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REVIEW

The Association Between the Clinical Frailty Scale and Adverse Health Outcomes in Older Adults in Acute Clinical Settings – A Systematic Review of the Literature

Hanna Falk Erhag[1–3], Gudny Guðnadóttir[3], Joakim Alfredsson[4], Tommy Cederholm[5,6], Niklas Ekerstad[7,8], Dorota Religa[9,10], Bengt Nellgård[11], Katarina Wilhelmson[2,3,12]

[1]Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [2]Centre for Ageing and Health (Agecap), University of Gothenburg, Gothenburg, Sweden; [3]Region Västra Götaland, Sahlgrenska University Hospital, Department of Acute Medicine and Geriatrics, Gothenburg, Sweden; [4]Department of Cardiology, and Department of Health, Medicine and Caring Sciences, Unit of Cardiovascular Sciences, Linköping University, Linköping, Sweden; [5]Clinical Nutrition and Metabolism Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden; [6]Theme Inflammation and Aging, Karolinska University Hospital, Stockholm, Sweden; [7]Department of Health, Medicine, and Caring Sciences, Unit of Health Care Analysis, Linköping University, Linköping, Sweden; [8]The Research and Development Unit, NU Hospital Group, Trollhättan, Sweden; [9]Department of Neurobiology, Care Sciences, and Society, Clinical Geriatrics, Karolinska Institute, Stockholm, Sweden; [10]Division for Clinical Geriatrics, Karolinska University Hospital, Stockholm, Sweden; [11]Department of Anesthesiology and Intensive Care, Institute of Clinical Studies, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [12]Department of Health and Rehabilitation, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Correspondence: Hanna Falk Erhag, Neuropsychiatric Epidemiology Unit, Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, Sahlgrenska Academy at the University of Gothenburg, Wallinsgatan 6, Gothenburg, SE 431 41, Sweden, Tel +46 760 476888, Fax +46 31 786 60 77, Email hanna.falk@gu.se

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Background: Frail older adults experience higher rates of adverse health outcomes. Therefore, assessing pre-hospital frailty early in the course of care is essential to identify the most vulnerable patients and determine their risk of deterioration. The Clinical Frailty Scale (CFS) is a frailty assessment tool that evaluates pre-hospital mobility, energy, physical activity, and function to generate a score that ranges from very fit to terminally ill.

Purpose: To synthesize the evidence of the association between the CFS degree and all-cause mortality, all-cause readmission, length of hospital stay, adverse discharge destination, and functional decline in patients >65 years in acute clinical settings.

Design: Systematic review with narrative synthesis.

Methods: Electronic databases (PubMed, EMBASE, CINAHL, Scopus) were searched for prospective or retrospective studies reporting a relationship between pre-hospital frailty according to the CFS and the outcomes of interest from database inception to April 2020.

Results: Our search yielded 756 articles, of which 29 studies were included in this review (15 were at moderate risk and 14 at low risk of bias). The included studies represented 26 cohorts from 25 countries (N = 44166) published between 2011 and 2020. All included studies showed that pre-hospital frailty according to the CFS is an independent predictor of all adverse health outcomes included in the review.

Conclusion: A primary purpose of the CFS is to grade clinically increased risk (i.e. risk stratification). Our results report the accumulated knowledge on the risk-predictive performance of the CFS and highlight the importance of routinely including frailty assessments, such as the CFS, to estimate biological age, improve risk assessments, and assist clinical decision-making in older adults in acute care. Further research into the potential of the CFS and whether implementing the CFS in routine practice will improve care and patients' quality of life is warranted.

Keywords: clinical frailty scale, risk stratification, acute clinical settings, literature review

Introduction

The functional heterogeneity of the growing older population is not captured by chronological age or morbidity estimates. The concept of frailty may add to the understanding and assessment of the aged individual by indicating biological age. Frailty develops due to age-related decline in multiple physiological systems.[1–4] It is a distinctive late-life condition where minor stress

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factors are associated with adverse health outcomes, including falls, cognitive impairment, disability, hospitalization, institutionalization, and death.[4,5] Although frailty is often clinically recognizable, operational criteria vary, and there is no golden standard for its detection.[6] Among persons ≥80 years accessing urgent care settings, about 25–50% are frail.[4] Assessing frailty early in the course of care is essential to identify the most vulnerable patients,[7–9] enabling patients to be directed towards appropriate clinical care and allowing targeted interventions to improve patients' medical, psychological, and functional capabilities, and prognosis.[10,11]

The frailty phenotype and the accumulated deficit model are the two dominating frameworks used to conceptualize frailty,[3,8] and various assessment tools have been developed to operationalize frailty, for example, judgment-based, summing the number of impairments, and performance measures.[1,12,13] The frailty phenotype is operationalized as the presence of at least three out of five criteria (i.e. unintentional weight loss, weakness, poor endurance, slowness, and low physical activity level).[1] Alternatively, the accumulated deficit model has been operationalized through the frailty index based on the accumulation of specific deficits (including functional limitations and disabilities, cognitive and sensory impairment, psychosocial variables, and diseases). The Clinical Frailty Scale (CFS) is a judgments-based assessment based on the cumulative deficit model that mixes items such as comorbidity, cognitive impairment, and disability and is validated against the Frailty Index.[12,14] The CFS focuses on items such as mobility, balance, the use of walking aids, and the ability to dress, shop, prepare meals, do housework, and handle finances.[3,8,12,13] The CFS is routinely used to screen pre-hospital frailty in patients ≥65 years admitted to hospitals via the Emergency Department in several European countries.[15,16] The scale is scored so that higher scores mean greater risk, has good criterion validity and inter-rater reliability, and it uses descriptors and figures to stratify older adults according to their level of vulnerability, ranging from very fit (i.e. robust, active, and energetic) to terminally ill.[12–15] The degree of frailty generally corresponds to the degree of dementia.[13] Mild dementia, for example, corresponds to mild frailty. In both cases, the individual is independent in their activities of daily living (ADLs) but dependent in one or more instrumental activities of daily living (IADLs). When dementia is suspected, although not diagnosed, the CFS assessment should be completed with validated cognitive tests. The CFS was developed to study frailty in older adults. Disability in younger people (including both acquired and life-long) does not have the same relevance for prognosis as for older adults and age-related disability. Numerous previous studies show a strong association between frailty and death in various clinical settings.[7,13,16–20] The key to CFS scoring is determining the baseline health state of the older adult, which is especially needed in clinical settings where health can change quickly. Many older adults in the emergency department who were physically fit two weeks previously (i.e. their baseline state) may appear frail while ill.

