

**Identifying older adults with frailty approaching end of life: a systematic review**

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# Key messages

* The NHS has an ambition to deliver the best possible care for those at the end of life. End of life services for people with cancer are well developed, but most older adults live with and die from non-malignant long-term conditions.
* Frailty is a health state characterised by a slow and gradual decline, which makes it difficult to identify when someone is entering the final 12 months of life.
* This systematic review aimed to synthesise evidence for how can we identify older people with frailty approaching end of life, and whether/how identification and associated intervention improves their experiences and outcomes.
* We included studies involving adults aged 65 and over, identified frail using the cumulative deficit or phenotypic models of frailty, or another established measure of frailty. We defined end of life as the final 12 months of life. We excluded studies with no established measure of frailty, those that used proxies for frailty (e.g. care home residence) or ‘frail’ as a synonym for old age. We also excluded studies involving people with cancer.
* The review found that there are no widely accepted, evaluated ways of identifying when older adults identified as frail are moving into the final 12 months of life.
* No evaluative evidence (specific to people with frailty) was identified for the application of established clinical tools such as the Gold Standards Framework Prognostic Indicator (GSF), the Necesidades Palitivas (NECPAL CCOMS-ICO© Tool Version 1) and the Supportive and Palliative Care Indicators Tool 9 (SPICT).™
* Strong evidence for identifying people with frailty who are approaching end of life came from a study of the electronic Frailty Index (eFI) in primary care. A distinct trajectory in eFI scores in the last 12 months of life (low baseline, followed by a rapid rise, then plateau) was associated with increased risk of death. More work would be required to develop an approach that is suitable for implementation in practice with individual patients.
* In this review, declining physical fitness in people with frailty admitted to emergency hospital care, and malnutrition or heart failure in care home residents with severe frailty have been shown to be indicators of approaching end of life. This evidence was limited to single studies from Sweden and Japan respectively.
* We found no studies of specific interventions for people who have been identified as frail (using an established measure of frailty) and at the end of life.
* Clear implications for policy and practice are hindered by the lack of evidence that relates to older adults explicitly identified as frail using established measures. Frailty is a well-established, distinct clinical entity with a series of measures developed in recent years. Future end of life research needs to use explicit approaches to the measurement and reporting of frailty.

# Executive summary

## Background and aim

The National Health Service (NHS) has a stated ambition to deliver the best possible care for those at the end of life. End of life services for people with cancer are well developed, but most older adults live with and die from non-malignant long-term conditions. Frailty is a common health state at older ages, characterised by a slow and gradual decline. People with frailty may have specific needs for end of life care, but there is no consensus on how to identify these people in a timely way, and once identified, whether they will benefit from specific interventions around end of life.

This systematic review aimed to synthesise evidence on how can we identify older people with frailty approaching end of life, and whether identification and associated intervention with this group improves their outcomes.

## Methods

We used a systematic review approach.

### Search strategy

A search strategy was developed, piloted and tested. Searches were carried out in the following databases: MEDLINE (Ovid), Embase (Ovid), Healthcare Management Information Consortium (Ovid), Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Controlled Register of Trials), CINAHL (EBSCO) and Epistemonikos.[[1]](#footnote-2) Searches were conducted in December 2019, with an additional search run in February 2020, with no date restrictions.

### Review criteria

Articles eligible for inclusion were those with adults aged 65 and over, identified as frail via either of the two main models of frailty (the phenotype model or the cumulative deficit model), or any other established measure. The end of life phase was defined as the final 12 months of life. Articles were excluded if they had used proxy definitions of frailty (such as long-term care residence) or ‘frail’ as a synonym for old age. Articles with mixed populations were included if those meeting the age and frailty criteria were distinguishable. Articles were excluded if they focused on older adults with cancer even if they were also identified as frail.

### Article selection

Titles and abstracts (n=5,844) were screened for relevance by two researchers independently, with decisions compared and discussed to clarify and resolve inconsistencies. Full texts of all selected articles (n=58) were assessed by two researchers independently, with a third researcher resolving inconsistencies.

### Data extraction and synthesis

Summary data were extracted, including: authors and date; country; aim; design; setting; definition of frailty; population characteristics (age; other diagnoses); description of prognostic model/factor or intervention; main findings; reported strengths and limitations; authors’ conclusions. Articles were appraised using quality appraisal tools appropriate to the design. A narrative summary was used.

### Patient and public involvement and engagement

This review used two approaches to engage with the public about their perspectives on discussions and support around end of life. A large network of public members who regularly contribute their perspectives on issues relating to ageing was used to facilitate an online discussion. Individuals with experience of supporting those at end of life (professional and public) were also consulted directly. The views expressed during these discussions were used to help interpret the findings of the review.

## Findings

Three articles met the inclusion criteria.

Strong evidence for identifying people with frailty who are approaching end of life came from a study of the electronic Frailty Index (eFI) in primary care. A distinct trajectory in eFI scores in the last 12 months of life (low baseline, followed by a rapid rise, then plateau) was associated with increased risk of death. This evidence was from a population-level study and it is therefore not clear from this study how this evidence would be translated into an approach that is suitable for use in practice with individual patients.

Evidence from a single Swedish study suggested that declining physical fitness amongst frail older people admitted to emergency hospital care was helpful to identify the end of life. This was particularly the case for men, people with high levels of comorbidity, or in those who showed a decline in fitness during an initial 3-month post-discharge period.

A study from Japan suggested that malnutrition or heart failure in nursing home residents with severe frailty could help to identify those who are approaching end of life.

We found no studies evaluating the use of established clinical tools—e.g. Gold Standards Framework Prognostic Indicator (GSF); Necesidades Palitivas (NECPAL CCOMS-ICO© Tool) Version 1; Supportive and Palliative Care Indicators Tool 9 (SPICT)™—with existing frail populations, i.e., older adults who have already been identified as frail using an established measure of frailty.

We found no evidence for end of life care interventions for people who have been identified as frail using an established measure of frailty and clearly identified as being in the last 12 months of life. Although there is a body of literature on advance care planning (ACP) with people with frailty, most of this research has relied on proxy measures of frailty.

