Geriatric Syndromes: Frailty

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Contents

H. Flaatten et al. (eds.), *The Very Old Critically Ill Patients*, Lessons from the ICU,
https://doi.org/10.1007/978-3-030-94133-8_11

Learning Objectives

Having read this chapter, you will be able to:

- Define frailty and explain its pathophysiology.
- Understand the two reference standard models of frailty: the phenotype model and cumulative deficit model.
- Appreciate the limitations of these two models for clinical practice and have an understanding of alternative simple instruments for assessing frailty in critically unwell older people.
- Understand the implications of our ageing population and the epidemiology of frailty in critical care units.
- Appreciate the clinical utility of frailty in critical care, including its role in triage decisions, predicting prognosis and identifying people for therapeutic interventions, as well as its potential future role as a therapeutic target.

11.1 Introduction

Population ageing worldwide is accelerating rapidly, with major implications for the planning and delivery of healthcare services. The ageing global demographic has been accompanied by a notable increase in the proportion of older people admitted to critical care facilities [1]. However, chronological age is not a universal predictor of inferior outcomes, and the concept of frailty more accurately identifies older people at increased risk of adverse outcomes, compared to people of the same chronological age. Frailty encapsulates the variable vulnerability to stressor events observed in older age, helping to explain why some older individuals are more resilient and are able to withstand stressors, whilst others only need a minor insult, such as a simple infection to trigger a sudden, disproportionate change in their health [2].

Globally, the prevalence of frailty in older adults is estimated to range from 7 to 26% [3], and this population with frailty is at increased risks of falls, disability and death. Older people with frailty are recognised as core users of health and social care services internationally, accounting for a considerable proportion of healthcare expenditure [4]. Over the past 20 years, there has been a considerable expansion in research to improve our understanding of the pathophysiology of frailty and its implications for healthcare services, which have historically mainly been designed to meet the needs of younger people with single long-term conditions. In this chapter, we discuss the definition, pathophysiology and epidemiology of frailty as well as present instruments to assess frailty in critically unwell older adults alongside an overall focus on the clinical importance of recognising frailty in critical care.

11.2 Frailty Definition and Pathophysiology

Frailty is a condition characterised by loss of biological reserves, failure of physiological mechanisms and increased vulnerability to a range of adverse outcomes. It develops as the result of accelerated ageing-associated decline across multiple physiological systems. This cumulative physiological decline diminishes homeostatic reserve, until stressor events trigger disproportionate and dramatic changes in health status [5]. For

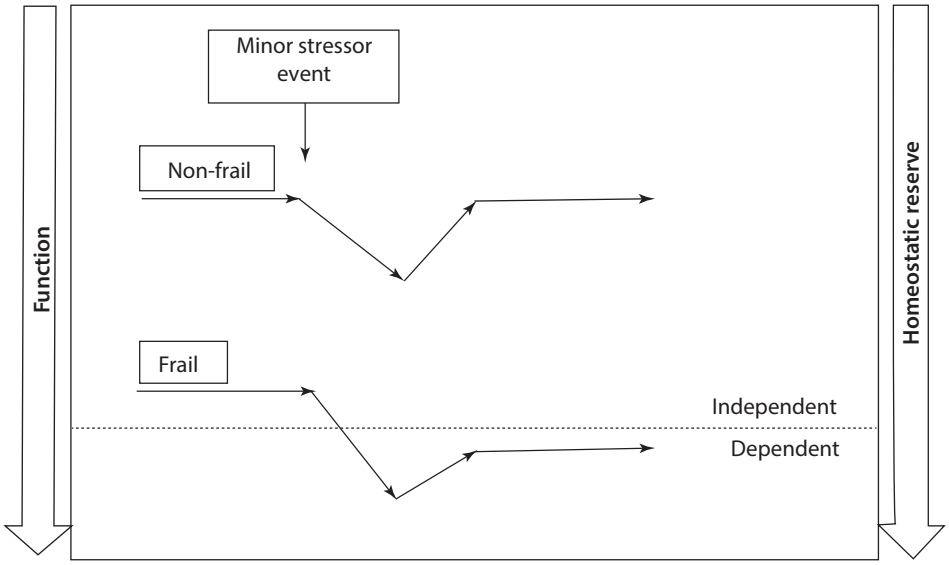

Fig. 11.1 Schematic epresentation of the typical clinical presentation of frailty [6]

