Clinical Interventions in Aging

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Predictive Value of Inflammation Markers for Frailty in Older Patients with CVD

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Background: Chronic inflammation plays a pivotal role in the development of frailty in patients with cardiovascular diseases (CVD). Systemic inflammatory response index (SIRI) has been shown to reflect the overall inflammatory status. This study aimed to investigate the relationship between SIRI and frailty in older patients with CVD, and to develop a nomogram for predicting the risk of frailty in this population.

Methods: A total of 234 older patients with CVD were included. Inflammation markers were derived from routine blood tests, and frailty status was assessed using the FRAIL scale. Clinical and laboratory characteristics were compared between patients with or without frailty. Multivariate logistic regression was employed to identify significant variables for inclusion in the nomogram. The performance of the nomogram, including its discrimination and calibration, was rigorously evaluated.

Results: A total of 98 cases were assigned to the frailty group and 136 to the non-frailty group. Patients in the non-frailty group were generally younger, more likely to have normal kidney function, and better blood pressure control. Frail patients exhibited a higher degree of systemic inflammation compared to non-frail patients ($P < 0.05$). Age, LDL-C and SIRI were identified as three independent risk factors with significant potential for predicting frailty in CVD patients. Therefore, we constructed a clinical nomogram model for frailty based on age, LDL-C and SIRI. The nomogram for frailty had considerable discriminative and calibrating abilities.

Conclusion: In summary, our study demonstrated a significant association between elevated levels of inflammation markers, particularly SIRI, and an increased risk of frailty. Furthermore, by integrating age, LDL-C and SIRI, we established a nomogram to predict the risk of frailty in older patients with CVD.

Keywords: inflammation markers, systemic inflammatory response index, frailty, cardiovascular diseases, nomogram

Introduction

Frailty is widely recognized as the most challenging manifestations of population ageing.[1] It is characterized by an increased vulnerability to poor resolution of homeostasis following stressors and results from a progressive decline across multiple physiological systems.[2,3] Studies have shown that the prevalence of frailty among adults aged 50 and older is approximately 12%.[4] Age-stratified meta-analyses conducted in Chinese communities revealed that the overall prevalence of frailty was 6% for individuals aged 65–74, 15% for those aged 75–84, and 25% for those aged 85 and older.[5] Given its high prevalence and substantial impact on health, frailty has increasingly been acknowledged as a critical issue in aging populations.

Frailty has emerged as a significant global health and economic burden for both clinical practice and public health.[6] It is associated with an increased risk of various adverse outcomes, including falls, cardiovascular disease, hospitalization, nursing home admission, poor surgical outcomes, disability, and mortality.[7–14] These negative outcomes not only impact individuals but also impose substantial burdens on healthcare systems. Identifying populations at higher risk for frailty is

Received: 24 October 2024
Accepted: 13 March 2025
Published: 8 April 2025

crucial in clinical practice to prevent these adverse outcomes. This is especially pertinent in the context of cardiovascular diseases (CVD), which share a complex relationship with frailty.[15–17]

Frailty was associated with a 2-fold increase in mortality among patients with CVD. Epidemiological studies have consistently demonstrated that frailty is closely related to a wide range of CVD conditions, including stable CVD, subclinical CVD, heart failure, and outcomes following surgical and transcatheter interventions.[15–17] For instance, the NHATS study demonstrated that both pre-frailty and physical frailty phenotypes were significantly associated with increased mortality and the development of major adverse cardiovascular events (MACE) over a 6-year follow-up period.[18] These findings underscore the importance of elucidating the mechanisms underlying the relationship between frailty and CVD, particularly the role of inflammatory processes.

Substantial evidence indicates that chronic inflammation significantly contributes to the development of frailty.[19–23] In recent years, researchers have endeavored to identify reliable biomarkers to assess inflammation and its impact on frailty. Systemic inflammatory response index (SIRI), a recently introduced composite marker that integrates neutrophil, monocyte, and lymphocyte counts, has garnered attention.[24] SIRI reflects the balance among these cell types and has been proved to effectively represent both local immune responses and systemic inflammation.[24] Notably, SIRI has demonstrated prognostic value in various conditions, including several cancers,[25–29] aneurismal subarachnoid hemorrhage,[30] acute ischemic stroke,[31] and has been correlated with the severity of coronary artery disease[32] as well as cardiovascular death and all-cause mortality.[33] Despite its potential, the relationship between SIRI and frailty remains underexplored, particularly in disease-specific populations.

