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Original Research

The Impact of Frailty on Clinical Outcomes in Patients With Non-ST-Elevation Acute Coronary Syndrome Treated With Percutaneous Coronary Intervention and an Analysis of Related Risk Factors

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Abstract

Background: Frailty strongly affects prognosis in patients with acute coronary syndrome (ACS), but its predictive value in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) treated with percutaneous coronary intervention (PCI) remains incompletely characterized. Conventional risk models often omit frailty and may underestimate the risk of adverse events. Thus, this study aimed to assess the prevalence of frailty and its independent prognostic association with multiple cardiovascular endpoints among patients with NSTE-ACS using the Hospital Frailty Risk Score (HFRS). **Methods:** This single-center retrospective cohort study included consecutive NSTE-ACS patients who underwent coronary angiography and PCI at People's Hospital of Ningxia Hui Autonomous Region from January 1 to December 31, 2022. Patients were stratified by HFRS into non-frail (HFRS <5, n = 132) and frail (HFRS ≥5, n = 297) groups. Kaplan–Meier survival curves with log-rank tests were used to assess event-free survival for major adverse cardiovascular events (MACEs), ACS rehospitalization, and gastrointestinal bleeding. Cox proportional hazards models were used to identify independent risk factors for each clinical endpoint. **Results:** Of 429 enrolled NSTE-ACS patients, 297 (69.2%) were classified as frail and 132 (30.8%) as non-frail. Frail patients were older, had a higher burden of metabolic–cardiovascular comorbidities, adverse cardiac structural parameters, a higher prevalence of three-vessel coronary disease, more repeat hospital admissions, and divergent discharge antiplatelet regimens. Over 36 months of follow-up, frail patients had a significantly higher cumulative incidence of major adverse cardiac and cerebrovascular events (MACCEs) (26.9% vs. 8.3%, log-rank $p < 0.001$). Frailty independently predicted long-term MACCEs (adjusted hazard ratio (aHR) 2.24, 95% confidence interval (CI) 1.09–4.62), along with peripheral vascular disease, complete coronary occlusion, right coronary stenosis, and repeat hospital admissions. Most secondary endpoints showed significant elevations, except cardiovascular death. **Conclusions:** Frailty is highly prevalent in NSTE-ACS and independently predicts long-term MACCEs, Although no significant difference in 3-year cardiovascular death was observed between the two groups in this cohort. Routine HFRS-based frailty screening facilitates risk stratification and individualized management in real-world NSTE-ACS populations.

Keywords: non-ST-segment elevation acute coronary syndrome; frailty; Hospital Frailty Risk Score; major adverse cardiovascular events

1. Introduction

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS), a major clinical phenotype of ischemic heart disease, comprises non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina pectoris [1,2]. Moreover, the high recurrence rate and long-term risk of adverse cardiovascular events pose a substantial public health burden [3]. Population aging has increased the proportion of elderly NSTE-ACS patients with multimorbidity and diminished physiological reserve, who face elevated procedural-complication risk and barriers to guideline-directed pharmacotherapy [4,5]. Conventional risk-stratification tools GRACE (Global Registry of Acute Coronary Events) and TIMI (Thrombolysis in Myocardial Infarction) (GRACE, TIMI) rely mainly on age, hemodynamics, and biochemical markers but incompletely capture geriatric physiological vulnerability, limiting predictive performance in older ACS populations [6,7,8]. Frailty is a geriatric syndrome characterized by multisystem physiological reserve depletion, stress intolerance, and increased susceptibility to adverse health outcomes [9,10]. Independent of comorbidity burden, frailty predicts poor prognosis in older ACS cohorts, correlating with in-hospital complications and long-term readmission and mortality [10]. Multiple frailty assessment instruments are available, including the Fried Frailty Phenotype, Clinical Frailty Scale (CFS), Edmonton Frail Scale (EFS), and the administrative data-derived Hospital Frailty Risk Score (HFRS) [11].

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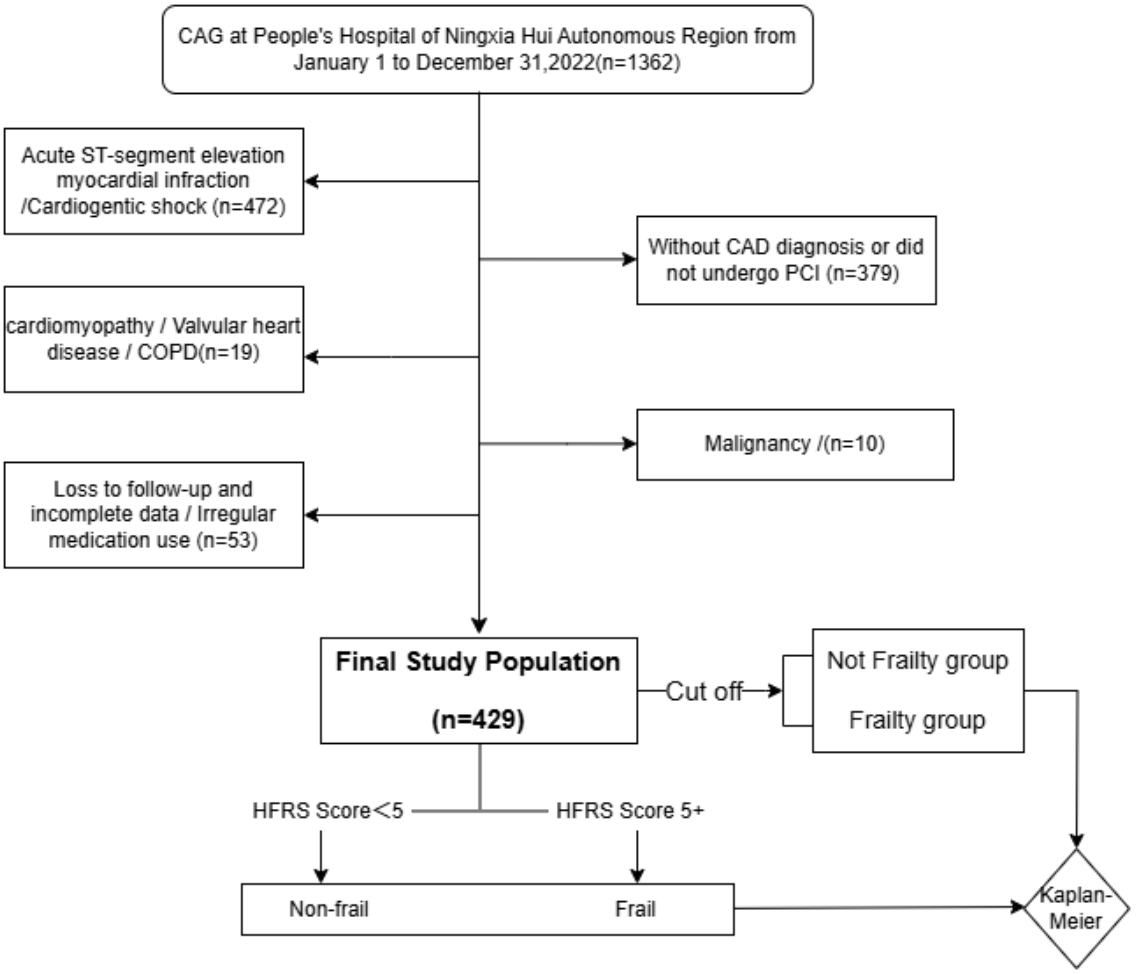


Fig. 1. Study flowchart for patient screening and grouping. CAG, coronary angiography; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

As an electronic health record-based algorithm, HFRS enables retrospective frailty identification without face-to-face geriatric assessment, making it suitable for retrospective real-world cohort research [11]. A recent prospective cohort study of 1174 older patients with ACS compared the relative predictive performance of the CFS, EFS, and Fried Frailty Phenotype criteria for mortality and prolonged hospital stay, identifying heterogeneous predictive efficacy across tools and suggesting that clinicians select assessment instruments tailored to specific clinical scenarios [9].

