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Association of platelet-to-HDL cholesterol ratio with frailty and all-cause mortality

Jianqiang Zhang[1,2*], Lele Chen[3] and Huifeng Zhang[4]

Abstract

Background Frailty often requires intensive care, and the admission outcomes of frail patients are often poor. However, owing to the lack of reliable diagnostic indicators, quickly identifying frailty is challenging. The present study aimed to explore the associations of the platelet/high-density lipoprotein cholesterol ratio (PHR; a novel inflammatory indicator) with frailty and all-cause mortality.

Methods The present study analyzed data from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018. Frailty was assessed on the basis of the 49-item Frailty Index. The associations of the PHR with frailty and long-term survival prognosis were explored through weighted logistic regression, weighted restricted cubic spline (RCS), and weighted Cox regression, with adjustments for demographic factors, lifestyle, blood lipids, medication history, and complications. In addition, subgroup and interaction analyses were conducted. Finally, several sensitivity analyses were performed.

Results A total of 15,615 adult participants were included, with 7,928 women (53.63%) and an average age of 60.76 years. After fully adjusting for confounding variables, the prevalence of frailty in the highest PHR quartile group of was significantly greater than that in the lowest quartile group (OR: 1.23, 95% CI: 1.04–1.47; $P=0.02$). The RCS showed that the inflection point was 166.7. Before and after the inflection point, the PHR was negatively associated (OR: 0.88, 95% CI: 0.80–0.97, $P=0.01$) and positively associated (OR: 1.10, 95% CI: 1.02–1.19, $P=0.01$) with frailty, respectively. Subgroup analysis suggested that the association between PHR and frailty was stronger in women than in men. A total of 5,544 frail participants were included in the survival analysis. The RCS revealed that the PHR was associated with the all-cause mortality risk of frail participants in a U-shaped manner, with an inflection point of 240.4. Before and after the inflection point, the PHR decreased (HR: 0.89, 95% CI: 0.81–0.97, $P=0.01$) and the all-cause mortality risk increased (HR: 1.08, 95% CI: 1.02–1.14, $P=0.01$), respectively.

Conclusion The present study suggests that there is a J-shaped association between PHR and frailty in the adult population of the United States and that the association between the PHR and frailty is stronger in women. In addition, the PHR has a U-shaped relationship with the all-cause mortality risk of frail patients.

Keywords Platelet/high-density lipoprotein cholesterol ratio, Frailty, All-cause mortality, NHANES, Observational study

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Introduction

Frailty is an age-related disease that is manifested mainly by a decline in the ability to cope with stressors, physical functions, and physiological reserves to varying degrees, leading to an increased risk of adverse health outcomes, including disability, death, and the need for long-term health care [1]. Frailty poses significant challenges to the current medical environment worldwide. In today's context of an aging society, early identification and intervention of frailty may greatly save medical resources.

Currently, various methods are used for assessing frailty in the general population, such as the Frailty phenotype, Frailty index, FRAIL scale, Tilburg frailty indicator, Edmonton frailty scale, and Groningen frailty indicator. Although these measurement methods differ, they have some similar core functions, such as cognition, physical health status, and social support [2, 3]. Although the relationship between age and frailty is relatively clear, frailty also exists in a considerable proportion of the young population, especially in less economically developed regions [4]. Additionally, studies have shown that frailty may change over time, making the identification of individual frailty even more challenging [5]. Inflammation is an important manifestation of aging in the body and may be related to frailty. Zhang et al. [6] suggested that two comprehensive inflammatory indicators in the American population have a potential relationship with frailty. Bilgin et al. [7] also suggested that the mean platelet volume/lymphocyte ratio (MPVLR) has a sensitivity of over 70% in predicting frailty in diabetic patients.

The platelet/high-density lipoprotein cholesterol ratio (PHR) was first proposed for use in the prediction model of metabolic syndrome (MetS) [8]. Insulin resistance is the core mechanism of MetS; evidence shows that insulin resistance may play a potential role in the pathogenesis of frailty [9]. Some recent studies have shown that the PHR may increase the incidence of kidney disease, liver disease, depression, and stroke, and it is negatively associated with serum α-klotho levels [10–14]. Klotho levels have been confirmed to be positively associated with muscle strength but negatively associated with osteoporosis, frailty, disability, and mortality [15–17]. However, the relationships of the PHR with frailty and the risk of death remain unclear.

The present study aimed to investigate the association of the PHR with frailty and risk of all-cause mortality, aiming to provide more references for the diagnosis of frailty.

Methods

Study participants

The present study included NHANES participants from 2005 to 2018. A total of 70,190 participants were involved in the 7 cycles. After individuals younger than 20 years (N=30,441), those with missing PHRs (N=3,974), those with fewer than 40 items for the frailty index (N=19,702), and those with missing covariables (N=458) were excluded, a total of 15,615 participants were included in the present study (Fig. 1).

Calculation of the PHR

The PHR is the ratio of the platelet count (PC) to the serum high-density lipoprotein cholesterol (HDL-C) level [13, 14]. Both PC (1000 cells/μL) and HDL-C concentrations (mmol/L) were obtained through laboratory tests. Considering the skewed distribution of the PHR, the present study standardized the PHR.

Diagnosis of frailty

In the present study, the definition of frailty was in accordance with the diagnostic criteria proposed by Hakeem et al. [6, 18]. Specifically, frailty was assessed on the basis of the 49-item Frailty Index (FI); this index reflects 49 items in multiple dimensions, comprehensively considering cognitive level, physical skills, daily activity level, depressive symptoms, physical health status, chronic disease conditions, laboratory test indicators, and health care status. The detailed assessment scale is provided in Supplementary Table 1. The scores of the above indicators were summed and standardized, and the resulting score ranged from 0 to 1. According to previous studies, the cutoff value of the FI was 0.21; FI≥0.21 was defined as frailty, whereas FI<0.21 was defined as non-frailty [19].

Survival outcome

In the present study, the survival outcome of interest was all-cause mortality. The NHANES database was matched with the death registration information of the Centers for Disease Control and Prevention through a unique subject identification symbol. Follow-up was until death or 12/31/2019 [20]. Moreover, the reason contributing to death was defined according to the ICD-10 code.