Two versions of the CFS have been extensively used in studies and clinical practice. Initially, it was scored from one (very fit) to seven (severely frail), and in 2007 it was modified to a nine-point scale to include very severely frail and terminally ill since these groups may need different care plans. By definition, CFS degrees 1–4 denote non-frailty (declining degrees of robustness), whereas degrees ≥5 indicate frailty. Previous systematic reviews have examined the psychometric properties of different frailty assessment tools in various clinical settings.[7,16–18,21,22] The CFS shows good accuracy and feasibility, a strong association with mortality, a higher care level,[23,24] and good inter-rater reliability.[19] Although these literature reviews on frailty suggest that the CFS is a promising frailty assessment tool, none of these have explicitly focused on the CFS in older patients in acute clinical settings in which frailty assessment is fundamental for guiding patient care and helping clinicians determine which interventions will be beneficial or harmful to the older patient. To our knowledge, this is the first systematic review of the research evidence focusing on the ability of the CFS to grade clinically increased risk (risk stratification), i.e. the association between the CFS and clinically relevant outcomes among older patients. Thus, this systematic review aims to synthesize the evidence of the association between pre-hospital frailty as determined by the CFS and all-cause mortality, all-cause readmission, length of hospital stay (LOS), adverse discharge destination (i.e. discharge to nursing homes, residential care, or settings with a higher level of care), and functional decline in patients ≥65 years in acute clinical settings.

Materials and Methods

This systematic review was registered in the prospective international register of systematic reviews PROSPERO (CRD42020178746) and reported in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) statement.[25]

Data Sources and Search Strategy

A computer-aided search strategy in PubMed, EMBASE, CINAHL, and Scopus was performed from database inception to April 2020. Prospective or retrospective observational studies that reported a relationship between the CFS scale and all-cause mortality, readmission, length of hospital stay, adverse discharge destination, and functional decline in older patients in acute care settings were considered. Studies were limited to the English language. All database search strategies are presented in Appendix 1.

Study Selection

A protocol was followed for study selection (Appendix 2). All identified citations were imported into Rayyan (rayyan.qcri.org). After removing duplicates, three authors independently screened the titles and abstracts of the studies and excluded those not meeting the inclusion criteria. Two out of three authors needed to be in favor in order for the study to be included. If the title and abstract seemed to fulfill the inclusion criteria, the full-text version of the study was retrieved and reviewed independently by at least two authors for a final decision on eligibility. Conference abstracts, editorial letters, commentaries, and pilot studies were excluded. Studies were also excluded if they had a cross-sectional design or a pre-test/post-test without predictive analysis, method development studies, qualitative studies, literature reviews, or study protocols not presenting data. Further exclusion criteria were studies investigating patients undergoing elective procedures or those living in long-term care facilities, nursing- or retirement homes.

Quality Assessment

The methodological quality of eligible studies was assessed by the Quality in Prognosis Studies (QUIPS) tool.[26] The Swedish Agency for Health Technology Assessment and Assessment of Social Services recommended the QUIPS as a suitable tool for evaluating the risk of bias in studies regarding risk prediction. Each QUIPS domain was evaluated as having a high, moderate, or low risk of bias (RoB). Seven authors were involved in the quality assessment, and at least two out of seven authors independently assessed each eligible study's methodological quality. All discrepancies were resolved by consensus or by a third author who independently assessed that specific study. To reach a decision, the majority rule was used. For QUIPS, no rules are available that indicate how a study's overall RoB should be assessed. In this review, we used criteria as suggested by Grooten et al.[27] If all domains were assessed as having low RoB or up to one moderate RoB, the study was classified as low RoB. If one or more domains were assessed as having high RoB, or ≥four moderate RoB, this study was classified as high RoB. All studies in between were classified as having moderate RoB. Only studies with an overall low or moderate RoB were included in this review.

Data Extraction and Synthesis

For each study, three authors independently extracted data on study design, participant demographics (sex and age), clinical setting, CFS version (i.e. seven- or the nine-item), CFS cut-offs, the prevalence of pre-hospital frailty, and whether pre-hospital frailty was treated as a discrete, dichotomous, or grouped variable. The association between CFS, all-cause mortality, all-cause readmission within 30 days, LOS, adverse discharge destination, and functional decline was reported as adjusted odds ratio (OR), hazard ratio (HR), and risk ratio (RR), with 95% confidence intervals and presented in a table. All-cause mortality was the most commonly used outcome in the included studies, and we therefore synthesized the estimates (i.e. OR and HR respectively) in two separate Forest Plots using the Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc.).

Results

Literature Flow

We found 756 potentially eligible studies. Fifty-seven studies were assessed for bias after removing duplicates and studies not meeting the inclusion criteria (i.e. wrong publication type, design, population, or outcome). A further 28 studies were excluded due to the high risk of bias. Finally, 29 were included in this review. The PRISMA flowchart is presented in Appendix 3.

