review article

Wien Klin Wochenschr (2020) 132:301–309
https://doi.org/10.1007/s00508-020-01650-9

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Frailty as a predictor of all-cause mortality and readmission in older patients with acute coronary syndrome

A systematic review and meta-analysis

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Received: 16 October 2019 / Accepted: 28 March 2020 / Published online: 27 April 2020

Summary
Background Evidence from longitudinal studies linking frailty and outcome after acute coronary syndrome (ACS) is mixed. This systematic review and meta-analysis aimed to examine whether frailty is a predictor of all-cause mortality and hospital readmission in older patients with ACS.
Methods A systematic search was carried out in PubMed, EMBASE and Web of Science databases for studies evaluating the association between frailty and outcomes in older patients with ACS. A meta-analysis was performed to determine the pooled effect estimate for the association between frailty and mortality and hospital readmission, respectively.
Results A total of 1459 articles were retrieved based on our search strategy. Fifteen studies involving 10,245 patients were included in the meta-analysis. The pooled prevalence of frailty was 32% (95% confidence interval [CI]: 25–39%), and the pooled prevalence of pre-frailty was 33% (95% CI: 26–40%) in elderly patients with ACS. Pooled analyses showed that frailty was associated with significantly higher risk of all-cause mortality and readmission (hazard ratios [HRs] = 2.43 and 2.32, respectively). Pre-frailty was also associated with significantly higher risk of all-cause mortality and readmission, respectively (HRs = 1.55 and 1.34, respectively).
Conclusions Both frailty and pre-frailty are risk factors for all-cause mortality and readmission in older patients with ACS. Therefore, frailty assessment should be given sufficient attention in the management of older patients with ACS to help improve survival and reduce readmission rate.

Keywords Frailty · Predictor · Acute coronary syndrome · Meta-analysis · Outcomes

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00508-020-01650-9) contains supplementary material, which is available to authorized users.

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Introduction

Frailty—a clinical syndrome characterized by reduced reserve and increased vulnerability to stressors— is associated with numerous adverse outcomes including falls, cognitive impairment, hospitalization, disability, and mortality [1]. Frailty develops as a consequence of age-related decline across multiple physiological systems. The prevalence of frailty increases rapidly with advancing age. As life expectancy is becoming longer, there will be an increasing number of frail older adults.

Ischemic heart disease (IHD) is the leading cause of death worldwide. According to the latest global burden of disease (GBD) study [2], about 9.48 million people died from IHD in 2016. Acute coronary syndrome (ACS) accounts for a large proportion of IHD deaths. Among the ACS patients admitted to hospital, more than half are older adults [3]. Moreover, about

10% of aged >65 years and more than 25% of those aged >85 years are considered frail [4, 5]. And that means a fair amount of ACS patients are prone to be frail.

An increasing number of studies have examined how frailty interplays with the provision of treatment and subsequent clinical outcomes among patients with ACS; however, evidence from longitudinal studies linking ACS and frailty is inconsistent and sample sizes of many studies were very small [6–10]. Demonstrating the value of frailty status for predicting mortality and hospital readmission among older ACS patients would be useful in making informed decisions about the treatment and management procedures.

In the present study a systematic review and meta-analysis were conducted to determine the association of frailty and adverse outcomes among older patients with ACS.

Methods

Search strategy

We conducted our systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11] and systematically searched the PubMed, Embase and Web of Science databases until 1 December 2018 for relevant studies using the following keywords and their variations: “frailty”, “ACS” and “acute coronary syndrome”. Additionally, we examined reference lists of included studies and reviews to find other relevant articles did not apply any language restrictions.

Eligibility criteria

Original research articles were included if they met the following criteria: (1) cohort studies; (2) study population was ACS patients, defined as acute myocardial infarction (either ST-segment elevation or non-ST-segment elevation) or unstable angina and (3) investigating the association between frailty and adverse outcomes among older patients with ACS. All titles and abstracts were reviewed by two reviewers (WX and YC) and potentially eligible studies were retrieved. These articles were reviewed in full-text reading according to the predefined eligibility criteria. Reference lists of articles passing the title and abstract screen were reviewed to identify additional articles.