Covariables

On the basis of existing publications and clinical practice, the present study included demographic factors, lifestyle habits, physical indicators, medication usage, comorbidities, and lipid levels [21, 22]. These factors may affect both the prevalence of frailty and the PHR. Among the demographic factors, age, sex, race/ethnicity, education attainment, marital condition, and economic level from the NHANES database were included. Lifestyle habits mainly included smoking, alcohol consumption, weekly exercise intensity, and daily dietary energy. The physical indicator was body mass index (BMI), and medication usage included lipid-lowering drugs or antiplatelet drugs. With respect to comorbidities, cancer, hypertension, diabetes mellitus (DM), and cardiovascular disease (CVD)

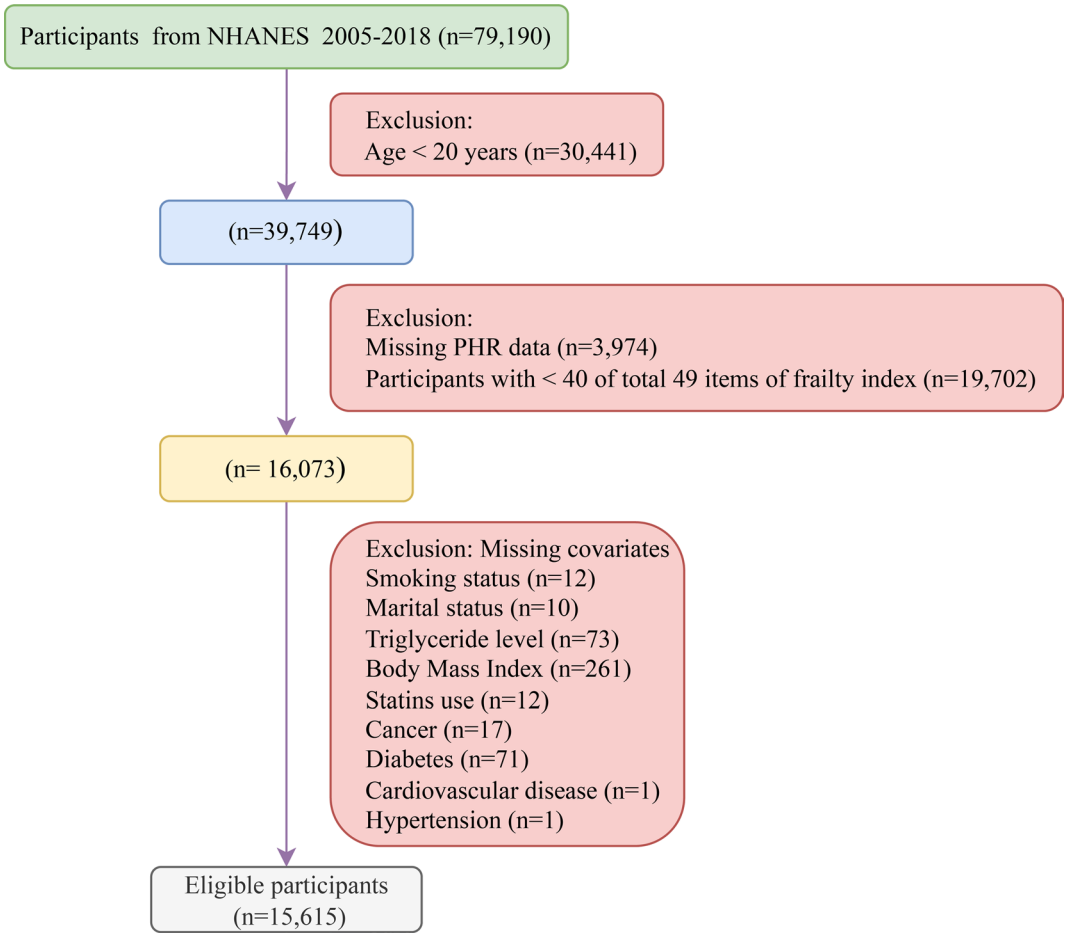

Fig. 1 Flow chart of participant recruitment. Notes: PHR, platelet/high-density lipoprotein cholesterol ratio; NHANES, National Health and Nutrition Examination Survey

were considered. Lipid levels included total blood cholesterol levels and triglyceride levels.

Statistical analysis

The NHANES employs complex probability sampling, and if weighted, it can represent the entire population. The sampling is divided into four levels, namely, county, segment, household, and individual (https://wwwn.cdc.gov/nchs/nhanes/tutorials/Weighting.aspx). Because the present study included participants from 7 cycles, one-seventh of the weight of laboratory tests was selected as the weight for analysis. The baseline characteristics of the included population were compared. One-way analysis of variance (ANOVA) or the Kruskal–Wallis test was used to compare the differences between continuous variables, whereas the chi-square test was used to compare the differences between categorical variables. The present study used the following four multivariable logistic regression or Cox regression models to estimate the associations between the PHR and frailty or survival: (1) no adjustments for confounding factors; (2) adjusted for demographic factors; (3) adjusted for demographic characteristics, lifestyle habits, and physical indicators; and (4) fully adjusted for demographic characteristics, lifestyle habits, physical indicators, medication history, comorbidities, and lipid levels. The adjustments of the four models were based on previous research experience. These factors may affect the PHR and the prevalence of frailty, and they may be related to all-cause mortality risk [21, 22]. In the logistic regression and Cox regression, the PHR was included in the model as a categorical variable based on quartiles. Considering that many covariables were included in the regression model and that there may be potential multicollinearity, a collinearity diagnosis of the model was performed. If collinearity existed, least absolute shrinkage and selection operator (LASSO) regression was used to screen important characteristic variables to simplify the model. The restricted cubic spline (RCS) method is a reliable method for analyzing nonlinear associations. In the present study, a 3-node RCS was fitted via weighted logistic regression or weighted Cox regression. If nonlinearity existed, the inflection point was determined by identifying the point where the second derivative was zero. Both the logistic

regression and Cox proportional risk models were subjected to collinearity diagnosis, and the Schoenfeld residual method was used to test whether the Cox regression model satisfied the proportional hazards assumption. In addition, subgroup analysis and likelihood ratio tests were performed to identify potentially susceptible populations. Three sensitivity analyses were conducted. First, considering the high incidence of frailty in people over 45 years of age, participants under 45 years of age were excluded. Second, the sample sampling weights during the NHANES design and survey were not considered. Finally, multiple imputation was performed for the missing covariables.

All the statistical procedures were implemented via R language version 4.40. The "nhanesR", "tidyverse", "rio", and "data.table" R packages were used for data cleaning. The "survival", "survey", and "rms" R packages were used to fit the regression models, and the "car" and the "survival" R packages were used for collinearity diagnosis and proportional hazards assumption testing. In addition, the "mice" R package was used for multiple imputation. In the present study, a two-sided $P<0.05$ was defined as significant.

Results

Population characteristics

After sequentially excluding those younger than 20 years, those with missing exposure variables and covariables, and those with fewer than 40 items for the frailty index, a total of 15,615 participants were included in the present study (Fig. 1). Table 1 presents the characteristics of the participants. The average age of the participants was 60.76 years, and there were 7,928 women (53.63%). Among the 15,615 participants, 5,550 were diagnosed with frailty. In terms of demographic characteristics, compared with participants in the lowest PHR quartile group, there were more men, more Mexican Americans, lower educational levels, more unmarried participants, and poorer economic levels among participants in the highest PHR quartile group. In terms of lifestyle, compared with those in the lowest quartile group, participants in the highest PHR quartile group were more likely to be currently smoking, were less likely to be currently drinking, had a lower level of daily activities, and had no significant difference in daily dietary energy. In addition, participants in the highest PHR quartile group had poor weight management. In terms of comorbidities and medication history, participants in the highest PHR quartile group had a greater incidence of diabetes and a lower prevalence of cancer compared to participants in the lowest PHR quartile group. In addition, participants in the highest PHR quartile group were less likely to use statins. However, there was no difference between the groups in terms of antiplatelet drugs, CVD, or hypertension.