example, a new medication, a 'minor' surgical procedure or an infection can translate into marked deteriorations in function and a transition from being independent to dependent, mobile to immobile and lucid to delirious (Fig. 11.1) [6]. The sudden, disproportionate change in health observed in frailty is typically followed by a prolonged period of recovery, frequently requiring an extended hospital stay, including a period of rehabilitation.

The brain, endocrine system, immune system and skeletal muscle are the physiological systems which have been most extensively investigated in frailty, [6] and cumulative decline in these systems has particular importance in the context of critical illness. In general, the cumulative decline across multiple systems in frailty identifies an individual whose homeostatic mechanisms are on the verge of a tipping point from which it may be impossible to recover, with an additional stressor of a critical illness leading to complete homeostatic failure and death. Considering specific organ systems, the gradual loss of skeletal muscle strength and function (sarcopenia) that is commonly observed in frailty can be particularly problematic with the addition of an acute severe illness, such as sepsis, or major surgical procedure. This is because the breakdown of muscle protein to produce amino acids for energy and antigenic peptides for the immune response to an inflammatory stimulus can further diminish already depleted skeletal muscle. When this is combined with additional muscle atrophy through immobility in hospital, the result can potentially be a major loss of independence that might not be recoverable, even with a prolonged period of rehabilitation. Furthermore, the changes to the brain that are observed with frailty can increase the risk of delirium, which is commonly encountered in the critical care setting, and an extremely unpleasant and upsetting experience for patients, families and staff.

Although the brain, endocrine system, immune system and skeletal muscle have been best studied, it is recognised that cumulative decline across other key systems

including the cardiovascular, respiratory and renal systems contributes to the overall development of frailty. Indeed, research has indicated that it is the total amount of decline across multiple organ systems that drives the development of frailty, as opposed to impairment in one particular system alone [7].

11.3 Frailty Models

Although the concept of frailty has been established in geriatric medicine for considerable time, it is only more recently that frailty models have been developed. The phenotype model and the cumulative deficit model are the two international models of frailty that are best established as reference standards. Both are extensively validated and, although conceptually different, have overlap in identification of frailty.

The phenotype model identifies frailty on the basis of the presence of three or more of the following physical characteristics: unintentional weight loss, self-reported exhaustion, low energy expenditure, low grip strength and slow walking speed (Table 11.1). Participants are classified as frail (three or more characteristics), pre-frail (one or two characteristics) or robust (no characteristics present). Although widely recognised as a reference standard, the main limitations of the phenotype model have been that the time required for assessment of the five characteristics means that it more suited as a research tool, rather than for routine clinical practice. An additional limitation is that the components can potentially conflate acute illness with frailty.

The cumulative deficit model identifies frailty on the basis of the accumulation of a range of health deficits (clinical signs, symptoms, diseases, disabilities, impairments), on the simple principle that the more small things an individual has wrong with them, the more likely they are to have frailty. The model is flexible in terms of the number and type of deficit variables that are required – a minimum number of 30 deficit variables is required for a valid model [9]. The deficit variables can be combined to calculate a frailty index (FI) score as the total number present in an individual as an equally weighted proportion of the total possible. A higher frailty index score is typically associated with worse outcomes [10]. With a theoretical range of

Table 11.1 The five phenotype model indicators of frailty and their associated measures [8]

Frailty indicator	Measure
Unintentional weight loss	Self-reported weight loss of more than 10 pounds or recorded weight loss of ≥5% per annum
Self-reported exhaustion	Self-reported exhaustion on CES-D score (3–4 days per week or most of the time)
Low energy expenditure	Energy expenditure <383 kcal/week (males) or <270 kcal/week (females)
Slow gait speed	Standardised cut-off times to walk 15 feet, stratified for sex and height
Weak grip strength	Grip strength, stratified by sex and BMI

between 0 and 1, a value of 0.70 represents a level of frailty beyond which further deficit accumulation is not sustainable [10]. Similar to the phenotype model, a key historical limitation of the cumulative deficit model is that it has been mainly suited to the research setting, although more recent research has extended the model to critical care.