Nevertheless, real-world evidence on HFRS prognostic performance in percutaneous coronary intervention (PCI)-treated NSTE-ACS populations remains limited, especially in Chinese cohorts. Whether frailty provides incremental prognostic value beyond established risk models requires further validation. Accordingly, this single-center retrospective cohort study was performed among PCI-treated NSTE-ACS patients [12]. Using HFRS, we compared baseline profiles between frail and non-frail subgroups, evaluated frailty-associated prognostic effects across multiple adverse endpoints, and identified independent risk factors for poor outcomes, with the aim of supporting frailty-oriented risk-stratification and individualized clinical decision-making for Chinese NSTE-ACS patients.

2. Methods

2.1 Study Population

Consecutive patients who underwent coronary angiography (CAG) at People's Hospital of Ningxia Hui Autonomous Region from January 1 to December 31, 2022, were initially screened (n = 1362). Inclusion criteria: (1) clinical diagnosis of NSTE-ACS according to the 2023 ESC NSTE-ACS guidelines [1]; (2) completion of coronary angiography and percutaneous coronary intervention; (3) complete electronic medical records and follow-up data. Exclusion criteria: (1) acute ST-segment elevation myocardial infarction (STEMI) or STEMI complicated by cardiogenic shock (n = 472); (2) no confirmed coronary artery disease or abandoned PCI (n = 379); (3) primary cardiomyopathy, valvular heart disease, or chronic obstructive pulmonary disease as the primary admission cause (n = 19); (4) active malignant tumor with a life expectancy of less than

1 year (n = 10); (5) loss to follow-up, incomplete clinical data, or irregular long-term medication (n = 53). The final study cohort comprised 429 NSTE-ACS patients. All participants were divided into a non-frail group (HFRS score <5, n = 132) and a frail group (HFRS score ≥5, n = 297). Fig. 1 presents the study flowchart.

HFRS Selection and Assessment

The HFRS was selected because this metric can be calculated solely from diagnostic code information stored in electronic medical records, without additional geriatric ward face-to-face assessment; this characteristic makes HFRS appropriate for retrospective real-world cohort analysis [11]. HFRS was selected for this retrospective cohort for two key reasons. First, HFRS is calculated solely from inpatient diagnostic codes extracted from electronic medical records without standardized bedside geriatric evaluation, which fits our historical dataset lacking dedicated frailty-scale records (Fried phenotype and CFS require face-to-face assessment that was not routinely collected during 2022 admission). Second, trained research investigators retrospectively extracted all 2022 inpatient diagnostic codes after follow-up completion and computed HFRS scores uniformly for all participants, with assessments conducted blind to clinical outcomes to avoid ascertainment bias. HFRS is a continuous risk metric constructed from 101 weighted International Classification of Diseases (ICD) diagnostic codes, and a validated cutoff value of ≥5 is applied to define frailty status. This score is generated by summing the weighted values of individual inpatient ICD diagnostic codes that reflect a spectrum of chronic conditions and geriatric-related health status. Several diagnostic components of HFRS, including diabetes mellitus, chronic kidney disease (CKD), prior stroke, and peripheral vascular disease (PVD), were included as independent covariates in the prognostic Cox model. Potential collinearity between HFRS and these covariates was carefully evaluated during variable selection. Although HFRS shares several individual disease items with the candidate covariates, it serves as an integrated composite score reflecting global multisystem physiological vulnerability rather than a single comorbidity. In this cohort of 429 NSTE-ACS patients, baseline comparisons and variable screening verified that the composite HFRS score was not highly or completely correlated with any of the above individual covariates. All variables retained in the final multivariate Cox model were screened through baseline intergroup comparisons and univariate analysis based on clinical relevance, and no prominent collinearity-induced instability that could interfere with model estimation and interpretation was identified. Accordingly, including HFRS and these individual comorbidity covariates simultaneously is clinically reasonable for evaluating the prognostic role of global frailty status alongside conventional single-disease risk factors.

2.2 Data Collection

Standardized electronic medical record extraction was performed to collect multidimensional variables: Demographic and metabolic indicators: age, gender, body mass index (BMI), obesity, and current smoking status; chronic comorbidities: diabetes mellitus, hypertension, hyperlipidemia, hyperuricemia, prior myocardial infarction, prior stroke, prior heart failure, prior PCI, CKD (defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 based on admission serum creatinine (SCr) according to KDIGO criteria), and PVD (defined as prior documented peripheral artery stenosis, intermittent claudication, or peripheral artery revascularization history). Echocardiographic parameters: left atrial (LA) diameter, left ventricular end-diastolic diameter (LVED), left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) functional classification. Notably, Killip classification was not systematically recorded in this historical dataset and, therefore, could not be analyzed. Biochemical markers: total cholesterol, low-density lipoprotein cholesterol (LDL-C), SCr, and serum uric acid. Coronary angiography and PCI procedural data: three-vessel disease, completely occluded lesions, chronic total occlusion (CTO), single-vessel stenosis (left anterior descending (LAD), left circumflex artery (LCX), right coronary artery (RCA)), left main trunk stenosis ≥50%, lesion length ≥60 mm, multivessel PCI, rotational atherectomy, intraoperative mechanical circulatory support. In-hospital events: cardiac arrest and new-onset heart failure during hospitalization.

Hospitalization characteristics: number of prior hospital admissions before the index NSTE-ACS admission and average length of stay. Discharge guideline-directed medications: aspirin, clopidogrel, ticagrelor, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEi/ARBs), statins, diuretics. ARNi, MRA, SGLT2i, GLP-1 receptor agonists, and oral anticoagulants were not routinely recorded as structured fields in our historical dataset, so these medication categories were not extracted for analysis. Polypharmacy and dedicated geriatric syndrome variables (cognitive impairment, sarcopenia) were also not systematically documented and could not be assessed in the present retrospective cohort. Continuous variables with non-normal distributions are reported as median (interquartile range, IQR); categorical variables are presented as n (%).

2.3 Follow-Up and Clinical Endpoint Definitions

All patients were followed up through outpatient review and telephone contact. Secondary readmission endpoints in this study are limited to inpatient events recorded in the electronic medical record system of our hospital, including ACS rehospitalization, acute heart failure (AHF) hospitalization, and gastrointestinal bleeding hospitalization. Comprehensive all-cause hospitalization data, including admissions at external medical institutions, cannot be

systematically retrieved due to a lack of inter-hospital medical record sharing. The follow-up endpoints were defined as follows: Major adverse cardiovascular events (MACEs): a composite endpoint of cardiovascular death, ischemic stroke, and unplanned revascularization. Secondary endpoints: individual components of major adverse cardiac and cerebrovascular events (MACCEs), ACS rehospitalization secondary to myocardial ischemia, AHF hospitalization, and gastrointestinal bleeding. ACS rehospitalization: readmission caused by recurrent angina or new-onset NSTEMI; gastrointestinal bleeding: overt gastrointestinal hemorrhage requiring medical intervention; cardiovascular death: death attributed to myocardial ischemia, heart failure, malignant arrhythmia, or stroke; ischemic stroke: new cerebral infarction confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI); unplanned revascularization: repeat PCI or coronary artery bypass grafting (CABG) due to refractory myocardial ischemia.

2.4 Statistical Analysis

Statistical analyses were conducted using SPSS 26.0 (IBM Corporation, Armonk, NY, USA) and R 4.3.0. (R Core Team, Vienna, Austria) For between-group comparisons: non-normally distributed continuous variables were analyzed using the Wilcoxon rank-sum test; categorical variables were analyzed using the chi-square test, and Fisher's exact test was used when the expected frequency was <5. Kaplan–Meier survival curves were plotted, and the log-rank test was used to compare event-free survival between groups. Cox proportional hazards models were fit to identify independent risk factors for each endpoint, and hazard ratios (HRs) and 95% confidence intervals (CIs) are reported; a two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics of Frail and Non-Frail NSTE-ACS Patients

The cohort included 429 NSTE-ACS patients: 132 (30.8%) non-frail and 297 (69.2%) frail. Table 1 summarizes baseline comparisons.

