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Frailty as an independent predictor of one-year outcomes in patients with HFpEF after acute myocardial infarction: insights from a multicenter retrospective cohort in China

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ABSTRACT

BACKGROUND Heart failure with preserved ejection fraction (HFpEF) following acute myocardial infarction (AMI) carries substantial morbidity and mortality, yet reliable prognostic markers beyond conventional cardiovascular factors remain limited. Frailty, reflecting diminished physiological reserve, has emerged as a potential determinant of adverse outcomes in this high-risk population. Therefore, the aim of this study was to address a critical knowledge gap and to provide evidence that may guide frailty-adapted management strategies to improve prognosis and quality of life in this high-risk population.

METHODS We conducted a multicenter retrospective cohort study including 4507 patients with HFpEF discharged after AMI across 82 hospitals in China (from January 2010 to March 2024). Frailty was assessed using the Hospital Frailty Risk Score (HFRS), with HFRS < 5 defined as non-frail and HFRS ≥ 5 as frail. Multivariable Cox proportional hazards models, adjusted for demographics, comorbidities, left ventricular ejection fraction, and therapies, were applied to evaluate associations between frailty and clinical outcomes. The primary endpoints were all-cause death and major adverse cardiovascular events (MACE), which defined as the composite of cardiovascular death and heart failure rehospitalization. Secondary endpoints included net adverse clinical events (NACE), which defined as the composite of all-cause death, stroke, recurrent myocardial infarction, revascularization, and major bleeding, as well as the individual components of MACE.

RESULTS Frailty was independently associated with a higher risk of all-cause death [adjusted hazard ratio (aHR) = 1.52, 95% CI: 1.31–2.03, *P* = 0.005] and NACE (aHR = 1.20, 95% CI: 1.02–1.41, *P* = 0.026). At one year, frail patients had higher unadjusted rates of all-cause death (9.0% *vs.* 2.9%) and NACE (19.8% *vs.* 13.7%) compared with non-frail patients. For cardiovascular death, the association did not reach statistical significance (aHR = 1.42, 95% CI: 0.99–2.03, *P* = 0.053). No significant associations were found for MACE (aHR = 1.05, 95% CI: 0.86–1.28, *P* = 0.636) or heart failure rehospitalization (aHR = 0.94, 95% CI: 0.75–1.19, *P* = 0.616).

CONCLUSIONS Frailty, as measured by the HFRS, is an independent predictor of one-year mortality and composite adverse events in post-AMI HFpEF patients. These findings support the use of HFRS at discharge to identify high-risk population who may benefit from closer follow-up, optimization of medical therapy, and targeted frailty-focused interventions.

Heart failure (HF) with preserved ejection fraction (HFpEF) accounts for nearly half of all HF cases and is associated with substantial morbidity and mortality, especially after acute myocardial infarction (AMI).[1] Despite advances in cardiovascular therapy, HFpEF remains a major clinical challenge due to its heterogeneous pathophysiology and the absence of disease-modifying treatments.[2] Current care focuses largely on symptom relief and comorbidity control, yet long-term outcomes remain poor, underscoring the need for reliable prognostic markers to guide individualized management.[1,3]

Frailty, a multidimensional syndrome reflecting redu-

ced physiological reserve and heightened vulnerability to stressors, has emerged as a key determinant of poor outcomes in cardiovascular disease.[4] In HFpEF, frailty is common and has been linked to impaired functional status, frequent hospitalizations, and excess mortality.[5] Recent reports suggest that incorporating frailty into risk stratification may improve prognostic accuracy in post-AMI patients, a population in whom conventional models often underperform.[6] Variability among frailty assessment tools and the lack of evidence-based interventions further limit its clinical application.[4,5]

Furthermore, the relationship between frailty and HFpEF-specific mechanisms, such as systemic inflammation, metabolic dysregulation, and neurohormonal imbalance, remains poorly defined.[5] Large, real-world, multicenter studies are therefore needed to validate frailty as a prognostic marker in clinically heterogeneous populations. However, little is known about its prognostic relevance specifically in patient who develop HFpEF after AMI, a subgroup with distinct clinical characteristics and disproportionately high vulnerability. Notably, no national, multicenter cohort has evaluated the applicability of a standardized frailty tool such as the Hospital Frailty Risk Score (HFRS) in this population, leaving its utility in post-AMI HFpEF largely uncertain.

