

**Supplementary Table 1: Studies assessing frailty in patients with cardiovascular disease**

<b>Authors, Year</b>	<b>N (% Male)</b>	<b>Age</b>	<b>Study cohort and design</b>	<b>Frailty tool</b>	<b>% Frail</b>	<b>Findings and outcomes for frail vs. non-frail</b>
Aguayo et al, <sup>35</sup> 2018	5294 (44.9%)	≥60	Comparative longitudinal secondary analysis of 35 frailty scores and CVD, cancer and mortality	4 frailty approach used: Frailty phenotype, multidimensional, accumulation of deficits and disability	None recorded	Multidimensional frailty scores may have a stronger and more stable association with mortality and incidence of cardiovascular events.
Veronese et al, <sup>11</sup> 2017	31343	≥65	Meta-analysis of 18 studies looking at proportion and incidence of CVD according to frailty status and proportion and rate of onset of CVD	15 used Modified version of Fried Phenotype 2 used CSHA CFS 1 used Gill's index	17.9%	Risk of having any-type CVD: adjusted OR= 2.85; 95% CI: 2.29–3.53, p < 0.001 Rate of onset of CVD: HR= 1.70; 95% CI: 1.18–2.45, p = 0.004 Cardiovascular mortality: HR= 3.89; 95% CI: 2.39–6.34, p < 0.001
Kamiya et al, <sup>27</sup> 2018	1474 (68%)	≥60	Prospective comparative study	Gait speed vs. six-minute walk distance	None recorded	All-cause mortality Gait speed: adjusted HR per 0.1 m/s increase: 0.87, 95% CI: 0.81–0.93, p < 0.001 Six-minute walk distance: adjusted HR per 10-metre increase: 0.96, 95% CI: 0.94–0.97, p < 0.001
Sergi et al, <sup>34</sup> 2015	1567 (39%)	≥65	Prospective cohort of study of community -	Modified Fried Pre frail= 1 or 2 from 5	0= 55.3% 1= 31.3% 2= 13.3%	Risk of CVD Participants meeting 1 criterion: HR= 1.25; 95% CI: 1.05 to 1.64

			dwelling at risk of CVD			Participants meeting 2 criteria: HR= 1.79; 95% CI: 1.27 to 2.52
Kulminski et al, <sup>36</sup> 2008	4721	≥65	Cohort study (patients from the CHS) comparing phenotypic frailty approach and cumulative deficit approach to predict mortality	CHS phenotypic frailty index (PFI) vs cumulative deficit index (DI-48 deficits)	PFI 361 (7.6%) DI 939 (19.9%)	PFI underestimated 720 at risk of mortality DI underestimated 134 DI predicts death significantly better than the PFI (i.e., RR DI=1.035, 95% CI=1.026–1.045 vs RR PFI=1.014, 95% CI=1.009–1.019).
Newman et al, <sup>29</sup> 2006	3075 (48%)	≥70	Observational cohort study of community-dwelling adults	Extended walking test= 400-m (Gait speed) [2680 eligible for test]	None recorded	Poorest quartile vs. best quartile Mortality- 14.2 vs. 39.9 per 1000 person-years: adjusted HR= 3.23; 95% CI: 2.11-4.94; P < 0.001 Risk of incident CVD- 27.7 vs. 36.0 per 1000 person-years: adjusted HR= 1.61; 95% CI: 1.05-2.45; P = 0.03 Mobility limitation (27.3 vs. 180.0 per 1000 person-years: adjusted HR= 4.43; 95% CI: 3.39-5.78; P < 0.001 Mobility disability (9.6 vs. 60.2 per 1000 person years: adjusted HR= 4.43; 95% CI: 2.88-6.82; P < 0.001
Newman et al, <sup>31</sup> 2001	4735 (42.8%)	≥65	Cross-sectional study of community dwelling older adults (CHS)	Fried scale ≥3	6.3% frail 45.3% pre-frail	Prevalent clinical CVD: 38% vs. 17%; OR= 2.79; 95% CI: 2.12–3.67

CFS= Clinical Frailty Scale; CI= Confidence interval; CHS= Cardiovascular Health Study; CSHA= Canadian Study of Health and Ageing; CVD= Cardiovascular disease; DI= Deficit Index; HR= Hazard ratio; OR= Odds ratio; PFI= Phenotypic frailty index; RR= relative risk.

