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Review

# Frailty for predicting all-cause mortality in elderly acute coronary syndrome patients: A meta-analysis

Changfeng Man, Shouyan Xiang, Yu Fan*

*Institute of Molecular Biology & Translational Medicine, The Affiliated People's Hospital, Jiangsu University, Zhenjiang, Jiangsu, 212002, China*

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ABSTRACT

*Background:* Frailty has been identified as a risk factor for mortality in patients with acute coronary syndrome (ACS). This meta-analysis aimed to evaluate the association between frailty and all-cause mortality outcome in patients with ACS.

*Methods:* Pubmed and Embase databases were searched up to September 26, 2018 for the observational studies evaluating the association between frailty and all-cause mortality in elderly ACS patients. Outcome measures were in-hospital death, short-term all-cause mortality (≤6 months),and long-term all-cause mortality (≥12 months).The impact of frailty on all-cause mortality was summarized as hazard ratios (HR) with 95% confidence intervals (CI) for the frail versus nonfrail patients.

*Results:* A total of 9 cohort studies involving 2475 elderly ACS patients were included. Meta-analysis showed that ACS patients with frailty had an increased risk of in-hospital death (HR 5.49; 95% CI 2.19–13.77), short-term all-cause mortality (HR 3.56; 95% CI 1.96–6.48), and long-term all-cause mortality (HR 2.44; 95% CI 1.92–3.12) after adjustment for confounding factors. In addition, prefrailty was also associated with an increased all-cause mortality (HR 1.65; 95% CI 1.01–2.69).

*Conclusions:* This meta-analysis demonstrates that frailty independently predicts all-cause mortality in elderly ACS patients. Elderly ACS patients should be assessed the frailty status for improving risk stratification.

## 1. Introduction

Acute coronary syndrome (ACS) encompasses a wide spectrum of ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), and unstable angina (Grech and Ramsdale, 2003). Elderly subjects over 75 years old represent a large proportion of patients hospitalized for ACS (McManus et al., 2011). Despite remarkable progress in medical care, ACS still causes greater morbidity and mortality among older patients (Veerasamy et al., 2015). As for elderly ACS patients had a worse prognosis than younger patients (Rosengren et al., 2006), risk stratification therefore is of paramount importance in this group of patients.

Frailty is a biological syndrome associated with ageing, characterized by weakness and decreased physiologic reserve (Bergman et al., 2007; Clegg et al., 2013). Estimates of frailty's prevalence among the general population aged 65 years and older ranged from 4.0%–59.1% (Collard et al., 2012). Frail older patients are at high risk for adverse outcomes in different specific medical conditions (Ritt et al., 2016). Frailty is also playing an important role in clinical risk stratification of ACS patients (Singh et al., 2014). Findings from observational studies have linked the frailty and all-cause mortality in elderly ACS patients (Bebb et al., 2018). However, no previous meta-analysis has thoroughly evaluated the association between the frailty and all-cause mortality in elderly patients with ACS. Nevertheless, the magnitude of prognostic value of frailty in these patients varied considerably due to different clinical settings.

Therefore, the aim of this meta-analysis was to evaluate the prognostic value of frailty among the elderly ACS patients in terms of in-hospital death, short-term all-cause mortality, and long-term all-cause mortality.

## 2. Methods

### 2.1. Literature search

This meta-analysis was conducted according to the checklists of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). A systematic literature

* Corresponding author at: Institute of Molecular Biology & Translational Medicine, The Affiliated People's Hospital, Jiangsu University, No. 8 Dianli Road, 212002, ZhenJiang, China.
*E-mail address:* jszjfanyu@163.com (Y. Fan).