Data extraction

Two investigators (WX and YC) independently extracted data on year of publication, study period, study design, operational definition of frailty, study population, sample size, follow-up duration, outcomes, and covariates adjusted in the multivariable models. Only multivariate adjusted hazard ratios (HR) with 95% confidence intervals (CI) were extracted and combined in the meta-analyses. Any disagreement was resolved by consensus.

Quality assessment

We used the Newcastle-Ottawa scale for observational study to assess the quality of all included studies [12]. Quality scores ranged from 0 to 9 points, with higher scores indicating better quality. Quality assessment was independently performed by two investigators (WX and YC). Any disagreement was resolved by consensus.

Outcomes of interest in this study

The primary outcome was all-cause mortality. Secondary outcome was readmission after discharge from hospital.

Statistical analysis

Both fixed effect and random effects models were used to evaluate the pooled HR for the association between frailty and adverse outcomes among older patients with ACS. Although both models yielded similar findings, results from the random effects model presented here assume that the true underlying effect varies among the included studies [13]. The proportion of inconsistency across included studies not explained by chance was evaluated by the I^2 statistic. An I^2 statistic >50% indicates the presence of substantial heterogeneity. Heterogeneity of included studies was assessed by the chi-square test. A $P<0.10$ for the χ^2-testindicates statistically significant heterogeneity [14]. We conducted subgroup analyses for all-cause mortality by study design, study design (prospective or retrospective), operational definition of frailty, population, sample size (>300 or <300), and follow-up period (>9 months or <9 months) to investigate potential source of heterogeneity. Subgroup analyses of hospital readmission were not conducted due to unavailability of data. We performed sensitivity analyses by excluding one study each time and re-running the analysis to verify the robustness of the overall results. We visually inspected the funnel plot to examine publication bias. Egger’s regression test [15] and Begg’s test [16] were used to statistically assess publication bias. A 2-tailed P-value <0.05 was considered statistically significant. We performed all analyses using Stata software version 12.0 (Stata Corp., College Station, TX, USA).

Results

A total of 1396 publications were identified from the literature search; 53 articles passed the title and abstract screen and 15 articles were included in the present study after full-text reviewing (Fig. 1). Of the

