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ORIGINAL RESEARCH

Development and Validation of a Diagnostic Nomogram Model for Predicting Cognitive Frailty in Acute Coronary Syndrome

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Background: Cognitive frailty (CF) is strongly associated with major adverse cardiovascular events, yet its assessment requires specialized equipment, limiting clinical practicality. This study aimed to develop and validate a nomogram model for predicting CF in patients with acute coronary syndrome (ACS) to enhance early identification and intervention.

Methods: Patients with ACS (N=547) were enrolled and randomly split into a training set (70%) and a testing set (30%). The training set was used to construct the nomogram, while the testing set was used for validation. Model performance was evaluated using the receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA) to assess discrimination, accuracy, and clinical utility, respectively.

Results: The nomogram included six predictors: education level, age, systolic blood pressure (SBP), Charlson Comorbidity Index (CCI), Short Physical Performance Battery (SPPB), and nutritional status. The model demonstrated strong discriminatory power, with an area under the ROC curve of 0.854 (95% CI: 0.741–0.861) in the training cohort and 0.733 (95% CI: 0.500–0.898) in the testing cohort. Calibration analysis confirmed high accuracy, and DCA indicated significant net benefits across both cohorts, supporting its clinical applicability.

Conclusion: The nomogram effectively predicts CF in ACS patients by considering education, age, SBP, CCI, SPPB, and nutritional status, serving as a visual aid for healthcare providers to facilitate the early identification and intervention of CF. Future research is needed to validate the nomogram's efficacy in diverse populations and explore standardized assessment methods that enhance its clinical applicability in mitigating CF in ACS patients.

Keywords: acute coronary syndrome, cognitive frailty, nomogram, predictive model, risk factors

Background

The global demographic landscape is undergoing a significant transformation, marked by a rapid increase in the older adult population. Projections indicate that by 2050, the number of individuals aged 60 and older will double.[1] This aging trend is closely linked to the rise of various geriatric syndromes, which, when coupled with cardiovascular diseases (CVDs), lead to a progressive and accelerated deterioration in patient health.[2] Among these syndromes, frailty and cognitive impairment (CI) are particularly consequential in older adults with CVDs. Research has shown that the concurrent development of frailty and CI significantly elevates the risk of major adverse cardiovascular events compared to the development of either condition alone.[3] In 2013, the International Academy of Nutrition and Aging and the International Association of Gerontology and Geriatrics introduced the concept of "cognitive frailty" (CF) to describe the co-occurrence of physical frailty and mild cognitive impairment, as indicated by a Clinical Dementia Rating of 0.5, in

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older adults who do not meet the criteria for a definitive dementia diagnosis, excluding other dimensions of frailty, such as social, psychological, and oral frailty.[4]

Acute coronary syndrome (ACS) is a more severe form of coronary heart disease (CHD) with a worse prognosis, particularly among patients aged 65 and older. The negative prognostic impact of frailty or CI in patients with ACS has been well-documented.[5] For instance, a study involving 2,041 patients aged 75 and older hospitalized with acute myocardial infarction (MI) revealed that 17% had CI, which was associated with higher risks of readmission and mortality.[6] Moreover, moderate-to-severe CI was linked to an even greater risk of death.[6] However, the specific impact of CF on ACS prognosis remains underexplored.[7,8] Mone P et al investigated the 5-year cardiovascular outcomes in older adults without prior coronary artery disease, categorizing participants based on the progression of frailty and CI. They found that the group classified as having CF exhibited the highest risk of experiencing major adverse cardiovascular events, followed by individuals who developed frailty or CI first.[9] Elderly ACS patients with CF experienced significantly higher rates of both in-hospital (including longer hospital stay, bleeding, ventricular arrhythmia, and a higher incidence of cardiogenic shock) and 6-month complications (including MI, stroke, Recurrent revascularization, and death).[10] These findings indicate that CF increases the risk of adverse cardiovascular events. Moreover, CF might affect treatment adherence and the adoption of secondary prevention behaviors post-ACS.

Assessing CF is challenging, given the increasing prevalence of ACS in the aging population. This assessment often involves tools like the Frail Score, which evaluates physical frailty based on several criteria, such as weight loss, exhaustion, and mobility, and the Mini-Mental State Examination (MMSE), which assesses the level of cognitive impairment based on 11 metrics, including orientation, memory, and attention. The existing diagnostic approaches for CF are complex, hindering effective diagnosis and prevention. Nomograms are simple yet effective visual tools for risk prediction that provide a solution. By integrating multiple factors into a statistical model, these tools estimate event risks, making them valuable for both cross-sectional and prospective studies in predicting disease risks.[11] This study aims to develop a nomogram-based risk prediction model that quantifies the likelihood of CF in patients with ACS, enabling early identification of high-risk elderly patients for targeted personalized prevention and treatment strategies to delay or prevent CF progression.[12]

Methods

Participants

This was a prospective observational single-center study conducted at Beijing Friendship Hospital in China. We prospectively recruited 1,267 participants aged over 65 years who were admitted to ACS from January 2020 to April 2022. The inclusion criteria were as follows: 1) elderly participants aged ≥ 65 years; 2) a primary diagnosis of ACS, including ST-Elevation MI (STEMI) and Non-ST-Elevation Acute Coronary Syndrome (NSTE-ACS); and 3) provided signed informed consent. Patients were excluded if they met any of the following criteria: 1) MI caused by other acute disease; 2) severe dementia or schizophrenia that prevented cooperation in completing the Comprehensive Geriatric Assessment; 3) severe liver dysfunction, kidney disease, or end-stage malignant tumors; or 4) totally disabled and bedridden.

According to the pre-established inclusion and exclusion criteria, we initially excluded 221 participants who were not diagnosed with ACS at discharge. Additionally, we excluded 185 participants who had severe comorbidities or refused to complete a frailty assessment and 314 patients who had not completed the MMSE. In the end, a total of 547 patients with frailty who completed the MMSE assessment were included in the study (Figure 1).

All participants provided informed consent, and the study received approval from the Ethics Committee of Beijing Friendship Hospital. The study was registered on ClinicalTrials.gov under the identifier NCT04580706 on March 26, 2024.