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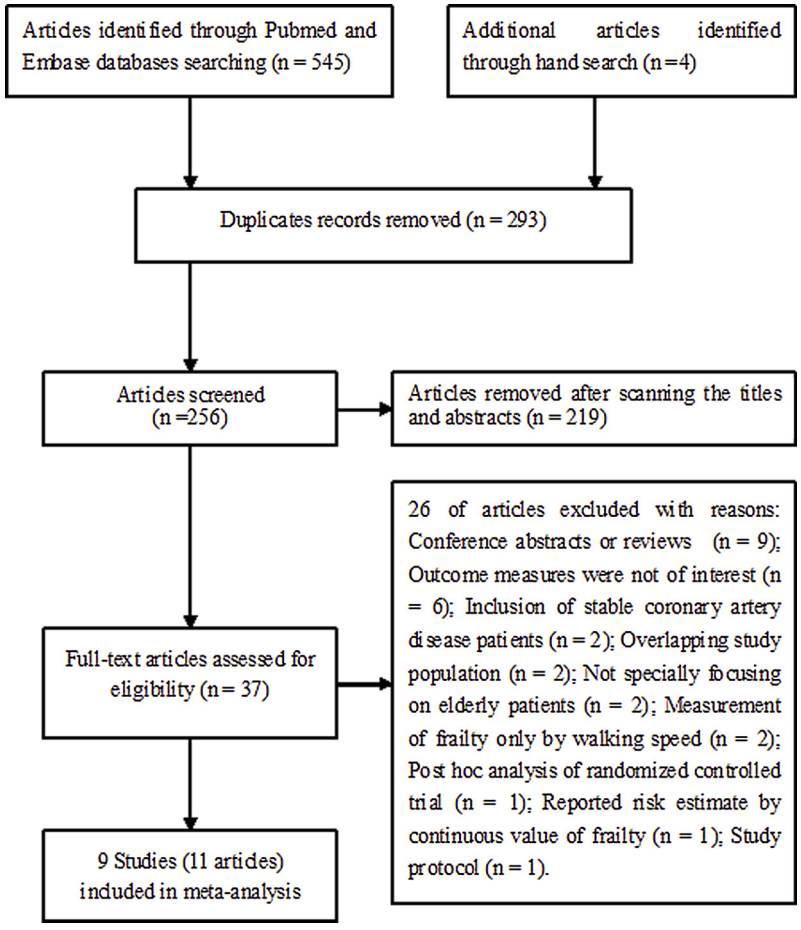


**Fig. 1.** Flow chart of studies selection process.

search was performed in Pubmed and Embase databases from their inception to October 1, 2018. The following keywords or Medical Subjective Headings were used for literature search: "frailty" AND "acute coronary syndrome" OR "unstable angina" OR "acute myocardial infarction" AND "mortality" OR "death". Additionally, reference lists of relevant article were also hand searched for any additional studies.

### 2.2. Study selection

Two authors independently searched the literature and evaluated the studies for eligibility. Disagreements were settled through discussion with a third author. Eligible studies should be satisfied the following inclusion criteria: 1) observational study design; 2) elderly patients (aged 65 years or older) with a diagnosis of ACS; 3) frailty defined by a validated method as exposure; and 4) reported adjusted hazard ratios (HR), risk ratio (RR) or odds ratios (OR) with 95% confidence intervals (CI) for all-cause mortality. According to the follow-up period, mortality was classified as in-hospital death, short-term all-cause mortality ($\leq$6 months), and long-term all-cause mortality ($>$ 12 months). Studies were excluded if: 1) post hoc analysis of randomized controlled trial; 2) measurement of frailty only by single domain items; and 3) reported risk estimate by continuous value of frailty.

### 2.3. Data extraction and quality assessment

Data from included studies were abstracted into a predefined standardized table. The extracted data included: last name of first author, year of publication, study design, origin of study, number of patients, proportion of men, type of ACS, age range, definition of frailty, prevalence of frailty, number of death events, fully adjusted risk estimate, follow-up period, adjustment for variables. Study quality was evaluated by two authors using a 9-star Newcastle-Ottawa Scale for cohort studies independently (Wells et al., 2018). High-quality studies were graded as those meeting 7 stars. Any disagreements in data extraction and quality evaluation were settled through discussion with a third author.