3.1.1 Demographics and Metabolic Comorbidities

Frail patients were markedly older than non-frail counterparts [66.00 (60.00, 72.00) vs. 55.00 (51.00, 62.00); $p < 0.001$]. No significant intergroup differences were observed in the proportion of females, BMI, obesity, or current smoking (all $p > 0.05$). Frail patients had a higher prevalence of diabetes (38.0% vs. 9.1%), hypertension (74.4% vs. 56.8%), and hyperuricemia (21.9% vs. 10.6%), with $p < 0.001$ or $p = 0.008$.

3.1.2 Cardiovascular History and Cardiac Structural Changes

Frail patients had a higher prevalence of prior stroke (24.6% vs. 8.3%; $p < 0.001$), CKD (10.8% vs. 0.0%; $p < 0.001$), and PVD (33.3% vs. 6.1%; $p < 0.001$). The proportion of patients with NYHA functional class >II was higher in the frail group (6.7% vs. 1.5%; $p = 0.030$). Echocardiographic measurements showed that frail patients had a larger LA diameter [36.30 (33.10, 38.80) vs. 33.65 (31.78, 37.42); $p < 0.001$] and a lower EF [62.00 (59.00, 65.20) vs. 64.50 (61.82, 67.00); $p < 0.001$]. LVED, serum lipids, SCr, and uric acid levels did not differ significantly between groups (all $p > 0.05$).

3.1.3 Coronary Lesion and Interventional Characteristics

All patients in the final cohort underwent coronary angiography and successful PCI; consequently, all subjects had angiographically confirmed obstructive coronary artery disease responsible for the index NSTE-ACS event. Three-vessel coronary disease was more common among frail NSTE-ACS patients (60.6% vs. 49.2%; $p = 0.037$). No significant differences were observed in complete vessel occlusion, CTO, single-branch stenosis rate, left main trunk stenosis, lesion length, multivessel PCI, or intraoperative auxiliary procedures (all $p > 0.05$).

3.1.4 Hospitalization and Discharge Medication

Frail patients had more prior hospital admissions before the index admission [2.00 (1.00, 3.00) vs. 1.00 (1.00, 1.00); $p < 0.001$], whereas length of hospital stay showed a borderline difference ($p = 0.063$). For antiplatelet regimens, frail patients received more clopidogrel (55.2% vs. 43.2%; $p = 0.028$) and less ticagrelor (42.4% vs. 54.5%; $p = 0.026$). Aspirin, β-blockers, ACEI/ARB, statins, and diuretics showed no group-level differences (all $p > 0.05$).

3.2 Kaplan–Meier Survival Analysis of Long-Term Endpoints

Kaplan–Meier survival analyses with log-rank tests were conducted to compare event-free survival stratified by frailty status, including 297 frail and 132 non-frail patients. Statistically significant disparities in cumulative event risks were observed across all four evaluated endpoints. The 36-month cumulative incidence of MACCEs was 8.3% (11/132) in the non-frail group and 26.9% (80/297) in the frail group. Kaplan–Meier curves showed consistent separation in MACCE-free survival throughout the 36-month follow-up period (log-rank $p < 0.001$; Fig. 2). Kaplan–Meier curves were constructed to compare cumulative event-free survival for all predefined secondary endpoints between frail and non-frail participants over the 36-month follow-up (Fig. 3A–F; Table 2). Fig. 3A–C presents event-free survival curves only for in-hospital readmissions verified by our institutional electronic health record (EHR); a full time-to-event analysis of all-cause hospitalization

Table 1. Baseline characteristics of frail and non-frail patients with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Variable	Overall (n = 429)	Non-frail (n = 132)	Frail (n = 297)	*p*-value
Age, years	64.00 (55.00, 70.00)	55.00 (51.00, 62.00)	66.00 (60.00, 72.00)	<0.001
Female	286 (66.7)	96 (72.7)	190 (64.0)	0.096
BMI (median, kg/m^2)	25.10 (23.41, 27.68)	25.10 (23.51, 27.69)	25.26 (23.32, 27.68)	0.760
Obesity	293 (68.3)	93 (70.5)	200 (67.3)	0.598
UA	316 (73.7)	98 (74.2)	218 (73.4)	0.855
NSTEMI	113 (26.3)	34 (25.8)	79 (26.6)	0.855
Current smoking	209 (48.7)	72 (54.5)	137 (46.1)	0.132
Diabetes mellitus	125 (29.1)	12 (9.1)	113 (38.0)	<0.001
Hypertension	296 (69.0)	75 (56.8)	221 (74.4)	<0.001
Hyperlipidemia	104 (24.2)	29 (22.0)	75 (25.3)	0.542
Hyperuricemia	79 (18.4)	14 (10.6)	65 (21.9)	0.008
Prior myocardial infarction	86 (20.0)	20 (15.2)	66 (22.2)	0.119
Prior stroke	84 (19.6)	11 (8.3)	73 (24.6)	<0.001
Prior heart failure	13 (3.0)	1 (0.8)	12 (4.0)	0.074
Prior PCI	122 (28.4)	30 (22.7)	92 (31.0)	0.103
Ef value ≥30%	429 (100.0)	132 (100.0)	297 (100.0)	NA
NYHA >II	22 (5.1)	2 (1.5)	20 (6.7)	0.030
LA (mm)	35.60 (32.60, 38.30)	33.65 (31.78, 37.42)	36.30 (33.10, 38.80)	<0.001
CKD	32 (7.5)	0 (0.0)	32 (10.8)	<0.001
PVD	107 (24.9)	8 (6.1)	99 (33.3)	<0.001
LVED (mm)	46.80 (44.00, 49.60)	46.80 (43.60, 49.60)	46.70 (44.10, 49.70)	0.590
LVEF (%)	63.00 (60.10, 65.90)	64.50 (61.82, 67.00)	62.00 (59.00, 65.20)	<0.001
Cholesterol (mmol/L)	3.94 (3.24, 4.70)	4.03 (3.28, 4.62)	3.86 (3.22, 4.70)	0.490
LDL-C (mmol/L)	2.11 (1.63, 2.71)	2.21 (1.75, 2.88)	2.05 (1.58, 2.65)	0.075
SCr (μmol/L)	73.00 (61.00, 86.00)	71.00 (61.00, 83.25)	74.00 (61.00, 88.00)	0.148
Uric acid (μmol/L)	322.00 (269.00, 382.00)	314.00 (269.00, 380.00)	323.00 (269.00, 387.00)	0.588
Three-vessel	245 (57.1)	65 (49.2)	180 (60.6)	0.037
Completely blocked	109 (25.4)	32 (24.2)	77 (25.9)	0.803
CTO	63 (14.7)	14 (10.6)	49 (16.5)	0.149
LCX	313 (73.0)	88 (66.7)	225 (75.8)	0.066
RCA	324 (75.5)	99 (75.0)	225 (75.8)	0.963
LAD	391 (91.1)	119 (90.2)	272 (91.6)	0.766
Left main trunk stenosis ≥50%	14 (3.3)	5 (3.8)	9 (3.0)	0.770
Lesion length ≥60 mm	151 (35.2)	48 (36.4)	103 (34.7)	0.820
Three-vessel PCI	17 (4.0)	7 (5.3)	10 (3.4)	0.496
Left main PCI	20 (4.7)	7 (5.3)	13 (4.4)	0.864
Rotational cutting	5 (1.2)	1 (0.8)	4 (1.3)	1.000
Dual-path	2 (0.5)	1 (0.8)	1 (0.3)	0.521
Mechanical support	3 (0.7)	1 (0.8)	2 (0.7)	1.000
Cardiac arrest during hospitalization	1 (0.2)	0 (0.0)	1 (0.3)	1.000
Whether experiencing heart failure during hospitalization	31 (7.2)	7 (5.3)	24 (8.1)	0.410
Number of hospitalization	1.00 (1.00, 2.00)	1.00 (1.00, 1.00)	2.00 (1.00, 3.00)	<0.001
Median length of hospital stay	8.00 (6.25, 11.00)	8.00 (6.00, 10.00)	8.00 (6.33, 11.50)	0.063
Medication				
Aspirin	421 (98.1)	129 (97.7)	292 (98.3)	0.706
Clopidogrel	221 (51.5)	57 (43.2)	164 (55.2)	0.028
Ticagrelor	198 (46.2)	72 (54.5)	126 (42.4)	0.026
β-blockers	292 (68.1)	89 (67.4)	203 (68.4)	0.938

Table 1. Continued.

