{cysc}$; (b) HRS: cystatin C and risk of frailty among individuals with a normal $eGFR_{scr}$; (c) CHARLS: creatinine and risk of frailty among individuals with a normal $eGFR_{cysc}$; (d) CHARLS: cystatin C and risk of frailty among individuals with a normal $eGFR_{scr}$.

5. Conclusion

In conclusion, this study demonstrates that cystatin C, but not creatinine, were significantly associated with an increased risk of frailty among individuals with normal kidney function. These findings highlight the potential of cystatin C as a sensitive biomarker for frailty risk assessment and underscore the need for a more nuanced approach to kidney function evaluation in aging populations. Incorporating cystatin C into routine clinical practice could improve the early identification and management of frailty, ultimately enhancing outcomes for older adults.

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Declaration of the use of generative AI and AI-assisted technologies in scientific writing and in figures, images and artwork

During the preparation of this work the authors used ChatGPT in order to optimize language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Fan Zhang: Writing – original draft, Formal analysis, Data curation. **Yue Xing:** Writing – original draft, Conceptualization. **Yan Bai:** Writing – original draft, Data curation. **Liuyan Huang:** Supervision. **Yifei Zhong:** Writing – review & editing, Project administration, Funding acquisition.

Declaration of competing 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 paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjfa.2026.100195.

Data availability

The data that support the findings of this study are available from the China Health and Retirement Longitudinal Study (CHARLS) (http://charls.pku.edu.cn) and Health and Retirement Study (HRS) (https://hrs.isr.umich.edu/) repository.

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