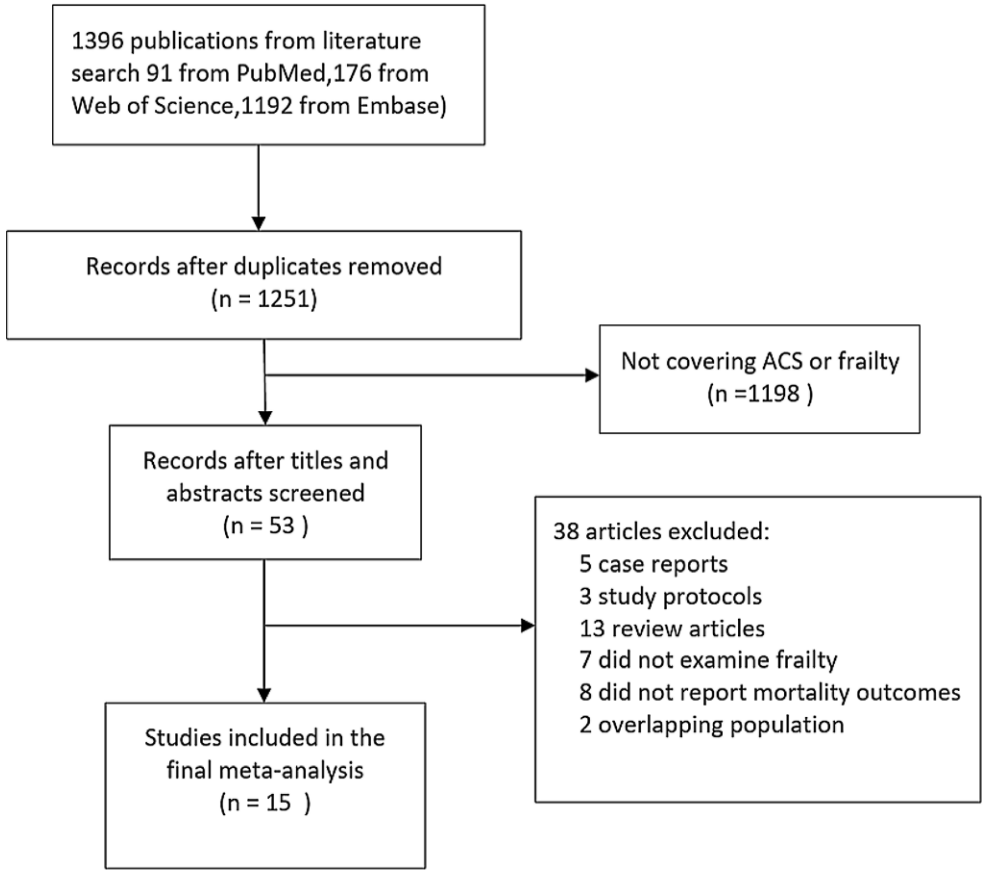

Fig. 1 Flowchart of study selection

38 publications excluded by full-text evaluation, 5 were case reports, 3 were study protocols, 13 were review articles, 7 did not examine frailty, 8 did not report mortality outcomes, and 2 used overlapping populations. A total of 15 studies involving 10,245 ACS patients were included in this meta-analysis. The main characteristics of the included studies are shown in Table 1.

Prevalence of frailty and pre-frailty

All 15 eligible studies reported the prevalence of frailty and 6 studies reported the prevalence of pre-frailty. The pooled prevalence of frailty was 32% (95% CI: 25–39%; Fig. 2). The pooled prevalence of pre-frailty was 33% (95% CI: 26–40%; Fig. 3). There was no evidence of publication bias according to Begg-Mazumdar's and Egger's tests (all $P > 0.05$).

The association between frailty and all-cause mortality

Fourteen studies investigated the association of frailty with all-cause mortality. Of these, 13 studies reported that frailty was associated with significantly higher mortality whereas one did not find a significant association. Results from the meta-analysis showed that the risk of death among older ACS patients who were frail was 2.43 times higher than among the non-frail (95% CI: 1.85–3.20, $P < 0.001$, $I^2 = 84.3\%$; Fig. 4). Egger's regression tests ($P > 0.05$) indicated no publication bias, whereas a small degree of asymmetry was observed from the funnel plot. Results did not change appreciably in the sensitivity analyses. Results of the subgroup analyses are shown in Table 2. We detected significant differences between the groups for all stratified characteristics including study design, operational definition of frailty, population, sample size, and follow-up period. The heterogeneity was substantially reduced after subgroup analysis.

Six studies reported the link between pre-frailty and all-cause mortality. Of these, four reported that pre-frailty was associated with higher mortality whereas two did not find a significant association. Results of the meta-analysis showed that older ACS patients who were prefrail were associated with a 1.55-fold risk of all-cause mortality than those who were non-frail (95% CI: 1.37–1.75, $P < 0.05$; Figure S1). We found a low level of heterogeneity across included studies ($I^2 = 1.0\%$). Begger's funnel plots did not show obvious asymmetry (Kendal Tau value = 1.69, $P = 0.091$), and Egger's test did not support the existence of publication bias ($t = 1.26$, $P = 0.276$). Sensitivity analysis showed that none of the individual studies substantially influenced the pooled HR.