11.4 Instruments for Assessing Frailty in Critically Unwell Older People

The limitations of the original phenotype and cumulative deficit models for routine assessment of critically unwell older people have led to interest in instruments that are feasible to complete in the time-pressured environment of an acute hospital but retain good reliability. Although there is a very extensive range of instruments for identifying frailty in community settings, many of these include performance-based items, such as measures of mobility (e.g. gait speed, timed-up-and-go test), which can conflate frailty with acute illness. Furthermore, frailty assessment in critically ill older people presents additional challenges, including the frequent presence of acute delirium, underlying dementia or reduced level of consciousness that can accompany critical illness. Useful instruments also need to take into account both the possibility of proxy completion and the challenges presented when there is no proxy available in the setting of an acute hospitalisation.

A 2018 systematic review of the feasibility and reliability of frailty assessment instruments in critically unwell older people identified six studies that assessed different frailty instruments in the critical care setting [11].

11.4.1 Modified Phenotype Model

A modified frailty phenotype model has been used in research studies investigating frailty in critical care. One version operationalised the five phenotype model domains for use in critical care, and a second version extended the modified domains to include cognitive impairment and sensory impairment (Table 11.2) [11].

In studies that have used the modified phenotype model, limitations in terms of difficulties completing some components, even with adaptations for critical care, were reported. Although the modified frailty phenotype has been used by both research and clinical staff, the time required for completion has not been reported, which means that resource required for routine implementation is currently uncertain.

11.4.2 Cumulative Deficit Model

A 43-item proxy-reported questionnaire based on the cumulative deficit model of frailty has been developed and tested in 610 critical care patients (Table 11.3) [13]. The questionnaire is completed using variables drawn from the health record, supplemented by proxy completion of variables collected from family members, based on the condition of the patient 2 weeks prior to hospital admission. Each deficit

Table 11.2 Assessment of frailty according to modified frailty phenotype model [12]

Frailty domain	Measure
Shrinking	Reported weight loss and BMI <24 or ≥5% weight loss
Weakness	Unable to rise from a chair without using arms
Slowness	Falls or need for assistance with mobility inside or outside the home in the past year
Low physical activity	Unable to climb flight of stairs or undertake moderate activity, e.g. pushing a vacuum cleaner or bowling
Exhaustion	Feeling that everything the patient does is an effort and/or the feeling that he could not get going, in past 4 weeks; number of times he/she had a lot of energy in past 4 weeks
Cognitive impairment	Memory impairment screen, or modified version of the short-form informant questionnaire on cognitive decline in the elderly
Sensory impairment	Problems in daily life because of poor vision or impaired hearing in last year

variable is coded as 0 (absent), 1 (present) or 0.5 (where intermediate values are possible).

The frailty index was a better predictor of adverse outcomes after critical care admission than age, illness severity or comorbidity. Higher baseline physical function and lower frailty index scores were robust predictors of survival and long-term physical function. In the validation study, the questionnaire was completed by trained researchers, and feasibility of use in routine clinical care requires further evaluation. A 52-item frailty index has also been operationalised for critical care, and validated in a sample of 155 patients, demonstrating good prediction of survival [14].