### 2.4. Data synthesis

All meta-analyses were conducted using Stata version12.0 (Stata Corporation, College Station, TX). Data analyses used most fully adjusted risk estimate. Patients were categorized as non-frail, pre-frail or frail. The effect of frailty on all-cause mortality was summarized by HR with 95% CI for the prefrail/frail versus non-frail group. Heterogeneity across studies was determined using the $I^2$ statistics and Cochran Q test. Value of $I^2$ statistics $\geq$50% or Cochran Q test $p < 0.10$ is considered to reflect significant heterogeneity. A random effects model was used when significant heterogeneity was found; otherwise, we selected a fixed-effect model. Subgroup analyses were conducted by follow-up duration (in-hospital versus short-term all-cause versus long-term mortality). Publication bias test was planned using the Begg's rank correlation (Begg and Mazumdar, 1994) and Egger's linear regression test (Egger et al., 1997). Sensitivity analyses were performed by removing individual study each time to explore the impact of each study on the overall risk estimate.

**Table 1**
Main characteristics of the included studies.

| Author./year | Region | Study design | Sample size (% men) | Type of ACS | Age (years) | Frailty criteria | Prevalence of frailty | Event number HR(95% CI) | Follow-up period | Variables adjustment | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Graham (2013) | Canada | Prospective cohort | 183 (67.2) | ACS | ≥65 | Edmonton Frail Scale | 30.0% | Total death:13 3.49 (1.08–7.61) F 1.31 (0.55–3.13) Pre | Up to 3 years | Mean burden of illness score | 6 |
| Sanchis 2014 | Spain | Prospective cohort | 342 (57) | ACS | ≥65 | Green score | 48% | Total death:74 3.4 (1.8–6.2) | 2.5 years | Age, sex, smoking, hypertension, DM, LVEF, WBC, hypercholesterolemia, MI, CAG, stroke, PAD, coronary surgery, use of anti-platelet drugs or statins, SBP, DBP, eGFR, HR, Killip class, troponin, hemoglobin, electrocardiogram, and invasive management | 8 |
| Sujino 2015 | Japan | Retrospective | 62 (58.1) | STEMI | ≥85 | CSHA-CFS | 35.5% | Total death:14 6.38 (1.21–44.7) | In-hospital | Age, BMI, WBC, albumin, primary PCI, Killip class, troponin, mechanical ventilation and blood transfusion. | 6 |
| Kang 2015 | China | Prospective cohort | 352 (57.7) | ACS | ≥65 | CFS (Rockwood) | 43.18% | Total death:18 5.39 (1.48–19.7) | 4 months | Age, gender, severity of coronary artery diseases, and co-morbidities | 7 |
| Alonso Salinas 2016 | Spain | Prospective, observational | 202 (60) | ACS | ≥75 | SHARE-FI | 35.1% | Total death:7 12.1 (1.4–103); 3.07(1.35–6.98)* | In-hospital | Age, gender, creatinine, GRACE index and DM | 7 |
| Blanco 2017 | France | Prospective cohort | 236 (51.7) | ACS | ≥80 | Edmonton Frail Scale | 20.8% | Total death:75 2.85 (1.19–6.82) F; 1.39 (0.64–3.01) Pre | 1.3 years | Age, sex, LVEF, severe renal failure, cardiogenic shock at admission; history of vascular disease, NYHA class, BMI, hemoglobin, statin, troponin, CAG, history of HF, and dual-antiplatelet therapy | 8 |
| Alegre 2018 | Spain | Prospective cohort | 532 (61.7) | ACS | ≥80 | FRAIL scale | 27.3% | Total death:63 2.99 (1.20–7.44) F; 2.71 (1.09–6.73) Pre | 6 months | Age, DM, previous stroke, HF, or depression, chronic treatments, troponin, HR, Killip class, hemoglobin, eGFR, LVEF, GRACE score, and CRUSADE score | 7 |
| Calvo 2018 | Spain | Prospective, observational | 259 (57.9) | STEMI | ≥75 | FRAIL scale | 19.7% | Total death:18 3.96 (1.16–13.56) | In-hospital | Age, DM, previous HF, depression, Killip class, LVEF, coronary arteries diseased number, mitral regurgitation, Barthel index, Lawton–Brody index, and Charlson index | 7 |
| Ekerstad 2018 | Sweden | Prospective, observational | 307 (51.1) | NSTEMI | ≥75 | CFS (Rockwood) | 48.5% | Total death:213 2.06 (1.51–2.81); 3.43(1.25–9.36) # | 6.7 years | CAD index score and cardiovascular risk | 8 |