Risk of Bias Within Studies

Out of the 57 studies reviewed for RoB using the QUIPS tool, 49% (n = 28) were overall high risk, often due to confounding and measurement bias, rendering study exclusion (Appendix 4). The overall RoB of the included studies is presented in Table 1, out

Table 1 Risk of Bias Within Studies

Study	Selection Bias	Attrition Bias	Measurement Bias Related to CFS	Measurement Bias Related to Outcomes	Confounding Bias	Analysis/ Presentation Bias	The Overall Risk of Bias
Anand et al 2020[28]	Low	Moderate	Moderate	Low	Moderate	Low	Moderate
Bagshaw et al 2014[43]	Low	Low	Low	Low	Low	Low	Low
Basic & Shanley 2015[44]	Low	Low	Low	Low	Low	Low	Low
Chan et al 2019[29]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Cheung et al 2017[30]	Moderate	Low	Low	Low	Moderate	Low	Moderate
Chong et al 2017[31]	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Chong et al 2018[32]	Moderate	Low	Moderate	Low	Low	Moderate	Moderate
Chua et al 2020[45]	Low	Low	Low	Low	Moderate	Low	Low
Curtis et al 2018[46]	Low	Low	Low	Low	Moderate	Low	Low
Darvall et al 2019[47]	Moderate	Low	Low	Low	Moderate	Low	Low
Darvall et al 2020[48]	Moderate	Low	Low	Low	Low	Low	Low
Ekerstad et al 2011[33]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Ekerstad et al 2014[34]	Low	Moderate	Moderate	Low	Low	Low	Moderate
Ekerstad et al 2018[35]	Low	Moderate	Low	Moderate	Moderate	Low	Moderate
Ellis et al 2020[36]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Evans et al 2019[49]	Low	Low	Low	Low	Moderate	Low	Low
Fernando et al 2019[37]	Low	Low	Moderate	Moderate	Low	Low	Moderate
Flaatten et al 2017[50]	Low	Low	Low	Low	Low	Low	Low
Fronczek et al 2018[51]	Low	Low	Low	Low	Moderate	Low	Low
Guidet et al 2020[52]	Low	Low	Moderate	Low	Low	Low	Low
Lewis et al 2019[38]	Low	Low	Moderate	Moderate	Low	Low	Moderate
Li et al 2018[39]	Low	Low	Moderate	Low	Moderate	Moderate	Moderate
MacKenzie et al 2019[53]	Low	Low	Low	Low	Low	Low	Low
Moore et al 2018[40]	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
Ritt et al 2017[41]	Low	Low	Moderate	Low	Moderate	Low	Moderate
Silva-Obregon et al 2020[54]	Low	Low	Moderate	Low	Low	Low	Low
Sze et al 2017[55]	Low	Low	Moderate	Low	Low	Low	Low
Ticinesi et al 2019[56]	Low	Low	Moderate	Low	Low	Low	Low
Wallis et al 2015[42]	Low	Moderate	Moderate	Low	Moderate	Low	Moderate

Notes: Risk of bias (RoB) according to the six domains of the Quality in Prognosis Studies (QUIPS) tool. [21] The overall RoB was determined using the following criteria as previously suggested by Grooten et al [22] If all domains were assessed as having low RoB or up to one moderate RoB, the study was classified as low RoB. If one or more domains were assessed as having high RoB, or ≥four moderate RoB, this study was classified as high RoB. All studies in between were classified as having moderate RoB.

of which 15 were at moderate risk,[28–42] and 14 were at low risk.[43–56] Common methodological strengths in studies with low or moderate RoB were detailed descriptions of study participants and thorough explanations of potential determinants, confounders, and outcome measurements.

Study Characteristics

The study details and characteristics are presented in Table 2. In total, the included studies represented 26 cohorts from 25 countries (N = 44,166) published between 2011 and 2020. Twenty-one (72%) of the studies were prospective[28,31–39,41,43–45,48–53,55] and eight (28%) studies were retrospective.[29,30,40,42,46,47,54,56] Sample sizes of the included studies ranged from 118[56] to15,613 participants.[47] The mean or median age of the samples ranged between 67 years[43] and 89 years,[31,32] and the proportion of females ranged between 38%[54,55] and 70%.[31,32,41] The follow-up period ranged from in-hospital (i.e. days or weeks) to the end of follow-up (i.e. years). Ten studies (34%) used the seven-item version,[28,30,33–35,38,39,44,46,56] and 19 studies (66%) used the nine-item version of the CFS scale.[29,31,32,36,37,40–43,45,47–55] The prevalence of pre-hospital frailty, defined as either CFS ≥4, CFS ≥5, or CFS ≥6, ranged between 14%[30] to 91%.[36] In all included