Table 1 Characteristic of the studies included in the meta-analysis

First Author/year	Study design	Frailty definition	Population	Sample size (*n*)	Follow-up (months)	Variables in multivariate model	Quality score
Batty 2018 [9]	Pro	Fried score	NSTEMI	280	12	NA	8
Vicent 2018 [28]	Pro	FRAIL scale	NSTEMI	535	6	Age, GRACE score, beta-blockers, angiotensin-converting enzyme inhibitors	9
Alegre 2017 [28]	Pro	FRAIL scale	NSTEMI	532	6	NA	8
Blanco 2017 [29]	Pro	EFS	Mixed	236	15	Age, sex, left ventricular ejection fraction, hemoglobin level, severe renal failure, history of vascular disease, cardiogenic shock at admission, and statin therapy at discharge	9
Salinas 2017 [8]	Pro	Frailty Index	Mixed	234	6	Age, diabetes, previous myocardial infarction, and GRACE score	9
Sanchis 2017 [30]	Pro	Green	Mixed	342	53	Age, sex, body mass index, dyslipidemia, diabetes mellitus, prior coronary artery bypass graft, Charlson index, prior treatment with antiplatelets and beta-blockers, admission diastolic blood pressure, admission heart rate, electrocardiogram ST-segment deviation, left bundle branch block, troponin elevation, left ventricular systolic function, and GFR	9
Zhang 2016 [31]	Pro	FRAIL scale	NSTEMI	181	3	Sex, age	8
Salinas 2016 [32]	Pro	Frailty Index	Mixed	202	In-hospital	Age, gender, creatinine, GRACE index and diabetes mellitus	8
Kang 2015 [33]	Pro	CSHA-CFS	Mixed	352	4	Sex, age, severity of coronary artery diseases (left main coronary artery lesion or not) and co-morbidities (CAD specific index)	8
White 2015 [34]	Retro	Fried score	NSTEMI	4996	30	Baseline characteristics and GRACE covariates	9
Myers 2014 [35]	Pro	Frailty Index	Mixed	1521	240	Age, sex, socioeconomic variables	9
Sujino 2014 [36]	Retro	CSHA-CFS	STEMI	62	NA	Body mass index, white cell count, hemoglobin, Troponin I, albumin, Killip class >III, primary PCI, mechanical ventilation, inotropes, blood transfusion	7
Ekerstad 2013 [37]	Pro	CSHA-CFS	NSTEMI	307	12	Diabetes mellitus, chronic heart failure, previous cerebrovascular accident/TIA, chronic obstructive pulmonary disease, and renal impairment	9
Graham 2013[38]	Pro	EFS	Mixed	183	12	Burden of illness	9
Matsuzawa 2013 [39]	Pro	Gait Speed	Mixed	472	66	Age, sex, height, weight, current smoking status, hypertension, diabetes mellitus, dyslipidemia, BNP, FRS, comorbidity index, eGFR, Killip class, left ventricular ejection fraction, angiotensin-converting enzyme-inhibitors/angiotensin II receptor blockers, hydroxymethylglutaryl-CoA reductase inhibitors, use of cane or walker, days in bed, days from admission to measurement of gait speed, and number of times of rehabilitation	8

Pro prospective; *Retro* retrospective; *NA* not available; *PCI* percutaneous coronary intervention; *TIA* transient ischemic attack; *GFR* glomerular filtration rate; *BNP* Brain-Type Natriuretic Peptide; *FRS* Framingham risk score; *GRACE* Global Registry of Acute Coronary Events; *CAD* coronary artery disease; *eGFR* estimated glomerular filtration rate

The association between frailty and hospital readmission

6 studies assessed the relationship between frailty and readmission. All of these studies reported higher rates of readmission. The meta-analysis indicated that frailty was associated with a 2.32-fold risk of readmission (95% CI: 1.93–2.80, $P<0.001$, $I^2=0\%$; Fig. 5). Results did not change appreciably in the sensitivity analyses. Visual inspection of the funnel plot revealed no serious publication bias. Begg's (Kendal Tau value = 0.19, $P=0.851$) and Egger's (t = 0.43, $P=0.687$) regression tests indicated no publication bias.

Two studies reported the association of pre-frailty with readmission. One study reported higher rates of readmission and the other one did not report a significant difference in readmission. Pooled analysis showed that pre-frailty was associated with a 1.34-fold risk of readmission (95% CI: 1.19–1.52, $P<0.001$, $I^2=0\%$; Figure S2).