However, limited research has specifically examined the association between SIRI and frailty in disease-specific study populations. This gap highlights the necessity for targeted studies, particularly among older adults with CVD, who are at high risk for both frailty and adverse cardiovascular outcomes. Thus, this study aims to explore the association between inflammation markers, with a focus on SIRI, and frailty in older patients with CVD. Additionally, we developed a nomogram to predict the risk of frailty in this population, aiming to enhance the management of frail CVD patients, reduce hospitalizations and mortality, and improve quality of life. By addressing this critical research gap, our findings may inform more effective clinical strategies for managing frailty in high-risk populations.

Material and Methods

Study Design

This study aimed to explore the association between the SIRI and frailty in older patients with CVD and to develop a nomogram for estimating the risk of frailty in this population. Clinical and laboratory features, including inflammation markers such SIRI, were compared between patients with and without frailty to identify potential predictors. Selected significant variables associated with frailty were subsequently incorporated into the nomogram to estimate the probabilities of frailty.

Study Population

This study included 234 patients treated in the inpatient department of Geriatrics from Peking University Third Hospital. The clinical data and blood samples were collected from May 28th 2023 to November 15th 2023. The trial is being carried out in compliance with the ethical principles of the Declaration of Helsinki. All patients have signed the informed consent forms, and the study has been approved by the institutional review board. All personal information was encrypted. For the analysis of different measurements, the sample size varied according to the number of missing data.

We selected patients $\geq$ 60 years with CVD, which included ischemic heart disease (IHD), stroke, heart failure, peripheral and aortic arterial disease, arrhythmias, and valvular diseases.[34] Patients with acute infections, autoimmune diseases, diseases of the hematopoietic system, malignancies and severe liver or kidney dysfunction were excluded.

Markers of Systemic Inflammation

The markers of systemic inflammation were obtained from routine blood tests at admission. The calculation formula is as follows:

- Systemic inflammation response index (SIRI) = neutrophil count (10^9/L) × monocyte count (10^9/L)/ lymphocyte count (10^9/L).
- The neutrophil-to-lymphocyte ratio (NLR) = neutrophil count (10^9/L)/ lymphocyte count (10^9/L).
- Derived NLR (dNLR) = neutrophil count (10^9/L)/(WBC count (10^9/L)-neutrophil count (10^9/L)).
- The platelet-to-lymphocyte ratio (PLR) = platelet count (10^9/L)/lymphocyte count (10^9/L).
- C-reactive protein/lymphocyte ratio (CLR) = C-reactive protein (mg/L)/lymphocyte count (10^9/L).
- Mean platelet volume (MPV) = mean platelet volume (fL).
- Monocyte-high density lipoprotein ratio (MHR) = monocyte count (10^9/L)/high-density lipoprotein (mmol/L).
- Systemic immune-inflammation index (SII) = platelet count (10^9/L) × neutrophil count (10^9/L)/lymphocyte count (10^9/L).
- Aggregate index of systemic inflammation (AISI) = neutrophil count (10^9/L) × monocyte count (10^9/L) × platelet count (10^9/L)/lymphocyte count (10^9/L).
- Atherogenic index of plasma (AIP) = log10 (triglyceride (mmol/L)/high-density lipoprotein (mmol/L)).
- C-reactive protein-to-prealbumin ratio (CPAR) = C-reactive protein (mg/L)/prealbumin (mg/L).
- Prognostic nutritional index (PNI) = albumin (g/L)+5×lymphocyte count (10^9/L).
- Triglyceride-glucose index of insulin resistance (TyG) = ln(triglyceride (mg/dL)×fasting blood glucose (mg/dL)/2).

Frailty Categories

Frailty status was assessed using the FRAIL scale. The FRAIL Scale was a simple and rapid screening tool for frailty, consisting of five dimensions, each assessed through a straightforward question or evaluation. Individuals who met three or more of the following five components were classified as frail: fatigue, resistance, ambulation, illness, and weight loss[35] (Box 1).

End Points and Other Covariate Data

Demographic and clinical characteristics, laboratory data and lifestyles were collected.

The demographic information (sex, age, body mass index, smoking habits), medical history (comorbidity: hypertension, diabetes and chronic kidney disease) were compiled from the electronic medical record system. Comorbidities were assessed using the age-adjusted Charlson comorbidity index (aCCI). At admission, the Barthel Index was used to assess activities of daily living (ADL).