Association of the PHR with frailty

As shown in Table 2, when the PHR was included in the model as a four-category variable and after fully adjusting for confounding factors (Model 3), only the odds of frailty in the quartile 4 group increased compared with the quartile 1 group (OR: 1.23, 95% CI: 1.04–1.47, $P=0.02$). However, the prevalence of frailty significantly increased among the four groups (P trend $=0.02$).

The RCS regression revealed a significant J-shaped association between PHR and frailty (nonlinear $P=0.0136$). When the PHR was 166.7, the prevalence of frailty was the lowest (Fig. 2). After fully adjusting for potential confounding variables (Model 3), the PHR was significantly negatively associated with the odds of frailty when the PHR was <166.7 (OR: 0.88, 95% CI: 0.80–0.97, $P=0.01$), and the PHR was significantly positively associated with the prevalence of frailty when the PHR was ≥166.7 (OR: 1.10, 95% CI: 1.02–1.19, $P=0.01$) (Table 2).

Stratified analysis revealed that the association between PHR and frailty was consistent in most subgroups; however, in the sex stratification, the association between PHR and frailty was stronger in women (P for interaction $=0.011$) (Fig. 3).

Association of the PHR with all-cause mortality in frail patients

In the present study, the association between the PHR and the risk of all-cause mortality in frail participants was also investigated. After excluding 6 participants who were lost to follow-up, a total of 5,544 frail participants were included; during the average follow-up period of 6.10 years, 1,575 participants died. The baseline characteristics of the patients in the nonsurviving group and the surviving group are shown in Supplementary Table 2.

The weighted Cox regression showed that when the PHR was included in the model as a categorical variable, the all-cause mortality risk of participants in the third and fourth PHR quartile groups was significantly lower in Model 0 without confounding factors ($P<0.05$; however, in the sequentially adjusted models (Model 1, Model 2, and Model 3), the PHR was not significantly associated with all-cause mortality risk (all $P>0.05$) (Table 3).

The potential nonlinear relationship was further analyzed through the RCS, which revealed that the PHR had a significant U-shaped association with all-cause mortality (nonlinear $P<0.0001$). The PHR corresponding to the lowest point of the HR was 240.4 (Fig. 4). Segmented weighted Cox regression revealed that before and after the inflection point, the PHR decreased (HR: 0.89, 95% CI: 0.81–0.97, $P=0.01$) and increased (HR: 1.08, 95% CI: 1.02–1.14, $P=0.01$) the risk of all-cause mortality in frail participants, respectively (Table 3).

Table 1 Weighted baseline characterization for cross-sectional study

Characteristics	Total (*N*=15615)	Quintile 1 (*N*=3908)	Quintile 2 (*N*=3898)	Quintile 3 (*N*=3900)	Quintile 4 (*N*=3909)	*P*-value
PHR, Median (IQR)	174.77(134.03,228.83)	110.12(93.13,122.81)	155.86(145.45,165.77)	199.12(187.10,212.61)	273.79(247.37,320.43)	< 0.0001
Frailty, n (%)	5550(31.26)	1237(26.59)	1291(28.58)	1365(31.33)	1657(38.62)	< 0.0001
Age(year), Mean (S.E.)	60.76(0.23)	64.98(0.29)	62.43(0.35)	59.88(0.41)	55.66(0.34)	< 0.0001
Total cholesterol level (mmol/L), Mean (S.E.)	5.04(0.02)	5.14(0.03)	4.99(0.03)	5.04(0.03)	4.99(0.02)	< 0.001
Triglyceride level (mmol/L), Mean (S.E.)	1.81(0.02)	1.21(0.01)	1.56(0.02)	1.92(0.02)	2.57(0.04)	< 0.0001
Sex, n (%)						< 0.0001
Female	7928(53.63)	2115(59.97)	2042(54.39)	1920(51.36)	1851(48.64)	
Male	7687(46.37)	1793(40.03)	1856(45.61)	1980(48.64)	2058(51.36)	
Race/Ethinicity, n (%)						< 0.0001
Mexican American	1946(5.06)	356(3.62)	477(4.66)	532(5.58)	581(6.42)	
Non-Hispanic Black	3250(9.60)	1007(11.08)	784(9.03)	771(9.55)	688(8.71)	
Non-Hispanic White	7680(75.02)	1954(77.42)	1925(76.92)	1877(73.24)	1924(72.39)	
Other Hispanic	1432(4.06)	268(2.71)	366(3.67)	406(4.93)	392(5.00)	
Other Race - Including Multi-Racial	1307(6.26)	323(5.17)	346(5.72)	314(6.70)	324(7.48)	
Educational level, n (%)						< 0.0001
No college	8455(44.95)	1923(40.14)	2060(42.68)	2171(46.99)	2301(50.11)	
College or equivalent	7160(55.05)	1985(59.86)	1838(57.32)	1729(53.01)	1608(49.89)	
Marital status, n (%)						0.004
No married	1608(10.26)	368(8.50)	365(10.08)	406(10.47)	469(12.01)	
Divorced or separated or widowed	5182(28.44)	1444(30.30)	1280(28.10)	1256(29.05)	1202(26.33)	
Already married or cohabitation	8825(61.30)	2096(61.20)	2253(61.83)	2238(60.47)	2238(61.67)	
PIR, n (%)						< 0.0001
<1.3	4919(22.23)	1059(17.70)	1109(20.11)	1287(23.85)	1464(27.37)	
1.3–3.5	5548(35.15)	1436(35.09)	1414(34.90)	1390(35.54)	1308(35.07)	
>3.5	3674(34.53)	1042(38.66)	1019(37.81)	851(31.76)	762(29.74)	
Not report	1474(8.09)	371(8.55)	356(7.18)	372(8.85)	375(7.82)	
Drinking status, n (%)						< 0.0001
Never drinked	2309(11.82)	526(10.69)	634(12.97)	566(11.68)	583(11.96)	
Former drinker	3341(18.14)	730(15.16)	742(15.76)	884(20.16)	985(21.58)	
Current drinker	8538(61.61)	2283(66.14)	2173(63.08)	2099(60.02)	1983(57.07)	
Not report	1427(8.43)	369(8.01)	349(8.19)	351(8.14)	358(9.38)	
Smoking status, n (%)						< 0.0001
Never smoked	7355(47.16)	1967(51.32)	1970(49.51)	1787(45.64)	1631(42.08)	
Former smoker	5181(33.35)	1333(35.37)	1310(34.87)	1337(33.13)	1201(29.98)	
Current smoker	3079(19.49)	608(13.31)	618(15.61)	776(21.23)	1077(27.94)	