Abbreviations: HRhazard ratio; CIconfidence intervals; Ffrailty; Preprefrailty; BMIbody mass index; DMdiabetes mellitus; ACSacute coronary syndrome; MImyocardial infarction; STEMIST segment elevated myocardial infarction; NSTEMInon-ST-elevation myocardial infarction; CFSClinical Frailty Scale; CSHA-CFSCanadian Study of Health and Aging Clinical Frailty Scale; SHARE-FISurvey of Health, Ageing and Retirement in Europe – Frailty Index; HFheart failure; CAGcoronary angiography; WBCwhite blood cell; PADperipheral arterial disease; GRACEGlobal Registry of Acute Coronary Events; LVEFleft ventricular ejection fraction; HRheart rate; SBPsystolic blood pressure; DBPdiastolic blood pressure; eGFRestimated glomerular filtration rate; NOSNewcastle-Ottawa Scale. #≤6 months data from Ekerstad et al. (2014) 24; *≥12 months data from Alonso Salinas 2018 [25].

## 3. Results

### 3.1. Search results and studies characteristics

Our initial electronic literature search yielded 545 potentially relevant articles. Four articles were identified through hand search. After scanning the titles and abstracts, 512 articles were excluded mainly due to duplicate publication or not irrelevant. Thus, 37 articles were retrieved for detailed evaluation. After assessment of full-text manuscript, 26 articles were further removed with various reasons. Finally, a total of 9 cohort studies from 11 articles (Alegre et al., 2018; Alonso Salinas et al., 2016, 2018; Blanco et al., 2017; Calvo et al., 2018; Ekerstad et al., 2018, 2014; Graham et al., 2013; Kang et al., 2015; Sanchis et al., 2014; Sujino et al., 2015) included in the meta-analysis. Fig. 1 shows the flow diagram of studies selection process.

Main characteristics of the included studies are summarized in Table 1. From these included studies 2475 elderly ACS patients were identified and analyzed. Sample sizes of individual studies ranged from 183 to 532. These studies were performed in Spain (Alegre et al., 2018; Alonso Salinas et al., 2016; Calvo et al., 2018; Sanchis et al., 2014), Sweden (Ekerstad et al., 2018), Canada (Graham et al., 2013), France (Blanco et al., 2017), China (Kang et al., 2015), and Japan (Sujino et al., 2015). Follow-up duration was up to 6.7 years. Six studies (Alegre et al., 2018; Alonso Salinas et al., 2016; Blanco et al., 2017; Graham et al., 2013; Kang et al., 2015; Sanchis et al., 2014) conducted in ACS patients, two studies (Calvo et al., 2018; Sujino et al., 2015) in STEMI patients, and one study (Ekerstad et al., 2018) in NSTEMI. The following definitions of frailty were used: FRAIL scale (Alegre et al., 2018; Calvo et al., 2018), Clinical Frailty Scale (Ekerstad et al., 2018; Kang et al., 2015; Sujino et al., 2015), Edmonton Frail Scale (Blanco et al., 2017; Graham et al., 2013), Green score (Sanchis et al., 2014), or Survey of Health, Ageing and Retirement in Europe- Frailty Index (Alonso Salinas et al., 2016). The prevalence of frailty ranged from 19.7 to 48.5%. The total NOS of the included studies ranged from 6 to 8 stars (Supplemental Table S1).