Accordingly, this study evaluated the independent prognostic value of frailty for one-year adverse outcomes in patients with HFpEF following AMI, using the HFRS as a validated and standardized tool. In addition to assessing adjusted hazard ratio (aHR), we also compared unadjusted event rates between frail and non-frail patients to provide a comprehensive view of frailty-related risk. By analyzing data from 82 hospitals across China, we aimed to address a critical knowledge gap and to provide evidence that may guide frailty-adapted management strategies to improve prognosis and quality of life in this high-risk population.

METHODS

Study Design

This was a multicenter, retrospective cohort study designed to evaluate the independent prognostic value of frailty for one-year adverse outcomes in patients with HFpEF following AMI. Data were obtained from electronic health records of 82 hospitals in China (from January 2010 to March 2024). The study protocol was approved by the Ethics Committee of the leading research institution, Second Hospital of Tianjin Medical University, Tianjin, China (No.KY-2025K010) and was conducted in accordance with the principles set forth in the Declaration of Helsinki. At the same time, the informed consent was waived owing to the retrospective nature of the analysis.

Study Population

Eligible patients were adults aged ≥ 18 years who were diagnosed with AMI according to the Fourth Universal Definition of Myocardial Infarction (2018), had a left ventricular ejection fraction (LVEF) ≥ 50% consistent with HFpEF, and received guideline-directed medical therapy (GDMT) during hospitalization. Patients were excluded if they had missing or incomplete data for key variables, died during the index hospitalization or discharged themselves against medical advice, or had comorbid conditions with a life expectancy less than one year (e.g., advanced malignancy). A total of 4507 patients met the criteria, of whom 1739 patients were classified as frail and 2768 patients as non-frail.

Frailty Assessment

Frailty status was assessed using the HFRS, an International Classification of Diseases-based algorithm comprising 32 frailty-related items. Based on the scoring framework originally proposed by Gilbert, *et al*.[7] and used in subsequent validation studies, an HFRS ≥ 5 was considered to indicate increased frailty risk, while HFRS < 5 were regarded as low risk.[8] The HFRS has been validated in multiple studies for its strong association with adverse outcomes and is suitable for large-scale retrospective analyses. To avoid over-adjustment in multivariable modeling, only major clinical comorbidities that were independent of HFRS-defining items were included as covariates.

Study Endpoints

The primary endpoints were all-cause mortality and major adverse cardiovascular events (MACE), which defined as the composite of cardiovascular death and HF rehospitalization. Secondary endpoints included net adverse clinical events (NACE), which defined as the composite of all-cause death, stroke, recurrent myocardial infarction, revascularization, and major bleeding, as well as the individual components of MACE.

Data Collection

Data were extracted from hospital records and included demographics (age, sex, and body mass index), clinical characteristics (LVEF, comorbidities such as hypertension,

diabetes mellitus, and chronic kidney disease), treatment information (use of aspirin, $P2Y_{12}$ inhibitors, statins, and other GDMT agents), and laboratory results (serum creatinine, hemoglobin, and N-terminal pro-B-type natriuretic peptide). Outcome events comprised all-cause death, MACE, NACE, and their individual components.

Statistical Analysis

Continuous variables were expressed as mean ± SD or medians (interquartile range) and compared between groups using the independent Student's *t*-test or the Mann-Whitney *U* test, as appropriate. Categorical variables were presented as counts (percentages) and compared using the Pearson's chi-squared test or the Fisher's exact probability test. Associations between frailty and study endpoints were assessed using Cox proportional hazards models. Multivariable models were adjusted for age, sex, comorbidities, LVEF, and all GDMT administered during hospitalization, including antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, statins, diuretics, spironolactone, calcium-channel blockers, sodium-glucose co-transporter-2 inhibitors, nitrates, and non-vitamin K antagonist oral anticoagulants, to minimize treatment-related confounding. Results were reported as aHR with 95% CI. Sensitivity analyses included stratified analyses across age, sex, and comorbidity subgroups, and multiple imputation was applied to account for missing data. Statistical analyses were conducted using R statistical software (version 4.2.1, R Foundation for Statistical Computing, Boston, MA, USA), and a two-sided *P*-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 4507 post-AMI HFpEF patients were included, of whom 1739 patients (38.6%) were classified as frail and 2768 patients (61.4%) as non-frail. Before multivariable adjustment, substantial imbalances were observed between the two groups [standardized mean difference (SMD) > 0.10 or $P < 0.05$].