Table 1 (continued)

Characteristics	Total (*N*=15615)	Quintile 1 (*N*=3908)	Quintile 2 (*N*=3898)	Quintile 3 (*N*=3900)	Quintile 4 (*N*=3909)	*P*-value
Physical activity (MET, minutes/week, n (%)						< 0.0001
<700	3129(20.31)	725(18.21)	768(19.46)	842(22.44)	794(21.21)	
700-2400	3303(22.70)	906(25.45)	885(23.50)	754(20.89)	758(20.87)	
>=2400	3813(27.22)	998(28.82)	940(27.82)	950(26.52)	925(25.67)	
Not report	5370(29.77)	1279(27.53)	1305(29.22)	1354(30.14)	1432(32.25)	
Energy intake (kcal/day), n (%)						0.22
Low	7737(46.01)	1939(47.53)	1932(45.85)	1921(46.04)	1945(44.59)	
High	7019(49.63)	1737(47.85)	1745(49.71)	1780(50.39)	1757(50.61)	
Not report	859(4.36)	232(4.62)	221(4.44)	199(3.57)	207(4.80)	
Body mass index, n (%)						< 0.0001
<25 kg/m^2	3932(25.61)	1504(39.57)	1049(26.94)	765(20.37)	614(15.17)	
>=25 kg/m^2	11,683(74.39)	2404(60.43)	2849(73.06)	3135(79.63)	3295(84.83)	
Statins use, n (%)	5343(32.92)	1380(34.58)	1399(34.85)	1352(32.00)	1212(30.20)	0.003
Antiplatelet drug use, n (%)	1088(5.75)	237(4.79)	285(6.22)	283(6.05)	283(5.94)	0.11
Cancer, n (%)	2604(18.82)	773(22.54)	642(18.73)	625(17.83)	564(16.10)	< 0.0001
DM, n (%)	4691(23.85)	930(17.52)	1120(23.06)	1231(24.83)	1410(30.09)	< 0.0001
CVD, n (%)	3281(18.94)	824(18.95)	817(18.83)	788(18.49)	852(19.48)	0.86
Hypertension, n (%)	9970(59.21)	2521(57.68)	2456(57.72)	2491(61.12)	2502(60.43)	0.06

Notes: PHR, platelet/high-density lipoprotein cholesterol ratio; IQR, Interquartile Range; SE, standard error; PIR, poverty-to-income ratio; MET, metabolic equivalent; DM, diabetes mellitus; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; CVD, cardiovascular diseases

Table 2 OR estimates for the association between PHR and frailty

		Model 0		Model 1		Model 2		Model 3	
		OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Frailty ~PHR	Quartile 1	reference		reference		reference		reference	
	Quartile 2	1.10(0.97,1.26)	0.15	1.16(1.01,1.33)	0.04	1.05(0.91,1.21)	0.54	1.00(0.85,1.18)	0.98
	Quartile 3	1.26(1.09,1.46)	0.003	1.31(1.12,1.52)	<0.001	1.07(0.92,1.25)	0.36	0.99(0.84,1.16)	0.87
	Quartile 4	1.74(1.49,2.02)	<0.0001	1.93(1.64,2.26)	<0.0001	1.47(1.24,1.74)	<0.0001	1.23(1.04,1.47)	0.02
	P for trend		<0.0001		<0.0001		<0.0001		0.02
	<166.7	0.96(0.89,1.04)	0.35	0.96(0.88,1.04)	0.32	0.91(0.83,0.99)	0.03	0.88(0.80,0.97)	0.01
	≥166.7	1.22(1.14,1.30)	<0.0001	1.25(1.17,1.33)	<0.0001	1.17(1.09,1.25)	<0.0001	1.10(1.02,1.19)	0.01

Notes: Model 0: Crude model. Model 1: Adjusted for age, sex, race, marital status, education, and poverty-income ratio. Model 2: Additionally adjusted for drinking, smoking, total energy intake, weekly physical activity level, and BMI. Model 3: Additionally, adjusted for diabetes, cancer, hypertension, CVD, blood cholesterol levels, blood triglyceride levels, lipid-lowering drugs and antiplatelet drugs. PHR, platelet/high-density lipoprotein cholesterol ratio; SD, standard deviation; BMI, body mass index; OR, odds ratio; CI, confidence interval

Sensitivity analysis

For the three sensitivity analyses, participants under 45 years of age were excluded, the sample sampling weights during the NHANES design and survey period were not considered, and the missing covariables were imputed multiple times. In all cases, the prevalence of frailty in the highest PHR quartile group was greater than that in the lowest quartile group. When 166.7 was considered as the inflection point, the PHR and frailty showed significant negative and positive associations on the left and right of the inflection point, respectively. Moreover, the effect strength of the association was similar to the main analysis results (Supplementary Table 3).

Discussion

The present study combined the large-scale cross-sectional survey data of the NHANES and the death registration information of the Centers for Disease Control and Prevention to investigate the relationships of the PHR with frailty and the long-term prognosis of frail patients. Among the 15,615 participants in the NHANES, the PHR was significantly positively associated with frailty, and this association had an inflection point at 166.7. Before

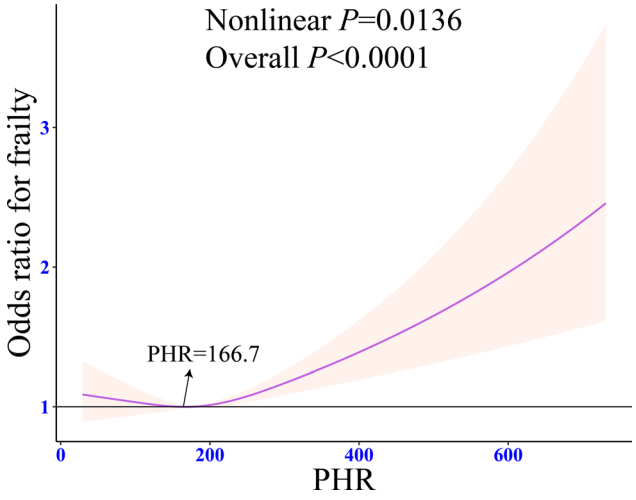

Fig. 2 Weighted restricted cubic spline regression of PHR with frailty. Notes: The adjusted restricted triple spline model was adjusted for age, sex, race, marital status, education, poverty-to-income ratio, drinking, smoking, total energy intake, weekly physical activity level, BMI, diabetes, cancer, hypertension, CVD, blood cholesterol levels, blood triglyceride levels, lipid-lowering drugs and antiplatelet drugs. PHR, platelet/high-density lipoprotein cholesterol ratio; BMI, body mass index; CVD, cardiovascular diseases; OR, odds ratio; CI, confidence interval

the inflection point, the PHR was significantly negatively associated with frailty, whereas after the inflection point, the PHR increased the prevalence of frailty. In the subgroup analysis, the association between the PHR and frailty was stronger in women than in men. In the average 6.10-year follow-up of 5,544 frail participants, the results suggested that the PHR had a significant U-shaped association with the risk of all-cause mortality, with an inflection point of 240.4. Before and after the inflection point, the PHR decreased and increased the risk of all-cause mortality in frail participants, respectively.