11.4.3 Clinical Frailty Scale

The Clinical Frailty Scale (CFS) is a method of summarising the overall level of fitness or frailty of an older individual after a clinical evaluation. The original CFS was a seven-item pictorial scale, ranging from level 1 (very fit) to level 7 (severely frail). More recently, a nine-item version has been developed, including two additional categories – very severe frailty (level 8) and terminally ill (level 9) (Fig. 11.2). The CFS has been used by a broad range of clinical and research staff, with high rates of completion in studies that evaluated reliability in critical care, reflecting its relative simplicity and ease of use. Furthermore, good inter-rater reliability has been reported for the CFS when used by different clinical staff, providing further support for its use [15]. It is gaining popularity in critical care as a frailty assessment instrument that is aligned with implementation in time-pressured clinical environments. One limitation of the CFS is that it mainly assesses function of an individual, so it may not account for the cumulative decline across multiple physiological systems that is characteristic of frailty. Despite this, the CFS correlates well with the research standard cumulative

Table 11.3 43 items included in a cumulative deficit frailty index developed for use in critical care, including items completed using information from the health record and proxy completion

#	Items contributed to the FI
1	Overall health of the patient?
2	Do you think the patient was depressed?
3	Do you think the patient worried a lot or got anxious?
4	Do you think the patient felt exhausted or tired all the time?
5	Did the patient have sleep problems?
6	Did the patient have problems with memory or thinking?
7	Did the patient have any problems speaking to make him−/herself understood?
8	Did the patient have difficulty hearing?
9	Did the patient have problems with eyesight (even when wearing glasses)?
10	Did the patient have problems with balance?
11	Did the patient complain of feeling dizzy or lightheaded?
12	Did the patient need assistance of a person or aid to prevent falling?
13	Did the patient hold on to furniture to keep from failing?
14	Was the patient able to walk alone?
15	Was the patient able to get out of a bed or chair alone?
16	Did the patient have problems with bowel control?
17	Did the patient have problems with bladder control?
18	Did the patient experience any unplanned weight loss in the last 6 months?
19	What was the patient's food intake in the week prior to ICU admission?
20	Was the patient able to carry out some day-to-day tasks?
21	Feed himself/herself?
22	Take a bath or shower?
23	Dress himself/herself?
24	Drive?
25	Look after his/her own medications?
26	Do day-to-day shopping?
27	Do day-to-day household cleaning?
28	Cook well enough to maintain his/her nutrition?
29	Look after his/her own banking and financial affairs?
30	Overall health of the patient?
31	Myocardial infarct

(continued)

Table 11.3 (continued)

#	Items contributed to the FI
32	Congestive heart failure
33	Peripheral vascular disease
34	Cerebrovascular disease +/– hemiplegia
35	Dementia
36	Chronic pulmonary disease
37	Connective tissue disease
38	Ulcer disease
39	Any liver disease
40	Diabetes
41	Moderate or several renal diseases
42	Diabetes with end organ damage
43	Any tumour