Variable	Overall (n = 429)	Non-frail (n = 132)	Frail (n = 297)	*p*-value
ACEi/ARB	296 (69.0)	87 (65.9)	209 (70.4)	0.419
Statins	427 (99.5)	131 (99.2)	296 (99.7)	0.521
Diuretics	52 (12.1)	11 (8.3)	41 (13.8)	0.109

Data are presented as the median (interquartile range, IQR) for non-normally distributed continuous variables, the mean (standard deviation, SD) for normally distributed continuous variables, and n (%) for categorical variables. All percentages are column percentages. n denotes sample size. The Wilcoxon rank-sum test was used for non-normally distributed continuous variables; the χ^2 test or Fisher's exact test (when the theoretical frequency <5) was used for categorical variables. The *p*-values are for between-group comparisons. NA, not applicable. No patients with chronic kidney disease were observed in the non-frail group. IQR, interquartile range; SD, standard deviation.

Abbreviations: BMI, body mass index; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; LA, left atrium diameter; CKD, chronic kidney disease; PVD, peripheral vascular disease; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LDL-C, low-density lipoprotein cholesterol; SCr, serum creatinine; CTO, chronic total occlusion; LCX, left circumflex artery; RCA, right coronary artery; LAD, left anterior descending artery.

across all external medical facilities cannot be performed due to data capture limitations of this single-center retrospective cohort. Frailty was associated with significantly elevated risk for most secondary endpoints, but cardiovascular death showed no group difference (1.7% frail vs. 0% non-frail; $p = 0.330$). Cumulative event rates for ACS rehospitalization, gastrointestinal bleeding, AHF hospitalization, ischemic stroke, and unplanned revascularization were higher among frail subjects (all corresponding $p < 0.05$).

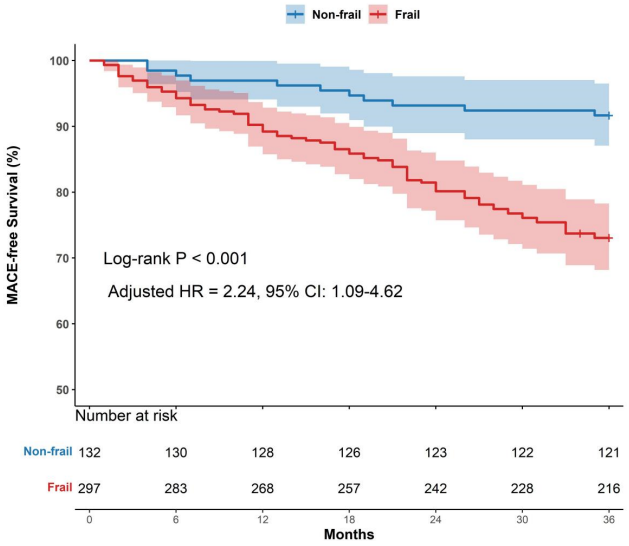


Fig. 2. Kaplan–Meier curves for major adverse cardiovascular event-free survival. The blue curve represents the non-frail group, and the red curve represents the frail group. Shaded bands surrounding each survival curve denote the 95% confidence intervals of the survival estimates. Tick marks on the curves indicate censored observations. The hazard ratio (HR) and 95% confidence interval shown were derived from a multivariable-adjusted Cox proportional hazards model. The table below the curve displays the number of patients at risk at each time point.

3.3 Cox Proportional Hazards Model Analysis for Independent Risk Factors

The Cox proportional hazards model was fitted to identify independent predictors of long-term MACEs, and the regression results are shown in the forest plot (Fig. 4), with the vertical red dashed line at HR = 1.0 denoting the null effect threshold. After adjusting for clinical, laboratory, and angiographic covariates, frailty, right coronary stenosis, PVD, complete coronary occlusion, and prior hospital admission count remained independent predictors of MACEs. Variables including SCr, prior stroke, CKD, age, three-vessel disease, and other traditional risk factors did not retain independent prognostic significance after multivariate adjustment.

4. Discussion

This study highlights the strong prognostic impact of frailty in patients with NSTE-ACS, showing that frailty is not merely a marker of advanced age but an independent predictor of MACEs. The finding that frailty confers more than a twofold increased risk of long-term MACEs (adjusted HR 2.24, 95% CI 1.09–4.62) aligns with the emerging consensus that physiological reserve, rather than chronological age alone, determines outcomes in older adults with acute coronary syndromes [3,13]. This robust association persists even after rigorous adjustment for traditional cardiovascular risk factors, underscoring frailty as a distinct and critical dimension of risk stratification that complements established models such as the GRACE score [6,14].

This study makes three distinct incremental contributions to the literature. First, we report real-world HFRS frailty prevalence and the associated independent long-term prognostic effects in a purely PCI-managed Chinese NSTE-ACS cohort, filling a gap in Asian ethnic data absent from European registries. Second, we systematically compare readmission risks (ACS, heart failure, gastrointesti-