## Implications for policy and practice

Our attempts to identify clear implications for policy and practice were hindered by the lack of evidence from studies that used an established approach to assessing frailty. Frailty is a well-established, distinct clinical entity, with a series of assessment measures developed over recent years, but there is a paucity of end of life research that employs any of these measures.

The research evidence considers very few prognostic models or factors that can identify when older adults who have specifically been identified as frail are moving into the final 12 months of life. Analysis of the eFI shows that there are clear trajectories in primary care patients. More work would be required to develop this into a practical tool for use with individual patients. Evidence from single, small studies in distinct populations identifies measures of physical fitness and assessment of malnutrition as potential indicators of end of life. Other potentially relevant models and factors have not been the subject of study. There is a lack of evidence for interventions for people who have been identified as frail, and clearly identified as being in the last 12 months of life.

This review found little evidence to further develop current policy and practice which is based on broad concepts of frailty that use proxy assessment measures. Given the importance of frailty in current policy, future end of life research should employ explicit measurement and reporting of frailty among study populations.

# Background

The National Health Service (NHS) has a stated ambition to deliver the best possible care for people at the end of life. End of life services for cancer are well developed (1), but most older adults live with and die from non-malignant long-term conditions. This population may have specific needs for end of life care but it is not clear how they can be identified in a timely way, and once identified, how they will benefit from intervention.

The national framework Ambitions for Palliative and End of Life Care highlights inequalities in access to end of life care (2). People with non-malignant conditions are a particular focus, with a need for better use of data to support clinical decision-making and planning for this population. Frailty is a non-malignant health state where people may have specific end of life care needs that should be carefully considered (3, 4). It is described in more detail in Box 1.

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| **Box 1.** What is frailty? |
| Frailty is ‘a state of vulnerability to poor resolution of homeostasis following a stress and is a consequence of cumulative decline in multiple physiological systems over a lifespan’ (5).There are two principal models of frailty. The**frailty phenotype** **model** (6) uses five criteria: exhaustion, weight loss, weakness/loss of muscular strength, reduced gait speed, and reduced energy/physical activity. A person is frail if they experience three or more of these criteria. The**cumulative deficit model**(7)considers that ‘the more things somebody has wrong with them, the more likely they are to be frail’. Frailty is measured using a Frailty Index (FI) containing 36 or more deficits. The number of deficits an individual has is divided by the total number in the index to give a score between 0 (no frailty) and 1 (extreme frailty). |

Estimates of the prevalence of frailty in the UK suggest that 3% of people aged 65 and over are severely frail and a further 12% are moderately frail (8).[[2]](#footnote-3) Frailty is a strong predictor of mortality (5), but identification that someone with frailty is approaching end of life—commonly defined as the final 12 months (9)—is difficult, because frailty is characterised by a slow and gradual decline (10). Since 2017, the General Medical Services contract in England has mandated general practice to identify and manage all patients aged 65 and over with moderate or severe frailty; all those with severe frailty should receive annual medication and falls reviews (8). A widely used tool in English primary care, is the electronic Frailty Index (eFI), which is based on the cumulative deficit model (see Box 1).

Identification of people with frailty who may benefit from end of life care would be useful at a population level, to support planning and equitable distribution of resources. At an individual level, accurate identification of end of life in frailty may facilitate advance care planning (ACP), care coordination and reduction in treatment burden. Although identification may lead to more appropriate services for patients, this is not necessarily straightforward. There is a literature on the views of professionals around early identification of end of life care needs that highlight some of the complexities (11, 12). These include a need to develop communication about end of life, so that it is an ongoing conversation, within an integrated team approach, that acknowledges patients’ wider considerations beyond medical implications.

Methods for end of life identification and intervention need to be based on strong conceptual and empirical foundations to ensure that they are a good use of health and care resources. Once identified, people should be offered appropriate care or effective interventions that will improve patient and carer experiences, quality of care and outcomes. Recent systematic reviews have focused on the ability of frailty measures to predict mortality over several years, as opposed to identifying entry into the end of life phase in people who have already been identified as frail. A recent review of reviews of frailty screening tools (26 assessments and eight indicators in total) found that the FI and gait speed were the most useful measures in routine care and community settings to predict adverse health outcomes including death (13). Another systematic review also found that the FI was a significant predictor of mortality (14), over two to 19 years.

This review evidence therefore shows that although the FI is the most useful measure for predicting mortality over relatively long periods of time, it remains unclear how patients already identified as frail may be identified as moving into the end of life phase. A common, generic approach to predicting entry into the end of life phase is the ‘surprise question’, in which clinicians reflect on whether they would be surprised if a particular patient were to die in the next 12 months. A systematic review and meta-analysis found that the surprise question performed only poorly-to-modestly, with worse performance in frailty, and recommended that it should not be used as a stand-alone tool (15). The British Geriatrics Society (16) currently recommends use of the Gold Standards Framework (GSF), the Necesidades Palitivas (NECPAL CCOMS-ICO© Tool Version 1) and the Supportive and Palliative Care Indicators Tool 9 (SPICT).™ The GSF and the NECPAL both start with use of the surprise question before considering indicators of frailty; the NECPAL CCOMS-ICO© Tool is intended to be used to identify patients who would benefit from palliative care, but is explicitly not intended to be used to determine prognosis. The SPICT rejects the time frame common to the surprise question and is an approach to holistic assessment and care planning in which prognostic uncertainty is accepted. None of these tools contain frailty-specific prognostic markers for end of life.

# Aims of the review

We aimed to synthesise evidence for how we can identify older people with frailty approaching end of life, and whether identification and associated intervention with older people with frailty approaching end of life improves their experiences and outcomes.

# Methods

We adopted a systematic review approach. This review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist for the reporting of systematic reviews (17). A protocol was registered on Prospero ([CRD42020462624](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=162624)).

## Search strategy

We developed and piloted a strategy and carried out searched in the following bibliographic databases: MEDLINE (Ovid), Embase (Ovid), Healthcare Management Information Consortium (Ovid), Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Controlled Register of Trials), CINAHL (EBSCO) and Episkemonikos.[[3]](#footnote-4)

The search strategy was based on combinations of search terms relating to four concepts:

1. frail older adults
2. end of life
3. prognosis
4. intervention

We combined concepts 1, 2 and 3 for identification and concepts 1, 2 and 4 for intervention. These two combinations were merged, and duplicates removed.