The diagnosis of frailty is a clinical challenge, and delayed identification of frailty may increase the consumption of medical resources. Consistent with the present conclusions, Zhang et al. [6] reported that the SII and SIRI have nonlinear J-shaped associations with frailty, but they excluded participants under 40 years of age, which may limit the generalizability of the findings concerning the association between inflammation and frailty. The present study revealed that the association between the PHR and frailty was robust in both the 20–40-year-old subgroup and the over 40-year-old subgroup. In addition, although Zhang et al. reported potential nonlinearity, they did not report the association characteristics between the inflammation index based on the inflection point and frailty. Tang et al. [23] explored the associations of whole blood cell-derived inflammatory markers with frailty and death in middle-aged and elderly people; they reported that the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), SII, and SIRI are positively associated with the risk of frailty, and increases in the NLR, MLR, PLR, SII, and SIRI are associated with an increased risk of death. However, similar to Zhang et al., Tang et al. explained the nonlinear associations of the discovered inflammatory indicators with frailty and all-cause mortality risk as simple linear relationships, but they ignored the potential complex relationship between inflammation and frailty. In addition, although the relationship between age and frailty is relatively clear, frailty also exists in a considerable proportion of the young population, especially in less economically developed regions [4]. However, the above two studies excluded people under 40 and 45 years of age, and the generalizability of their conclusions is limited.

As a new indicator, the PHR reflects the inflammatory state of the body by combining blood cells and blood lipid levels. Previous studies have shown that the PHR may serve as an effective marker for metabolic syndrome (MetS), nonalcoholic fatty liver disease (NAFLD), stroke, chronic kidney disease (CKD), kidney stones, serum klotho levels, and depression [8, 10, 12, 13, 24–26]. In 2022, two meta-analyses consistently reported a significant positive association between MetS and frailty [27, 28]. In 2023, a longitudinal cohort study from Ireland revealed that MetS patients over 50 years old have a 29-57% increased likelihood of developing frailty within four years [29]. Obesity, an important characteristic of MetS, leads to the body being in a long-term chronic low-grade inflammatory state. Chronic inflammation accelerates the consumption of muscle mass and strength, thereby leading to frailty [30–32]. In addition, MetS leads to insulin resistance, which is related to skeletal muscle atrophy, fatigue, and slow gait, and it may eventually lead to frailty [33, 34]. Therefore, an increase in the PHR may increase the prevalence of frailty through MetS. Moreover, MetS is the strongest risk factor for NAFLD, and the prevalence of frailty in individuals with NAFLD is high. As a new marker of NAFLD, the PHR may lead to frailty by aggravating the progression of NAFLD [12, 35, 36]. Despite heterogeneity, the systematic review by Burton et al. [37] revealed that frailty assessed in various ways is common in acute stroke patients and is associated with adverse outcomes. Our previous study also revealed a significant J-shaped association between the PHR and stroke [13]. A low PHR usually means a high HDL-C concentration and low platelet count. A high HDL-C concentration may increase the risk of all-cause and cardiovascular-specific mortality [38–41]. In addition, studies have shown that platelet counts are lower in elderly adults than in younger adults [42]. This may explain the negative association between the PHR and frailty when the PHR was less than 166.7 in the present study because the platelet count was low. Frailty