Data Collection

Data were prospectively collected by investigators before discharge using standardized case report forms to ensure consistency and reliability. The systematically recorded information included demographic data, baseline clinical

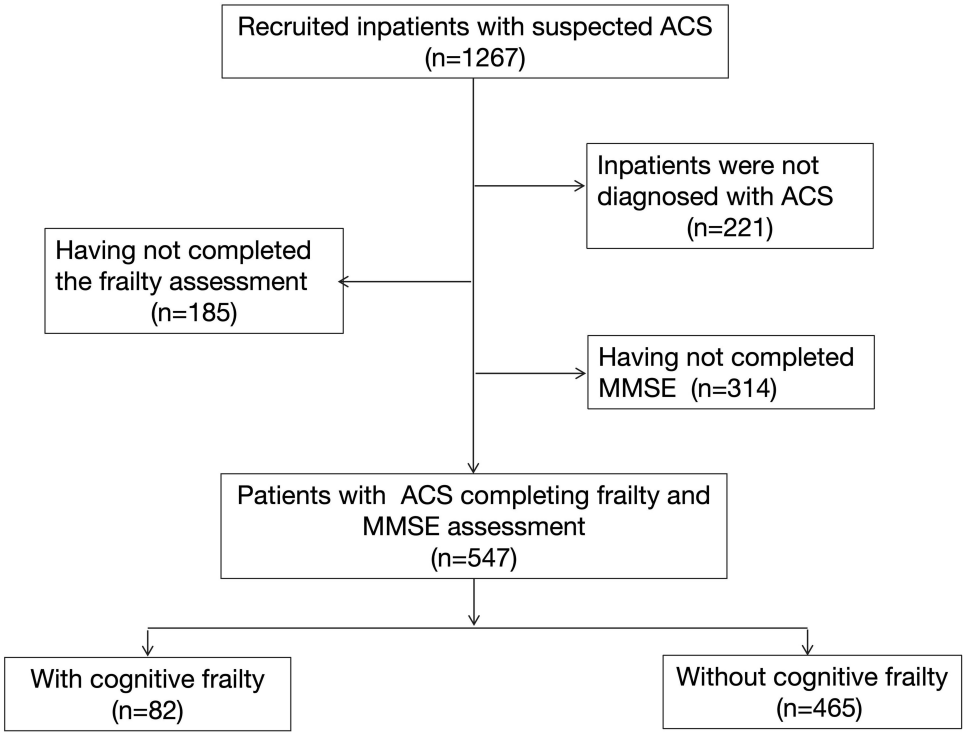

Figure 1 Flowchart of the recruitment process for the study population.
Abbreviations: ACS, acute coronary syndrome; MMSE, mini-mental state examination; n, number of participants in the study.

characteristics, detailed medical history, dietary habits, comorbidities, electrocardiogram results, laboratory tests, echocardiographic findings, coronary angiographic data, treatment modalities, and duration of hospital stay. Global Registry of Acute Cardiac Events (GRACE) risk scores were calculated to estimate in-hospital and out-of-hospital mortality risk.

Cardiovascular outcomes, including major adverse cardiac events (MACE), were monitored during hospitalization. MACE was defined as recurrent myocardial ischemia, unplanned revascularization, all-cause death, and recurrent arrhythmia.

Assessment of Frailty and Cognitive Function

Trained personnel conducted assessments to evaluate physical frailty and cognitive impairment at the time of admission. For the assessment of physical frailty, the FRAIL Scale was utilized. This widely recognized five-item questionnaire evaluates the following domains: fatigue, resistance, ambulation, illness, and loss of weight. Each item is scored as 0 (indicating the absence of the characteristic) or 1 (indicating the presence of the characteristic).[13] The scoring system categorizes individuals based on their level of frailty: a total score ranging from 1 to 2 represents pre-frailty, indicating that the individual may be at risk for further decline in health. In contrast, a total score of 3 or higher signifies frailty, which is associated with increased vulnerability and a higher risk of adverse health outcomes.

Cognitive function was evaluated using the MMSE, which is designed to evaluate various aspects of cognitive ability. The MMSE consists of 11 items that are categorized into five domains, each contributing to the overall score: orientation (10 points), memory registration (3 points), attention and calculation (5 points), recall (3 points), and language (10 points). The total score on the MMSE ranges from 0 to 30, with higher scores indicating better cognitive function. A cutoff score of 27 has been established for identifying cognitive impairment, particularly in populations with higher educational attainment. This suggests that individuals scoring below this threshold may exhibit signs of cognitive decline or impairment.[14]

Comprehensive Geriatric Assessment

This assessment was conducted by two trained medical staff members at the time of admission and included evaluations of comorbidities, functional status, lower extremity function, and nutritional risk. Functional status was assessed using the activities of daily living (ADL) Scale, which measures basic self-care abilities, such as bathing, dressing, and feeding, as well as the Instrumental ADL (IADL) Scale, which assesses complex activities necessary for independent living, including managing finances, preparing meals, and transportation. Lower extremity function was evaluated through the Short Physical Performance Battery (SPPB) test, which evaluates standing balance (0 to 4 points), gait speed (0 to 4 points), and chair stands (0 to 4 points).

Nutritional risk was screened using the Mini Nutritional Assessment-Short Form, which incorporates anthropometric measurements, dietary intake evaluations, and subjective assessments of the individual's nutritional status. All assessments were performed at the time of hospital discharge to facilitate appropriate follow-up care and interventions.

Statistical Analysis

All data were analyzed using SPSS version 25.0 and R version 4.4.1. Patient characteristics are presented as the mean ±standard deviation (x±SD), median (interquartile range) [M (Q1, Q3)], or percentages (%). The Pearson's χ^2 test was used to assess associations between selected factors and CF status.

The dataset, comprising a total of 547 participants, was divided into training and validation cohorts using stratified sampling at a 7:3 ratio by CF status, resulting in 382 participants in the training cohort and 165 in the validation cohort. Logistic regression analysis was conducted to identify predictive risk factors for CF within the training cohort. Significant risk factors were then used to construct a nomogram, with the length of each line representing the relative influence of the variable on CF outcomes.