Table 2 Included Study Details and Characteristics

Study	Country	Design	Sample	Setting	Age, Years Mean (SD), or Median [IQR]	Female (%)	CFS Version	CFS Cut-Off	Pre-Hospital Frailty (%)
Anand et al 2020[28]	UK	P	198	TC	79 (6)	42	7-item	CFS ≥5	20
Bagshaw et al 2014[43]	Canada	P	421	ICU	67 (10)	39	9-item	CFS ≥4	33
Basic & Shanley 2015[44]	Australia	P	2125	TC	83 (8)	60	7-item	CFS ≥5	89
Chan et al 2019[29]	Canada	R	423	TC	83 (8)	63	9-item	CFS ≥6	83
Cheung et al 2017[30]	Canada	R	260	TC	77 (8)	47	7-item	CFS ≥6	14
Chong et al 2017, 2018[31,32]	Singapore	P	206	TC	89 (5)	70	9-item	CFS ≥5	81
Chua et al 2020[45]	Singapore	P	314	ED	84 (7)	60	9-item	CFS ≥5	65
Curtis et al 2018[46]	US	R	1403	TC	78 (9)	NS	7-item	NS	NS
Darvall et al 2019[47]	Australia	R	15613	ICU	85 [82–88]	47	9-item	CFS ≥5	40
Darvall et al 2020[4]	Australia	P	218	TC	74 [69–80]	45	9-item	CFS ≥5	28
Ekerstad et al 2011, 2014, 2018[33–35]	Sweden	P	307	TC	83 (NS); 85 (NS)	49	7-item	CFS ≥5	49
Ellis et al 2020[36]	UK	P	2254	ED	85 (14)	55	9-item	CFS ≥5	91
Evans et al 2019[49]	UK	P	433	TC	83 [77–86]; 87 [83–92]	48–63	9-item	CFS ≥5	54
Fernando et al 2019[37]	Canada	P	1510	TC	73 (7); 80 (8)	44	9-item	CFS ≥5	34
Flaatten et al 2017[50]	ESICM	P	5021	ICU	84 [81–86]	48	9-item	CFS ≥5	43
Fronczek et al 2018[51]	Poland	P	272	ICU	84 [81–87]	59	9-item	CFS ≥5	63
Guidet et al 2020[52]	ESICM	P	3920	ICU	84 [81–87]	47	9-item	CFS ≥5	40
Lewis et al 2019[38]	Australia	P	899	ED	80 (8)	51	7-item	CFS ≥5	44
Li et al 2018[39]	Canada	P	308	TC	75 [65–94]	45	7-item	CFS ≥5	22
MacKenzie et al 2019[53]	Canada	P	400	TC	81 (8)	57	9-item	CFS ≥5	79
Moore et al 2018[40]	UK	R	924	TC	85 (9); 87 (9)	54–69	9-item	CFS ≥5	71–84
Ritt et al 2017[41]	Germany	P	305	TC	85 (7); 82 (6)	60–70	9-item	CFS ≥5	72
Silva-Obregon et al 2020[54]	Spain	R	285	ICU	78 (4)	38	9-item	CFS ≥5	19
Sze et al 2017[55]	UK	P	265	TC	80 [72–86]	38	9-item	CFS ≥4	53
Ticinesi et al 2019[56]	US	R	118	TC	84 (5)	61	7-item	CFS ≥5	45
Wallis et al 2015[42]	UK	R	5764	TC	84 (6)	56	9-item	CFS ≥5	57

Abbreviations: ESICM (European Society of Intensive Care Medicine) includes Austria, Belgium, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Italy, Libya, the Netherlands, Norway, Poland, Portugal, Romania, Russia, Spain, Sweden, Switzerland, Turkey, United Kingdom; P, prospective; R, retrospective; ICU, intensive care unit; ED, emergency department; TC, tertiary care including specialized medical care, trauma care, surgical care, University Hospitals, or tertiary referral hospitals; NS, not stated; SD, standard deviation; IQR, interquartile range.

studies, frail patients were older, more likely to be female, had more comorbid diseases, greater functional dependence, and had fewer social contacts than non-frail patients.

The association between frailty as determined by the CFS and all-cause mortality, all-cause readmission, LOS, adverse discharge destination, and functional decline is presented in Table 3. Fourteen studies treated the CFS as a dichotomous variable.[30–35,37,38,40,42,44,48,51,54] Seven studies treated the CFS as a discrete variable where each point increase predicted an increased risk or probability of the adverse health outcome of interest.[28,36,41,46,49,52,55] Three studies created separate CFS groups (i.e. mild, moderate, or severe frailty),[50,53,56] and five studies used mixed approaches.[29,39,43,45,47] All included studies adjusted their analysis using different confounders. Twenty-two studies adjusted their analyses for age,[28–46,48,50,52] 20 studies for sex,[28,29,31–36,38–45,47,50,53,54] and 18 studies adjusted for both age and sex.[28,29,31–36,38–45,48,50]

Association Between CFS and All-Cause Mortality

The difference in odds of all-cause mortality between frail and non-frail patients and the risk of all-cause mortality in-hospital, at 1-, 3-, 6-, 12- months, and end of follow-up are presented in Figure 1. Ten studies[31–33,37,43,44,46–48,51,53] reported a significant difference in the odds of in-hospital mortality, with the largest difference reported by MacKenzie et al[53] (OR 16.6, 95% CI 5.4–50.9), and Darvall et al[48] (OR 5.43, 95% CI 1.15–25.59). At 1-month follow-up, the largest difference was reported by Ekerstad et al[33] (OR 4.7, 95% CI 1.7–13.0), at 6 and 12 months, the largest difference was reported by Chong et al[32] (OR 4.37, 95% CI 2.44–7.83 and OR 5.78, 95% CI 3.19–10.48). In two studies, a single point increase in the CFS scale showed an increased likelihood of dying at both 1-month (OR 1.03, 95% CI 1.01–1.05),[49] and 3-months (OR 1.56, 95%

Table 3 Association Between CFS Degree and All-Cause Mortality, All-Cause Readmission, LOS, Adverse Discharge Destination, and Functional Decline