**Supplementary Table 2: Studies assessing frailty in patients with ACS.**

Authors, Year	N (% Male)	Age	Study cohort and design	Frailty tool	% Frail	Findings and outcomes for frail vs. non-frail
Nunez et al, <sup>46</sup> 2020	488 (58.3%)	>65	Prospective observational single centre study of ACS patients (79.1% NSTEMI)	Fried scale $\geq 3$	41.4%	Mortality for Fried $\geq 3$ : HRs= 1.41; 95% CI:1.01–1.94, p = 0.043 Mortality for Fried per increase in 1: HR= 1.25; 95% CI:1.08–1.47, p = 0.004 All-cause death males Fried $\geq 3$ : HR= 1.89; 95%CI :1.25–2.85, p = 0.003 All-cause death females Fried $\geq 3$ : HR= 0.92; 95% CI :0.57–1.49, p = 0.726
Damluji et al, <sup>41</sup> 2019	469,390 (47%)	$\geq 75$	Retrospective study of patients with acute MI	Claims-based Frailty Index (CFI) [21 variables cut off 0.20]	19%	PCI: 15% vs 33%, P<0.001 CABG: 1% vs 9%, P<0.001 Overall mortality rate: 13.2% vs 9.6%, P<0.001 In-hospital mortality: adjusted OR= 1.25, 95% CI: 1.22–1.28
Dou et al, <sup>37</sup> 2019	8554	$\geq 65$	Systematic review and meta-analysis of frailty in ACS (15 studies)	4 CSHA-CFS 4 SHARE-FI 2 Green score 2 EFS 1 Fried scale 1 FRAIL 1 computer program	CSHA CFS 35.50-48.50% SHARE-FI 35.10-40.20% Green 48% EFS 20.8-30.05% Fried scale 4.70%	Risk of mortality in STEMI: adjusted HR= 6.51; 95% CI: 2.01–21.10 Risk of mortality in NSTEMI: adjusted HR= 2.63; 95%CI: 1.51–4.60

					FRAIL 27.3% Computer 35.5%	
Nguyen et al, <sup>40</sup> 2019	324 (60.8%)	≥60	Prospective cohort study of patients with ACS (37.0% STEMI, 41.0% NSTEMI and 21.9% unstable angina)	Reported EFS	48.1%	In-hospital mortality: adjusted OR= 3.02; 95%CI: 1.35–6.75 30-day mortality: adjusted OR= 3.28; 95% CI: 1.59–6.76 30-day readmission: adjusted OR= 2.53; 95% CI: 1.38–4.63 PCI: 41.7% vs. 58.3%, P= 0.003 Arrhythmia risk: adjusted OR= 2.24; 95% CI: 1.32–3.8 HAP: adjusted OR= 2.27; 95% CI: 1.24 4.17
Campo et al, <sup>47</sup> 2019	402 (66%)	≥70	Prospective cohort study of patients admitted with ACS (33% STEMI, 45% NSTEMI and 22% unstable angina)	7 scales used: Fried scale ≥3 Handgrip strength SPPB ≤3 CFS ≥5 Columbia frailty index ≥6 MPI EFS ≥8	Fried scale 31% Handgrip strength 14-40% SPPB 15% CFS 33% Columbia frailty index 17% MPI 3% EFS 9%	Associated with all-cause mortality SPPB: adjusted OR= 0.74, 95% CI: 0.63–0.85 EFS: adjusted OR= 1.33, 95% CI: 1.13–1.56 Fried: adjusted OR= 1.58, 95% CI: 1.14–2.18 SPPB is the best predictor for MACCE ( $\Delta$ C-statistic 0.043, p = 0.04; integrated discrimination improvement (IDI) 0.054, p = 0.001; net reclassification improvement (NRI) 0.752, p < 0.001) and all-cause mortality ( $\Delta$ C-statistic 0.063, p = 0.02; IDI 0.061, p < 0.001; NRI 1.022, p < 0.001).
Kwok et al, <sup>43</sup> 2019	7,398,572	>50	Retrospective cohort study of ACS	Hospital Frailty Risk	LRS 86.5% IRS 13.4%	Comparing HRS to LRS, there was a significant increase in

			patients (66.8% NSTEMI or unstable angina and 33.2% STEMI)	Score based on ICD-9 codes using the cut-offs <5, 5 to 15, and >15 for low-(LRS), intermediate - (IRS), and high-risk (HRS) frailty scores, respectively	HRS 0.1%	Bleeding complications: OR= 2.34, 95% CI: 2.03-2.69 Vascular complications: OR= 2.08, 95% CI: 1.79-2.41 In-hospital stroke: OR= 7.84, 95% CI: 6.93-8.86 In-hospital death: OR= 2.57, 95% CI: 2.18-3.04 Medical management: LRS= 31.0%, IRS= 54.8%, and HRS= 70.9%
Alonso Salinas et al, <sup>15</sup> 2017	234 (59.4%)	≥75	Prospective cohort study of ACS patients (37.1% STEMI)	SHARE- FI	40.2% frail 28.2% pre-frail	Combination of death or nonfatal myocardial reinfarction: adjusted HR= 2.54, 95% CI: 1.12-5.79 Combination of death, nonfatal myocardial reinfarction, or major bleeding: adjusted HR= 2.14, 95% CI: 1.13-4.04 Readmission: adjusted HR= 1.80, 95% CI: 1.00-3.22
Blanco et al, <sup>38</sup> 2017	236 (51.7%)	≥80	Prospective observational study of ACS patients (32.2% STEMI and 67.8% NSTEMI)	EFS score >7	20.8%	All-cause death: adjusted HR= 4.03; 95% CI: 2.02-8.04; P < 0.001 Survival rate was 82.4% in the EFS 0-3 group, 64.7% in the EFS 4-6 group, and 38.8% in the EFS > 7 group (log-rank test P < 0.001).
White et al, <sup>42</sup> 2016	9326 [4996]	≥65	TRILOGY ACS trial- ACS patients	Fried scale ≥3	4.7% frail 23.0% pre-	All-cause mortality: 30.2% vs 15.0%; HR= 1.98; 95% CI: 1.47–2.68; p<0.001