Box 1 FRAIL Scale Items

Fatigue: **Question**: Did you often feel tired during the recent month? **Scoring**: Yes (1 point) / No (0 points)
Resistance: **Question**: Did you have any difficulty climbing up 10 steps by yourself and without using aids? **Scoring**: No (1 point) / Yes (0 points)
Ambulation: **Question**: Did you have any difficulty walking 200 or 300 meters by yourself and without using aids? **Scoring**: No (1 point) / Yes (0 points)
Illnesses: **Question**: Did a doctor tell you that you have the following 11 illnesses? The illnesses included hypertension, diabetes, angina, heart attack, congestive heart failure, stroke, chronic lung disease, asthma, arthritis, cancer (other than a minor skin cancer) and kidney disease **Scoring**: Yes (≥5 illnesses) / No (<5 illnesses)
Loss of Weight: **Question**: How much weight did you lose in the past year? **Scoring**: Yes (≥ 5%) / No (< 5%)

Laboratory data included white blood cells count (WBC), hemoglobin (HB), platelets (PLT), mean platelet volume (MPV), serum albumin (ALB), prealbumin, lactate dehydrogenase (LDH), serum creatinine (Cr), estimated glomerular filtration rate (eGFR), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), ultra-sensitive C-reactive protein (US-CRP), brain natriuretic peptide (BNP) and D-Dimer levels.

Statistical Analysis

Descriptive statistical analyses were performed to compare characteristics between patients with or without frailty. Continuous variables with a normal distribution were presented as mean ± standard deviation, and the differences were analyzed by T-test. Non-normally distributed measurement data were presented as the median (lower and upper quartiles), and intergroup comparisons were analyzed by Mann–Whitney-U test. Categorical variables were presented as absolute numbers (%), group differences were analyzed by Chi-square tests or Fisher's test.

Stratification analysis was used to explore the influencing factors of SIRI. Stratification was based on the median value of every category. Items which were affected by frailty but independent of SIRI were included in the Multivariate binary logistic regression.

Multivariate binary logistic regression was used to estimate the association of frailty with systemic inflammation. The data was presented using odds ratios (ORs) with 95% CI.

We constructed a nomogram for frailty according to the variables screened. Multivariate binary logistic regression was used to select variables for inclusion in the nomogram. Using the nomogram, the probabilities of frailty were estimated. We used concordance area under the time-dependent receiver operating characteristic curve (time-dependent AUC) calculated by bootstrapping to evaluate discriminative ability. Specially, AUC values greater than 0.7 was considered reasonable.

The two-tailed P value of <0.05 was considered significant. All analyses were conducted with SPSS 22.0 and R (version 4.2.3).

Results

Population Characteristics

Table 1 shows patient characteristics, which has been categorized based on the frailty parameters. In our study, a total of 234 individuals were included and analyzed in cross-sectional setting. Of all the patients, 53.42% were males and the mean (±SD) age was 76.28 years (±9.62), mean score on the FRAIL scale was 1.99 (±1.42), with 50% having diabetes, 17.95% having chronic kidney diseases, 67.95% having hypertension, and 29.49% having a history of smoking. In our study, the majority of patients presented with a spectrum of severities of ischemic heart disease, heart failure, and degenerative valvular heart disease, while a smaller proportion of patients also had comorbid conditions such as atrial fibrillation and lower extremity arterial stenosis.

According to the results of FRAIL scale, 98 cases were assigned to the frailty group and 136 to the non-frailty group. Patients without frailty were younger, more likely to have a normal kidney function and good blood pressure control. Frail patients had lower body mass index (BMI) and aADL score but higher aCCI score than non-frail patients. Frail patients exhibited higher WBC, LDH, Cr, BNP and D-Dimer levels. In contrast, lower HB, ALB, eGFR, TG and LDL-C levels were seen in frail patients ($P < 0.05$). In addition, no significant differences were found in sex, diabetes, history of smoking, PLT and US-CRP between the two groups ($P > 0.05$).

Association of the Markers of Systemic Inflammation with Frailty

Table 2 shows the association of the markers of systemic inflammation with frailty.

Frail patients exhibited high systemic inflammation, with higher SIRI, NLR, dNLR, CLR, AISI, AIP, PNI and TyG levels than non-frail patients.

Stratification analysis revealed that SIRI was positively associated with age, aCCI score, WBC, US-CRP, BNP and D-Dimer levels. Male patients with chronic kidney disease and a history of smoking showed elevated SIRI. SIRI was negatively associated with aADL score and ALB. Furthermore, SIRI was independent of diabetes, hypertension, BMI, HB, PLT, eGFR and LDL-C (all $P < 0.05$, Table 3).