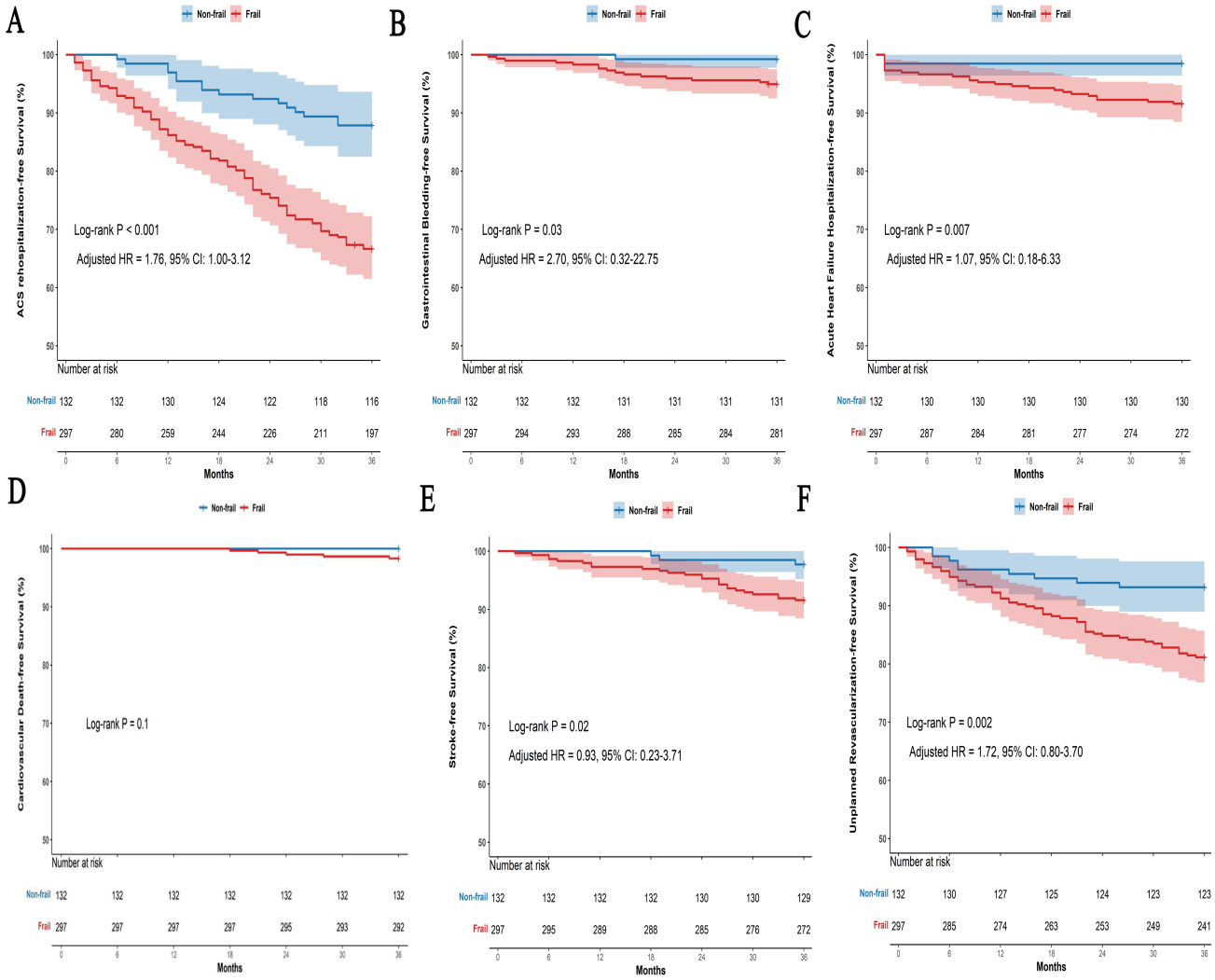


Fig. 3. Kaplan–Meier curves for secondary endpoint-free survival. Blue curves represent non-frail patients; red curves represent frail patients. Shaded regions surrounding survival curves indicate 95% confidence intervals. Tick marks on curves denote censored observations. Hazard ratios (HRs) presented in each panel are multivariable-adjusted. (A) ACS rehospitalization-free survival. (B) Gastrointestinal hemorrhage-free survival. (C) Acute heart failure (AHF) hospitalization-free survival. (D) Cardiovascular death-free survival. (E) Stroke-free survival. (F) Unplanned revascularization-free survival. Of the six endpoints shown, four demonstrated statistically significant differences, and two showed no significant difference.

Table 2. Comparison of clinical outcomes between frail and non-frail patients.

Outcomes	Non-frail (n = 132)	Frail (n = 297)	*p*-value
MACCEs	11 (8.3)	80 (26.9)	<0.001
Cardiovascular death	0 (0.0)	5 (1.7)	0.330
Unplanned revascularization	9 (6.8)	56 (18.9)	0.001
Stroke	3 (2.3)	25 (8.4)	0.017
ACS rehospitalization	16 (12.1)	99 (33.3)	<0.001
AHF	2 (1.5)	25 (8.4)	0.007
Gastrointestinal hemorrhage	1 (0.8)	15 (5.1)	0.029

MACCEs, major adverse cardiovascular and cerebrovascular events; ACS, acute coronary syndrome; AHF, acute decompensated heart failure.

nal bleeding) stratified by frailty status using Kaplan–Meier and Cox regression analyses. Third, we identify right coronary stenosis and cumulative prior hospitalization count as novel independent predictors of MACEs in this population, providing a new reference for risk stratification among older Chinese NSTE-ACS patients.

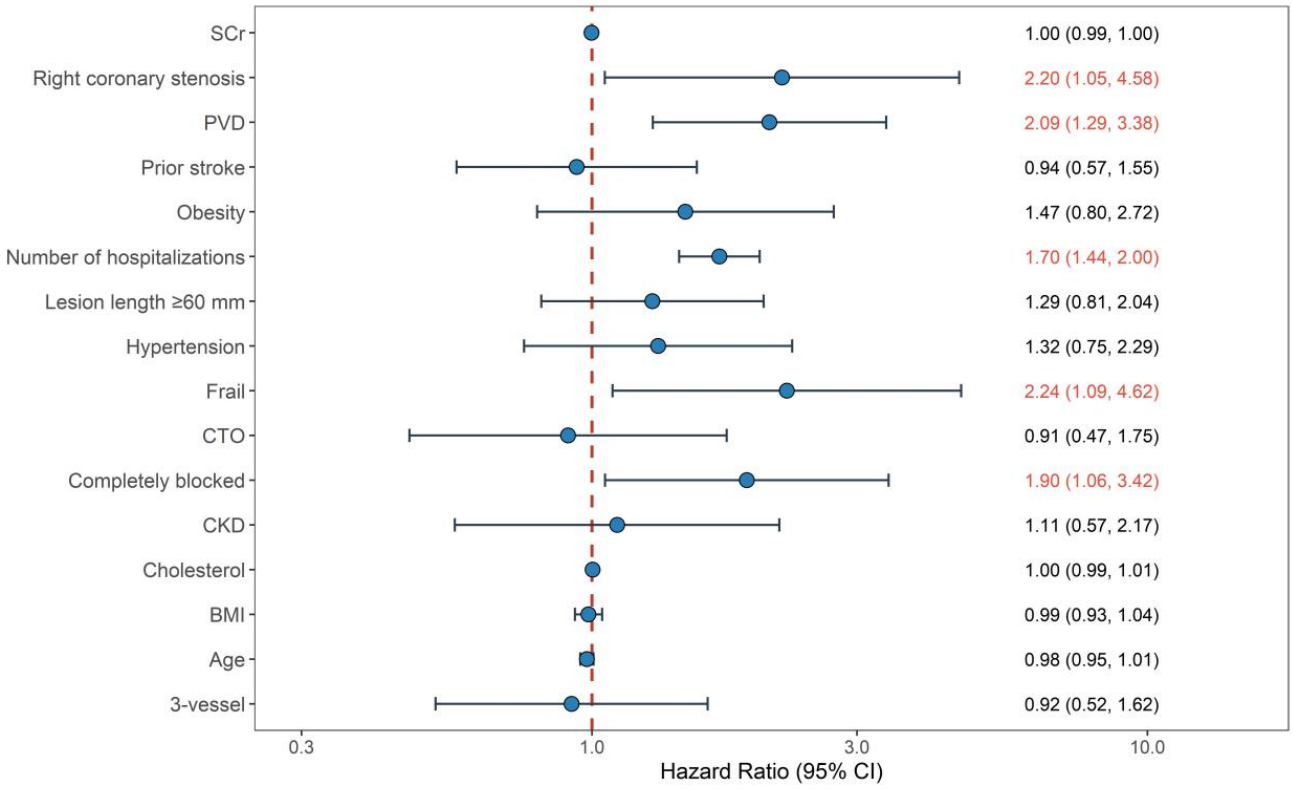


Fig. 4. Forest plot of the Cox proportional-hazards model for major adverse cardiovascular events. Each blue circle represents the hazard ratio (HR), and horizontal lines represent the corresponding 95% confidence intervals (CIs). The vertical red dashed line at HR = 1 is the null reference line; intervals crossing this line indicate no statistically significant association. Red-colored HR values denote statistically significant results ($p < 0.05$), whereas black HR values indicate non-significant results. For continuous variables: HR of age corresponds to per 1-year increment, BMI per 1 kg/m^2 increment, and SCr (serum creatinine) per 1 μmol/L increment.

4.1 Baseline Frailty Prevalence Comparison With Existing Registries

Our HFRS-defined frailty proportion (69.2%) is substantially higher than in large European nationwide registries (15.1% in the German ACS registry, 16.3% in the UK retrospective cohort) [15,16]. Three major reasons account for this inter-cohort divergence: (1) Selection bias: our cohort was restricted to patients undergoing invasive coronary angiography and PCI, a subgroup with inherently greater multimorbidity and physiological frailty, whereas European registries recruited unselected hospitalized ACS patients, including those managed conservatively. (2) Ethnic and EHR coding heterogeneity: Chinese inpatient diagnostic coding rules and reimbursement-driven documentation habits capture more chronic geriatric comorbidity codes that elevate HFRS scores, whereas European electronic health record systems use standardized, simplified diagnostic coding for the registry population. (3) Limited single-center sample size (n = 429) versus millions-scale European national registries, leading to potential sampling fluctuation in the frailty proportion.