### 3.2. Association between frailty and all-cause mortality

All the included studies reported all-cause mortality outcomes in frail versus nonfrail patients. As shown in Fig. 2, meta-analysis showed that frailty was associated with an increased risk of in-hospital mortality (HR 5.49; 95%CI 2.19–13.77; $I^2$ = 0%; $p$ = 0.665), short-term all-cause mortality (HR 3.56; 95% CI 1.96–6.48; $I^2$ = 0%; $p$ = 0.763), and long-term all-cause mortality (HR 2.44; 95% CI 1.92–3.12; $I^2$ = 0%; $p$ = 0.527) in a fixed-effect model, without evidences of significant heterogeneity. The sensitivity analysis showed that the pooled risk estimates remained reliable after removal of anyone study at each time. Publication bias test was not performed due to less than recommended arbitrary number of studies analyzed (Lau et al., 2006).

### 3.3. Association between prefrailty and all-cause mortality

Three studies (Alegre et al., 2018; Blanco et al., 2017; Graham et al., 2013) reported the association between prefrailty and all-cause mortality. As shown in Fig. 3, meta-analysis indicated that prefrailty was associated with an increased risk of all-cause mortality (HR 1.65; 95% CI 1.01–2.69) in a fixed-effect model, without evidences of significant heterogeneity ($I^2$ = 0%; $p$ = 0.449).

## 4. Discussion

The main findings of this meta-analysis are that frailty is an independent predictor of in-hospital death and follow-up all-cause mortality in elderly ACS patients. The reported prevalence of frailty ranged from 19.7%–48.5%. Elderly ACS patients with frailty had an 5.49-fold higher risk of in-hospital death, 3.56-fold higher risk of short-term mortality, and 2.39-fold higher risk of long-term mortality. In addition, elderly ACS patients with prefrailty increased by 1.65-fold higher all-cause mortality risk. This meta-analysis further consolidates the growing evidence for use of frailty in risk stratification of elderly patients with ACS.

An important concern of interpreting these results is the various methods of frailty assessment.The phenotype model (Fried et al., 2001) and multiple deficits model (Rockwood et al., 2005) are the two well-established international frailty models. However, there was no consensus on a definition of frailty. The phenotype model determines frailty on the following physical characteristics: weight loss; exhaustion; low energy expenditure; slow gait speed; and reduced grip strength. However, use of a single domain or multi-domain frailty tools in ACS patients showed similar predictive value. As a component of the