Table 1 Patient Characteristics Between the Frailty Group and the Non-Frailty Group

Categories	Frailty Group (n=98)	Non-Frailty Group (n=136)	P
Gender(male,%)	54(55.10)	71(52.21)	0.661
Age≥75 years(%)	87(88.78)	33 (24.26)	<0.001
Diabetes(%)	42(42.86)	75(55.15)	0.064
Chronic kidney disease(%)	33(33.67)	9(6.62)	<0.001
Hypertension(%)	78(79.59)	81(59.56)	0.001
History of smoking(%)	23(23.47)	46(33.82)	0.087
BMI<24 kg/m^2(%)	50(51.02)	47(34.56)	0.012
aCCI≥7(%)	85(86.73)	43(32.33)	<0.001
aADL<87.5(%)	84(85.71)	33(24.26)	<0.001
WBC≥5.88×10^9/L(%)	59(60.20)	58(42.65)	0.008
HB<120g/L(%)	63(64.29)	37(27.21)	<0.001
PLT≥195×10^9/L(%)	46(46.94)	72(52.94)	0.365
ALB<37.7g/L(%)	65(67.01)	51(37.50)	<0.001
LDH(U/L)	194.50(173.50,230.25)	173.00(152.50,195.50)	<0.001
Cr(umol/L)	82.50(63.75,111.00)	71.00(59.00,85.00)	<0.001
eGFR<79mL/min/$1.73m^2$(%)	66(67.35)	48(35.56)	<0.001
TG(mmol/L)	1.04(0.76,1.55)	1.32(0.95,1.82)	0.008
LDL-C<2.05mmol/L(%)	52(61.90)	55(41.35)	0.003
US-CRP≥1.34mg/L(%)	39(58.21)	47(45.19)	0.097
BNP≥450pg/mL(%)	49(52.13)	12(10.08)	<0.001
D-Dimer≥0.185ug/mL(%)	68(69.39)	48(35.82)	<0.001

Abbreviations: BMI, body mass index; aCCI, the age-adjusted Charlson Comorbidity Index; aADL, activities of daily living at admission; WBC, white blood cells count; HB, hemoglobin; PLT, platelets; ALB, serum albumin; LDH, lactate dehydrogenase; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; TG, triglyceride; LDL-C low-density lipoprotein cholesterol; US-CRP, ultra-sensitive C-reactive protein; BNP brain natriuretic peptide.

Table 2 Markers of Systemic Inflammation Between the Frailty Group and the Non-Frailty Group

Categories	Frailty Group (n=98)	Non-Frailty Group (n=136)	P
SIRI	1.06(0.62,2.28)	0.78(0.50,1.07)	<0.001
NLR	2.46(1.54,4.53)	1.89(1.42,2.44)	<0.001
dNLR	1.72(1.13,2.90)	1.43(1.11,1.78)	0.002
PLR	114.01(86.39,189.06)	114.45(87.35,162.75)	0.565
CLR	1.61(0.30,9.37)	0.61(0.26,1.62)	0.011
MPV	10.20(9.40,11.20)	10.20(9.60,10.70)	0.439
MHR	0.43(0.31,0.59)	0.38(0.28,0.50)	0.087
SII	474.20(235.18,943.71)	387.91(276.86,530.97)	0.057
AISI	207.21(95.06,402.91)	149.66(93.91,228.67)	0.007
AIP	0.04(0.28)	0.12(0.26)	0.036
CPAR	0.0097(0.0025,0.0750)	0.0051(0.0026,0.0147)	0.082
PNI	43.33(7.50)	47.08(4.82)	<0.001
TyG	8.50(0.70)	8.70(0.58)	0.041

Abbreviations: SIRI, systemic inflammation response index; NLR, the neutrophil-to-lymphocyte ratio; dNLR, derived NLR; PLR, the platelet-to-lymphocyte ratio; CLR, C-reactive protein/lymphocyte ratio; MPV, mean platelet volume; MHR, monocyte-high density lipoprotein ratio; AISI, the aggregate index of systemic inflammation; AIP, atherogenic index of plasma; CPAR, C-reactive protein-to-prealbumin ratio; PNI, prognostic nutritional index; TyG, triglyceride-glucose index of insulin resistance.