The relatively low 3-year cardiovascular mortality observed in our cohort is multifactorial. We acknowledge that a 73.7% proportion of unstable angina (UA) is unreasonable in contemporary high-sensitivity cardiac troponin-era NSTE-ACS registries. This high UA proportion can largely be attributed to improved national public health awareness and the comprehensive development of chest pain centers in China in recent years. Such progress enables patients with early, mild coronary ischemic symptoms to seek medical care promptly, resulting in many patients being admitted at the unstable angina stage rather than progressing to NSTEMI or STEMI. The predominance of unstable angina in this cohort further accounts for its relatively low cardiovascular mortality.

4.2 Frailty as a Multifaceted Risk Determinant in NSTE-ACS

The baseline characteristics show that frail NSTE-ACS patients have a significantly higher burden of multimorbidity, including diabetes, hypertension, and PVD. This clustering of comorbidities reflects shared pathophysiological pathways between frailty and cardiovascular disease, particularly systemic inflammation and endothelial dysfunction [17,18]. The markedly higher prevalence of PVD in the frail cohort (33.3% vs. 6.1%) is noteworthy, as PVD emerged as an independent predictor of MACE (adjusted HR 2.09, 95% CI 1.29–3.38). This suggests that frailty may

serve as a clinical surrogate for widespread atherosclerotic burden and systemic vascular vulnerability [19,20]. The interplay between frailty and PVD underscores the importance of comprehensive vascular assessment in this population, as both conditions contribute to reduced functional capacity and impaired recovery from ischemic insults [21,22]. Furthermore, the observed differences in cardiac structure, specifically larger LA diameter and lower ejection fraction in frail patients, indicate that frailty is associated with more advanced cardiac remodeling and subtle systolic dysfunction [23]. These structural changes likely contribute to the significantly higher rates of AHF hospitalization observed in the frail group, as evidenced by the Kaplan–Meier analysis [3,24].

Notably, well-established prognostic covariates, including age, three-vessel disease, CKD, prior stroke, and SCr, did not retain independent predictive significance in multivariate Cox models. CKD did not emerge as an independent predictor of MACEs in multivariate regression, inconsistent with most prospective cohorts. The primary explanation is the low absolute number of CKD events (only 32 frail patients and zero non-frail patients with CKD), which creates extreme imbalance between groups and limits statistical power to detect an independent prognostic effect after adjusting for HFRS frailty and other multimorbidity covariates. A core contributing factor is the low absolute number of cardiovascular death events (only five cases in the frail group, zero in the non-frail group), which substantially reduces statistical power to detect independent associations of these conventional risk factors. This limitation indicates that findings from small, retrospective, single-center cohorts cannot replace evidence from large, multicenter, prospective registries with abundant hard endpoint events [25].

4.3 Angiographic Complexity and Revascularization Challenges

The angiographic findings show that frail patients are more likely to present with three-vessel coronary disease (60.6% vs. 49.2%), yet right coronary stenosis emerged as an independent risk factor for MACEs (adjusted HR 2.20, 95% CI 1.05–4.58). While multivessel disease is common in older adults, the prognostic significance of right coronary involvement in the context of frailty warrants further investigation. Table 1 reports only categorical coronary disease burden indicators (single/three-vessel disease), whereas individual vessel stenosis status (LAD, circumflex, RCA) was extracted as independent covariates and entered directly into multivariate Cox regression models;RCA stenosis independently predicted long-term MACEs after full covariate adjustment. Pathophysiologically, severe RCA lesions impair right ventricular filling and systemic hemodynamic stability. Frail patients inherently possess depleted multisystem physiological reserve; superimposed RCA ischemia increases the risk of circulatory decompensation, amplifying adverse cardiovascular outcomes even after adjusting for multimorbidity, lesion complexity, and revascularization strategy [19,26]. Most individuals have a right-dominant coronary circulation. The RCA is anatomically thick and supplies critical cardiac blood flow; thus, severe stenosis or ischemia of this vessel is more likely to trigger adverse cardiovascular endpoints. The lack of significant differences in CTO between groups, despite complete vessel occlusion being an independent risk factor (adjusted HR 1.90, 95% CI 1.06–3.42), suggests that any significant occlusive disease, regardless of chronicity, poses a substantial threat in the frail population [27,28]. Managing these complex anatomical substrates in frail patients remains challenging. Indeed, the current data show that frail patients were less likely to receive potent P2Y12 inhibitors like ticagrelor and more likely to be prescribed clopidogrel. This prescribing pattern likely reflects clinician caution regarding bleeding risk, a concern supported by the significantly higher incidence of gastrointestinal bleeding in the frail cohort (log-rank $p = 0.03$) [29]. The POPular AGE data support using clopidogrel in older adults to reduce bleeding without compromising ischemic protection, suggesting that the treatment approach in this cohort may align with contemporary evidence favoring safety in vulnerable populations [30]. However, frail patients have a higher rate of ACS rehospitalization, and frailty is an independent risk factor, indicating that this conservative antiplatelet strategy, while safer regarding bleeding, may not fully mitigate the high underlying ischemic risk driven by their frailty status [31].

4.4 Clinical Implications and Future Directions

Identifying frailty, PVD, right coronary stenosis, complete vessel occlusion, and prior hospitalization frequency as independent predictors of MACE provides a refined risk profile for NSTE-ACS patients. Traditional risk scores often fail to capture the vulnerability associated with frailty, potentially underestimating risk in this subgroup [6,32]; thus, incorporating frailty assessment into routine clinical practice could enhance risk stratification and guide more personalized management strategies. For instance, the elevated risks of ACS rehospitalization, repeat revascularization, stroke, heart failure hospitalization, and bleeding in frail patients, alongside the independent predictive effect of frailty on recurrent ACS admission, suggest a need to carefully balance antithrombotic therapy intensity and to implement closer post-discharge monitoring [33]. Moreover, the strong association between frailty and adverse outcomes highlights the potential benefit of multidisciplinary interventions, including cardiac rehabilitation and nutritional support, tailored to improve physiological reserve [24,34]. While invasive management remains standard for NSTE-ACS, frailty should prompt a comprehensive evaluation of the risks and benefits of revascularization, considering both anatomical complexity and the capacity of the patient to

tolerate procedural stress and adhere to long-term medical therapy [35]. Future research should examine whether targeted prehabilitation or modified revascularization strategies can mitigate the excess risk conferred by frailty in this high-risk population [36,37].

4.5 Study Limitations

This study has several inherent limitations. First, it is a single-center retrospective observational cohort with potential selection bias; multi-center prospective cohorts are needed to validate the conclusions. Second, frailty was evaluated using an electronic medical record-based HFRS without a standardized face-to-face geriatric assessment, which may introduce minor measurement bias. Third, this 2022 historical EHR dataset lacked structured recording for several medication categories (ARNi, MRA, SGLT2i, GLP-1 RA, oral anticoagulants), polypharmacy indicators, and other key geriatric syndrome markers, including cognitive impairment and sarcopenia, precluding subgroup analysis stratified by these critical geriatric vulnerability indicators. Fourth, absolute cardiovascular death event numbers were relatively small, limiting statistical power for certain endpoint analyses; the proportion of unstable angina versus NSTEMI in this cohort may partly shape observed mortality patterns. Fifth, quality of life metrics were not collected. Medication adherence assessment relied on chart documentation rather than objective monitoring. Further multicenter prospective real-world studies are warranted to replicate our findings. Sixth, complete time-to-event data for all-cause rehospitalization could not be systematically collected in this retrospective single-center cohort. Our institutional electronic medical record system archives only inpatient encounters generated within our hospital; many participants received unplanned inpatient care at external county, municipal, or provincial medical facilities throughout the 36-month follow-up window, and our dataset cannot access accurate admission timestamps, primary discharge diagnoses, or length-of-stay records for these off-site admissions. We exclusively analyzed three categories of adjudicated, timestamped rehospitalization events fully captured within our institution, including ACS-related readmission, acute decompensated heart failure hospitalization, and gastrointestinal bleeding hospitalization. Therefore, the overall long-term readmission burden among frail NSTE-ACS patients may be underestimated, and future multicenter prospective registries with integrated cross-hospital admission linkage are warranted to quantify frailty-associated all-cause hospitalization risks.