The model's discrimination ability was evaluated using the receiver operating characteristic (ROC) curve, while calibration was assessed via the calibration curve. Decision curve analysis (DCA) was employed to determine the clinical utility and net benefits of the model.

Results

Baseline Characteristics of the Study Population

Of the 547 patients enrolled, the mean age was 71 years, and 42.2% of the study population was female. The average years of education received was 9 year and the average body mass index (BMI) was 25.0 kg/m^2. Approximately 81.7% of the study population was living with hypertension, and 41.9% had diabetes. Among these participants, 462(84.5%) were diagnosed with unstable angina pectoris (UAP), with a non-ST elevated MI (NSTEMI) of 55(10.1%) and ST elevated MI (STEMI) of 30(5.5%). The majority of this older population had multiple chronic conditions, and 6.1% of the cohort had four or more chronic commodities. Additionally, 248 (45.34%) patients were classified as pre-frail, and 50(9.14%) patients were identified as having physical frailty according to the FRAIL Scale.

The overall prevalence of CF was 82(14%), with pre-frailty and frailty prevalence of 50.42% and cognitive impairment prevalence of 126 (23%). Full characteristics of the study population are shown in Table 1. Patients who

Table 1 Characteristics of ACS Patients with and Without CF

Characteristic	Total (n=547)	Cognitive Frailty (n=82)	Non-Cognitive Frailty (n=465)	*P*-value
Age, years	71(68,75)	76(70,82)	71(68,74.5)	<0.001*
Female, n%	231(42.2%)	52(63.4%)	179(38.5%)	<0.001*
BMI, kg/m^2	25.0(23.2,27.7)	25.0(22.5,27.6)	25.0(23.3,27.7)	0.539
Education, yrs	9(6,12)	9(6,9)	9(9,12)	<0.001*
Living alone, n%	62 (11.33%)	9 (11.39%)	53 (11.88%)	0.901

(*Continued*)

Table 1 (Continued).

Characteristic	Total (n=547)	Cognitive Frailty (n=82)	Non-Cognitive Frailty (n=465)	*P*-value
Annual income (¥)				0.019*
<60,000	319(58.3%)	58(70.7%)	261(56.1%)	
≥60,000	228(41.7%)	24(29.3%)	204(43.9%)	
Hypertension, n%	447(81.7%)	71(86.6%)	376(80.9%)	0.216
Diabetes, n%	229(41.9%)	38(46.3%)	191(41.1%)	0.373
SBP, mmHg	134(124,145)	139(129,153)	133(122,144)	0.001*
DBP, mmHg	72(65,80)	70(65,80)	72(65.5,80)	0.454
Hgb, g/dL	131(121,142)	123(115,136)	132(122,142)	<0.001*
D-dimer, ng/mL	0.4(0.3,0.6)	0.5(0.4,0.9)	0.4(0.3,0.6)	<0.001*
Albumin, g/L	38(36,40)	37(35,40)	38(36,40)	0.007*
CRP, mg/L	1.1(0.4,3.6)	1.3(0.4,7.1)	1.1(0.4,3.2)	0.15
Cr, mmol/L	74.2(63.35,85.75)	75.05(62.75,97.18)	74.2(63.35,85.05)	0.49
CHOL, mmol/L	3.79(3.21,4.61)	3.78(3.19,4.97)	3.79(3.22,4.56)	0.559
TG, mmol/L	1.19(0.9,1.61)	1.18(0.93,1.59)	1.19(0.89,1.61)	0.707
HDL, mmol/L	1.02(0.89,1.17)	1.1(0.94,1.24)	1.02(0.88,1.16)	0.023*
LDL, mmol/L	2.11(1.73,2.71)	2.12(1.71,2.98)	2.11(1.74,2.69)	0.858
Glucose, mmol/L	5.44(4.83,6.54)	5.88(5.06,6.96)	5.39(4.79,6.49)	0.006*
HbA1C	6.1(5.7,7.1)	6.2(5.8,7.2)	6.1(5.7,7)	0.222
ProBNP	154(73,381)	227(101.75,606.75)	147(68.7,333)	0.066
Diagnosis				0.003*
UAP	462(84.5%)	65(79.3%)	397(85.38%)	
NSTEMI	55(10.1%)	16(19.5%)	39(8.39%)	
STEMI	30(5.5%)	1(1.2%)	29(6.24%)	
CCI n,%				0.002*
0–1	406(74.2%)	50(61.0%)	356(76.6%)	
2–3	129(23.6%)	27(32.9%)	102(21.9%)	
≥4	12(2.2%)	5(6.1%)	7(1.5%)	
Cardiac dysfunction	253(46.3%)	54(65.8%)	199(42.8%)	<0.001*
Ejection fraction	0.65(0.61,0.68)	0.64(0.58,0.68)	0.65 (0.61,0.68)	0.310
Number of lesion branches				0.680
1	125(22.9%)	21 (25.6%)	104(22.4%)	
2–3	174(31.8%)	23(28%)	151(32.5%)	
≥4	248(45.3%)	38(46.3%)	210(45.2%)	
GRACE score	119(106–131)	125(112,141)	118(105,128)	<0.001*
Estimated death risk in-hospital				<0.001*
Low risk	163(29.9%)	13(15.9%)	150(32.3%)	
Middle risk	306(56.1%)	47(57.3%)	261(56.1%)	
High risk	76(13.9)	22(26.8%)	54(11.6%)	
Estimated death risk out-hospital				0.025*
Low risk	8(1.5%)	0	8(1.7%)	
Middle risk	256(47%)	29(35.4%)	227(49.0%)	
High risk	281(51.6%)	53(64.6%)	228(49.2%)	
Hospitalization days	5.00(4.0;7.0)	5.0(4.0;7.0)	5.0(4.0;7.0)	0.292
Expenses	26,023 (10,604;49,160]	20,076(11,108;44,220]	27,255(10,495;50,024)	0.554
MACE in-hospital (n,%)	9(1.6%)	2(2.4%)	7(1.5%)	0.54

Notes: *, $p < 0.05$.