	frailty assessed (53.9%)]		(unstable angina and NSTEMI) randomised to clopidogrel or prasugrel		frail	Likelihood of cardiovascular death, MI, or stroke events: Pre-frail vs not-frail: adjusted HR= 1.33; 95% CI: 1.15–1.54; p<0.001 Frail vs not-frail: adjusted HR= 1.52; 95% CI: 1.18–1.98; p=0.002
Kang et al, <sup>48</sup> 2015	352 (57.7%)	≥65	Prospective single centre cohort study on ACS patients (STEMI and NSTEMI)	CFS (5-7)	43.18% frail (5-7) 26.42% moderately or severely frail (6-7)	All-cause mortality: HR=5.393; 95% CI: 1.477-19.692, P = 0.011 Unscheduled return visit: HR= 2.832; 95% CI: 1.140-7.037, P = 0.025 ICCU treatment: 32.89% vs 20.50%, p=0.009 Coronary angiography: 75.66% vs 85%, p=0.027
Murali-Krishnan et al, <sup>49</sup> 2015	745 (70%)	62.2 (mean)	Prospective cohort study of stable angina or ACS (39.6% STEMI) patients undergoing PCI	CSHA CFS ≥5	11%	30-day mortality: HR= 4.8, 95% CI: 1.4 to 16.3, p=0.013 1-year mortality: HR= 5.9, 95% CI: 2.5 to 13.8, p<0.001
Sanchis et al, <sup>45</sup> 2014	342 (57%)	≥65	Prospective single centre cohort study of ACS patients (21% STEMI, 79% NSTEMI or unstable angina)	Fried ≥ 3/5 Green score ≥ 5/12	Fried 34% Green 48%	All-cause mortality: Green ≥ 5: HR= 3.4, 95% CI 1.8 to 6.2, P = 0.0001 Fried: P = 0.4 after adjusting for the Green score

Graham et al, <sup>39</sup> 2013	183 (67.2%)	≥65	Prospective single centre study of ACS patients (19.1% STEMI and 80.9% NSTEMI)	EFS ≥7	30.1%	One-year mortality: adjusted HR= 3.49; 95% CI: 1.08-7.61; P = 0.002 Mean length of stay: 12.7 days vs 7.0 days, p=0.03
Gharachoulou et al, <sup>51</sup> 2012	629 [545 frailty assessed (69%)]	≥65	Prospective study of coronary artery disease patients (11.9% STEMI and 15.4% NSTEMI undergoing PCI)	Fried scale ≥3	18.6%	30 days: no statistically significant differences in any of the clinical events by frailty category (death, myocardial infarction, and revascularization) Frail vs non-frail: poorer health status and QOL (P < 0.001), higher frequency of multivessel or left main coronary artery disease (74% vs 60%, p=0.019)
Singh et al, <sup>50</sup> 2011	629 (69%)	≥65	Prospective, multicenter cohort of elderly coronary artery disease patients post-PCI	Fried scale ≥3	18.6%	3-year mortality: 28% vs. 6%; HR= 2.74; 95% CI: 1.12–6.71

ACS= Acute coronary syndrome; CABG= Coronary Artery Bypass Graft; CFI= Claims-based Frailty Index; CFS= Clinical Frailty Scale; CI= Confidence interval; EFS= Edmonton Frail Scale; HAP= Hospital acquired pneumonia; HFRS= Hospital Frailty Risk Score; HR= Hazard ratio; ICCU= intensive coronary care unit; IDI= integrated discrimination improvement; IRS= Intermediate-risk frailty scores; LRS= Low-risk frailty scores; MACCE= Major adverse cardiovascular and cerebrovascular events; MI= myocardial infarction; MMSE= Mini Mental State Examination; MPI= Multidimensional prognostic index; NRI= net reclassification improvement; NSTEMI= Non ST-elevation myocardial infarction; OR= Odds ratio; PCI= Percutaneous coronary intervention; QOL= Quality of life; SHARE-FI= Survey of Health Ageing and Retirement in Europe Frailty Index; SPPB= Short Physical Performance Battery; STEMI= ST-elevation myocardial infarction.