As shown in Table 1, frail patients were significantly older (68.8 ± 11.7 years *vs.* 64.0 ± 11.7 years) and less often male (63.5% *vs.* 69.1%). They presented with more severe hemodynamic compromise, with Killip class III–IV on admission being nearly three times more common (21.6% *vs.* 7.9%), and had a slightly lower mean LVEF (58.7% ± 4.7% *vs.* 59.4% ± 4.6%). Although body mass index differed statistically between the two groups (25.45 ± 3.16 kg/m^2 *vs.* 25.67 ± 3.51 kg/m^2, $P = 0.028$), the SMD was minimal (SMD = 0.07), indicating negligible clinical imbalance.

Moreover, comorbidities were more prevalent in frail patients, including hypertension (72.9% *vs.* 60.3%), diabetes mellitus (40.3% *vs.* 34.0%), atrial fibrillation (15.0% *vs.* 8.6%), peripheral vascular disease (14.3% *vs.* 7.0%), cerebrovascular disease (48.9% *vs.* 9.9%), and malignancy (6.0% *vs.* 2.0%). Acute respiratory failure on admission was also more frequent (7.8% *vs.* 0.6%). In addition, frail patients exhibited substantially higher N-terminal pro-B-type natriuretic peptide levels, with a median of 1198 pg/mL (interquartile range: 323.6–1917 pg/mL) compared with 685 pg/mL (interquartile range: 294–1632 pg/mL) in non-frail patients (SMD = 0.25, $P < 0.001$), indicating greater baseline neurohormonal activation. The frail group also had a slightly higher prevalence of prior percutaneous coronary intervention (4.8% *vs.* 2.8%), whereas prior coronary artery bypass grafting was rare and similar between groups (0.2% *vs.* 0.2%).

In-hospital Treatments

Treatment patterns differed systematically between groups. Non-frail patients were more likely to receive secondary prevention therapies, including aspirin (96.3% *vs.* 88.2%), $P2Y_{12}$ inhibitors (98.6% *vs.* 94.5%), statins (98.5% *vs.* 95.6%), beta-blockers (83.4% *vs.* 78.9%), and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (84.8% *vs.* 80.0%, all $P < 0.001$). In contrast, frail patients more frequently received agents reflecting congestion or blood pressure control, including loop diuretics (74.2% *vs.* 59.5%), thiazide diuretics (77.2% *vs.* 63.0%), spironolactone (54.7% *vs.* 43.4%), and calcium-channel blockers (24.2% *vs.* 16.7%, all $P < 0.001$). Uptake of sodium-glucose co-transporter-2 inhibitors was only modestly higher in frail patients (8.6% *vs.* 6.8%, $P = 0.036$), while nitrates were slightly less used (94.1% *vs.* 96.9%, $P < 0.001$). Consistent with the greater baseline prevalence of atrial fibrillation, frail patients also received non-vitamin K antagonist oral anticoagulants more often (3.4% *vs.* 1.4%, $P < 0.001$). Collectively, these patterns suggest a shift toward symptom-directed management in frail patients, whereas non-frail patients were more likely to receive guideline-directed secondary prevention. Full details are provided in Table 2.

One-year Outcomes

During one-year follow-up, frail patients experienced substantially higher unadjusted event rates compared with

Table 1 Baseline characteristics of post-AMI HFpEF patients.