Study	CFS Variable	Control Factors	Outcome (95% CI)
Anand et al 2020[28]	CFS (discrete)*	Age, sex, comorbidity, cardiovascular risk	• All-cause mortality at 12 months post-discharge HR 1.72 (1.37–2.16)
Bagshaw et al 2014[43]	CFS (dichotomous) CFS groups (i.e. mild, moderate, severe)	Age, sex, comorbidity, severity of illness, hospital type	• All-cause mortality in hospital OR 1.81 (1.09–3.01). All-cause mortality at 12 months post-discharge HR 1.82 (1.28–2.60), in CFS 4 HR 1.86 (1.15–3.00), CFS 5 HR 2.31 (1.30–4.10), CFS 6–8 HR 2.77 (1.67–4.58). • Adverse discharge destination ** OR 1.98 (1.22–3.23) • Functional decline at 12 months post-discharge OR 2.25 (1.03–4.89)
Basic & Shanley 2015[44]	CFS (dichotomous)	Age, sex, comorbidity	• All-cause mortality in hospital OR 2.44 (1.77–3.36) and OR 2.97 (2.11–4.17) • LOS HR 0.88 (0.82–0.94) and HR 0.87 (0.81–0.93)
Chan et al 2019[29]	CFS (dichotomous) CFS (discrete)*	Age, sex, time to surgery, mode of anesthesia	• Death or discharge to a nursing home OR 23.0 (3.0–173.5) • LOS in CFS 4 RR 1.4 (1.2–1.6), in CFS 5 RR 1.6 (1.4–1.7), in CFS 6; RR 2.2 (2.0–2.4)
Cheung et al 2017[30]	CFS (dichotomous)	Age, severity of injury, comorbidity	• Death or discharge to long-term care, chronic care, or another acute facility OR 5.1 (2.0–13.2)
Chong et al 2017[31]	CFS (dichotomous)	Age, sex, comorbidity	• All-cause mortality in hospital OR 2.57 (1.14–5.83)
Chong et al 2018[32]	CFS (dichotomous)	Age, sex, comorbidity	• All-cause mortality in hospital OR 3.69 (1.19–11.43), at 6 months OR 4.37 (2.44–7.83), and 12 months OR 5.78 (3.19–10.48) • Functional decline at 12 months OR 1.35 (1.09–1.81) • Institutionalization or death at 6 months OR 3.14 (1.94–5.07) • Institutionalization or death at 12 months OR 3.69 (2.31–5.88)
Chua et al 2020[45]	CFS (dichotomous) CFS groups (i.e. mild, moderate, severe)	Age, sex, comorbidity, discharge placement	• All-cause mortality at 6 months HR 1.27 (1.05-1.53) • All-cause mortality at 6 months CFS7–8 HR 2.09 (1.01-4.33)
Curtis et al 2018[46]	CFS (discrete)*	Age, consciousness at hospital admission	• All-cause mortality at three months OR 1.56 (1.39–1.73) • Adverse discharge destination OR 1.54 (1.4–1.7)
Darvall et al 2019[47]	CFS (dichotomous) CFS (discrete)*	Sex, region, hospital type, and severity of illness	• All-cause mortality in hospital OR 1.87 (1.65–2.11) • Adverse discharge destination **OR 1.61 (1.34–1.95)
Darvall et al 2020[48]	CFS (dichotomous)	Age, sex, admission source, comorbidity	• All-cause mortality in hospital OR 5.43 (1.15–25.59), at 1 month OR 4.30 (1.09–16.98), and 6 months OR 3.28 (1.54–6.96) • All-cause readmission within 30 days OR 3.70 (1.46–9.41) • Adverse discharge destination RR 2.66 (1.15–6.13), OR 3.70 (1.46–9.41)
Ekerstad et al 2011[33]	CFS (dichotomous)	Age, sex, previous myocardial infarction, ejection fraction, diabetes, cardiovascular risk, classification of myocardial infarction, comorbidity	• All-cause mortality at 1 month OR 4.7 (1.7–13.0) • Death or discharge to a long-term care facility OR 2.2 (1.3–3.7)
Ekerstad et al 2014[34]	CFS (dichotomous)	Age, sex, previous myocardial infarction, ejection fraction, diabetes, cardiovascular risk, classification of myocardial infarction, comorbidity	• All-cause mortality at 12 months HR 4.3 (2.4–7.8)
Ekerstad et al 2018[35]	CFS (dichotomous)	Age, sex, ejection fraction, cardiovascular risk, comorbidity	• All-cause mortality at end of follow-up HR 2.06 (1.51–2.81)
Ellis et al 2020[36]	CFS (discrete)*	Age, sex, delirium, laboratory tests	• All-cause mortality at end of follow-up HR 1.39 (1.28–1.51) • All-cause readmission within 30 days HR 1.26 (1.17–1.37) • LOS RR 1.43 (1.35–1.52) • Adverse discharge destination **OR 1.30 (1.16–1.47)
Evans et al 2019[49]	CFS (discrete)*	Thrombolysis, illness severity	• All-cause mortality at 1 month OR 1.03 (1.01–1.05)
Fernando et al 2019[37]	CFS (dichotomous)	Age, long-term care recipient, illness severity, comorbidity	• All-cause mortality in hospital OR 1.81 (1.34–2.49) • All-cause readmission within 30 days OR 1.83 (1.38–2.34)
Flaatten et al 2017[50]	CFS groups (i.e. mild, moderate, severe)	Age, sex, illness severity	• All-cause mortality at 1 month in CFS 4; HR 1.19 (1.03–1.38), CFS ≥5 HR 1.54 (1.38–1.73)
Fronczek et al 2018[51]	CFS (dichotomous)	Illness severity, urgency	• All-cause mortality in hospital OR 2.25 (1.26–4.01)
Guidet et al 2020[52]	CFS (discrete)*	Age, admission source, urgency, illness severity, comorbidity	• All-cause mortality at one month HR 1.11 (1.09–1.15)
Lewis et al 2019[38]	CFS (dichotomous)	Age, sex, comorbidity, urgency	• Death, poor or fair self-reported health, poor or fair quality of life, new presentation to an emergency department, or need for community services OR 2.20 (1.55–3.12)

(*Continued*)

Table 3 (Continued).