The search was designed by an experienced information specialist (FB) in collaboration with other members of the project team (AH and EB). We designed the search in MEDLINE, using MeSH headings and title and abstract key words (Appendix A), and translated to other databases. The prognosis concept was informed by a tested filter published in the evidence synthesis methodology literature (18). Searches were conducted in December 2019, with no date restrictions.

To achieve more comprehensive results, we ran additional searches in MEDLINE, Embase and CINAHL using manipulations of the search term ‘mortality’. The MEDLINE design is shown in Appendix A. These additional searches were conducted in February 2020, again with no date restrictions.

## Review criteria

The review design drew upon PICOTS guidance for systematic reviews of prediction models (19). Review criteria are summarised in Table 1. Key criteria for inclusion were studies involving adults aged 65 and above, who were explicitly defined as frail (using the frailty phenotype model, the cumulative deficits model, or any other established measure). The rationale for using explicit definitions of frailty was to acknowledge that although frailty overlaps with disability and comorbidity, it is a distinct clinical entity with a series of specific measures developed in recent years (20). Studies with mixed populations were included if those meeting the age and frailty criteria were distinguishable. Key criteria for exclusion were studies where frailty was inferred by a proxy (e.g. long-term care residence), and studies that focused on people who had a diagnosis of cancer, even if they were also identified as frail, because end of life care identification and subsequent care pathways for cancer are well developed (1). We defined the end of life phase as the final 12 months of life, which is widely used and is reflected in NICE Quality Standards for end of life care (9).

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| **Table 1. Inclusion and exclusion criteria** |
|  | **Inclusion criteria** | **Exclusion criteria** |
| **Population** | Older adults (aged ≥65)Sample explicitly defined as frail via one of the two major models of frailty: Fried’s **frailty phenotype** (6)**;** Rockwood and Mitnitski’s **cumulative deficits model** (7)Studies where frailty is defined using **other established measures** | Older adults with cancerStudies using the term ‘frail’ as a generic adjective without justification or clear definition of frailtyOlder adults with major life-limiting diagnoses (e.g. dementia, heart disease, COPD, stroke, renal disease) who are not also explicitly identified as frail Studies with mixed populations where results from older adults who are identified as frail are indistinguishable from results from older adults who are not identified as frail |
| **Interventions and Comparators** | **Prognostic prediction models** for the identification of end of life in frailty. We defined a prognostic prediction model as one which estimates ‘the individualised probability or risk that a certain condition will occur in the future by combining information from multiple prognostic factors from an individual’ (21); Prognostic prediction models linked to interventions (**prediction model impact studies**), through comparative studies where one group receives usual care provided without the model and the other has model predictions made available to guide decision-making;**Interventions** where people with frailty identified as being at the end of life are treated with an intervention compared with usual care or another suitable comparator. |  |
| **Study design** | Reviews or individual studies of prognostic prediction models Reviews or single comparative studies of prediction model impact studiesReviews or single comparative studies of interventions | Case studies, case series, non-controlled before and after studies, qualitative studiesAbstracts and studies not in full form. |
| **Outcomes** | Prognostic models: model performance, including discrimination (the ability of the model to distinguish between patients needing end of life care and those who do not) and calibration (accuracy of predicted risk of end of life care, in terms of how the expected outcomes predicted from the model diverge from the observed outcomes). Interventions: patient outcomes (clinical outcomes, quality of life); health care utilisation and cost-effectiveness; patient experience. |  |
| **Time span of prediction** | Individuals likely to die within 12 months  | Models that predict survival beyond 12 monthsInterventions for people expected to live beyond 12 months |
| **Setting** | All health care settings |  |

The application of the key inclusion criteria is summarised in Figure 1.

Prognosis

Life expectancy ≤ 12 months

Established measure of frailty

Age ≥ 65

Intervention

**Figure 1. Application of key inclusion criteria**

## Article selection

Records were screened in two stages: (i) titles and abstracts were screened for relevance by two researchers independently (AH and EB), with decisions compared and discussed to clarify and resolve inconsistencies; (ii) we retrieved the full texts of all records selected at stage one and assessed them for inclusion against the review criteria, by two researchers independently (AH and EB) with a third researcher resolving inconsistencies (PK or PB). During retrieval of full-texts, other relevant texts not identified during our database searches were also reviewed if potentially eligible.

## Data extraction, quality appraisal and synthesis

A data extraction form was developed and piloted. Data were extracted as follows: authors and date; country; aim; design; setting; definition of frailty; population characteristics (age; other diagnoses); description of prognostic model/factor or intervention; main findings; reported strengths and limitations; authors’ conclusions. Data were extracted by one researcher (AH) and checked by a second (EB).

We identified the following quality appraisal tools for use where appropriate:

* Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) (22)
* Prognostic studies: Prediction Model Risk of Bias Assessment Tool (PROBAST) (23); Quality in Prognostic Studies (QUIPS) (24)
* Randomised controlled studies: Cochrane Risk of Bias (RoB) 2.0 (25)
* Non-randomised comparative studies: Cochrane Risk of Bias in Non-Randomised Studies-of Intervention (ROBINS-I) (26).

Quality appraisal was conducted by one researcher (AH) and checked by a second (EB or PK). We produced a narrative summary of findings.

## Patient and public involvement and engagement (PPIE)

We consulted with patients and the public to find out their opinions on end of life care for people with frailty. Our main approach was via the Valuing Our Intellectual Capital and Experience (VOICE) network to facilitate an online discussion.[[4]](#footnote-5) VOICE is a large network of public members across the UK who regularly contribute their perspectives on issues relating to ageing. Existing members of the VOICE network were made aware of the opportunity to contribute to our discussion via their usual weekly bulletin. We also circulated the link to the VOICE discussion among our existing stakeholder networks.

The introductory text of the discussion board is in Appendix B. We specified that we were interested in the views of older people with frailty, or those who provide support to an older person with frailty. We requested that people with a diagnosis of cancer, or those providing support to someone with a diagnosis of cancer, did not take part.