https://doi.org/10.2147/CIA.S502617

Table 3 Stratification Analysis

Categories	Number of Cases	SIRI	P
Gender			
Male	124	1.07 (0.70,1.71)	<0.001
Female	109	0.66 (0.40,0.99)	
Age			
<75 years	113	0.83(0.50,1.11)	0.021
≥75 years	120	0.89(0.58,1.77)	
Diabetes			
Yes	117	0.84(0.53,1.21)	0.626
No	116	0.86(0.51,1.44)	
Chronic kidney disease			
Yes	42	1.11(0.66,2.37)	0.019
No	191	0.84(0.51,1.21)	
Hypertension			
Yes	158	0.87(0.51,1.34)	0.569
No	75	0.81(0.56,1.31)	
History of smoking			
Yes	68	1.06(0.68,1.65)	0.002
No	165	0.78(0.48,1.20)	
BMI			
<24kg/m^2	97	0.84(0.54,1.41)	0.919
≥24kg/m^2	136	0.86(0.53,1.24)	
aCCI			
<7	102	0.76(0.46,1.06)	<0.001
≥7	128	0.98(0.63,1.79)	
aADL			
<87.5	117	1.06(0.61,2.24)	<0.001
≥87.5	116	0.78(0.50,1.04)	
WBC			
<5.88×10^9/L	117	0.63(0.40,0.89)	<0.001
≥5.88×10^9/L	116	1.12(0.83,2.16)	
HB			
<120g/L	100	0.91(0.50,1.77)	0.179
≥120g/L	133	0.84(0.54,1.15)	
PLT			
<195×10^9/L	116	0.76(0.50,1.20)	0.106
≥195×10^9/L	117	0.92(0.56,1.36)	
ALB			
<37.7g/L	116	1.05(0.65,1.77)	<0.001
≥37.7g/L	116	0.76(0.43,1.03)	
eGFR			
<79mL/min/1.73m^2	114	0.88(0.56,1.41)	0.207
≥79mL/min/1.73m^2	118	0.83(0.50,1.23)	
LDL-C			
<2.05mmol/L	107	0.91(0.58,1.46)	0.058
≥2.05mmol/L	109	0.81(0.50,1.12)	
US-CRP			
<1.34mg/L	84	0.65(0.45,0.91)	<0.001
≥1.34mg/L	86	0.99(0.67,1.66)	

(*Continued*)

Table 3 (Continued).

Categories	Number of Cases	SIRI	P
BNP			
<450pg/mL	151	0.81(0.51,1.12)	<0.001
≥450pg/mL	61	1.15(0.64,2.55)	
D-Dimer			
<0.185ug/mL	115	0.75(0.50,1.01)	<0.001
≥0.185ug/mL	116	1.10(0.65,2.25)	

Abbreviations: SIRI, systemic inflammation response index; BMI, body mass index; aCCI, the age-adjusted Charlson Comorbidity Index; aADL, activities of daily living at admission; WBC, white blood cells count; HB, hemoglobin; PLT, platelets; ALB, serum albumin; eGFR, estimated glomerular filtration rate; LDL-C low-density lipoprotein cholesterol; US-CRP, ultra-sensitive C-reactive protein; BNP brain natriuretic peptide.

Table 4 Multivariate Binary Logistic Regression Analysis

	β	S.E.	Wald	P	OR	95% CI	
						Lower	Upper
Male	−0.309	0.443	0.486	0.486	0.734	0.308	1.751
Age	0.170	0.030	32.625	<0.001	1.185	1.118	1.256
Hypertension	0.431	0.451	0.916	0.339	1.539	0.636	3.721
BMI	−0.079	0.068	1.386	0.239	0.924	0.809	1.054
HB	−0.019	0.012	2.460	0.117	0.981	0.958	1.005
eGFR	−0.009	0.012	0.617	0.432	0.991	0.968	1.014
LDL-C	−0.658	0.250	6.910	0.009	0.518	0.317	0.846
SIRI	0.730	0.279	6.833	0.009	2.075	1.200	3.587

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval. BMI, body mass index; HB, hemoglobin; eGFR, estimated glomerular filtration rate; LDL-C low-density lipoprotein cholesterol; SIRI, systemic inflammation response index.

Influencing Factors Related to Frailty in CVD Patients by Logistic Regression Analysis

The occurrence of frailty served as the dependent variable in our study, while factors such as gender, age, hypertension, BMI, HB, eGFR, LDL-C, and SIRI were included in multivariate binary logistic regression analysis. It was found that age, LDL-C and SIRI were three independent risk factors leading to frailty in CVD patients (Table 4).