Study	CFS Variable	Control Factors	Outcome (95% CI)
Li et al 2018[39]	CFS (discrete)* CFS groups (i.e. mild, moderate, severe)	Age, sex, type of surgery	• All-cause readmission or death within 30 days OR 1.35 (1.03–1.77), at 6 months OR 1.39 (1.11–1.75) • Death or readmission at 1-month CFS 3–4 OR 4.60 (1.29–16.45), CFS >5 OR 4.51 (1.13–17.94), and at 6 months CFS 3–4 OR 2.15 (1.01–4.55), CFS >5 OR 3.27 (1.32–8.12) • 30-day readmission CFS 3–4 OR 4.23 (1.20–14.97), CFS >5 OR 3.97 (1.00–15.78)
MacKenzie et al 2019[53]	CFS groups (i.e. mild, moderate, severe)	Sex, admission glucose	• All-cause mortality in hospital CFS 6 OR 3.9 (1.2–12.4) • All-cause mortality in hospital CFS ≥7 OR 16.6 (5.4–50.9) • LOS CFS 5 OR 2.1 (1.0–4.2), CFS 6 OR 3.6 (1.8–7.3), CFS >7 OR 2.5 (1.1–5.6)
Moore et al 2018[40]	CFS (dichotomous)	Age, sex, delirium, living alone, discharged to a higher level of care	• LOS OR 1.74 (1.15–2.63), ie, discharge occurring >24 h after last recorded clinical fit date
Ritt et al 2017[41]	CFS (discrete)*	Age, sex, comorbidity, disability (IADL/ADL)	• All-cause mortality at 12 months HR 3.67 (2.59–5.19)
Silva-Obregon et al 2020[54]	CFS (dichotomous)	Sex, comorbidity, illness severity, treatment intensity, complications	• All-cause mortality in hospital HR 4.44 (1.72–11.45), at 1 month HR 6.07 (1.76–20.89), at 3 months HR 4.08 (1.54–10.79), at 6 months HR 4.30 (1.74–10.65), at t12 months HR 4.04 (1.65–9.89)
Sze et al 2017[55]	CFS (discrete)*	Malnourishment	• All-cause mortality at end of follow-up HR 1.56 (1.35–1.81)
Ticinesi et al 2019[56]	CFS groups (i.e. mild, moderate, severe)	Comorbidity	• All-cause mortality at end of follow-up CFS >7; RR 2.0 (1.1–3.8)
Wallis et al 2015[42]	CFS (dichotomous)	Age, sex, comorbidity	• All-cause mortality in hospital OR 1.60 (1.48–1.74) • LOS OR 1.19 (1.14–1.23) • Adverse discharge destination **OR 1.33 (1.24–1.42)

Notes: *CFS used as a discrete variable meant that each point increase in CFS score predicted an increased risk or probability of the adverse health outcome of interest. **Adverse discharge destinations included nursing homes, residential care, hospitalization, or higher level of care.
Abbreviation: CI, confidence interval.

CI 1.39–1.73).[46] The increased risk of all-cause mortality in-hospital, within 1-, 3- 6-, 12-months, and end of follow-up are presented in Figure 2. Silva-Obregón et al[54] showed that frail patients suffered more than a four-fold increased risk of dying in hospital (HR 4.44, 95% CI 1.72–11.45), a six-fold increased risk within 1 month (HR 6.07, 95% CI 1.76–20.89), and a four-fold increased risk within 3 months (HR 4.08, 95% CI 1.54–10.79), and 6 months (HR 4.30, 95% CI 1.74–10.65). Nine studies[28,34–36,41,43,54–56] reported that pre-hospital frailty increased the risk of dying within 12 months or at the end of follow-up, with the largest risk reported by Ekerstad et al[34] (HR 4.3, 95% CI 2.4–7.8). A single point increase in the CFS showed a nearly four-fold increased risk of dying within 12 months or at the end of follow-up as reported by Ritt et al[41] (HR 3.76, 95% CI 2.59–5.19), and a nearly two-fold increase in risk as reported by Anand et al[28] (HR 1.72, 95% CI 1.37–2.16).

Association Between CFS and All-Cause Readmission

Four studies[36,37,39,48] showed a significant difference in the odds of all-cause readmission within 30 days between frail and non-frail patients, with the most significant difference reported by Li et al[39] (OR 3.97, 95% CI 1.00–15.78). In the study by Ellis et al[36] an additional point increase on the CFS scale increased the risk of hospital readmission (HR 1.26, 95% CI 1.17–1.37).

Association Between CFS and LOS

Three studies[40,42,53] showed a significant difference in the odds of an extended LOS between frail and non-frail patients, with the most significant difference reported by MacKenzie et al[53] (OR 3.6, 95% CI 1.8–7.3). Two studies[29,36] showed a dose-response relationship between increasing pre-hospital frailty and LOS, with the most significant risk observed by Chan et al[29] (RR 2.2, 95% CI 2.0–2.4).

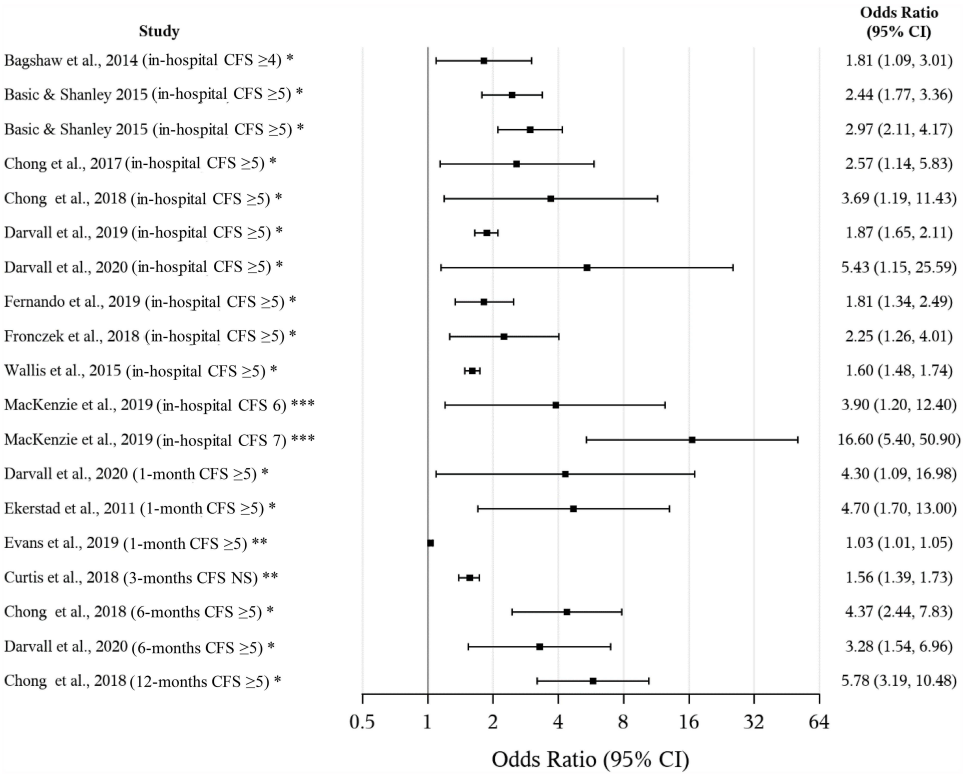

Figure 1 The adjusted difference in the odds of all-cause mortality between frail and non-frail patients (in-hospital, within 1-, 3-, 6-, 12-months, or end of follow-up). *CFS was treated as a dichotomous variable, **as a discrete variable, ***or a grouped variable in the analysis.