We invited discussion around two broad questions:

* Have health or social care professionals discussed end of life with you/the person you support?
	+ If so, how did these discussions happen? What services, support or care have been offered following these discussions? Has anything changed?
	+ If not, do you think these sorts of discussion would be helpful? What would you like to discuss?
* In terms of services, support and care, what is important to you/the person you support at the end of life? What would you like to see happen?

We ran the discussion board for two weeks, from 21st September to 4th October 2020. One researcher (AH) facilitated the discussion by checking the board daily and responding to posts. In total three people made posts. We also spoke directly to professionals and older adults with experience of supporting people at end of life.

# Findings

## Number of articles

Database searches yielded 5,844 unique articles. Three articles met the inclusion criteria (Figure 2).



**Figure 2. PRISMA flow diagram** (17)

## Characteristics of included articles

Table 2 summarises the characteristics of the three included articles (27-29). These articles focused on the identification of the end of life phase in people with frailty. A list of the 58 articles excluded at full-text review (30-87), with reasons, is provided in Appendix C.

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| **Table 2. Characteristics of included studies** |
| **Study; country** | **Study type, design and setting** | **Aim** | **Measure of frailty** | **Population characteristics; *other diagnoses*** | **Prognostic tool / intervention description** |
| Ahlund et al. 2019; Sweden (27) | Prognostic (factor)Sub-study from a prospective controlled clinical trialHospital (inpatient emergency medical care) | To analyse (1) the association between physical fitness measurements and 1-year mortality, and (2) the association between a preserved physical fitness during the first three months after discharge from emergency hospital care and 1-year prognosis | Frail Elderly Support Research Group (FRESH) screening instrument | n=408 (56.7% female, mean age 85.7, range 75-99); 18 died during hospital stay therefore final total n=390 in analysis. *Renal failure (87%), hypertension (71%), heart failure (40%), ischemic heart disease (30%) and cerebrovascular disease (26%)* | Six-minute walk test (6MWT); handgrip strength test (HS) |
| Kamo et al. 2017; Japan (28) | Prognostic (factor)1-year prospective studyLong term care (nursing homes) | To explore the relationship of coexisting severe frailty and malnutrition with all-cause mortality among the oldest old in nursing homes | Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) | **Total**: n=160, 88.75% female, mean 90.9 (sd 3.8). **Mild or moderate frailty** (CFS score 5-6): n=37, 100% female, mean age 91.0 (sd 4.4). *Dementia (n=5), cerebrovascular disease (n=5), cancer (n=3), osteoarthritis (n=3), hypertension (n=10), heart failure (n=2), hip fracture (n=5), diabetes (n=1).* **Severe frailty** (CFS score 7+): n=123, 85.4% female, mean age 90.9 (sd 3.7). *Dementia (n=51), cerebrovascular disease (n=33), cancer (n=6), osteoarthritis (n=9), hypertension (n=48), heart failure (n=12), hip fracture (n=17), diabetes (n=14).* **Co-existing severe frailty & malnutrition**: n=75, 86.6% female, mean age 92.1 (sd 3.9). *Dementia (n=40), cerebrovascular disease (n=24), cancer (n=6), osteoarthritis (n=7), hypertension (n=39), heart failure (n=11), hip fracture (n=14), diabetes (n=6)* | Nutritional status assessed using Mini Nutritional Assessment - Short Form (MNA-SF); health status assessed through medical reports; overall mortality measured over 12-month follow up period via telephone/medical records |
| Stow et al. 2018; England (29) | Prognostic (model)LongitudinalPrimary care | To determine if changes in frailty measured by the eFI could be useful in primary care to indicate increased risk of dying and the need to consider palliative care | eFI | n=26,928 (13,149 cases, 13,149 controls), 55.6% female, mean age at death 85.14 (sd 5.98) (cases) | eFI was calculated automatically by ResearchOne (extracts data from SystmOne clinical information system which hold records on half the UK population) at monthly intervals for 1 year, based on the information contained in each participant’s clinical record |

## Quality appraisal

Table 3 shows the risk of bias assessments of the three studies. All were all judged to be of low risk of bias.

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| **Table 3. Risk of bias assessments of included studies** |
| **Study** | **Stow et al. 2018** (29) | **Ahlund et al. 2019** (27) | **Kamo et al. 2017** (28) |
| **Overall RoB judgement** | Low | Low | Low |
| **Appraisal tool** | PROBAST | QUIPS | QUIPS |
| **RoB judgements by domain of tool** | **Domain** | **Judgement**RoB/Applicability concern | **Domain** | **Judgement** | **Domain** | **Judgement** |
| Participants | Low/Low | Study participation | Low | Study participation | Low |
| Predictors | Low/Low | Study attrition | Moderate | Study attrition | Low |
| Outcome | Low/Low | Prognostic factor assessment | Low | Prognostic factor assessment | Low |
| Analysis | Low/Low | Outcome measurement | Low | Outcome measurement | Low |
|  | Adjustment for other prognostic factors | Low | Adjustment for other prognostic factors | Low |
| Analysis | Low | Analysis | Low |

## Primary care: clear trajectories in electronic Frailty Index scores

The prognostic model study by Stow et al. (29) was a longitudinal case-control study of 26,928 primary care patientsto determine if changes in eFI scores over a 12-month period could identify those at increased risk of dying. Stow et al. found that repeat measurement of frailty using the eFI can support the identification of people with frailty who are approaching end of life. The study found three distinct trajectories of eFI score. A small but clear proportion of the sample (2.2%) had a frailty trajectory characterised by a rapid initial rise from a low baseline, followed by a plateau. People in this group showed an initial increase of 0.022 eFI per month, slowing from a baseline eFI of 0.21. This was associated with a mortality increase of 180% (OR 2.84, 95% CI 2.34–3.45). This trajectory had 99.1% specificity and 3.2% sensitivity (positive predictive value 19.8%, negative predictive value 93.3%) for predicting individual mortality risk. Just under a quarter of the sample (21.2%) showed a pattern of moderately increasing frailty (eFI increase of 0.007 per month, baseline 0.26). This was associated with a mortality increase of 65% (OR 1.65, 95% CI 1.54–1.76). The largest group, around three-quarters of the sample (76.6%), showed a stable frailty profile, with an eFI increase of 0.001 from a baseline of 0.26.