Nomogram Construction and Validation

We constructed a nomogram for frailty based on age, LDL-C and SIRI. Figure 1 shows an example of using the nomogram to predict frailty probability of a given patient. The total score was determined based on the individual scores calculated using the nomogram. The model was internally verified using 100 repetitions of bootstrap sample corrections.

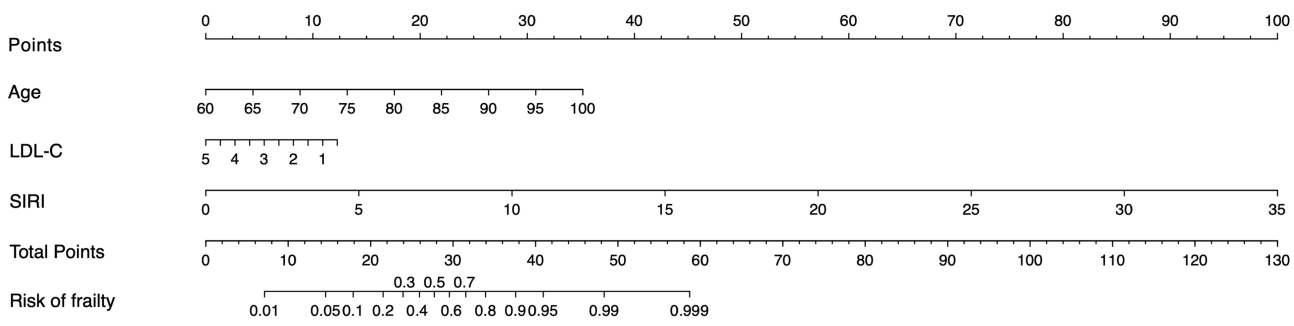

Figure 1 Nomogram of frailty risk.

https://doi.org/10.2147/CIA.S502617

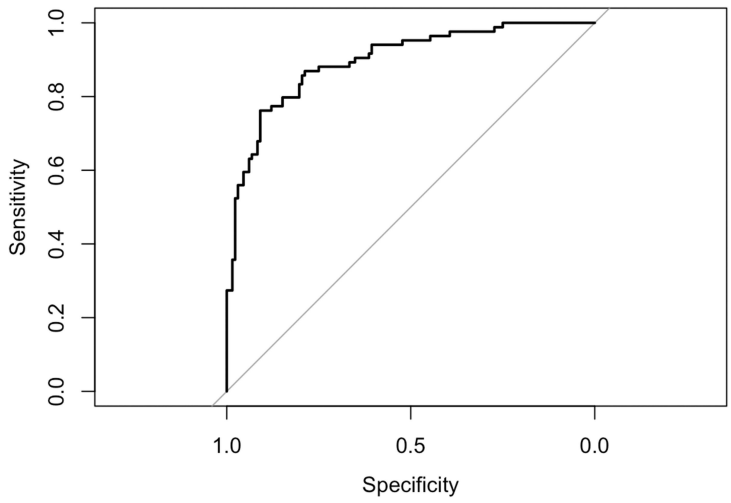

Figure 2 Internal validation of the nomogram.

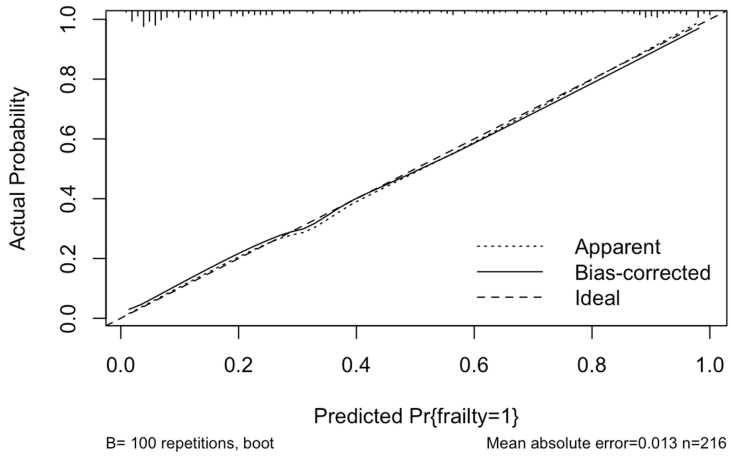

Figure 3 Calibration plot of the nomogram.