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CCI, Charlson Comorbidity Index; CF, cognitive frailty; CHOL, total cholesterol; Cr, creatinine; CRP, C reactive protein; DBP, diastolic blood pressure; GRACE, Global Registry of Acute Coronary Events; HbA1c, hemoglobin A1c; Hgb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MACE, Major Adverse Cardiac Events; NSTEMI, non-ST elevated myocardial infarction; SBP, systolic blood pressure; STEMI, ST elevated myocardial infarction; TG, triglycerides; UAP, unstable angina pectoris.

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had CF were older, more likely to be women, and less educated as compared to non-CF (NCF) patients. Compared to NCF subjects, subjects with CF had slightly higher systolic blood pressure (SBP) (139 [129,153] vs 133(122,144], $P<0.001$), significantly lower hemoglobin (Hgb) (123[115–136] vs 132[122,142] g/dL, $P<0.001$) and ALB (37[35,40] vs 38[36,40])g/dL, $P=0.007$), a significantly higher level of D-dimer (0.5[0.4,0.9] vs 0.4[0.3,0.6] ng/dL, $P<0.001$).

CF patients also had a higher prevalence of NSTEMI (19.5%) compared to NCF patients. The overall number of chronic comorbidity conditions was also higher among CF patients, with approximately 40% reporting two or more chronic medical conditions. Patients with CF had poorer cardiac function (65.8% vs 42.8%, $P<0.001$), higher GRACE scores (125 [112–141] vs 118[10–5,128], $P<0.001$). The estimated high risk of mortality, both in-hospital(26.8% vs 11.6%, $P<0.001$) and out-hospital (64.6% vs 49.2%, $P<0.001$), were much higher in CF patients. The mean length of hospital stay was 5 days, and the incidence of in-hospital MACE was 1.6%. There was no significant difference in the number of lesions or MACE.

When evaluating measures of disability, including self-care, mobility disability, and household activities disability, patients with CF had poorer activity including ADL and IADL scores. Compared with NCF patients, the lower extremity function and mobility were poorer in patients with CF of lower SPPB scores (7 vs 10, $P<0.001$), and step speed of 4 m (0.6[0.5,0.8] vs 0.8[0.7,1.0]s, $P<0.001$). The incidence of malnutrition in the CF group was as high as 28.05%, which was higher than that observed in the NCF group. Furthermore, patients with CF consumed fewer carbohydrates and nuts of their dietary habit (Table 2).

Table 2 The Relationship Between Cognitive Frailty, Nutrition, and Diet

Characteristic	Total (n=547)	Cognitive Frailty (n=82)	Non-Cognitive Frailty (n=465)	*P*-value
Frail state				<0.001*
No frailty	249(45.5%)	0(0.00%)	249(53.6%)	
Pre frailty	248(45.34%)	55(67.07%)	193(41.5%)	
Frailty	50 (9.14%)	27(32.93%)	23(4.9%)	
ADL scores	5.94±0.36	5.71±0.78	5.98±0.20	<0.001*
IADL scores	7.71±1.01	6.87±1.90	7.86±0.66	<0.001*
SPPB score	10(8,11)	7(5,10)	10(8,11)	<0.001*
Step speed of 4m	0.8(0.6,1.0)	0.6(0.5,0.8)	0.8(0.7,1.0)	<0.001*
Malnutrition	91(16.6%)	25(30.5%)	66(14.2%)	<0.001*
Diet				
Carbohydrate				0.002*
50–100 g/d	10(1.8%)	4(4.88%)	6(1.29%)	
100–200 g/d	151(27.6%)	32(39.02%)	119(25.59%)	
200–300 g/d	264(48.3%)	35(42.68%)	229(49.25%)	
>300 g/d	122(22.3%)	11(13.41%)	111(23.87%)	
Vegetables				0.297
<100 g/d	5(0.9%)	1(1.4%)	4(0.9%)	
100–300 g/d	148(27.1%)	28(38.9%)	120(27.2%)	
300–500 g/d	267(48.8%)	33(45.8%)	234(52.9%)	
500–700 g/d	78(14.3%)	9(12.5%)	69(15.6%)	
>700 g/d	16(2.9%)	1(1.4%)	15(3.4%)	
Nuts				0.023*
None	101(18.5%)	21(58.3%)	80(35.1%)	
<175 g/w	127(23.2%)	12(33.3%)	115(50.4%)	
175–350 g/w	28(5.1%)	1(2.8%)	27(11.8%)	
350–700 g/w	8(1.5%)	2(5.6%)	6(2.6%)	

(*Continued*)

Table 2 (Continued).

Characteristic	Total (n=547)	Cognitive Frailty (n=82)	Non-Cognitive Frailty (n=465)	*P*-value
Milk				0.764
200–600 mL	105(19.2%)	15(18.3%)	90(19.35%)	
600–1,400 mL	71(13.0%)	8(9.8%)	63(13.54%)	
≥1,400 mL	336(61.4%)	49(59.8%)	287(61.72%)	
Meat				0.594
None	75(13.71%)	13(18.57%)	62(14.09%)	
50–100g/d	345(63.07%)	48(68.57%)	297(67.50%)	
100–200 g/d	79(14.44%)	8(11.43%)	71(16.14%)	
>200 g/d	11(2.01%)	1(1.22%)	10(2.15%)	

Notes: *, $p < 0.05$.
Abbreviations: ADL, activities of daily living; g/d, grams per day; g/w, grams per week; IADL, instrumental activities of daily living; mL, Milliliters; SPPB, Short Physical Performance Battery.

Baseline Characteristics of Patients in Training Group and Validation Group

The laboratory and clinical data of the training and validation sets are presented in Table 3. Notably, the only significant difference between the training and testing sets was observed in SBP levels ($P<0.05$). Other clinical indicators did not exhibit significant differences between the two groups.