## Emergency hospital care: physical fitness

The prognostic factor study by Ahlund et al. (27) investigated the predictive value of physical fitness among frail older patients who had received emergency hospital care. Physical fitness measures used were to test aerobic capacity (via the six-minute walk test (6MWT)) and muscle strength (via a handgrip strength test). Participants completed tests on three occasions: at baseline, at 3-month follow up, and at 12-month follow up.

Performance on both tests, at baseline and at 3-month follow up, was associated with 1-year mortality. On the 6MWT, people who walked less than 100m in the index test were over three times more likely to die than those who walked over 200m (HR 3.31, 95% CI 1.89–5.78, p=0.001). People with low handgrip strength at index (<20kg women; <30kg men) had over twice the risk of dying than those with normal strength (HR 2.39, 95% CI 1.33–4.27, p=0.003). Changes on both tests over the 0–3-month period were also associated with 1-year mortality, with those whose performance deteriorated having a poorer prognosis than those whose performance improved (6MWT: HR 3.80, 95% CI 1.44–10.06, p=0.007; handgrip strength: HR 2.21, 95% CI 1.07–4.58, p=0.032). A higher comorbidity burden (Charlson’s Comorbidity Index (CCI) score of 8+) or being male were associated with slightly higher mortality (6MWT: CCI 8+ HR 1.69, 95%CI 1.05-2.70, p=0.03; male gender HR 1.69, 95% CI 1.19-2.38, p=0.003; handgrip strength: CCI 8+ HR 1.70, 95% CI 1.07-2.68, p=0.024; male gender HR 1.76, 95% CI 1.25-2.48, p=0.001). However, severity of frailty and age were not associated with higher mortality.

## Nursing homes: malnutrition or heart failure

The prognostic factor study by Kamo et al. (28) investigated the predictive value of coexisting malnutrition and severe frailty among nursing home residents.[[5]](#footnote-6) Nutritional status of residents was assessed using the Mini Nutritional Assessment - Short Form (MNA-SF), health status was assessed via medical reports, and mortality measured over 12-month follow up. Residents were stratified according to frailty level (mild/moderate or severe). The vast majority (n=123/160) were severely frail, and nearly half (n=75/160) had coexisting severe frailty and malnutrition. Cox regression analysis showed that after adjusting for age, gender, and other diagnoses, coexisting severe frailty and malnutrition was significantly associated with mortality. Specifically, the risk was ten times greater, although there was a wide margin of uncertainty (adjusted HR 10.89, 95% CI 4.04–29.33, p<0.0001). Across all levels of frailty, heart failure was also significantly associated with mortality; this risk was nearly eight times greater, but again, there was a significant uncertainty (adjusted HR 7.83, 95% CI 3.25–18.88, p<0.0001).

## PPIE

In total three people made posts on the VOICE platform discussion board. We also spoke directly with a palliative care programme manager in a local clinical network, to learn more about how frailty was viewed within this region’s approach to palliative care, and with an older adult with experience of supporting a loved one at end of life.

Our PPIE consultees advocated discussions around end of life care and ACP, including documentation of wishes. There was recognition that the initiation and timing of these conversations could be difficult, through a lack of clear prognosis (particularly apparent in frailty) or where the frail person may be reluctant (a more generic challenge). Such conversations would be best held on an ongoing, layered and subtle basis, simply starting by focusing on what is important to the person now and what would they like to happen or not happen in future. An emphasis on quality of life was important. The programme manager reinforced the picture that primary care clinicians found identification of end of life in people with frailty very difficult, even in discussion with colleagues. They highlighted ongoing quality improvement work to address inequalities in access to palliative care for conditions other than cancer, and a specific focus on frailty which included people of all ages, not just older adults.

# Discussion

## Review focus

Frailty is a health state where people may have specific end of life care needs and where existing provision of end of life care may be suboptimal. Identifying that someone with frailty is approaching end of life is difficult because frailty is characterised by a slow and gradual decline. Identification of people with frailty who may benefit from end of life care would be useful at a population level, to support planning and equitable distribution of resources. At an individual level, accurate identification of end of life in frailty may facilitate ACP, care coordination and reduction in treatment burden. This review focused on how older people with frailty can be identified as approaching end of life, and whether identification and associated intervention with such people improves their experiences and outcomes. We adopted strict inclusion criteria, in particular regarding frailty, non-cancer and end of life. We focused on populations who had been identified as frail using an established measure of frailty, rather than by proxy measures, because frailty is a distinct clinical entity and there have been a series of frailty measures developed in recent years (20). We excluded studies that focused on people who had a diagnosis of cancer, even if they were also identified as frail, because end of life care identification and subsequent care pathways for cancer are well developed (1). We defined the end of life phase as the final 12 months of life, which is widely used and is reflected in NICE Quality Standards for end of life care (9).

## Summary of findings

We found one prognostic model and two prognostic factor studies.[[6]](#footnote-7) The prognostic model study provided evidence for use of the eFI in primary care to identify when people with frailty are approaching end of life. There was a subset of frail people with clear trajectory in eFI scores during their final 12 months of life, characterised by a low baseline, followed by a rapid rise, before reaching a plateau. People with this trajectory would be the most likely candidates for palliative care. However, this evidence was from a population-level study that was not designed to produce practical tools for use with individual patients.

Two small studies identified potential prognostic factors that are common in later life and unlikely to be of practical use.

We found no studies evaluating the use of established clinical tools—e.g. Gold Standards Framework Prognostic Indicator (GSF); Necesidades Palitivas (NECPAL CCOMS-ICO© Tool) Version 1; Supportive and Palliative Care Indicators Tool 9 (SPICT)™—with existing frail populations, i.e., older adults who have already been identified as frail using an established measure of frailty.

We did not find any studies evaluating any end of life care interventions for older people who had been identified as frail via an established measure, and who had been clearly identified as being at end of life.