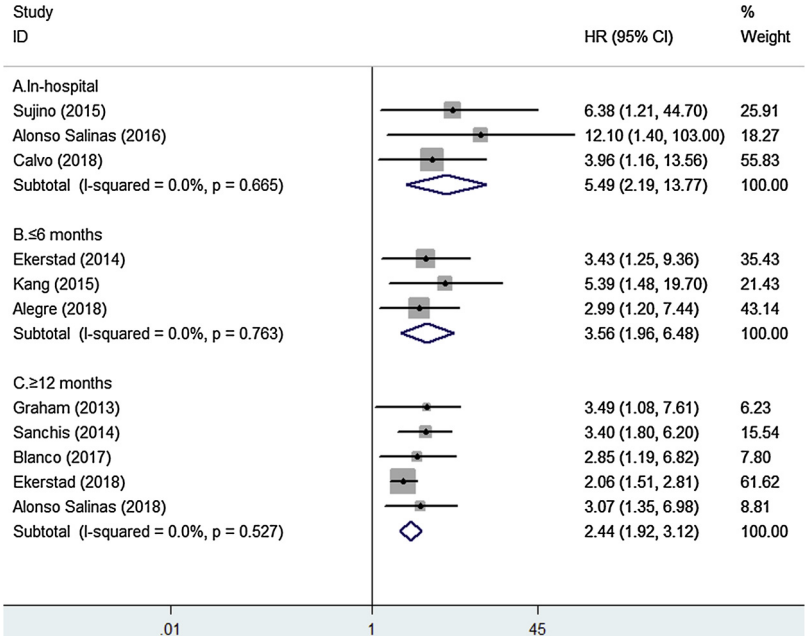


**Fig. 2.** Forest plots showing the effect of frailty on all-cause mortality stratified by the follow-up duration.

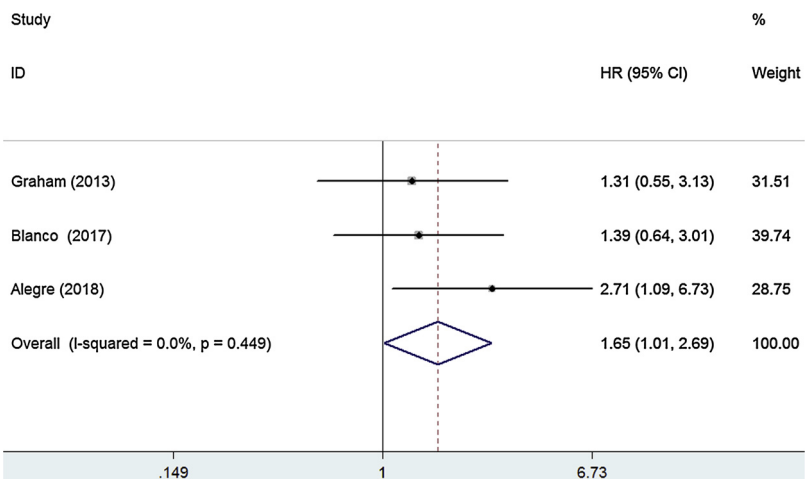


**Fig. 3.** Forest plots showing the effect of prefrailty on all-cause mortality.

five frailty phenotype diagnostic criteria, slow gait speed has been shown to be associated with an increased risk of cardiovascular events in patients after STEMI (Matsuzawa et al., 2013).

In line with our meta-analysis, previous meta-analytical studies have confirmed that frailty increased mortality in cardiac patients undergoing percutaneous coronary intervention (Tse et al., 2017) and those undergoing transcatheter aortic valve implantation (Anand et al., 2017). Additionally we did not include a hoc analysis of randomized controlled trial (White et al., 2016) from our analysis. In this study, elderly NSTEMI patients with frailty based upon the Fried score had an 1.98-fold higher risk of all-cause mortality when compared with not-frail patients. In relatively younger (mean age 55 years) myocardial infarction population, patients in the frailest group ($\geq 0.25$) at baseline had twice all-cause mortality risk than those in the least frail group ($< 0.1$) over 13 years of follow up. This finding indicated that identification of frailty among younger ACS patients may also improve clinical decision-making.

ACS patients represent a heterogeneous clinical group. However, evidence for managing elderly ACS patients is especially limited. Elderly ACS patients were less likely to receive evidence based therapies (Zaman et al., 2014). As for frailty is dynamic and potentially reversible (Morley et al., 2013), all elderly ACS patients should be assessed for frailty status. Frailty evaluation in ACS patients has potential to improve preventive interventions. However, frailty has not yet achieved the formal guideline recommendations as a strong risk factor for adverse outcomes in patients with ACS. This meta-analysis highlights the important aspects of clinical guidelines regarding frailty management to improve in-hospital and long-term outcomes among elderly ACS patients. To translate this evidence into specific recommendations in guidelines, there is an undisputable need to evaluate frailty in randomized controlled trials among these high risk patients.

Several potential limitations in our meta-analysis should be pointed out. First, despite no significant heterogeneity detected by $I^2$ statistics and Cochran Q test, inherent clinical heterogeneity was present because of adoption of various frailty assessment tools. Nevertheless, there were different severities of ACS (represented by peak creatine kinase or Killip class) and ranges of age (the definition of elderly varied substantially). Second, included patients were whole spectrum of ACS and therefore prognostic significance of frailty in STEMI, NSTEMI and unstable angina patients should be confirmed in future studies. Finally, we failed to perform subgroup analysis and publication bias test due to the small number of studies analyzed.

## 5. Conclusions

This meta-analysis provided preliminary evidence that elderly ACS patients with frailty had an increased risk of all-cause mortality, even after adjustment for conventional confounding factors. Therefore, determination of frailty has potential to improve risk stratification among elderly ACS patients and help in the clinical decision-making process. Given the higher morbidity and mortality among elderly ACS patients, more studies are warranted addressing the association cardiovascular mortality and other health outcomes.

## Conflict of interest

None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.03.003.

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