Table 3 Baseline Characteristics of the Training Set and Validation Set

	Total (n=547)	Testing Set (n=165)	Training Set (n=382)	*P*-value
CF, n(%)	0.15(0.36)	0.17(0.38)	0.14(0.35)	0.410
Age, yrs	71.0(68.0,75.0)	72.0(68.0,76.0)	71.0(68.0,75.0)	0.185
Education, yrs	9(9,12)	9(9,12)	9(9,12)	0.903
Female, n(%)	231(42.2%)	67(40.6%)	164(42.9%)	0.681
Income <60,000	319(58.32%)	100(60.61%)	219(57.33%)	0.536
SBP, mmHg	134(124,145)	136(125,149)	133(123,143)	0.017*
Albumin	38.0(36.0,40.0)	37.9(36.1,40.4)	38.0(35.9,39.9)	0.791
Hgb, g/dL	131(121,142)	132(119,141)	131(121,142)	0.837
HDL, mmol/L	1.0(0.9,1.2)	1.0(0.9,1.1)	1.0(0.9,1.2)	0.155
Glucose, mmol/L	5.4(4.8,6.5)	5.4(4.8,6.3]	5.4(4.8,6.7)	0.460
Diagnosis, n(%)				0.110
UAP	462(84.46%)	135(81.82%)	327(85.60%)	
NSTEMI	55(10.05%)	23(13.94%)	32(8.38%)	
STEMI	30(5.48%)	7(4.24%)	23(6.02%)	
CCI, n(%)				0.839
0–1	406(74.22%)	121(73.33%)	285(74.61%)	
2–3	129(23.58%)	41(24.85%)	88(23.04%)	
≥4	1(2.19%)	3(1.82%)	9(2.36%)	
GRACE score	119(106,131)	118(104,132)	119(108,130)	0.511
SPPB	10.0(8.0,11.0)	10.0(8.0,11.0)	10.0(8.0,11.0)	0.263
Step speed of 4 m	0.80(0.7,0.9)	0.8(0.6,1.0)	0.8(0.7,0.9)	0.220
Malnutrition, n(%)	456(83.36%)	13(81.82%)	321(84.03%)	0.608

Notes: *, $p < 0.05$.
Abbreviations: CCI, Charlson Comorbidity index; CF, cognitive frailty; GRACE, Global Registry of Acute Coronary Events; SBP, systolic blood pressure; Hgb, hemoglobin; HDL, high-density lipoprotein; NSTEMI, non-ST elevated myocardial infarction; STEMI, ST elevated myocardial infarction; UAP, unstable angina pectoris; SPPB, Short Physical Performance Battery.

Table 4 Potential Risk Factors Identified by Univariate and Multivariate Logistic Regression Analysis in the Training Group

	Univariate Analysis		Multivariate Analysis	
Characteristics	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age	1.157(1.096–1.224)	<0.001	1.130(1.032–1.242)	0.009
Sex	3.125(1.723–5.849)	<0.001		
Education	0.742(0.66–0.824)	<0.001	0.798(0.689–0.915)	0.002
Income	0.468(0.241–0.865)	0.019		
SBP,mmHg	1.028(1.012–1.046)	0.001	1.034(1.008–1.062)	0.01
Albumin	0.922(0.847–1.005)	0.063		
HgB	0.961(0.941–0.98)	<0.001		
D-dimer	1.423(0.966–2.061)	0.059		
CCI≥4	2.387(1.439–3.935)	0.001	2.275(1.167–4.400)	0.014
GRACE scores	1.018(1.005–1.03)	0.005		
ADL scores	0.139(0.043–0.331)	<0.001		
IADL scores	0.48(0.355–0.615)	<0.001		
SPPB	0.799(0.728–0.877)	<0.001	0.832(0.713–0.973)	0.02
Step speed of 4m	0.083(0.018–0.359)	0.001		
Malnutrition	0.218(0.115–0.417)	<0.001	0.179(0.072–0.434)	<0.001

Abbreviations: ADL, activities of daily living; SBP, systolic blood pressure; CCI, Charlson Comorbidity Index; CI, 95% confidence interval; GRACE, Global Registry of acute coronary events; HgB, hemoglobin; IADL, instrumental activities of daily living; OR, odds ratio; SPPB, Short Physical Performance Battery.

Derivation of the Predictive Factors in the Training Set

Univariate analysis identified years of age, sex education, income, SBP, Hgb, CCI>4, GRACE score, ADL, IADL scores, SPPB, and malnutrition were significantly associated with cognitive impairment. In multivariate regression analysis, age (1.130; 95% CI, 1.03–21.242), education (0.798, 95% CI, 0.68–90.915), SBP (1.034, 95% CI, 1.008–1.062), CCI>4 (2.275, 95% CI 1.167–4.400), SPPB (0.832, 95% CI, 0.713–0.973) and malnutrition (0.179, 95% CI, 0.072–0.434) were independently associated with CF (see Table 4). Older patients with higher SBP and CCI were more likely to have CF, while education and SPPB were identified as protective factors against cognitive frailty.

Establishment of the Diagnostic Nomogram Model

The nomogram for CF was developed based on all the independent significant factors in the training set (Figure 2). For each independent variable, corresponding values were obtained by drawing vertical lines to the scoring scale at the top of

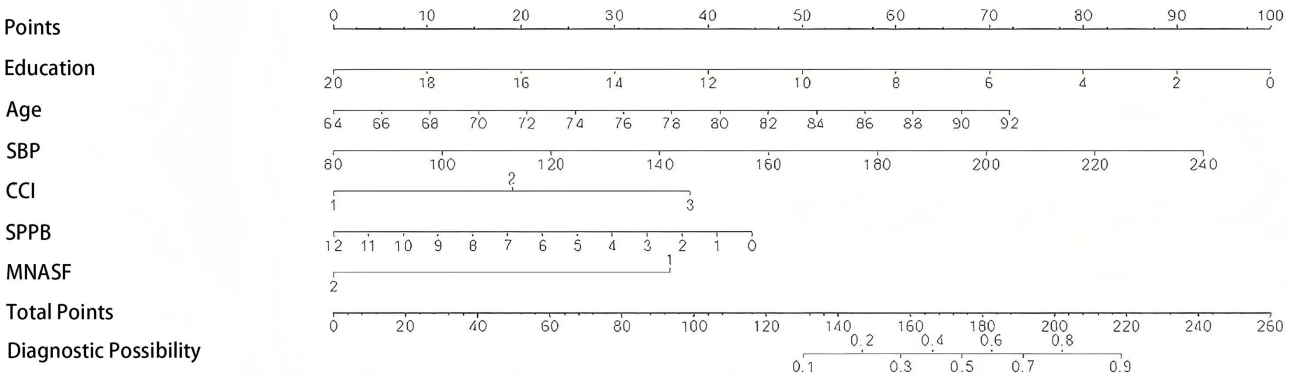

Figure 2 Nomogram for predicting CF based on the training cohort (n=382).
Abbreviations: Education, years of education; Age, the number of years; SBP, systolic blood pressure; CCI, Charlson Comorbidity Index (1, CCI of 0–1; 2, CCI of 2–3; 3, CCI of more than 3); CF, cognitive frailty; SPPB, score on the Short Physical Performance Battery assessment; MNA-SF, Mini Nutritional Assessment Short Form (1, malnutrition, 2, risk of malnutrition).