## Key finding: lack of use of frailty measures

The key finding from this review is the lack of use of established frailty measures in the literature on end of life identification and intervention for frail older adults. Our inclusion criteria meant that we necessarily excluded research that had used proxy indicators of frailty, such as long-term care residence. One example was the study of Heppenstall et al. (53), which aimed to develop methods for predicting 12-month mortality by testing the performance of geriatricians (similar to the surprise question) and the performance of a logistic regression model. Both approaches had mediocre performance, only slightly better than chance (geriatricians: AUC=0.64; model: AUC=0.65). The authors made repeated mention that long-term care residents constituted a frail population, yet also stated that markers of frailty were not available. While it may seem intuitive that such a population is frail, this is equivocal; a recent systematic review and meta-analysis of the prevalence of frailty and prefrailty in nursing homes found that only around half of residents were frail according to validated criteria and definitions (89).

Two recent reviews have synthesised the literature on ACP for people who are frail (90, 91), but the vast majority of this literature has not used established measures of frailty. Combes et al. (90) conducted an integrative review of implementation of ACP with frail older people in the community; of the 11 intervention studies included, only one used an established measure of frailty, which was the study by Overbeek et al. (68). However, this study did not use any prognostic model or factor to identify participants at end of life phase; the assumption was based on the fact that participants had a mean age of 87, were in receipt of formal care and were frail (69). Overbeek et al. highlighted that they were surprised by a low mortality rate of 10% during the 12-month study period, and reflected that their participants were in better health than they had assumed (69). Hopkins et al. (91) conducted a systematic review of ACP in acute inpatient settings, including 14 studies with adults aged 75 or over without a disease-specific focus; none of these studies used an established measure of frailty. Combes et al. (90) reflected that use of long-term care residence as a proxy measure for frailty may have skewed findings away from people living in their own homes. Hopkins et al. (91) called for better characterisation of study populations in frailty research as a priority. This call is not limited to frailty-specific research; routine measurement and reporting of frailty is largely missing in trials of novel pharmacological interventions for long-term conditions, but appears to be identifiable and prevalent in study populations from middle age and older (92).[[7]](#footnote-8)

In their cross-sectional study of prognostic indicators of end of life trajectories, Amblas-Novellas et al. (30) reported that in the group of people with advanced frailty and no other illness, there was no indicator that was especially prevalent or infrequent, and that professionals had low perceptions of palliative needs in these patients. This was echoed by our PPIE consultees. Amblas-Novellas et al. recommended the development of new measuring systems for frailty and the need for alternative conceptual models by defining new end of life trajectories. Stow et al. findings on use of the eFI (29) appear to go some way to demarcating a new end of life trajectory in this population. Overall the lack of evidence for prognostic models and absence of prognostic markers in this population, suggests that formal assessment of needs should be prioritised over a search for prognostic indicators. In the case of advanced cancer patients, a recent systematic review of 50 good-quality studies found that patient and informal carers have a wide range of context-bound unmet needs (93); similar levels of pain and distress experienced by these patients are seen in people with frailty (4).

It is possible that intervention at end of life for people with frailty takes the form of lower-key interventions, such as small incremental enhancements to usual care, that are generally not captured in the published literature and are rarely evaluated in their own right, but nonetheless are likely to be of value. We did not find any studies that had evaluated such lower-key interventions for this specific population.

In light of this increased attention on end of life care for people with frailty, it is perhaps worth reflecting that in the guidance for doctors certifying cause of death in England and Wales (94), ‘frailty’ is an example of a ‘very vague statement’ which is not acceptable as the sole cause of death; ‘frailty of old age’ is acceptable when the doctor has been involved in the patient’s care for a long period and has observed a gradual decline in the absence of any other identifiable disease.

## Strengths and limitations

In this review, we adopted transparent, pre-specified criteria, including the need for studies to have applied an established measure of frailty. This is a strength as it is aligned with English health policy position that advocates routine measurement and monitoring of frailty (8) and the recognition that people with frailty may have specific end of life care needs (4). However, it necessarily excluded research that was relevant to but did not directly address the specific focus of the review. We found a very limited literature meeting our specific criteria, and it should be noted that two out of the three studies meeting the criteria were studies of single prognostic factors, rather than multivariable models.

We were hopeful that our approaches to PPIE would lead to a higher level of engagement than achieved. Only three people posted to the VOICE discussion. It is possible that the topic of end of life care was simply not particularly appealing compared to other participation opportunities available on the VOICE network at the time. However, it is also possible that given the challenges in recognising frailty, the specific focus upon end of life care in frailty meant that there were very few people who felt they had eligible experiences upon which to comment; one member posted that they felt their experiences would be irrelevant as they were in the context of dementia.

## Implications for policy and practice

The best evidence for identifying when people with frailty may be entering the end of life phase comes from use of the eFI. However, this evidence was from a population-level study and it is not currently clear how this evidence would be translated into an approach that is amenable to implementation in practice with individual patients. Clear implications for policy and practice around end of life identification and intervention are hindered by the lack of evidence that relates to older adults explicitly identified as frail by an established approach to assessing frailty. Frailty is a well-established, distinct clinical entity, with a series of assessment measures developed over recent years, but there is a scarcity of end of life research that employs any of these measures. Future research should adopt explicit measurement and reporting of frailty among study populations.

The low number of studies included in our review, and the lack of demographic information other than age and gender, mean that we are unable to offer detailed comment on issues of inequalities. Recent work using the eFI with a sample of 13,510 older adults in London has shown that there are differences in the prevalence of frailty between ethnic groups (95). The Stow et al. study (29) applied eFI to data from 26,298 older adults via the SystmOne clinical information system which holds records on half the UK population, and is therefore likely to be representative. Given the current evidence base, it may be useful to think about needs assessment approaches to end of life care in frailty through a lens of equality of access to palliative care.

# Conclusions

There are currently very few prognostic models or factors that can identify when older adults who have specifically been identified as frail are moving into the final 12 months of life. Use of the electronic Frailty Index shows that there is a clear trajectory in primary care patients, but more work would be required to translate this evidence into a practical application. Measures of physical fitness and assessment of malnutrition may also be able to indicate entry into the end of life phase, but this evidence is currently limited to single studies with small samples in Swedish acute care and Japanese nursing homes respectively. There is a lack of evidence for interventions for people who have been identified as frail using an established measure of frailty and clearly identified as being in the final 12 months of life. Clear implications for policy and practice are hindered by the lack of evidence that relates to older adults explicitly identified as frail by an established measure of frailty. Future end of life research should adopt explicit measurement and reporting of frailty among study populations.