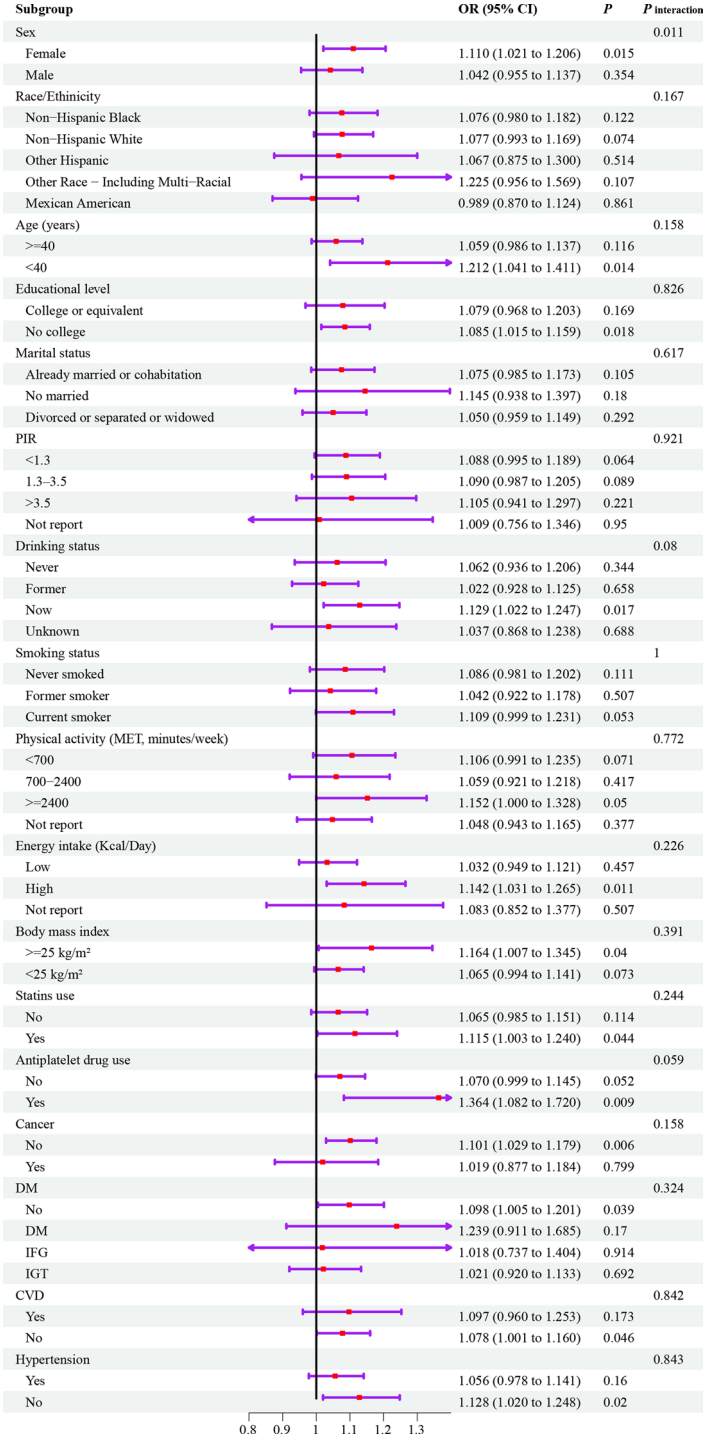

Fig. 3 Weighted subgroup analyses for the association between PHR and frailty. Notes: Models were adjusted for age, sex, race, marital status, education, poverty-to-income ratio, drinking, smoking, total energy intake, weekly physical activity level, BMI, diabetes, cancer, hypertension, CVD, blood cholesterol levels, blood triglyceride levels, lipid-lowering drugs and antiplatelet drugs. OR, odds ratio; PHR, platelet/high-density lipoprotein cholesterol ratio; BMI, body mass index; CVD, cardiovascular diseases; PIR, poverty-to-income ratio; MET, metabolic equivalent; DM, diabetes mellitus; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; OR, odds ratio; CI, confidence interval

Table 3 HR estimates for the association between PHR and all-cause mortality in patients with frailty

		Model 0		Model 1		Model 2		Model 3	
		HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
All-cause mortality~PHR	Quartile 1	reference		reference		reference		reference	
	Quartile 2	0.87(0.72,1.03)	0.11	0.90(0.76,1.07)	0.25	0.88(0.74,1.06)	0.18	0.89(0.74,1.07)	0.21
	Quartile 3	0.68(0.57,0.82)	<0.0001	0.86(0.71,1.04)	0.12	0.84(0.69,1.03)	0.09	0.83(0.68,1.03)	0.09
	Quartile 4	0.60(0.50,0.72)	<0.0001	0.96(0.80,1.16)	0.68	0.91(0.75,1.10)	0.33	0.88(0.70,1.10)	0.26
	P for trend		<0.0001		0.51		0.25		0.2
	< 240.4	0.83(0.76,0.89)	<0.0001	0.91(0.83,0.98)	0.02	0.90(0.82,0.98)	0.01	0.89(0.81,0.97)	0.01
	≥ 240.4	1.04(0.95,1.14)	0.41	1.06(1.01,1.12)	0.03	1.07(1.01,1.13)	0.02	1.08(1.02,1.14)	0.01

Notes: Model 0: Crude model. Model 1: Adjusted for age, sex, race, marital status, education, and poverty-income ratio. Model 2: Additionally adjusted for drinking, smoking, total energy intake, weekly physical activity level, and BMI. Model 3: Additionally, adjusted for diabetes, cancer, hypertension, CVD, blood cholesterol levels, blood triglyceride levels, lipid-lowering drugs and antiplatelet drugs. PHR, platelet/high-density lipoprotein cholesterol ratio; SD, standard deviation; BMI, body mass index; HR, hazard ratio; CI, confidence interval

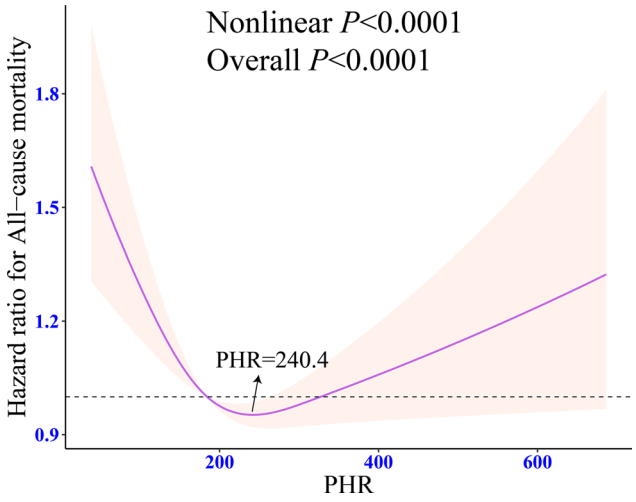

Fig. 4 Weighted restricted cubic spline regression of PHR with all-cause mortality in patients with frailty. Notes: The adjusted restricted triple spline model was adjusted for age, sex, race, marital status, education, poverty-to-income ratio, drinking, smoking, total energy intake, weekly physical activity level, BMI, diabetes, cancer, hypertension, CVD, blood cholesterol levels, blood triglyceride levels, lipid-lowering drug and antiplatelet drugs. PHR, platelet/high-density lipoprotein cholesterol ratio; BMI, body mass index; CVD, cardiovascular diseases HR, hazard ratio; CI, confidence interval

is common in CKD patients and increases the risk of adverse consequences. Hannan et al. [43] reported that in the Chronic Renal Insufficiency Cohort (CRIC) study, the frailty state of patients with CKD is associated with an increased risk of atherosclerotic events, heart failure incidents, and death. In addition, in a cross-sectional study of the NHANES, Jiang et al. [44] reported a U-shaped association between the serum α-Klotho level and frailty. Huang et al. [25] reported a linear negative association between the PHR and α-Klotho in the NHANES. These findings explain the nonlinear association between the PHR and frailty in the present study. The present findings also suggested that the association between the PHR and frailty is stronger in female participants. Generally, women have a greater proportion of adipose tissue and a lower proportion of muscle mass than men [45, 46]. This difference in body composition may lead to women being more likely to experience frailty symptoms when facing metabolic changes. A greater amount of adipose tissue may be related to a chronic low-grade inflammatory state, and chronic inflammation is an important factor leading to frailty [47, 48]. The PHR reflects the inflammatory state of the body. A greater amount of adipose tissue in women may more likely be strongly associated with frailty. In addition, as women age, their muscle mass may decline faster than that of men, especially after menopause [49, 50]. The weakening of muscle strength is an important sign of frailty, which may make women more susceptible to changes in the PHR and thus show a stronger association.

In terms of prognosis, the PHR had a significant U-shaped relationship with the risk of all-cause mortality in frail participants, indicating that both high and low PHRs reduce the long-term survival probability of this group of people. Studies have shown that high HDL-C levels (>3.0 mmol/L) increase the risk of all-cause mortality [38–41]. In the present study, when the PHR was lower than 240.4 (which may indicate high HDL-C), the risk of all-cause mortality in frail patients decreased as the PHR increased. A high PHR generally indicates a greater systemic inflammatory state, and inflammation is known to be a risk marker for death [51]. In addition, the PHR has been reported to increase the risk of cardiovascular death in stroke patients and is negatively associated with the α-Klotho level in the general population. α-Klotho, as a longevity protein, can prolong the human lifespan [13, 14, 52].