Discussion

In this systematic review and meta-analysis, we synthesized evidence of the association of pre-frailty and frailty with all-cause mortality and hospital read-

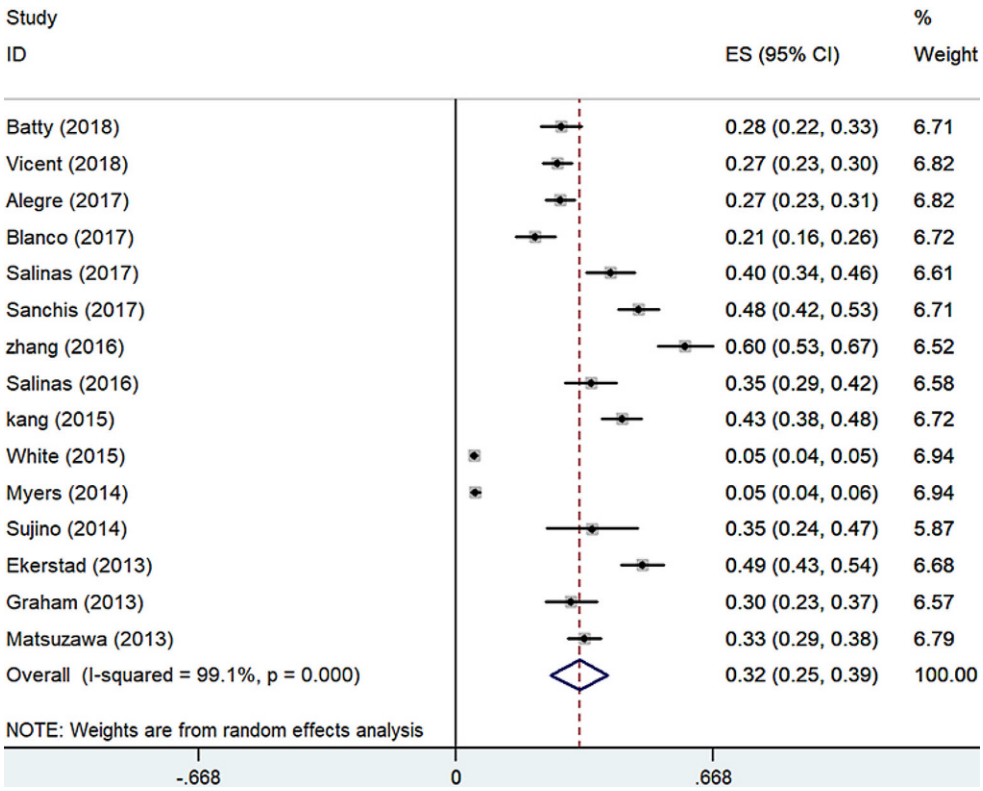

Fig. 2 Forest plot of prevalence of frailty in patients with ACS. The *dotted red line* represented the pooled ES. *ES* effect size