# Conflict of interest statement

Authors of the Stow et al. prognostic model study included in this review (29) are members of the NIHR Older People and Frailty Policy Research Unit, including Professor Barbara Hanratty who is a co-author of this review. None of these authors were involved in the search, selection, quality appraisal or data extraction stages of this review.

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Appendices

Appendix A: MEDLINE search strategies

The table below shows the full search strategy including the additional manipulation of the term ‘mortality’ conducted in February 2020. The original search strategy is in rows 1-26; the additional strategy is from row 27 onwards.

|  |  |  |
| --- | --- | --- |
| **#** | **Searches** | **Results** |
| 1 | Frail elderly/ | 10985 |
| 2 | Frailty/ | 2077 |
| 3 | frail\*.ti,ab,kw. | 20344 |
| 4 | 1 or 2 or 3 | 24440 |
| 5 | Terminal Care/ | 27514 |
| 6 | Hospice Care/ | 6332 |
| 7 | Palliative Care/ | 52750 |
| 8 | Terminally Ill/ | 6419 |
| 9 | ("end of life" or end stage or late stage or deterioriat\* or declin\* or dying or palliat\* or life limiting or life-limiting or terminal\*).ti,ab,kw. | 966012 |
| 10 | or/5-9 | 994189 |
| 11 | (Stratification or Discrimination or Discriminate or c-statistic or "c statistic" or "Area under the curve" or AUC or Calibration or Indices or Algorithm or Multivariable).ti,ab,kw. | 747655 |
| 12 | ROC Curve/ | 55872 |
| 13 | "Predictive Value of Tests"/ | 198365 |
| 14 | observer variation/ | 41825 |
| 15 | (predict\* or scor\* or observ\*).ti,ab,kw. | 5212233 |
| 16 | or/11-15 | 5755012 |
| 17 | (adaptive clinical trial or clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial).pt. | 2603782 |
| 18 | exp epidemiologic studies/ or feasibility studies/ or pilot studies/ | 2565475 |
| 19 | ((intervention\* or program\* or strateg\* or initiative\* or project?) and (evaluat\* or effect\* or measur\* or assess\*)).ti,ab,kw. | 1595158 |
| 20 | or/17-19 | 5642691 |
| 21 | 4 and 10 and 16 | 1429 |
| 22 | 4 and 10 and 20 | 1842 |
| 23 | 21 or 22 | 2352 |
| 24 | exp neoplasms/ | 3283100 |
| 25 | 23 not 24 | 2158 |
| 26 | limit 25 to (english language and humans) | 1674 |
| 27 | mortality/ or hospital mortality/ | 80862 |
| 28 | mo.fs. | 561375 |
| 29 | 27 or 28 | 605629 |
| 30 | 4 and 29 and (16 or 20) | 2103 |
| 31 | 30 not 24 | 1736 |
| 32 | limit 31 to (english language and humans) | 1659 |
| 33 | 32 not 26 | 1382 |
| 34 | 4 and 27 and (16 or 20) | 702 |
| 35 | 34 not 24 | 677 |
| 36 | limit 35 to (english language and humans) | 646 |
| 37 | 36 not 26 | 545 |
| 38 | 4 and 28 and (16 or 20) | 1671 |
| 39 | 38 not 24 | 1312 |
| 40 | limit 39 to (english language and humans) | 1260 |
| 41 | 40 not 26 | 1053 |
| 42 | 41 not 37 | 837 |
| 43 | from 42 keep 1-837 | 837 |
| 44 | Frailty/mo [Mortality] | 191 |
| 45 | 44 and (16 or 20) | 180 |
| 46 | limit 45 to (english language and humans) | 178 |
| 47 | 46 not 24 | 164 |
| 48 | 47 not 26 | 142 |
| 49 | 37 not 48 | 518 |
| 50 | 41 not (48 or 37) | 722 |
| 51 | 33 or 48 | 1382 |

Appendix B: Text used on the VOICE network discussion platform

**Overview**

Share your thoughts and experiences on end-of-life care for people with frailty to support policy research.

--------------------------------------------------------------------------------------------------------------------------

The [NIHR Older People and Frailty Policy Research Unit](https://www.opfpru.nihr.ac.uk/) are conducting a project to understand how we can identify older people with frailty who are approaching end-of-life, and whether identifying and subsequently supporting these people improves their experiences and outcomes.

We are interested in end-of-life care for those with diagnoses other than cancer. This is because end-of-life care for people with cancer is much better developed, and better understood, than end-of-life care with frailty.

The majority of older people live with and die from complex combinations of frailty, disability, and long-term conditions. These people are likely to need end-of-life care, but it is not clear how they can be identified in a timely way, and whether they will benefit from intervention.

We would like to invite**older people with frailty**, or**those who provide support to an older person with frailty**, to take part in a discussion about end-of-life care.

Please **do not** take part in this discussion if you or the person you support has a diagnosis of cancer.

**What is frailty?**

Frailty is a specific health state that is characterised by low energy, slow walking speed, and poor strength, which makes people more vulnerable to serious health problems after a seemingly minor event or change. Frailty is associated with ageing, but it is not an inevitable part of ageing or a short-hand term for ‘old age’. For more information about frailty, [click here to take a look at the British Geriatrics Society’s website](https://www.bgs.org.uk/resources/frailty-what%E2%80%99s-it-all-about).

**What is end-of-life care?**

People are usually considered to be approaching end-of-life if they are expected to die within 12 months. End-of-life care includes palliative care, which is focused on making people comfortable, addressing pain and symptoms, and involving psychological, social and spiritual support. For more information about end-of-life care, [click here to take a look at the NHS website](https://www.nhs.uk/conditions/end-of-life-care/what-it-involves-and-when-it-starts/).

**Discussion questions**

* Have health or social care professionals discussed end-of-life with you/the person you support?
	+ If so, how did these discussions happen? What services, support or care have been offered following these discussions? Has anything changed?
	+ If not, do you think these sorts of discussion would be helpful? What would you like to discuss?
* In terms of services, support and care, what is important to you/the person you support at the end-of-life? What would you like to see happen?