Advantages and limitations

The present study had several advantages. First, it had a large sample size and was nationally representative after the sampling weights of the samples were considered in the statistical analysis. Second, three sensitivity analyses were conducted to further demonstrate the nonlinear association between the PHR and frailty. The association between the PHR and the prevalence of frailty showed

opposite characteristics before and after the inflection point. Third, the present study explored the relationship between the PHR and the risk of all-cause mortality in patients with frailty. In this cohort, 5,544 frail participants were included, and the average follow-up time was as long as 6.10 years; thus, the results were relatively reliable. Fourth, previous frailty studies have often excluded young participants. The present study included all participants over 20 years of age, and it identified a strong association between the PHR and frailty in both the 20–40 and over 40 years of age subgroups, further confirming the effectiveness of the PHR as a frailty marker.

The present study also had several limitations. First, a cross-sectional design cannot determine the temporal sequence between the PHR and frailty, preventing a causal relationship to be determined. Owing to the inability to determine the causal direction, there is a certain degree of uncertainty in the present study for guiding clinical interventions and formulating public health strategies. It is difficult to determine whether interventions targeting the PHR can effectively prevent or improve frailty status or whether interventions targeting frailty status will have a positive impact on the PHR, which limits the in-depth understanding of potential mechanisms. The inability to determine the causal relationship makes further exploration of the biological, physiological, or behavioral mechanisms involved in the relationship between the PHR and frailty difficult. In future research, a longitudinal study design is needed to better explore the causal relationship between the PHR and frailty. Second the present study was unable to exclude the interference of potential confounding factors on the association. Third, the present study was conducted with individuals over 20 years old, indicating that the conclusion should not be extended to minors. Finally, both the PHR and frailty status are dynamic and may change over time. Using only a single measurement may not accurately reflect the true situation of an individual at different time points, thus potentially introducing biases. This single-measurement method increases the risk of misclassification bias, and it may misclassify some individuals whose PHR or frailty status changes over time, thereby affecting the accuracy and reliability of the research results.

Conclusion

In the American population over 20 years old, the PHR has J-shaped and U-shaped associations with frailty and the risk of all-cause mortality, respectively. In addition, the association between the PHR and frailty is robust in the younger group (<40 years old). Given the cross-sectional design and single-time-point PHR measurement in the present study, further longitudinal studies are needed to determine the qualification of the PHR as a reliable frailty marker. In addition, the mechanism underlying the relationship between the PHR and frailty needs to be further explored in the future to confirm the long-term impact of the PHR on frailty and mortality.

Abbreviations

ANOVA	One-way analysis of variance
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CRIC	Chronic Renal Insufficiency Cohort
CVD	cardiovascular diseases
DM	diabetes mellitus
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
ICD-10	The International Statistical Classification of Diseases and Related Health Problems 10th Revision
IQR	Interquartile Range
LASSO	least absolute shrinkage and selection operator
MECS	Mobile Examination Centers
MetS	metabolic syndrome
MLR	monocyte-to-lymphocyte ratio
MPVLR	mean platelet volume/lymphocyte ratio
NAFLD	non-alcoholic fatty liver disease
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NLR	neutrophil-to-lymphocyte ratio
OR	odds ratio
PC	Platelet count
PHR	platelet/high-density lipoprotein cholesterol ratio
PIR	poverty income ratio
PLR	platelet-to-lymphocyte ratio
RCS	restricted cubic spline
SE	standard error
SII	systemic immune-inflammation index
SIRI	systemic inflammation response index

Supplementary Information

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Supplementary Material 1

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Author contributions

J.Q.Z.: Designing topics, funding, literature search and writing. L.L.C.: Data cleansing, writing and statistical analysis. H.F.Z.: Image portfolio, writing, review and literature search.

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Data availability

The website for cross-sectional data is https://wwwn.cdc.gov/nchs/nhanes/; the website for survival data is https://www.cdc.gov/nchs/ndi/index.htm.

Declarations

Competing interests

The authors declare no competing interests.