Variable	Non-frail group (n = 2768)	Frail group (n = 1739)	SMD	P-value
Demographics				
Age, yrs	64.02 ± 11.70	68.78 ± 11.65	0.408	< 0.001
Male	1912 (69.1%)	1105 (63.5%)	0.117	< 0.001
Body mass index, kg/m^2	25.67 ± 3.51	25.45 ± 3.16	0.070	0.028
Smoking history	826 (29.8%)	563 (32.4%)	0.055	0.041
Clinical features				
Killip class			0.471	< 0.001
I	1115 (40.3%)	421 (24.2%)		
II	1436 (51.9%)	942 (54.2%)		
III	157 (5.7%)	277 (15.9%)		
IV	60 (2.2%)	99 (5.7%)		
LVEF, %	59.36 ± 4.61	58.70 ± 4.65	0.144	< 0.001
Acute respiratory failure	17 (0.6%)	135 (7.8%)	0.363	< 0.001
Comorbidities				
Hypertension	1669 (60.3%)	1267 (72.9%)	0.269	< 0.001
Diabetes mellitus	940 (34.0%)	701 (40.3%)	0.132	< 0.001
Atrial fibrillation	239 (8.6%)	260 (15.0%)	0.197	< 0.001
Peripheral vascular disease	193 (7.0%)	249 (14.3%)	0.240	< 0.001
Cerebrovascular disease	275 (9.9%)	851 (48.9%)	0.947	0.002
Chronic lung disease	232 (8.4%)	194 (11.2%)	0.094	0.002
Gastrointestinal bleeding	54 (2.0%)	68 (3.9%)	0.116	< 0.001
Malignancy	52 (1.9%)	62 (3.6%)	0.104	0.001
Connective tissue disease	6 (0.2%)	11 (0.6%)	0.064	0.049
Chronic kidney disease	66 (2.4%)	203 (11.7%)	0.37	< 0.001
Liver disease	11 (0.5%)	36 (2.1%)	0.14	< 0.001
Prior percutaneous coronary intervention	77 (2.8%)	84 (4.8%)	0.104	0.003
Prior coronary artery bypass grafting	6 (0.2%)	4 (0.2%)	0.003	0.912
Laboratory measurements				
N-terminal pro-B-type natriuretic peptide, pg/mL	685.1 (294–1632)*	1198.0 (323.6–1917)*	0.47	< 0.001

Data are presented as means ± SD or n (%). *Presented as median (interquartile range). AMI: acute myocardial infarction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; SMD: standardized mean difference.

non-frail patients (Table 3). The incidence of all-cause death was 9.0% in the frail group versus 2.9% in the non-frail group, and NACE occurred in 19.8% versus 13.7%, respectively (both P < 0.001). Cardiovascular death was also more frequent in frail individuals (5.2% *vs.* 2.9%, P < 0.001). The incidence of myocardial infarction was also slightly higher in frail patients (6.3% *vs.* 4.8%, P = 0.038), whereas revascularization showed no significant between-group differences (7.4% *vs.* 7.8%, P = 0.612). MACE (12.4% *vs.* 10.9%, P = 0.082) and HF rehospitalization (11.2% *vs.* 10.5%, P = 0.284) likewise showed no significant between-group differences.

After multivariable adjustment, frailty remained independently associated with all-cause mortality (aHR = 1.52, 95% CI: 1.31–2.03, P = 0.005) and NACE (aHR = 1.20, 95% CI: 1.02–1.41, P = 0.026). By contrast, associations with cardiovascular death (aHR = 1.42, 95% CI: 0.99–2.02, P = 0.053), MACE (aHR = 1.05, 95% CI: 0.86–1.28, P = 0.636), and HF rehospitalization (aHR = 0.94, 95% CI: 0.75–1.19, P = 0.616) were not statistically significant. These adjusted results are summarized in Figure 1.

Table 2 In-hospital treatments.

Variable	Non-frail group (*n* = 2768)	Frail group (*n* = 1739)	SMD	*P*-value
Antiplatelet therapy				
Aspirin	2665 (96.3%)	1533 (88.2%)	0.307	< 0.001
$P2Y_{12}$ inhibitors	2730 (98.6%)	1644 (94.5%)	0.227	< 0.001
Neurohormonal blockade				
Beta-blockers	2308 (83.4%)	1372 (78.9%)	0.115	< 0.001
Angiotensin-converting enzyme inhibitor/Angiotensin II receptor blocker	2347 (84.8%)	1391 (80.0%)	0.126	< 0.001
Spironolactone	1201 (43.4%)	951 (54.7%)	0.227	< 0.001
Diuretics				
Loop diuretics	1647 (59.5%)	1291 (74.2%)	0.317	< 0.001
Thiazide diuretics	1745 (63.0%)	1343 (77.2%)	0.314	< 0.001
Other agents				
Statins	2726 (98.5%)	1662 (95.6%)	0.172	< 0.001
Calcium-channel blockers	461 (16.7%)	421 (24.2%)	0.188	< 0.001
Sodium-glucose co-transporter-2 inhibitors	189 (6.8%)	149 (8.6%)	0.065	0.036
Nitrates	2681 (96.9%)	1637 (94.1%)	0.132	< 0.001
Non-vitamin K antagonist oral anticoagulants	38 (1.4%)	59 (3.4%)	0.133	< 0.001

Data are presented as *n* (%). SMD: standardized mean difference.

Table 3 One-year clinical outcomes in frail and non-frail patients after AMI with HFpEF.