Please leave your comments in the discussion section below.

The discussion will run from **Monday 21st September**until **Sunday 4th October 2020.**

Appendix C: List of excluded studies

|  |  |  |
| --- | --- | --- |
| **Study** | **Reason** | **Notes** |
| Amblas-Novellas et al. 2016 | Wrong population | Not already identified as frail |
| Amella 2003 | Wrong study design | Not prognostic or intervention |
| Armstrong et al. 2010 | Wrong publication type | Research letter |
| Arora et al. 2010 | Wrong population | Not already identified as frail - 'vulnerable hospitalised elders' |
| Barclay et al. 2014 | Wrong population | Not defined as frail |
| Brown et al. 2016 | Wrong time span | > one year |
| Buchman et al. 2009 | Wrong time span | > one year |
| Butcher et al. 2019 | Wrong time span | > one year |
| Cardona-Morrell et al. 2015 | Wrong study design | Review paper |
| Cardona-Morrell et al. 2017 | Wrong study design | Narrative 'state of play' |
| Cardona et al. 2018 | Wrong population | Not already identified as frail |
| Carey et al. 2008 | Wrong population | Not clear that the population are all frail; not clear that people with cancer are disaggregated |
| Cole et al. 2019 | Wrong population | Not defined as frail |
| Conroy et al. 2011 | Wrong intervention | Not prognostic; interventions not specifically for end of life |
| Covinsky et al. 2003 | Wrong population | Not clear that the population are all frail; not clear that people with cancer are disaggregated |
| Curtin et al. 2019 | Wrong publication type | Conference abstract |
| Deng 2017 | Wrong publication type | Conference abstract |
| Dent et al. 2016 | Wrong study design | Review of frailty scales, not prognostic models |
| Ekerstad et al. 2017 | Wrong population | Identified as frail but not as being in end of life phase |
| Espinoza et al. 2012 | Wrong time span | > one year |
| Evans et al. 2016 | Wrong publication type | Conference abstract |
| Giannini et al. 2007 | Wrong intervention | Not prognostic; interventions not specifically for end of life |
| Glajchen et al. 2011 | Wrong population | Cannot disaggregate cancer patients |
| Heppenstall et al. 2015 | Wrong population | Long term care residence as proxy for frailty |
| Huang et al. 2007 | Wrong population | Not defined as frail |
| Huijberts et al. 2016 | Wrong population | Long term care residence as proxy for frailty |
| Iwata et al. 2006 | Wrong population | Not defined as frail |
| Jakobsson et al. 2011 | Wrong population | Long term care residence as proxy for frailty |
| Kaehr et al. 2016 | Wrong population | Not already identified as frail |
| Kagansky et al. 2005 | Wrong population | Frailty as synonym for old age |
| Kinley et al. 2014 | Wrong study design | Implementation study |
| Landi et al. 2007 | Wrong population | Not clear that the population are frail |
| Lunney et al. 2003 | Wrong population | Long term care residence as proxy for frailty |
| Ma et al. 2013 | Wrong population | Not already identified as frail |
| Mendonca et al. 2019 | Wrong time span | > one year |
| Mukamel et al. 2004 | Wrong population | Not clear that the population are all frail; not clear that people with cancer are disaggregated |
| Nouvenne et al. 2016 | Wrong intervention | Biomarker study |
| O'Caoimh et al. 2014 | Wrong population | Less than half the population clearly defined as frail |
| Overbeek et al. 2016 | Wrong publication type | Conference abstract |
| Overbeek et al. 2018 | Wrong intervention | Participants not clearly identified as being at end of life |
| Overbeek et al. 2019 | Wrong intervention | Participants not clearly identified as being at end of life |
| Romoren et al. 2003 | Wrong outcome | Not predicting entry into end of life phase |
| Salamanca-Balen et al. 2018 | Wrong population | Frailty as synonym for old age |
| Sanchez-Rodriguez et al. 2019 | Wrong population | Not clear that the population are frail |
| Stolz et al. 2019 | Wrong population | Not identified as frail |
| Stow et al. 2018 | Wrong population | Not already identified as frail |
| Sullivan et al. 1991 | Wrong population | No access to article, but from 1991 which predates the conceptions of frailty in our criteria |
| Thomazeau et al. 2017 | Wrong study design | Review; article in French |
| Todd et al. 2019 | Wrong time span | > one year |
| van der Steen et al. 2005 | Wrong population | Long term care residence as proxy for frailty |
| van Kempen et al. 2015 | Wrong outcome | Not end of life |
| Vermeiren et al. 2016 | Wrong population | Review; four papers of relevance but not identified as frail |
| Woods et al. 2019 | Wrong publication type | Conference abstract |
| Wu et al. 2018 | Wrong time span | > one year |
| Yash Pal et al. 2017 | Wrong study design | Descriptive |
| Zasadzka et al. 2019 | Wrong population | Not already identified as frail |

1. <https://www.epistemonikos.org/> — a source of systematic reviews relevant to health decision-making [↑](#footnote-ref-2)
2. Our Policy Research Unit is conducting work to further understand frailty distributions in England: <https://www.opfpru.nihr.ac.uk/our-research/project-2-frailty-data/> [↑](#footnote-ref-3)
3. <https://www.epistemonikos.org/> — a source of systematic reviews relevant to health decision-making [↑](#footnote-ref-4)
4. <https://www.voice-global.org/> [↑](#footnote-ref-5)
5. The definition of ‘nursing home’ in Japan is broadly similar to that of England, providing long-term care for people with the most complex needs (88). (88. Curry N, Castle-Clarke S, Hemmings N. What can England learn from the long-term care system in Japan? London: Nuffield Trust; 2018. [↑](#footnote-ref-6)
6. The difference between a prognostic model and a prognostic factor is that a prognostic model uses a combination of multiple prognostic factors. [↑](#footnote-ref-7)
7. Our Policy Research Unit has recently responded to a request from the Department of Health and Social Care to review tools to identify frailty in younger adults: <https://www.opfpru.nihr.ac.uk/our-research/rapid-responses/> [↑](#footnote-ref-8)