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References

1. Canevelli M, Jackson-Tarlton C, Rockwood K. Frailty for neurologists: perspectives on how frailty influences care planning. Lancet Neurol. 2024.
2. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet. 2019;394(10206):1365–75.
3. Hanlon P, Politis M, Wightman H, Kirkpatrick S, Jones C, Khan M, et al. Frailty and socioeconomic position: a systematic review of observational studies. Ageing Res Rev. 2024;100:102420.
4. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. Lancet Public Health. 2018;3(7):e323–32.
5. Welstead M, Jenkins ND, Russ TC, Luciano M, Muniz-Terrera G. A systematic review of Frailty trajectories: their shape and influencing factors. Gerontologist. 2020;61(8):e463–75.
6. Zhang H, Liu X, Wang X, Jiang Y. Association of two novel systemic inflammatory biomarkers and frailty based on NHANES 2007–2018. Front Public Health. 2024;12:1377408.
7. Bilgin S, Aktas G, Kahveci G, Atak BM, Kurtkulagi O, Duman TT. Does mean platelet volume/lymphocyte count ratio associate with frailty in type 2 diabetes mellitus? Bratisl Lek Listy. 2021;122(2):116–9.
8. Jialal I, Jialal G, Adams-Huet B. The platelet to high density lipoprotein -cholesterol ratio is a valid biomarker of nascent metabolic syndrome. Diabetes Metab Res Rev. 2021;37(6):e3403.
9. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. Lancet Diabetes Endocrinol. 2018;6(9):743–52.
10. Ni J, Lv L, Wu P, Xu C. Associations between the platelet/high-density lipoprotein cholesterol ratio and likelihood of nephrolithiasis: a cross-sectional analysis in United States adults. Front Endocrinol (Lausanne). 2024;15:1289553.
11. Li X, Cui L, Xu H. Association between systemic inflammation response index and chronic k idney disease: a population-based study. Front Endocrinol.15:1329256.
12. Lu CF, Cang XM, Liu WS, Wang LH, Huang HY, Sang SM, et al. Association between the platelet/high-density lipoprotein cholesterol ratio and nonalcoholic fatty liver disease: results from NHANES 2017–2020. Lipids Health Dis. 2023;22(1):130.
13. Zhang H, Xu Y, Xu Y. The association of the platelet/high-density lipoprotein cholesterol ratio with self-reported stroke and cardiovascular mortality: a population-based observational study. Lipids Health Dis. 2024;23(1):121.
14. Huang C, Guan Y, Chen L, Xu Y, Yang H. The association of platelet count, high-density lipoprotein cholesterol, and platelet/high-density lipoprotein cholesterol ratio with serum soluble Klotho. Lipids Health Dis. 2024;23(1):251.
15. Veronesi F, Borsari V, Cherubini A, Fini M. Association of Klotho with physical performance and frailty in middle- aged and older adults: a systematic review. Exp Gerontol.154:111518.
16. Guan Z, Ma L, Wu C. Association between serum Klotho and Physical Frailty in Middle-aged a nd older adults: finding from the National Health and Nutrition Examin ation survey. J Am Med Dir Assoc.24(8):1173–e82.
17. Jiang Z, Wang J, Cai X, Wang P, Liu S. L-shaped association of serum α-Klotho and frailty among the middle-ag ed and older adults: results from NHANES 2007–2016. BMC Geriatr.23(1):716.
18. Hakeem FF, Bernabé E, Sabbah W. Association between Oral Health and Frailty among American older adults. J Am Med Dir Assoc. 2021;22(3):559–e632.
19. Joo SH, Song JW, Shin K, Kim MJ, Lee J, Song YW. Knee osteoarthritis with a high grade of Kellgren–Lawrence score is associated with a worse frailty status, KNHANES 2010–2013. Sci Rep. 2023;13(1):19714.
20. Zhang X, Ma N, Lin Q, Chen K, Zheng F, Wu J, et al. Body roundness index and all-cause Mortality among US adults. JAMA Netw Open. 2024;7(6):e2415051.
21. Ye C, Chen G, Huang W, Liu Y, He Z, Hu M et al. Association between the platelet/high-density lipoprotein cholesterol ratio and depression: a cross-sectional analysis in United States adul ts. Journal of affective disorders. S0165-327(24)01612-4.
22. Zhang H, Xu Y, Xu Y. The association of the platelet/high-density lipoprotein cholesterol r atio with self-reported stroke and cardiovascular mortality: a populat ion-based observational study. Lipids Health Dis.23(1):121.
23. Tang Y, Zhai Y, Song W, Zhu T, Xu Z, Jiang L, et al. Association between complete blood count-derived inflammatory markers and the risk of frailty and mortality in middle-aged and older adults. Front Public Health. 2024;12:1427546.
24. Li X, Cui L, Xu H. Association between systemic inflammation response index and chronic kidney disease: a population-based study. Front Endocrinol (Lausanne). 2024;15:1329256.
25. Huang C, Guan Y, Chen L, Xu Y, Yang H. The association of platelet count, high-density lipoprotein cholestero l, and platelet/high-density lipoprotein cholesterol ratio with serum soluble Klotho. Lipids Health Dis.23(1):251.
26. Zhang H, Xu Y, Xu Y. The value of the platelet/high-density lipoprotein cholesterol ratio i n predicting depression and its cardiovascular disease mortality: a Po pulation-based observational study. Front Endocrinol.15:1402336.
27. Jiang X, Xu X, Ding L, Lu J, Zhu H, Zhao K et al. The association between metabolic syndrome and presence of frailty: a systematic review and meta-analysis. Eur Geriatr Med.13(5):1047–56.
28. Dao HHH, Burns MJ, Kha R, Chow CK, Nguyen TN. The relationship between metabolic syndrome and Frailty in older Peopl e: a systematic review and Meta-analysis. Geriatr (Basel).7(4):76.
29. McCarthy K, Laird E, O'Halloran AM, Fallon P, Ortuño RR, Kenny RA. Association between metabolic syndrome and risk of both prevalent and incident frailty in older adults: Findings from The Irish Longitudinal Study on Ageing (TILDA). Experimental gerontology.172:112056.
30. Stranahan AM. Visceral adiposity, inflammation, and hippocampal function in obesity. Neuropharmacology. 2022;205:108920.
31. Divella R, Gadaleta Caldarola G, Mazzocca A. Chronic inflammation in obesity and Cancer Cachexia. J Clin Med. 2022;11(8).
32. Mehta M, Louissaint J, Parikh NS, Long MT, Tapper EB. Cognitive function, Sarcopenia, and inflammation are strongly Associated with Frailty: a Framingham Cohort Study. Am J Med. 2021;134(12):1530–8.
33. Luo L, Qin R, Liu T, Yu M, Yang T, Xu G. OsASN1 plays a critical role in asparagine-dependent Rice Development. Int J Mol Sci. 2018;20(1).
34. Perkisas S, Vandewoude M. Where frailty meets diabetes. Diabetes Metab Res Rev. 2016;32(Suppl 1):261–7.
35. Naimimohasses S, O'Gorman P, McCormick E, Ferguson D, Monaghan A, McGrath M et al. Prevalence of frailty in patients with non-cirrhotic non-alcoholic fatty liver disease. BMJ Open Gastroenterol. 2022;9(1).
36. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018;24(7):908–22.
37. Burton JK, Stewart J, Blair M, Oxley S, Wass A, Taylor-Rowan M et al. Prevalence and implications of frailty in acute stroke: systematic review & meta-analysis. Age Ageing. 2022;51(3).
38. Hamer M, O'Donovan G, Stamatakis E. High-density lipoprotein cholesterol and mortality: too much of a good thing? Arterioscler Thromb Vasc Biol. 2018;38(3):669–72.
39. Ko DT, Alter DA, Guo H, Koh M, Lau G, Austin PC, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous Cardiovascular conditions: the CANHEART Study. J Am Coll Cardiol. 2016;68(19):2073–83.
40. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J. 2017;38(32):2478–86.
41. Hirata A, Sugiyama D, Watanabe M, Tamakoshi A, Iso H, Kotani K, et al. Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: the EPOCH-JAPAN study. J Clin Lipidol. 2018;12(3):674–e845.
42. Hernández B, Fuentes E, Palomo I, Alarcón M. Increased platelet function during frailty. Exp Hematol.77:12–e252.

43. Hannan M, Chen J, Hsu J, Zhang X, Saunders MR, Brown J, et al. Frailty and Cardiovascular outcomes in adults with CKD: findings from the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis. 2024;83(2):208–15.
44. Jiang Z, Wang J, Cai X, Wang P, Liu S. L-shaped association of serum α-Klotho and frailty among the middle-aged and older adults: results from NHANES 2007–2016. BMC Geriatr. 2023;23(1):716.
45. Chang E, Varghese M, Singer K. Gender and sex differences in adipose tissue. Curr Diab Rep. 2018;18(9):69.
46. Nuzzo JL. Sex differences in skeletal muscle fiber types: a meta-analysis. Clin Anat.37(1):81–91.
47. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev. 2016;31:1–8.
48. Mraz M, Haluzik M. The role of adipose tissue immune cells in obesity and low-grade infla mmation. J Endocrinol.222(3):R113–27.
49. Shin MJ, Jeon YK, Kim IJ. Testosterone and Sarcopenia. World J Mens Health.36(3):192–8.
50. Critchlow AJ, Hiam D, Williams R, Scott D, Lamon S. The role of estrogen in female skeletal muscle aging: a systematic review. Maturitas. 2023;178:107844.
51. Singh-Manoux A, Shipley MJ, Bell JA, Canonico M, Elbaz A, Kivimäki M. Association between inflammatory biomarkers and all-cause, cardiovascular and cancer-related mortality. CMAJ. 2017;189(10):E384–90.
52. Xu Y, Sun Z. Molecular basis of Klotho: from gene to function in aging. Endocr Rev.36(2):174–93.

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