Outcomes	Non-frail group (*n* = 2768)	Frail group (*n* = 1739)	SMD	*P*-value
All-cause death	81 (2.9%)	156 (9.0%)	0.258	< 0.001
Cardiovascular death	55 (2.0%)	104 (6.0%)	0.205	< 0.001
Myocardial infarction	134 (4.8%)	110 (6.3%)	0.065	0.038
Revascularization	209 (7.6%)	142 (8.2%)	0.023	0.488
MACE	204 (7.4%)	272 (15.6%)	0.261	< 0.001
NACE	379 (13.7%)	344 (19.8%)	0.164	< 0.001
Heart failure rehospitalization	162 (5.9%)	187 (10.8%)	0.178	< 0.001

Data are presented as *n* (%). AMI: acute myocardial infarction; HFpEF: heart failure with preserved ejection fraction; MACE: major adverse cardiovascular events; NACE: net adverse clinical events; SMD: standardized mean difference.

DISCUSSION

In this large multicenter retrospective cohort of 4507 post-AMI HFpEF patients, frail individuals exhibited consistently higher crude event rates compared with their non-frail counterparts. These unadjusted differences were reinforced by multivariable Cox regression analyses, which identified frailty, measured by the HFRS, as an independent predictor of adverse outcomes. Specifically, frailty was associated with an increased risk of all-cause mortality and NACE, whereas its associations with cardiovascular death, MACE, and HF rehospitalization were not statistically significant. This pattern suggests that frailty may exert its strongest influence through systemic vulnerability and multi-organ stress rather than through strictly cardiovascular pathways, aligning with the increasingly recognized concept that HFpEF is a systemic syndrome. The disproportionately higher burden of comorbidities such as cerebrovascular disease and acute respiratory failure among frail patients may partly account for this excess risk.

Our findings are broadly consistent with previous literature. Pandey, *et al.*[9] demonstrated a 1.4- to 1.8-fold increased mortality risk in frail HFpEF patients independent of age and comorbidities, and Segar, *et al.*[10] similarly reported that frailty nearly doubled the risk of death in older HF cohorts. In contrast, Mentz, *et al.*[5] identified frailty as a pr-

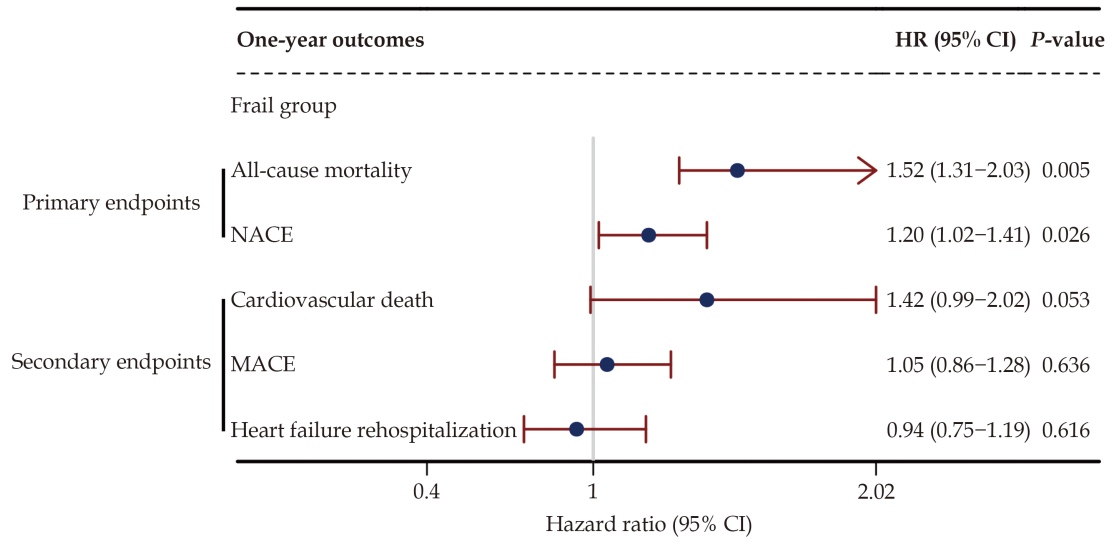

Figure 1 Adjusted hazard ratios for one-year outcomes according to frailty status in patients with HFpEF after AMI, derived from multivariable Cox regression analysis. AMI: acute myocardial infarction; HFpEF: heart failure with preserved ejection fraction; MACE: major adverse cardiovascular events; NACE: net adverse clinical events.

edictor of both mortality and HF hospitalization. These discrepancies may reflect differences in frailty tools, healthcare systems, patient characteristics, and population comorbidity profiles. Importantly, our cohort consisted of patients with HFpEF following AMI, a subgroup in which acute injury superimposed on chronic diastolic dysfunction may amplify the influence of systemic frailty, possibly explaining why all-cause mortality showed stronger associations than cardiovascular-specific outcomes.