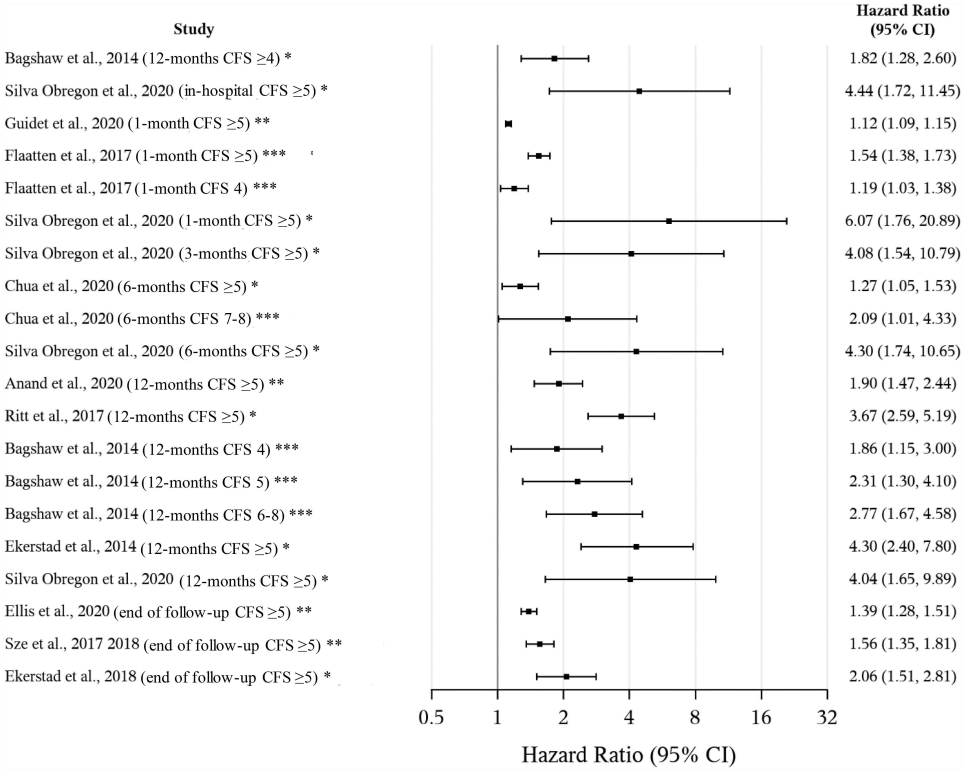

Figure 2 The adjusted risk of all-cause mortality (in-hospital, within 1-, 3-, 6-, 12-months, or end of follow-up). *CFS was treated as a dichotomous variable, **as a discrete variable, ***or a grouped variable in the analysis.

Association Between CFS and Adverse Discharge Destination

Six studies[36,42,43,46–48] showed a significant difference in the odds of adverse discharge destination between frail and non-frail participants, with the largest difference reported by Darvall et al[48] (OR 3.70, 95% CI 1.46–9.41), as well as a nearly three-fold increased risk (RR 2.66, 95% CI 1.15–6.13). Ellis et al[36] reported that a single point increase in the CFS increased the odds of adverse discharge destination by 30% (OR 1.30, 95% CI 1.16–1.47).

Association Between CFS and Functional Decline

Two studies[32,43] reported a difference in the odds of functional decline at 12 months post-discharge between frail and non-frail patients, with the largest difference reported by Bagshaw et al[43] (OR 2.25, 95% CI 1.03–4.89).

Association Between CFS and Composite Outcome

Six studies reported differences in odds of various composite outcomes between frail and non-frail patients.[29,32,33,35,38,39] A difference in the odds of death or discharge to a nursing home or long-term facility was reported by Chan et al[29] (OR 23, 95% CI 3.0–173.5), Chong et al[32] (OR 3.14, 95% CI 1.94–5.07 and OR 3.69, 95% CI 2.31–5.88), and Ekerstad et al[33] (OR 2.2, 95% CI 1.3–3.7). Lewis et al[38] reported a difference in the odds of death, poor or fair self-reported health, poor or fair quality of life, new presentation to an emergency department, or need for community services (OR 2.20, 95% CI 1.55–3.12). Li et al[39] reported a difference in the odds of being readmitted or deceased one-month post-discharge (OR 4.51, 95% CI 1.13–17.94), and a single-point increase in the CFS more than tripled the odds (OR 3.27, 95% CI 1.32–8.12).

Discussion

The explicit purpose of this systematic review was to study the ability of the CFS to grade clinically increased risk (risk stratification), i.e. the association between the CFS and clinically relevant outcomes in patients >65 years in acute clinical settings. Twenty-nine studies were included out of which 15 were at moderate risk of RoB,[28–42] and 14 at low risk of RoB.[43–56] Our results show that there is a significant difference between frail and non-frail patients in the risk of mortality in-hospital, at 1-, 3-, 6-, and 12 months, and at the end of follow-up (i.e. 6.7 years) and that the CFS is a strong and independent predictor of mortality at all time-points. Our result also showed a significant difference in the odds of all-cause readmission within 30 days, extended LOS, adverse discharge destination, and functional decline between pre-hospital frail and non-frail patients as defined by the CFS, and CFS was an independent risk factor. Taken together, this is a strong indication that the CFS provides robust risk predictions in patients >65 years in acute clinical settings.