The AUC was 0.897 (95% CI = 0.854–0.940), indicating favorable discrimination by the nomogram (Figure 2). The calibration curves of the nomogram showed high consistencies between the predicted and observed frailty probability (Figure 3). In summary, the nomogram for frailty had considerable discriminative and calibrating abilities.

Discussion

Frailty is a prevalent condition among older adults, marked by reductions in physiological reserve and function across various systems due to aging, which diminishes their capacity to manage daily demands or respond to acute stressors. Clinical manifestations of frailty are frequently linked to increased risks for adverse outcomes including falls, incident disability, hospitalization, and mortality.[36] In our regression analysis, we found that advanced age, high blood pressure, and high SIRI levels all contributed to frailty, while male, higher levels of BMI, hemoglobin, kidney function, and blood lipid delayed the occurrence of frailty. In older patients, high BMI and blood lipid levels tend to indicate better nutrition status and a lower risk of malnutrition,[37] and thus are inversely associated with frailty. In our study, high level of inflammation markers was found to be associated with increased frailty incidence in older patients with CVD. Moreover, we developed and validated a nomogram to predict risk of frailty in older patients with CVD, which could assist clinicians in evaluating prognosis in such population. It was demonstrated that age, LDL-C and SIRI were significant predictors for frailty in older patients with CVD.

It has been confirmed in previous studies that inflammation markers were associated with the risk of frailty.[38,39] It was widely recognized that c-reactive protein, interleukin-6 and tumor necrosis factor α were associated with frailty.[1] In patients with maintenance hemodialysis (MHD), NLR and PLR were of a certain diagnostic value for frailty. MHD patients with frailty had high NLR and PLR levels and an unfavorable prognosis.[40] A prospective study demonstrated a positive association between SII, NLR and PLR level with frailty. The frailty phenotype partially mediated the association between systemic inflammation and osteoporosis and fracture risks.[41] The correlation between frailty and inflammation markers, in particular NLR were also observed in older patients with CHD and cancer.[42–44] The relationship between inflammation and frailty involves several key mechanisms: 1. Cytokine imbalance, with elevated pro-inflammatory cytokines (eg, IL-6, TNF-α, CRP)[45,46] and reduced anti-inflammatory cytokines (eg, IL-10), causes systemic inflammation and tissue damage.[47] 2. Chronic inflammation increased reactive oxygen species (ROS), accelerating cell damage and frailty.[48,49] 3. Inflammatory pathways (eg, NF-κB, MAPK) promote muscle wasting by enhancing protein breakdown and inhibiting synthesis, impairing muscle function.[48,50–52] 4. Endocrine dysregulation disrupts hormonal balance (eg, HPA axis, IGF-1),[53–55] reducing anabolic activity and tissue repair. 5. Immune dysfunction, including immunosenescence and inflammasome activation, perpetuate chronic inflammation, further exacerbating tissue damage and frailty.[56] 6. Cellular senescence promotes the secretion of pro-inflammatory factors (SASP), impairing tissue regeneration.[57,58] 7. Neuroinflammation contributes to cognitive decline and neurodegeneration, which are often associated with frailty.[59–61] 8. Vascular dysfunction reduces blood flow and nutrient delivery to tissues.[62,63] 9. Age-related gut microbiota increase gut permeability, triggering systemic inflammation.[56] 10. Inflammatory cytokines (eg, IL-6, TNF-α) stimulate osteoclast activity, leading to osteoporosis and increased fracture risk, further contributing to frailty.[64]