Mechanistic studies further support the plausibility of these findings. Elevated inflammatory cytokines and impaired mitochondrial function in frail HFpEF patients have been linked to reduced functional capacity and worse prognosis.[11–13] Chronic low-grade inflammation promotes endothelial dysfunction and myocardial fibrosis,[14] while sarcopenia and impaired muscle–heart axis regulation contribute to diminished exercise tolerance and increased hemodynamic stress.[15] Metabolic abnormalities such as insulin resistance and mitochondrial dysfunction further exacerbate the HFpEF phenotype.[16,17] Neurohormonal dysregulation, including heightened sympathetic activity and renin-angiotensin-aldosterone system activation, worsens myocardial remodeling and may reduce tolerance to standard therapies.[18,19] In the post-AMI setting, these systemic deficits may limit physiological reserve and predispose frail patients to multi-organ complications, infectious events, and functional decline, which may contribute more to early mortality than recurrent cardiovascular events alone.

Treatment patterns differed markedly between groups, with frail patients more often receiving symptom-oriented therapies (e.g., spironolactone, loop diuretics, calcium-channel blockers, nitrates) and non-frail patients more frequently prescribed guideline-directed therapies such as aspirin and statins. This suggests that frailty may influence real-world prescribing through medication intolerance, polypharmacy concerns, and clinician risk–benefit judgments. Although all GDMT variables were included in the multivariable models, treatment-related confounding cannot be fully excluded due to unmeasured clinical factors.

LIMITATIONS

The strengths of this study include its large sample size across 82 hospitals, the use of a validated and standardized frailty measure, and comprehensive adjustment for major confounders. Nonetheless, several limitations should be acknowledged. The retrospective design may leave residual confounding from unmeasured factors such as socioeconomic and nutritional status. The HFRS primarily captures physical frailty and may not reflect cognitive or psychosocial domains assessed by other instruments.[20,21] In addition, the study population was derived from Chinese hospitals, which may limit generalizability to other regions. Although all GDMT variables were included in the multivariable models, some treatment-related confounding due to clinical tolerance or physician decision-making may still remain. In particular, frail patients may have had more contraindications or reduced tolerance to certain therapies,

and these clinical considerations were not fully captured in our dataset, so residual treatment-related confounding cannot be entirely excluded. Finally, heterogeneity in medication use and adherence, particularly with newer therapies such as sodium-glucose co-transporter-2 inhibitors, could have influenced outcomes.

Clinically, these findings suggest that frailty assessment should be incorporated into post-AMI care pathways for HFpEF patients to enhance risk stratification and guide individualized management. In practical terms, frailty can be screened at discharge using the HFRS, which requires no additional testing and can be extracted directly from routine clinical data. Patients identified as frail may benefit from closer follow-up, medication tolerance checks, and earlier involvement of geriatrics, rehabilitation, or nursing support. Importantly, several components reflected in higher HFRS scores, such as anemia, infections, dehydration, mobility impairment, or polypharmacy, are potentially modifiable, providing a clinical rationale for frailty-adapted management rather than treating frailty as a fixed trait. Using frailty status to guide decisions, such as setting more cautious therapeutic targets or prioritizing functional recovery, may help clinicians anticipate problems that are not captured by cardiovascular parameters alone. Beyond cardiovascular therapies, attention to frailty-related vulnerabilities, such as sarcopenia, polypharmacy, and cognitive decline, may be essential for improving outcomes. Future research should explore targeted frailty interventions, such as multimodal rehabilitation and nutritional support, and mechanistic studies integrating multi-omics approaches to better elucidate pathways linking frailty and HFpEF progression.[22]

CONCLUSIONS

In conclusion, frailty is a powerful and independent determinant of one-year all-cause mortality and NACE in patients with HFpEF following AMI. By capturing systemic vulnerability beyond conventional cardiovascular risk factors, frailty provides critical prognostic information and supports a shift toward holistic, patient-centered models of care. Future work should aim to integrate frailty into routine clinical practice and develop targeted interventions to mitigate its adverse impact.

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