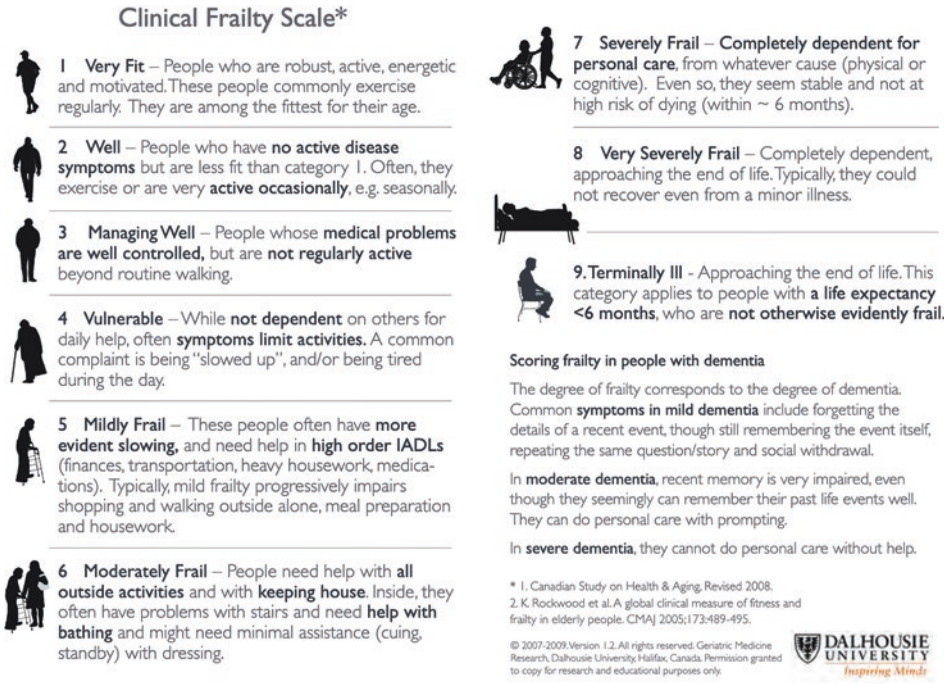

Fig. 11.2 Nine-item CFS

deficit model, which includes variables that span the range of systems that are typically impaired in frailty.

11.4.4 Identifying Frailty Using Routine Electronic Health Record Data

The use of routine electronic health record data to identify frailty in critically unwell older people is an attractive option but has a range of considerations. In the UK, an electronic frailty index (eFI) has been developed using routinely available primary care electronic health record data, and implemented nationally, but is not currently available in secondary care health record systems [16] and requires validation in a critical care context. A Hospital Frailty Risk Score (HFRS) has also been developed and validated using International Classification of Diseases version 10 (ICD-10) coding, [17] but has not yet been validated in critical care or been widely implemented. A modified frailty index (mFI), constructed using 11 and 19 items, has been developed and tested using critical care registry data from 129,680 patients in Brazil, with higher scores demonstrating good prediction of in-hospital mortality and lower likelihood of returning home [18]. However, the index included fewer items than the recommended minimum of 30 variables required for a valid frailty index, and only 1 item assessing physical function was included in the shorter version, meaning that the index mainly includes comorbidities, rather than aligning with the wider multidimensional construct of frailty [19]. The use of routine electronic health record data to identify frailty in critically unwell older adults is an attractive area of ongoing work.

11.5 Epidemiology of Frailty

A notable consequence of the increased global life expectancy observed across the twentieth century is the demographic shift towards an ageing population, which has been most marked in higher-income countries [20]. By 2070, it is predicted that 18.9% of the global population will be older than 65 years and 28.7% in high-income countries [20].

Globally the prevalence of frailty amongst community-dwelling older adults (≥50) ranges from 7 to 26%, depending on the definition used and population examined [21]. Prevalence is associated with social and economic factors and has consistently been demonstrated to be greater in women independent of age [8, 21]. Frailty is a dynamic process whereby people transition between different frailty states over time. The most common trajectory is for individuals to progress to a worse frailty state, although frailty has been observed to improve to some degree in almost a quarter of people. However, transitioning from established frailty to a non-frail state is typically very rare [22]. Older people typically comprise up to two-thirds of the acute inpatient population, and estimates indicate that around half of these patients have frailty [23].

11.5.1 Epidemiology of Frailty in Critical Care Units

One of the consequences of population ageing is that older critically ill patients are a rapidly expanding group in critical care units. A growing older population with frailty at risk of sudden, dramatic changes in health with acute illness has major implications for the design and operational delivery of critical care, and robust information on epidemiology of frailty in critical care is required for planning services. A landmark 2017 systematic review of the prevalence of frailty in critical care facilities and its impact on outcomes of critically ill patients identified 10 studies, with a total of 3050 patients [22]. These ten studies along with additional key studies that were conducted following this review are summarised in ◘ Table 11.4. The frailty rates in patients admitted to critical care units differ considerably between studies, with rates ranging between 12 and 60%. This likely represents different eligibility criteria and frailty scores used across studies, alongside differences in service model delivery in different countries globally. A large, transnational study spanning 21 European countries investigating the impact of frailty in 5021 intensive care unit patients used a standardised assessment of frailty – the Clinical Frailty Scale – and reported notable differences in frailty prevalence [24]. Rates of frailty in older intensive care unit patients were lowest in Western Europe (35.1%) compared to Eastern Europe (55.3%), with intermediate rates in Central Europe (48.9%), Northern Europe (48.4%) and Southern Europe (38.6%). As the frailty assessment measure was standardised across settings, these differences most likely reflect how service models have been established in these geographical regions, with a greater emphasis on triage of critically unwell older patients prior to transfer to intensive care units in Western and Southern Europe.