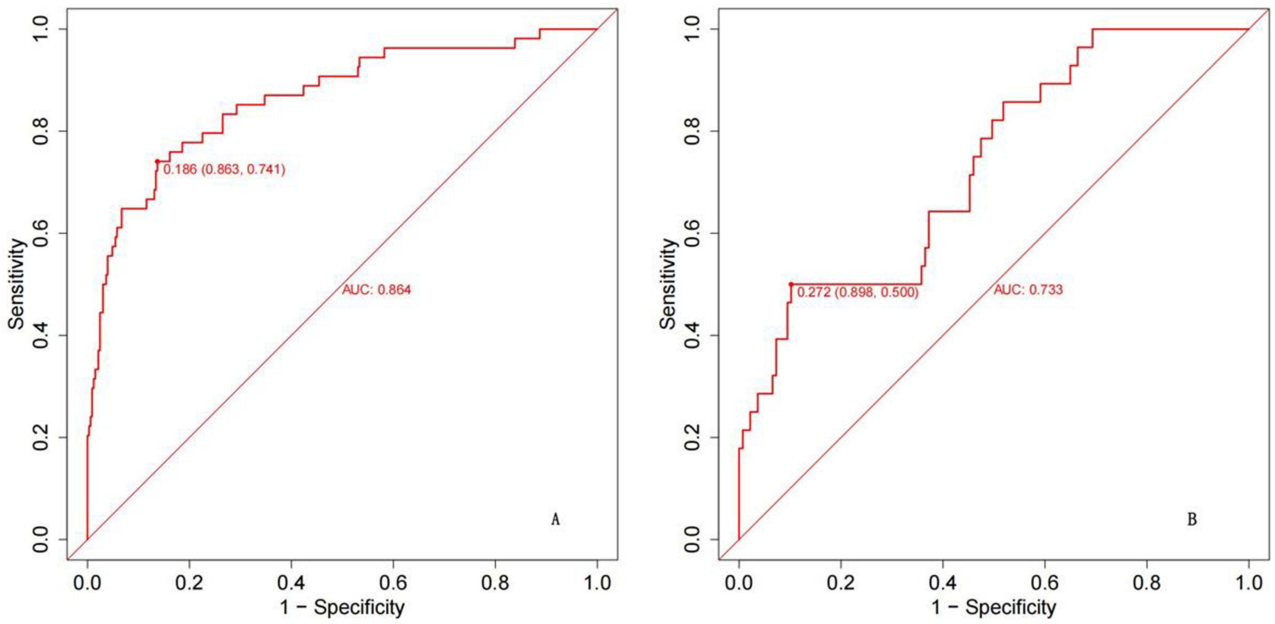

Figure 3 ROC curves of the nomogram for predicting CF in the training (**A**) n=382 and testing (**B**) n=165 sets.
Abbreviations: AUC, area under the curve; CF, cognitive frailty; n, number of participants in the study; ROC, receiver operating characteristic.

the nomogram, which ranges from 0–100. The scores for each variable were then summed to obtain the total score, which was used to find the corresponding predicted probability values on the prediction line at the bottom of the monogram's column graph. For a 76-year old patient with 9 years of education, a SBP of 140 mmHg, a CCI of 3, malnutrition, and a SPPB of 4, the total score was 204, indicating a greater than 81% probability of CF. It is recommended that this patient receive prevention measurement.

Differentiation, Calibration, and Clinical Applicability of the Diagnostic Nomogram Model

To validate the efficacy of our nomogram model, we employed ROC analysis. The AUC values for the CF nomogram were 0.854 (95% CI, 0.741–0.861) in the training cohort and 0.733 (95% CI, 0.500–0.898) in the validation cohort, indicating a good ability to discriminate between patients with and without CF (Figure 3). However, the wide CI in the validation cohort suggests potential instability, which may be attributed to a smaller sample size and heterogeneity.

The calibration of the nomogram was assessed using the calibration curve (Figure 4), which showed agreement between the observed and predicted values, with absolute errors of 0.01 and 0.03 in the training and testing sets, respectively, indicating that there was no deviation from the perfect fit.

DCA was conducted for the prediction nomogram (Figure 5). The results for both the training and testing sets indicate that the nomogram is a promising tool for predicting CF.

Discussion

CF presents significant challenges for patients with ACS, their caregivers, and clinicians due to atypical symptoms and a heightened risk of complications. This study explored the prevalence and characteristics of CF in ACS patients and developed a predictive nomogram model. Key findings include: 1) Approximately 15% of ACS patients exhibited CF, as assessed by the FRAIL Scale and MMSE. These patients were typically older, female, less educated, economically disadvantaged, and had higher SBP and glucose levels. 2) Patients with CF had a higher prevalence of multiple chronic conditions and more severe health statuses. They showed a greater incidence of NSTEMI, cardiac dysfunction, baseline disability, and higher GRACE scores compared to non-cognitive frail participants. 3) CF patients had poorer nutrition, as indicated by lower hemoglobin (Hgb) and albumin (Alb) levels, and consumed fewer carbohydrates and nuts in their