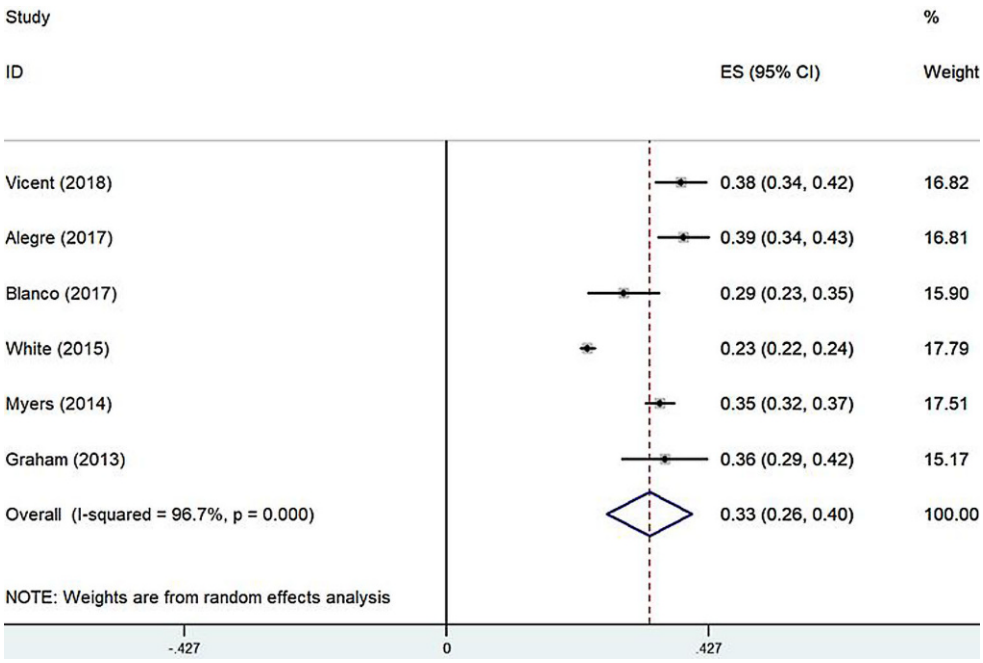

Fig. 3 Forest plot of prevalence of pre-frailty in patients with ACS. The *dotted red line* represented the pooled ES. *ES* effect size

mission among older patients with ACS. The results showed that the prevalence of frailty was significantly higher among ACS patients as compared to community-dwelling older persons. Results of the meta-analyses suggested that both pre-frailty and frailty were associated with significantly increased risk of all-cause mortality and hospital readmission among older patients with ACS.

In the past two decades, numerous frailty assessment tools have been developed and used to stratify the risk of adverse outcomes, such as mortality, disability and falling among community-dwelling older adults [17–21]. Researchers have demonstrated the prognostic value of the frailty status among older patients with specific chronic diseases, such as hypertension, diabetes, and heart failure. [22–24]. Our

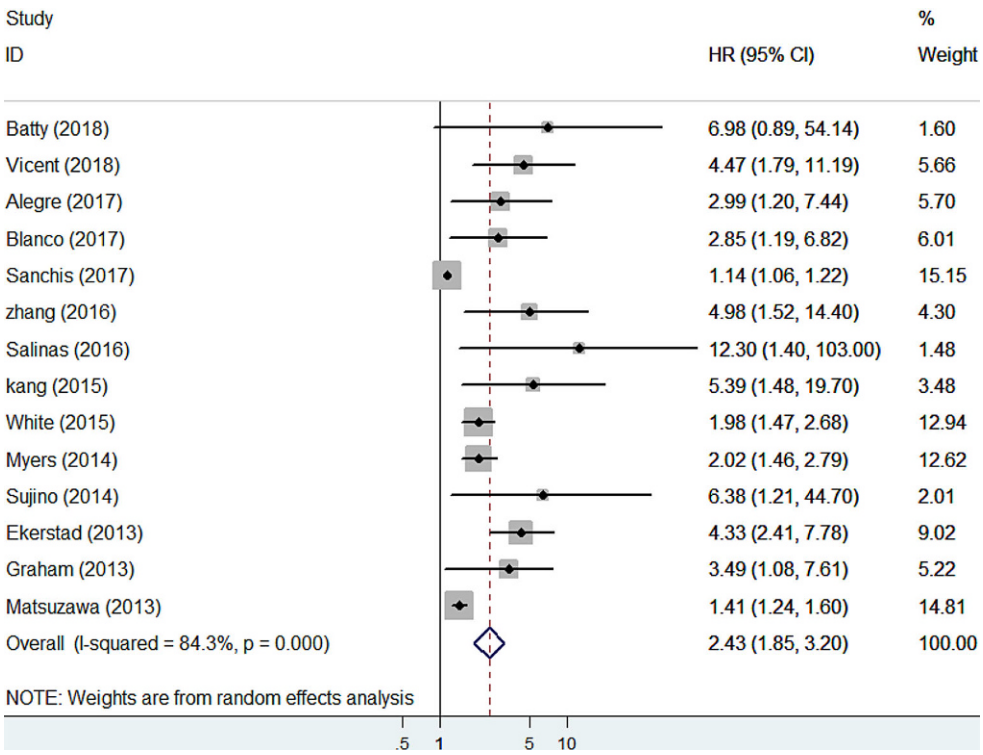

Fig. 4 Forest plot of association between frailty and all-cause mortality. The *dotted red line* represented the pooled ES. *ES* effect size, *HR* hazard risk