11.6 Clinical Utility of Frailty in Critical Care

Interest in identifying frailty in critical care has grown in recent years, particularly in view of triage decisions potentially required in the COVID-19 pandemic [41]. The most common scale used clinically is the Clinical Frailty Scale, aligned with the evidence for its feasibility and reliability in critical care settings as it is considered easy to estimate with minimal training and even without the involvement of a patient's family [11]. A major concern with the use of frailty scores on ICU is that patients may be far from their baseline and this could cloud judgement. Although the CFS appears to have a high inter-rater reliability, a 2019 study reported a difference of one category or more in 47% of cases [15].

11.6.1 Prognosis

There are many scoring systems which predict outcomes in critical care, but in the main these are only recommended for use in aggregate and not for individuals [42]. Frailty as measured by CFS and frailty index predicts mortality independent of age and acute scoring systems such as APACHE II and SOFA [24, 36]. In the Muscedere et al. meta-analysis, [43] frailty was a predictor of hospital (risk ratio (RR), 1.71; 95%

Table 11.4 Major studies exploring frailty prevalence in the critically ill

Reference	Year	Country	Cohort size (N)	Age criteria (years)	Prevalence (%)	Frailty criteria
Bagshaw [25]	2014	Canada	421	≥50	33	9-point CFS (≥5 points)
Brummell [26]	2020	USA	567	≥18	24	7-point CFS (≥5 points)
Brummel [27]	2017	USA	1040	≥18	30	7-point CFS (≥3 points)
Darvall [28]	2019	New Zealand, Australia	15,613	≥80	40	8-point CFS (≥5 points)
Ferrante [29]	2016	USA	391	≥70	55	FP (≥3 points)
Fisher [30]	2015	Australia	205	≥18	28	9-point CFS (≥5 points)
Flaatten [24]	2017	21 European countries	5021	≥80	43	9-point CFS (≥5 points)
Geense [31]	2020	The Netherlands	1300	≥18	12	9-point CFS (≥5 points)
Hessey [32]	2020	Canada	11,816	≥18	29	9-point CFS (≥5 points)
Heyland [13, 33]	2015	Canada	610	≥80	32 (CFS) 59 (FI)	7-point CFS (≥5 points) 43-item FI (>0.2)
Hope [34, 35]	2015	USA	84	≥18	35 (CFS) 27 (FAT-ICU)	9-point CFS (≥5 points) FAT-ICU (>3 points)
Hope [12]	2017	USA	95	≥18	36	9-point CFS (≥5 points)
Kizilarslanoglu [36]	2017	Turkey	122	>60	21	55-item FI (>0.4)
Le Maguet [3]	2014	France	196	>65	41 (FP) 24 (CFS)	FP (≥3 points) 9-point CFS (≥5 points)
Lopez [37]	2019	Spain	132	≥65	35	FRAIL scale (≥3 points)
Montgomery [38]	2019	Canada	15,238	≥18	28	9-point CFS (≥5 points)

(continued)

Table 11.4 (continued)

Reference	Year	Country	Cohort size (N)	Age criteria (years)	Prevalence (%)	Frailty criteria
Mueller [39]	2016	USA	102	>18	38	50-item FI FI (>0.25)
Takaoka [40]	2020	Canada	66	≥18	26	9-point CFS (≥5 points)
Zampieri [18]	2018	Brazil	129,680	≥18	19	11-point modified FI (≥3 points)
Zeng [14]	2015	China	155	>65	60	52-item FI (>0.22)

CFS, clinical frailty scale; FI, frailty index; FP, frailty phenotype; FAT-ICU, frailty assessment tool for intensive care unit

confidence interval (CI), 1.43 to 2.05) and long-term (RR, 1.53; 95% CI, 1.40 to 1.68) mortality independent of age, illness severity and comorbidity. Additionally, frail patients were less likely to be discharged home (RR 0.59; 95% CI 0.49 to 0.71) and reported a reduced quality of life at 1 year.