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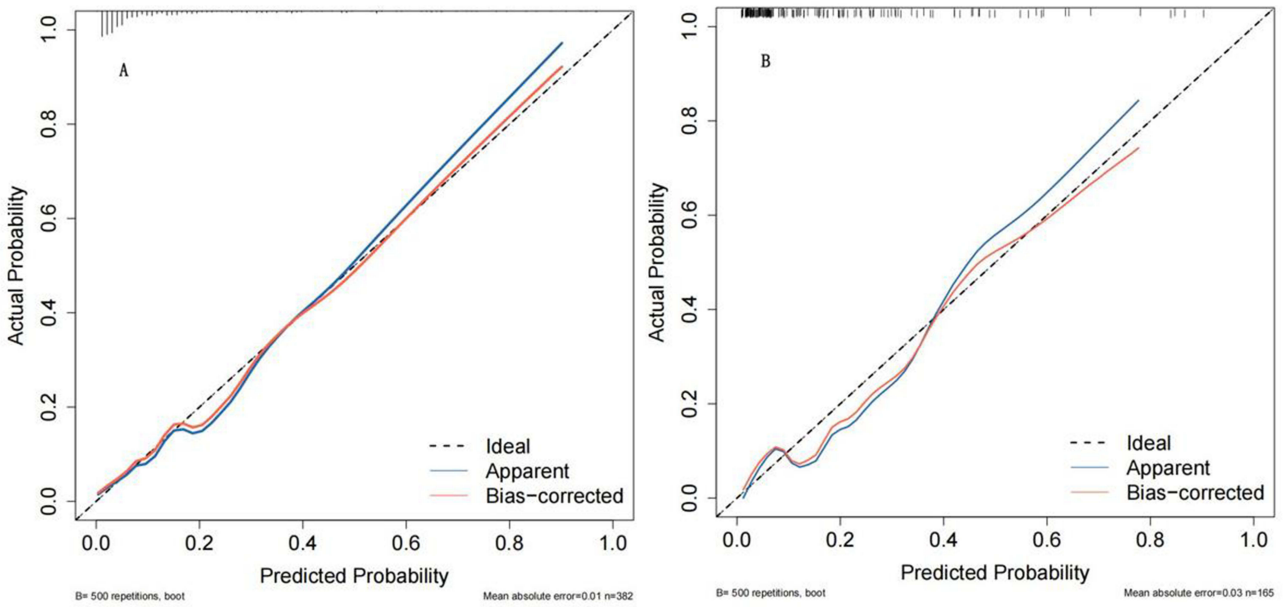

Figure 4 Calibration curves for predicting CF in the training (**A**) n=382 and validation (**B**) n=165 sets.
Abbreviations: CF, cognitive frailty; n, number of participants in the study.

diet. 4) Education, age, SBP, CCI, SPPB scores, and nutritional status were identified as independent predictors of CF. A diagnostic nomogram incorporating these factors demonstrated good accuracy and discrimination in predicting CF.

CF is notably prevalent among post-ACS patients, particularly in older adults with a mean age of 71 years (range 68–75). The condition is associated with advancing age, lower educational attainment, female gender, reduced income, elevated blood pressure, and higher glucose levels. Cognitive impairment, frailty, and CVD share common risk factors such as diabetes, hypertension, obesity, and smoking, as well as pathophysiological pathways like systemic inflammation, oxidative stress, and neuroendocrine dysregulation. In this study, CF patients exhibited higher SBP and glucose levels, along with a greater incidence of comorbidities. The relationship between CF and CVD is complex and bidirectional. CVD can lead to CF through the role of atherosclerosis in the pathogenesis of cerebral small vessel disease, while CF can exacerbate the progression of CVD, worsening prognosis through mechanisms such as reduced treatment compliance.[8,15–17]

In our study, patients with NSTEMI were more likely to experience CF. Pasquale Mone et al explored the relationship between physical and cognitive dysfunction in frail STEMI patients, finding a significant correlation between gait speed and MMSE scores (r: 0.771; $p < 0.001$).[9] Similarly, Valerie Josephine et al studied 239 NSTEMI patients with a median age of 80.9 years, revealing that 82% were pre-frail or frail, and 39.7% had CF[18.] Richardson et al linked MI to brain microinfarcts in postmortem studies, suggesting that small vessel disease may contribute to cognitive decline.[19]

Although CF status was not associated with the number of lesion branches, CF patients had higher GRACE scores, reflecting factors such as SBP and kidney function, and were at greater risk both during and after hospitalization. Current European Society of Cardiology guidelines for ACS management lack specific recommendations for elderly patients, particularly considering frailty and cognitive impairment, likely due to their exclusion from major clinical trials.[20] Our findings highlight a strong link between CF and cardiac dysfunction. While no significant difference in in-hospital MACE was observed, likely due to short hospital stays (5 days), studies like Cammalleri's show that ACS patients with severe cognitive and functional impairments face the highest 6-month mortality rates.[21] Similarly, Hajduk et al's multicenter study of more than 3,000 elderly ACS patients (mean age 82 years) found that moderate to severe cognitive impairment was associated with increased 6-month post-discharge mortality.[6]

This study highlights a link between nutrition and CF, with lower Hgb and ALB levels observed in affected individuals. Malnutrition, characterized by imbalances in calories, protein, and other nutrients, significantly impacts body composition, physical function, and overall health.[22] Inadequate intake of carbohydrates and nuts was also