Although the CFS is commonly used in research and clinical care, there is currently only one previous scoping review showing that it is widely used in multiple settings and has a good predictive ability for mortality, length of stay, and functional decline.[7] The results of this review, also judging the bias in the included studies, confirms these results and further support the use of the CFS in clinical practice.

Since the population of frail older adults is growing and healthcare utilization among this population is increasing, prevention of frailty, maintenance, or reduction of the level of frailty should be prioritized. Dementia confers a unique challenge, although the degree of frailty generally corresponds to the degree of dementia.[13] When dementia is suspected, although not diagnosed, the CFS assessment should be completed with cognitive tests. There is a pressing need to understand how a population with potentially complex medical, physical, and psychosocial concerns could be supported. Therefore, an assessment tool with good clinimetric properties is needed. The CFS provides a simple clinical measure of biological age, combining comorbidity, disability, and cognitive impairment. The use of the CFS to stratify risk is not particularly time-consuming and is relatively easy to implement in daily clinical practice.[7,8,12] Although one primary purpose of the CFS is risk stratification, it may also be used as a screening tool to identify frail patients needing further geriatric evaluation, i.e. comprehensive geriatric assessment (CGA). In addition, reliable information on long-term prognosis may improve informed decision-making on the individual level for patients and their families.

It is beyond the scope of this review to compare the CFS with other frailty instruments, as well as to comprehensively describe the different concepts or models of frailty, including multidimensionality and different components or domains. Measuring the level of frailty may be challenging for several reasons. Multiple theoretical and operational frailty

definitions have been suggested in the last decade,[21,22,] and there is no international standard measurement for frailty.[6,9,18] Different frailty models (and corresponding instruments) serve different purposes and it is important to point out that measuring frailty has several objectives requiring different forms of assessment. Some measures are better for population-level frailty screening (e.g. self-reported questionnaires), whereas others are best suited for clinical assessment.[9] In addition, there are some measures that are better suited to direct the patient toward a more complex multidimensional, interdisciplinary diagnostic process. In contrast, others are best suited to describe health status changes over time. In a recent consensus document from the European Society of Cardiology, the following was stated:

> Therefore, albeit under the same definition, these two different concepts (accumulated deficit-model and phenotype-model) currently recognize entirely different subjects and, more importantly, generate different clinical and prognostic implications that may be considered as complementary.[57]

Frail patients pose particular challenges, have higher rates of adverse outcomes, and have complex healthcare needs.[4,19] In several hospitals in Sweden, the CFS scale is routinely included in the assessment of all patients older than 65 years in emergency departments and other acute settings. A primary purpose of the CFS is to grade clinically increased risk (i.e. risk stratification), and in these contexts, the CFS is generally used to identify patients presenting an increased risk profile that warrants comprehensive assessments allowing care plans to be more tailored and holistic.[12] Our results indicate that the CFS is a robust tool for predicting adverse health outcomes and that it is essential to report the accumulated knowledge on the risk-predictive performance of CFS in a scientific review that can guide clinical decision-making. Since the CFS has been validated against the Frailty Index, and the correlation between the two scales is high,[14] it is argued that the CFS also can be used to identify older patients' capacity to accumulate deficits which lies beyond categorically defining the presence/absence of frailty or risk of frailty.[6] Our results report the accumulated knowledge on the risk-predictive performance of CFS and highlight the importance of routinely including frailty assessments, such as the CFS, to estimate biological age, improve risk assessments, and assist clinical decision-making in older adults in acute care.

Limitations

Firstly, there was large variability between the studies regarding how the CFS was used in the analysis (i.e. dichotomous, discrete, grouped), controlling factors, and study settings. Therefore, we chose to present our comprehensive overview of the research evidence in a narrative synthesis using tables and figures instead of performing a meta-analysis, which would have strengthened our results. Also, the lack of adjustment for psychosocial factors and polypharmacy across studies might have influenced our results. Although most studies controlled for age, frail patients tend to be older than non-frail patients, and the risk of mortality generally increases with advancing age which might have affected the predictive performance of CFS. Frail patients might not receive the same level of care/care interventions as non-frail patients, which might influence the predictiveness of the CFS. However, there are studies that show that although the type of therapy or level of care is used as a controlling factor in the analysis, the predictive ability of the CFS remains unchanged.[20,24,56,58] Secondly, we used the QIUPS tool as recommended by the Swedish Agency for Health Technology Assessment and Assessment of Social Services. It is possible that utilizing another quality assessment tool would have influenced our final sample of included studies. Instead of using GRADE to weigh the results of the included studies against each other, three authors independently screened and extracted the data. Seven authors independently assessed the risk of bias using the QUIPS tool. In addition, the data extracted from the included studies were reviewed and discussed by the authors, who all have extensive clinical and scientific experience of frailty and the use of different frailty assessment tools. Thirdly, the literature review was stopped in 2020 with the plan of publishing in 2021. Due to the Covid-19 pandemic, the methodological quality assessment of eligible studies and publication of the final literature review was delayed. Including research studies published after 2020 would have further strengthened our literature review.

Conclusion

A primary purpose of the CFS is to grade clinically increased risk (i.e. risk stratification). Our results report the accumulated knowledge on the risk-predictive performance of CFS and highlight the importance of routinely including frailty assessments, such as the CFS, to estimate biological age, improve risk assessments, and assist clinical decision-making in older adults in acute care. This review revealed that frailty, according to the CFS, is a strong predictor of

adverse health outcomes in patients >65 years in acute settings. Further research into the potential of the CFS and whether implementing the CFS in routine clinical practice will improve care outcomes and patients' quality of life is warranted. Due to the strong association between frailty according to the CFS and adverse health outcomes, more research on acute management and rehabilitation potential in frail older adults is needed.

Disclosure

Dr Joakim Alfredsson reports personal fees from Boehringer Ingelheim, MSD, and Astra Zeneca, outside the submitted work. Dr Tommy Cederholm reports personal fees from Nutricia, Nestle, Fresenius-Kabi, Abbott, and Pfizer, outside the submitted work. The authors report no other conflicts of interest in this work.

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