5. Conclusions

In summary, frailty is a core determinant of poor prognosis in patients with NSTE-ACS, with prognostic effects that exceed those of traditional cardiovascular risk factors. Clinical practice should shift from isolated management of coronary artery lesions to a patient-centered holistic care model. Routine frailty screening at admission is recommended to identify high-risk individuals. For frail patients, treatment decisions should balance the benefits of revascularization against procedural risks, with individualized antithrombotic regimens tailored to reconcile ischemic and bleeding risks [38,39]. Furthermore, given the elevated readmission and heart failure risks among frail patients, intensified multidisciplinary follow-up is warranted post-discharge, encompassing cardiac rehabilitation, nutritional support, and medication adherence management, to augment physiological reserve and optimize long-term quality of life [19,25]. Future research should explore frailty-targeted interventions for ACS populations, drawing on evidence from the work by van den Broek et al. [40].

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to the strict management and protection requirements for patient data under hospital policies, but are available from the corresponding author upon reasonable request.

Author Contributions

JL designed the study, performed statistical analysis and drafted the manuscript. YZ and XW collected clinical data. JM and QZ assisted with data curation and manuscript revision. HT participated in data interpretation, critical revision of the manuscript, and helped polish the academic expression of this article, supervised the project, revised the manuscript. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All methods were carried out in accordance with the Declaration of Helsinki. This study involves human participants and was approved by the Ethics Committee of the People's Hospital of Ningxia Hui Autonomous Region. (Ethics Approval Number: [2026]-LL-269). Due to the retrospective nature of this study, written informed consent was waived by the Ethics Committee of the People's Hospital of Ningxia Hui Autonomous Region.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During manuscript preparation, the authors used AI-based large language models (ChatGPT [version 4.0] and Doubao [ByteDance, version 2026]) for language polishing and readability improvement. The tool did not contribute to study design, data collection, analysis, or interpretation. All scientific content was independently generated and approved by the authors, who take full responsibility for the work.

References

[1] Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. European Heart Journal. 2023; 44: 3720–3826. https://doi.org/10.1093/eurheartj/ehad191

[2] Rao SV, O'Donoghue ML, Ruel M, Rab T, Tamis-Holland JE, Alexander JH, et al. 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2025; 85: 2135–2237. https://doi.org/10.1016/j.jacc.2024.11.009

[3] Shi J, Tang W, Wang S, Hou X, Xing Y, Kan J, et al. The role of frailty in older adults with Non-ST-elevation acute coronary syndrome: a Chinese population-based cohort study. Aging Clinical and Experimental Research. 2025; 37: 312. https://doi.org/10.1007/s40520-025-03207-0

[4] Morici N, De Servi S, De Luca L, Crimi G, Montalto C, De Rosa R, et al. Management of acute coronary syndromes in older adults. European Heart Journal. 2022; 43: 1542–1553. https://doi.org/10.1093/eurheartj/ehab391

[5] Damluji AA, Forman DE, van Diepen S, Alexander KP, Page RL, 2nd, Hummel SL, et al. Older Adults in the Cardiac Intensive Care Unit: Factoring Geriatric Syndromes in the Management, Prognosis, and Process of Care: A Scientific Statement From the American Heart Association. Circulation. 2020; 141: e6–e32. https://doi.org/10.1161/CIR.0000000000000741

[6] Anand A, Cudmore S, Robertson S, Stephen J, Haga K, Weir CJ, et al. Frailty assessment and risk prediction by GRACE score in older patients with acute myocardial infarction. BMC Geriatrics. 2020; 20: 102. https://doi.org/10.1186/s12877-020-1500-9

[7] Ekerstad N, Swahn E, Janzon M, Alfredsson J, Löfmark R, Lindenberger M, et al. Frailty is independently associated with short-term outcomes for elderly patients with non-ST-segment elevation myocardial infarction. Circulation. 2011; 124: 2397–2404. https://doi.org/10.1161/CIRCULATIONAHA.111.025452

[8] Ekerstad N, Swahn E, Janzon M, Alfredsson J, Löfmark R, Lindenberger M, et al. Frailty is independently associated with 1-year mortality for elderly patients with non-ST-segment elevation myocardial infarction. European Journal of Preventive Cardiology. 2014; 21: 1216–1224. https://doi.org/10.1177/2047487313490257

[9] Langsted A, Benatar J, Kerr A, Bloomfield K, Devlin G, Sasse A, et al. Comparison of frailty instruments for predicting mortality and prolonged hospitalization in acute coronary syndrome patients. PLoS One. 2025; 20: e0318656. https://doi.org/10.1371/journal.pone.0318656

[10] Jiménez-Salva M, Carmona-Segovia A, Molina-Ramos AI, García-Rodríguez L, Puyol-Ruiz F, Doncel-Abad V, et al. Older adults with acute coronary syndrome: the impact of frailty and nutritional status on in-hospital complications. European Journal of Cardiovascular Nursing. 2025; 24: 595–605. https://doi.org/10.1093/eurjcn/zvaf006

[11] Nguyen VT, Tran MH, Ngo TKT. Comparative clinical frailty scale and hospital frailty risk score in identifying frailty and predicting mid-term outcomes in older patients with acute coronary syndrome: a multicenter cohort study in Vietnam. BMC Geriatrics. 2025; 25: 125. https://doi.org/10.1186/s12877-025-05690-6

[12] Wontor R, Rudnicka ŁM, Ołpińska B, Dudek KD, Lisiak M, Bańkowski T, et al. Impact of Frailty Syndrome on Early and Midterm Adverse Events in Patients With Acute Coronary Syndrome. Medical Science Monitor. 2026; 32: e952737. https://doi.org/10.12659/MSM.952737

[13] Ratcovich H, Beska B, Mills G, Holmvang L, Adams-Hall J, Stevenson H, et al. Five-year clinical outcomes in patients with frailty aged ≥75 years with non-ST elevation acute coronary syndrome undergoing invasive management. European Heart Journal Open. 2022; 2: oeac035. https://doi.org/10.1093/ehjopen/oeac035

[14] Georgiopoulos G, Kraler S, Mueller-Hennessen M, Delialis D, Mavraganis G, Sopova K, et al. Modification of the GRACE Risk Score for Risk Prediction in Patients With Acute Coronary Syndromes. JAMA Cardiology. 2023; 8: 946–956. https://doi.org/10.1001/jamacardio.2023.2741

[15] Völschow B, Goßling A, Kellner C, Neumann JT. Frailty prevalence, invasive treatment frequency, and in-hospital outcome in patients hospitalized for acute coronary syndrome in Germany (2005-2022): a nationwide registry study. The Lancet Regional Health. Europe. 2024; 49: 101168. https://doi.org/10.1016/j.lanepe.2024.101168

[16] Roman M, Miksza J, Lai FYL, Sze S, Poppe K, Doughty R, et al. Revascularization in frail patients with acute coronary syndromes: a retrospective longitudinal study. European Heart Journal. 2025; 46: 535–547. https://doi.org/10.1093/eurheartj/ehae755

[17] Calila H, Bălășescu E, Nedelcu RI, Ion DA. Endothelial Dysfunction as a Key Link between Cardiovascular Disease and Frailty: A Systematic Review. Journal of Clinical Medicine. 2024; 13: 2686. https://doi.org/10.3390/jcm13092686