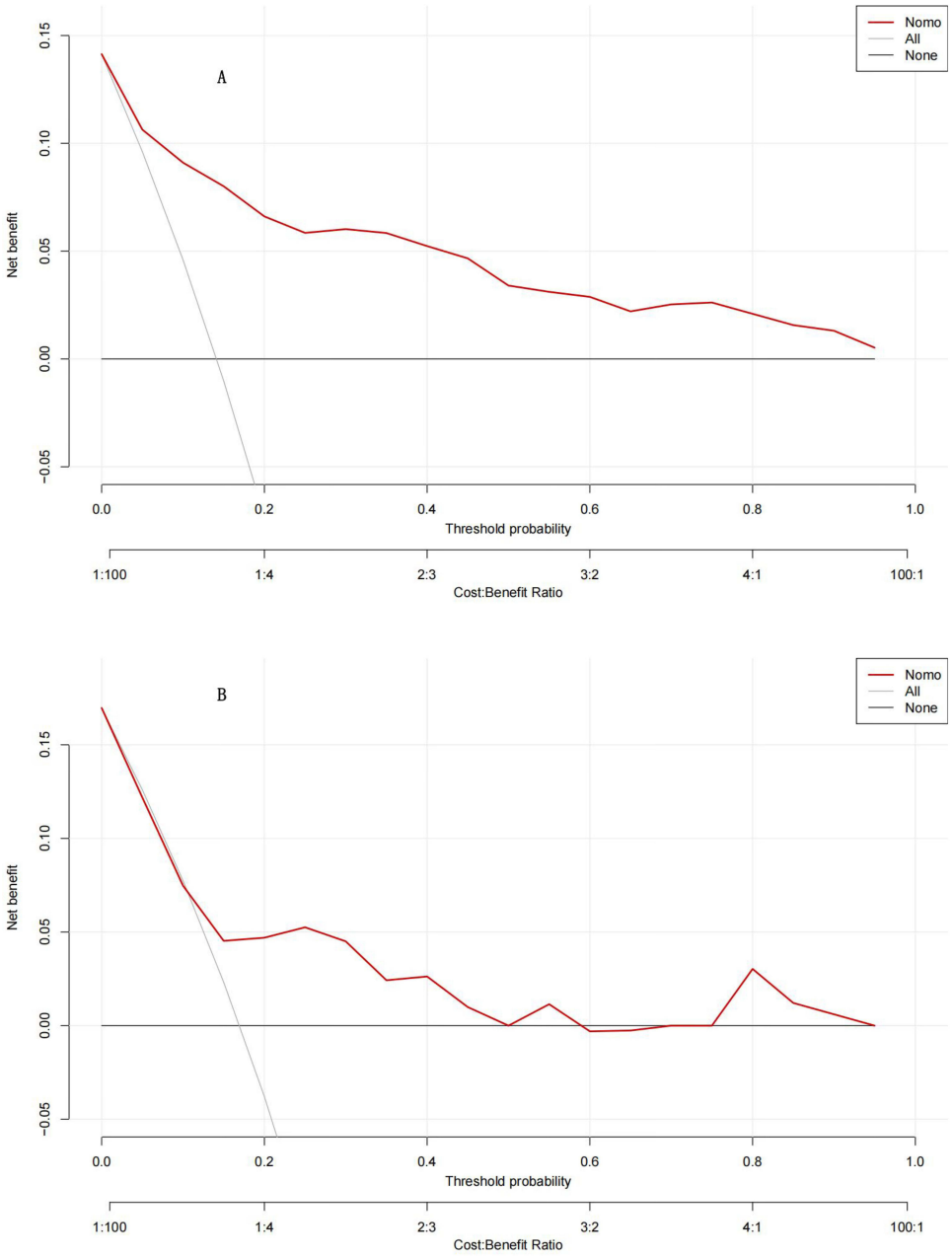

Figure 5 Decision curves for the proposed nomogram model in the training (**A**) n=382 and testing (**B**) n=165 sets.
Abbreviations: n, number of participants in the study; Nomo, nomogram.

identified as a predictor of CF. Carbohydrates are a primary energy source, and insufficient consumption can lead to malnutrition and weight loss, which are critical factors in CF development among older adults. Notably, 58.33% of participants in this study reported no nut consumption. Nuts, a globally recommended food rich in protein, healthy fats, and satiety-promoting properties, have been associated with a reduced risk of chronic conditions, including CVD.[23,24] Further mechanistic studies are needed to explore causal relationships involved.

For clinicians, a cost-effective and simplified method for rapidly predicting CF is highly valuable. In this study, we identified education, age, SBP, CCI, SPPB scores, and nutritional status as predictive indicators of CF. These factors were used to develop a nomogram model, which demonstrated strong predictive accuracy, with an AUC of 0.854 for the training cohort and 0.733 for the validation cohort. Since these variables can be easily obtained through routine

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assessments, the nomogram could be utilized at the time of admission for patients with ACS to identify those with CF. Additionally, it is practical for both regular evaluation and ongoing monitoring.

The current research has several limitations. First, although the data were of high quality, they were collected from a single center in China, potentially restricting the generalizability of the findings for the geographic constraints and heterogeneity. Second, CF was assessed using MMSE and Frail scores, which introduced variability due to differences in screening tools, cut-off values, and measurement time points. Third, although the nomogram model demonstrated good predictive accuracy in the study, it remains uncertain whether its performance might differ in populations with higher educational attainment or varying prevalence of frailty. Lastly, the conclusions are primarily based on baseline data analysis and in-hospital follow-up. Future long-time follow-up assessments are planned to address these limitations.

Conclusions

The present study demonstrates that in elderly patients with ACS, the coexistence of frailty and cognitive impairment is frequent and is associated with age, female, less educated, worse economic, higher SBP, and glucose. Patients with CF were more likely to have worse cardiac function and malnutrition. Intaking more carbohydrates and nuts will improve nutrition, thereby alleviating CF. This study explored a simple and practical nomogram for providing patients with an early warning about the risk of hypertension based on the associated risk factors.

Abbreviations

CF, Cognitive frailty; ACS, acute coronary syndrome; ROC, receiver operating characteristic; DCA, decision curve analysis; SBP, systolic blood pressure; CCI, Charlson Comorbidity Index; SPPB, Short Physical Performance Battery; CVDs, cardiovascular diseases; CI, cognitive impairment; MMSE, Mini-Mental State Examination; STEMI, ST-Elevation myocardial infarction; NSTEMI, non-ST elevated myocardial infarction; NSTE-ACS, Non-ST-Elevation Acute Coronary Syndrome; GRACE, Global Registry of Acute Cardiac Events; MACE, major adverse cardiac events; ADL, activities of daily living; IADL, Instrumental activities of daily living; SPPB, Short Physical Performance Battery; BMI, body mass index; CHO, cholesterol; Cr, creatinine; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; Hgb, hemoglobin; LDL, low-density lipoprotein; TG, triglycerides; UAP, unstable angina pectoris; AUC, area under the curve.

Human Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee for Clinical Research of Beijing Friendship Hospital before the performance of the analyses (code: 2022-P2-045-01). All procedures involving human participants were performed in accordance with the ethical standards of the Ethics Committee for Clinical Research of Beijing Friendship Hospital and with the Declaration of Helsinki and its later amendments.

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Disclosure

The authors declare that they have no competing interests.

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