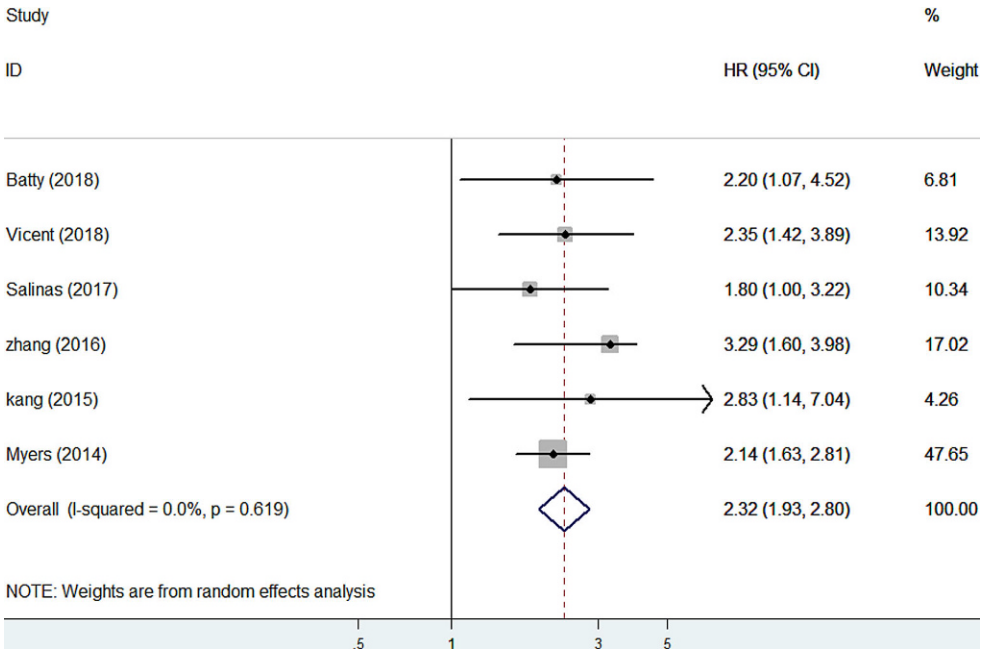

Fig. 5 Forest plot of association between frailty and readmission. The *arrow* represented the actual value was larger than shown in the figure and was limited by the size of the graph. The *dotted red line* represented the pooled ES. *ES* effect size, *HR* hazard risk

study showed that the frailty assessment tools were also of great predictive value for acute disease, which is ACS. Among the included studies, several assessment tools were used, including Fried's physical frailty phenotype approach, FRAIL scale, Edmonton frail scale (EFS), frailty index, Green score, and clinical frailty scale (CFS). Subgroup analyses in the present study showed that frailty, as assessed by most frailty assessment tools, was associated with increased risk of mortality and hospital readmission among older patients with ACS. These findings highlight the importance of frailty screening in routine management of older patients with ACS because screening for frailty status may help clinicians to identify patients with a high risk for a poor prognosis and to develop tailored interventions to improve the clinical outcomes. It should be noticed that frailty assessed by the physical phenotype approach or frailty index was not associated with a higher risk of mortality in our meta-analysis; however, these results should be interpreted

Table 2 Subgroup analyses of association between frailty and all-cause mortality in older patients with acute coronary syndrome