[18] Poznyak AV, Victoria A, Vakili-Ghartavol R, Glanz VY, Beloyartsev DF, Sukhorukov VN, et al. Interplay And Causative Relationship Between Frailty And Atherosclerosis. Journal of Angiotherapy. 2024; 8: 1–11. https://doi.org/10.25163/angiotherapy.829449

[19] Beska B, Ratcovich H, Bagnall A, Burrell A, Edwards R, Egred M, et al. Angiographic and Procedural Characteristics in Frail Older Patients with Non-ST Elevation Acute Coronary Syndrome. Interventional Cardiology (London, England). 2023; 18: e04. https://doi.org/10.15420/icr.2022.20

[20] Damluji AA, Chung SE, Xue QL, Hasan RK, Moscucci M, Forman DE, et al. Frailty and cardiovascular outcomes in the National Health and Aging Trends Study. European Heart Journal. 2021; 42: 3856–3865. https://doi.org/10.1093/eurheartj/ehab468

[21] Taylor JA, Greenhaff PL, Bartlett DB, Jackson TA, Duggal NA, Lord JM. Multisystem physiological perspective of human frailty and its modulation by physical activity. Physiological Re-

views. 2023; 103: 1137–1191. https://doi.org/10.1152/physrev.00037.2021

[22] Monil M, KP N, Rajkumar D, Doshi R, Mehta H, Vindhyal MR, et al. Prognostic Value of Hospital Frailty Risk Score and Clinical Outcomes in Patients Undergoing Revascularization for Critical Limb-Threatening Ischemia. Journal of the American Heart Association. 2023; 12: e030294. https://doi.org/10.1161/JAHA.123.030294

[23] Halim GA, Rampengan SH, Jim EL. Relationship Between Left Ventricular Ejection Fraction And Age With Major Cardiovascular Incidence In Nste-Acs Patients. Jurnal Impresi Indonesia. 2025; 4: 1080–1096. https://doi.org/10.58344/jii.v4i1.6269

[24] Díez-Villanueva P, Jiménez-Méndez C, Cepas-Guillén P, Vilches L, Rivero F, García-Pardo H, et al. Personalized management and decision-making for non-ST-segment elevation acute coronary syndrome in vulnerable populations. Expert Review of Cardiovascular Therapy. 2025; 23: 809–820. https://doi.org/10.1080/14779072.2025.2583939

[25] Lu YY, Lee CH, Chen CC, Chen DY, Ho MY, Yeh JK, et al. Comparison of long-term outcomes of complete vs. incomplete revascularization in elderly patients (≥75 years) with acute coronary syndrome and multi-vessel disease undergoing percutaneous coronary intervention. Frontiers in Cardiovascular Medicine. 2023; 10: 1037392. https://doi.org/10.3389/fcvm.2023.1037392

[26] Inohara T, Kohsaka S, Fukuda K, Menon V. The challenges in the management of right ventricular infarction. European Heart Journal: Acute Cardiovascular Care. 2013; 2: 226–234. https://doi.org/10.1177/2048872613490122

[27] Ng AKY, Ng PY, Siu CW, Jim MH. Factors associated with long-term major adverse cardiac events of coronary bioresorbable vascular scaffold. Cardiovascular Intervention and Therapeutics. 2021; 36: 462–469. https://doi.org/10.1007/s12928-020-00723-w

[28] Ko D, Evans PT, Lin KJ, Pande AN, Cervone A, Lee SB, et al. Frailty and Clinical Outcomes of Ticagrelor Versus Clopidogrel in Older Adults With Acute Myocardial Infarction. Journal of the American Heart Association. 2024; 13: e034529. https://doi.org/10.1161/JAHA.124.034529

[29] van den Broek WWA, van Paassen JG, Gimbel ME, Deneer VHM, Ten Berg JM, Vreman RA. Cost-effectiveness of clopidogrel versus ticagrelor in patients of 70 years or older with non-ST-elevation acute coronary syndrome. European Heart Journal. 2022; 43: ehac544.2846. https://doi.org/10.1093/eurheartj/ehac544.2846

[30] Gimbel M, Qaderdan K, Willemsen L, Hermanides R, Bergmeijer T, de Vrey E, et al. Clopidogrel versus ticagrelor or prasugrel in patients aged 70 years or older with non-ST-elevation acute coronary syndrome (POPular AGE): the randomised, open-label, non-inferiority trial. Lancet. 2020; 395: 1374–1381. https://doi.org/10.1016/S0140-6736(20)30325-1

[31] The Nguyen Q, Van Nguyen T, Viet Phuong Nguyen T, Minh Tran H, Ngoc Dang S, Ngoc Hoan Nguyen B, et al. Frailty as an independent predictor for midterm adverse outcomes in the elderly undergoing primary percutaneous coronary intervention: A longitudinal cohort study. Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions. 2025; 105: 335–344. https://doi.org/10.1002/ccd.31251

[32] Giallauria F, Di Lorenzo A, Venturini E, Pacileo M, D'Andrea A, Garofalo U, et al. Frailty in Acute and Chronic Coronary Syndrome Patients Entering Cardiac Rehabilitation. Journal of Clinical Medicine. 2021; 10: 1696. https://doi.org/10.3390/jcm10081696

[33] van Wyk GW, Berkovsky S, Fraile Navarro D, Coiera E. Comparing health outcomes between coronary interventions in frail patients aged 75 years or older with acute coronary syndrome: a systematic review. European Geriatric Medicine. 2022; 13: 1057–1069. https://doi.org/10.1007/s41999-022-00667-9

[34] Coughlan JJ, Durand R, Byrne RA. An initial invasive strategy in older patients with non-ST elevation acute coronary syndromes: it is never too late. European Heart Journal. 2024; 45: 2063–2065. https://doi.org/10.1093/eurheartj/ehae255

[35] Chad T, Koulouroudias M, Layton GR, Fashina O, Sze S, Roman M, et al. Frailty in acute coronary syndromes. A systematic review and narrative synthesis of frailty assessment tools and interventions from randomised controlled trials. International Journal of Cardiology. 2024; 399: 131764. https://doi.org/10.1016/j.ijcard.2024.131764

[36] Díez-Villanueva P, Cepas-Guillén P, López Lluva MT, Jurado-Román A, Bazal-Chacón P, Negreira-Caamaño M, et al. One-year clinical events according to frailty in older patients with non-ST elevation acute coronary syndrome undergoing coronary angiography: an analysis of the IMPACT-TIMING-GO study. Journal of Geriatric Cardiology: JGC. 2025; 22: 159–168. https://doi.org/10.26599/1671-5411.2025.01.003

[37] Kohansal E, Jamalkhani S, Hosseinpour A, Yousefimoghaddam F, Askarinejad A, Hekmat E, et al. Invasive versus conservative strategies for non-ST-elevation acute coronary syndrome in the elderly: an updated systematic review and meta-analysis of randomized controlled trials. BMC Cardiovascular Disorders. 2025; 25: 96. https://doi.org/10.1186/s12872-025-04560-8

[38] Damluji AA, Nanna MG, Mason P, Lowenstern A, Orkaby AR, Washam JB, et al. Coronary Artery Revascularization in the Older Adult Population: A Scientific Statement From the American Heart Association. Circulation. 2025; 152: e494–e525. https://doi.org/10.1161/CIR.0000000000001387

[39] Popat A, Vempati R, Kodali LSM, Sai Santhosha Mrudula A, Haddad F, Jain A, et al. Frailty status and outcomes of percutaneous coronary intervention in elderly patients with non-ST-elevation myocardial infarction. World Journal of Cardiology. 2025; 17: 111870. https://doi.org/10.4330/wjc.v17.i10.111870

[40] van den Broek WWA, Gimbel ME, Hermanides RS, Runnett C, Storey RF, Knaapen P, et al. The impact of patient-reported frailty on cardiovascular outcomes in elderly patients after non-ST-acute coronary syndrome. International Journal of Cardiology. 2024; 405: 131940. https://doi.org/10.1016/j.ijcard.2024.131940