Our results highlight the potential utility of SIRI for identifying frailty in CVD patients. Neutrophils, one of the primary members of the innate immune system, are the traditional index to reflect inflammatory status. Circulatory monocytes, which can migrate out of the bloodstream and become tissue macrophages, were involved in immune defense and the damage-repairment process. While lymphocytes play a key role in adaptive immune responses.[65] SIRI comprises three components from hemograms, including neutrophils, monocytes, and lymphocytes. SIRI demonstrates strong associations with various diseases, including cardiovascular conditions,[33] cancers,[66,67] and frailty,[39] due to its reliance on standard blood tests. It may serve as a more sensitive and representative inflammatory biomarker compared to single parameters, as it incorporates both the NLR and MLR.[33] SIRI exhibits distinct advantages over other inflammation parameters in predicting outcomes for diseases like CVD and cancers. In patients with acute coronary syndrome who underwent PCI, SIRI outperformed four other lymphocyte-based inflammatory indices including PLR, NLR, MLR and SII in predicting MACE combining SIRI with the Global Registry of Acute Coronary Events (GRACE) risk score improved the accuracy of MACE prediction.[68] Elevated SIRI, but not SII, was independently associated with an increased risk for myocardial infarction.[69] Furthermore, SIRI showed superior predictive power for stroke prognosis compared to NLR, PLR, LMR, and RDW.[70] In obese populations, SIRI significantly outperformed SII in predicting both all-cause and CVD mortality.[71] Elevated SIRI was independently associated with an increased risk of CVD in diabetic patients with high BMI, demonstrating greater clinical value than hs-CRP.[72] Moreover, SIRI predicted survival in patients with pancreatic cancer receiving gemcitabine chemotherapy better than NLR, LMR, tumor stage or CA 19–9 levels.[24] Preoperative SIRI clearly predicted the efficacy and prognosis of neoadjuvant chemoradiotherapy in patients with rectal cancer. Compared to NLR and SII, only the SIRI was found to be an independent prognostic factor for overall survival and disease-free survival.[73] However, SIRI has several limitations, such as the lack of standardized cut-off values,[67] potential susceptibility to external influences like infections or medications, and unclear biological mechanisms. Additionally, it cannot differentiate specific sources of inflammation.

There are various methods for assessing frailty, with common assessment tools including: Fried Frailty Phenotype, Frailty Index, FRAIL Scale, Edmonton Frailty Scale and Clinical Frailty Scale, etc.[74,75] The FRAIL Scale was a simple and efficient tool for rapid frailty screening, particularly useful in resource-limited clinical and community settings.[76] Its advantages include simplicity, no need for special equipment, reliance on patient self-reporting, and quick completion, making it ideal for large-scale screening and epidemiological studies. The FRAIL Scale was widely applicable and easy to implement, especially in busy or resource-constrained environments. Our study investigated the association between SIRI and frailty in older patients with CVD, introducing a novel nomogram-based method to estimate risk of frailty. This tool can be integrated into routine clinical visits for ongoing frailty risk monitoring. The risk calculations facilitate the identification of high-risk patients,

enabling targeted interventions. Interventions are customized according to frailty risk levels: low-risk patients receive lifestyle modifications and education; moderate-to-high risk patients undergo comprehensive geriatric assessments, individualized care plans, supervised exercise programs, medication optimization such as statin therapy, and nutritional support. Greater awareness should be raised among older CVD patients with elevated SIRI levels to encourage early interventions aimed at reducing the incidence of frailty.

The limitations were also presented in our study. First, considering the broad spectrum of cardiovascular diseases, there was potential heterogeneity among the CVD patients included in our study, which may influence the findings to some extent. Second, in our study, frailty status was assessed using the FRAIL scale in which most of measures were relatively subjective. For more precise assessments, it may be necessary to combine it with other tools like the Fried Frailty Phenotype or Frailty Index to achieve a comprehensive evaluation of frailty. Third, though we adjusted for several confounding factors, we could not eliminate other potential factors for frailty such as medication use, nutritional status, and cognitive function. These factors often interact and significantly contribute to frailty in older adults. Forth, since this was a cross-sectional study, we only captured inflammation markers at one point, thus we were unable to assess the relationship between frailty and changes in these markers. Longitudinal studies in the future would further illustrate possible relationship.

Conclusions

Our findings indicate that that elevated levels of inflammation markers are significantly associated with an increased risk of frailty, thereby supporting the role of inflammation in the development of frailty. Further research is warranted to fully elucidate the underlying mechanisms involved. Moreover, integrating frailty assessment into routine clinical cardiovascular practice is crucial for enhancing cardiovascular risk prediction in older adults. By employing a nomogram based on age, LDL-C, and SIRI, we were able to predict the risk of frailty in older patients with cardiovascular disease. Further research with larger and more populations with diverse CVD subtypes is warranted to confirm these findings and further explore the clinical utility of SIRI and the nomogram in frailty prediction and management.

Data Sharing Statement

All data relevant to the study are included in the article.

Ethics Approval and Informed Consent

All patients have signed the informed consent forms, and the study has been approved by Peking University Third Hospital Medical Science Research Ethics Committee (No. 696-02).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; SH, XL, and CC took part in drafting, YS, HC, ZG and DL revising or critically reviewing the article; all authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Beijing Research Ward Excellence Program, BRWEP (BRWEP2024W014090208), Research Project of Peking University Third Hospital in State Key Laboratory of Vascular Homeostasis and Remodeling (Peking University, No.2024-VHR-SY-11).

Disclosure

All authors declare no competing interests in this work.

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