Subgroups	No. of studies	HR (95% CI)
Frailty definition		
Fried score	2	2.43(0.98, 6.02)
FRAIL scale	3	3.95(2.25, 6.91)
EFS	2	3.12(1.63, 5.98)
Green score	1	1.14(1.06, 1.22)
FI	2	3.6(0.69, 18.78)
CSHA-CFS	3	4.62(2.77, 7.71)
Gait speed	1	1.41(1.24, 1.60)
Population		
NSTEMI	6	3.29(2.13, 5.09)
STEMI	1	6.38(1.05, 38.78)
MIXED	7	1.75(1.32, 2.31)
Sample size (n)		
<300	7	3.46(1.59, 7.55)
>300	7	2.43(1.71, 3.46)
Follow-up (months)		
<9	6	4.51(2.79, 7.31)
>9	8	1.94(1.48, 2.56)
Study design		
Prospective	12	2.45(1.82, 3.29)
Retrospective	2	2.50(1.00, 6.24)

EFS Edmonton Frail Scale; *FI* Frailty Index; *CSHA-CFS* Chinese-Canadian study of health and aging clinical frailty scale; *NSTEMI* non ST-segment elevation myocardial infarction; *STEMI* ST-segment elevation myocardial infarction

with caution because only very few studies adopted these two frailty measures.

All included studies assessed the frailty status during admission or before discharge; however, this might not be proper in all circumstances. ACS is a serious acute disease that could have an immediate and devastating influence on patients. Patients need a long time, usually several months, to recover from the disease. Thus, the performance of grip strength and gait speed test might be significantly affected by the ACS. This may lead to overestimation of the pre-frailty/frailty prevalence among older patients with ACS, and underestimation of the association between pre-frailty/frailty and adverse outcomes. Our study found that frailty defined by frailty assessment tools contained grip strength and gait speed test as the main part, e.g. Fried score and Green score, or gait speed test alone was associated with lower risk of future adverse outcomes than that defined by tools which did not included physical function test, e.g. FRAIL scale and CFS. Frailty defined by EFS, which included functional performance (timed up and go test) as one of its nine items and may be less affected by ACS, was associated with higher mortality risk than that defined by Fried score and Green score. The frailty status assessed by FRAIL scale, EFS and CFS may better reflect the real status of frailty before the onset of ACS. Thus, FRAIL scale, EFS and CFS may be more clinically relevant for frailty assessment of older patients with ACS.

Studies in the present review and meta-analysis mainly focused on the prognostic value of frailty for adverse outcomes among older patients with ACS. Whether frail older ACS patients may benefit more from invasive treatment than conservative treatment is poorly understood. Julio et al. reported that PCI was associated with a significant reduction in the risk of hospital readmission but not all-cause mortality in patients who were frail [25]. More studies are warranted to provide a more definite conclusion.

To the best of our knowledge, our meta-analysis was the first to summarize the evidence of the association of pre-frailty and frailty with mortality and hospital readmission in older patients with ACS. We found that pre-frailty and frailty are risk factors for mortality and readmission among older patients with ACS. These findings highlight the importance of frailty assessment in routine management of older patients with ACS.

Several limitations of our study should also be acknowledged. First, different frailty assessment tools were used in the included studies, which led to substantial heterogeneity across studies. Second, all included studies were combined for the overall prevalence of frailty; however, previous studies showed that the frailty prevalence differed when different frailty assessment tools were used [26]. Thus, the estimates of the prevalence of pre-frailty and frailty among older patients with ACS might not be very accurate. Finally, subgroup analysis by different frailty assessment tools showed that the number of included studies in each subgroup was small. Therefore, the results are likely to be imprecise [27]. Conclusions drawn from these meta-analyses should be considered preliminary.

Conclusion

In summary, our meta-analysis provides evidence that both frailty and pre-frailty are associated with higher risk of all-cause mortality and readmission among older patients with ACS. Further studies are needed to explore whether frail patients would benefit more from invasive treatment than conservative treatment and the most applicable frailty assessment tools for ACS patient.

Conflict of interest W. Xu, Y. Cai, H. Liu, L. Fan, and C. Wu declare that they have no competing interests.

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