Even as a strong prognostic factor, it is not clear that frailty can be used on its own to identify futility in critical care decision making. Survival is possible even for patients considered 'very severely frail', [24] and acceptable outcomes will vary by patient, so frailty must for now remain as one factor in a comprehensive assessment and discussion which incorporates patient wishes and acute illness severity [44].

11.6.2 Identifying People for Therapeutic Interventions

Admission to critical care is itself a therapeutic intervention, and many scoring systems are validated on patients already admitted to critical care, making it problematic to use them to guide admission [42]. It has therefore not historically been recommended that any scoring system be used to guide critical care admission, [45] though during the COVID-19 pandemic, UK guidance from the National Institute for Health and Care Excellence (NICE) suggested critical care treatment may be inappropriate for patients with a CFS score of 5 or more [41, 44]. The use of prognostic indicators in general to guide decisions to intervene with admission to critical care or an escalation of treatment, when failing to intervene, may result in death, risks becoming a self-fulfilling prophecy even when based on reliable evidence [46].

Recognising that it is not usually possible to accurately determine which patients may respond best to the initiation of critical care treatment, there is interest in 'ICU trials' where a patient is admitted to critical care but treatment is withdrawn early if they are not responsive in the first 24–48 hours [47, 48]. However, whilst medical and bioethical literature frequently combines withdrawal and withholding of life-sustaining

treatment by invoking the 'Equivalence Thesis', it appears that most doctors feel on safer ground withholding rather than withdrawing treatment [49]. This may risk patients missing out on treatments who may have benefitted, or subjecting patients to the indignity and discomfort of futile treatment, and work to reduce the disparity between ethical theory and medical practice could produce real patient benefit.

Despite these ethical concerns, it is clear that both treatment withdrawal and treatment withholding are used in critical care when limiting life-sustaining treatments (LSTs) [47]. As might be expected, frailty, age and acute organ failure all predict LST limitation in older adults in critical care. However, this varies across Europe, where LST limitation appears to be more common in countries where there are greater levels of religious atheism, or higher GDP per capita, and highest in Northern Europe.

11.6.3 The Future: Frailty as a Therapeutic Target?

As we improve our understanding of frailty as a syndrome distinct from ageing, there is interest in identifying treatments which can target underlying elements [50].

Box 11.1

Inflammation	Inflammatory cytokines may perpetuate frailty, but no therapy has yet proven helpful; monoclonal antibodies can reduce inflammation but may worsen infection. Statin therapy has been studied without outcome improvement. Omega-3 fatty acid supplementation shows some promising signs but needs further study in this population
Myopathy	Early mobilisation may improve later function, but interventions on the ward or later after ICU have not been shown to be beneficial. Electrical stimulation and in-bed cycling in ICU also seem to have limited effect on critical illness myopathy. Medications targeting muscle atrophy are of interest, but not yet in human trials
Neuroendocrine	Frailty and prolonged ICU stay can be associated with hormone suppression, and this may potentiate muscle loss, weakness and fatigue. Therapeutics targeting the somatotrophic and gonadal axes have not been tested. Targeting the adrenal axis is more problematic because of cortisol's role as an immunosuppressant along with evidence it may increase mortality, but vitamin D supplementation may affect cortisol regulation, and trials are ongoing, though so far without improvement being demonstrated

Conclusion

Frailty is a common condition in older age that has clinical utility in guiding complex clinical decisions in the context of critical care admission and life-sustaining treatment decisions. A range of frailty instruments are available for use in critical care, with the CFS being one example of a tool that is simple to use, with evidence for predictive validity, feasibility and reliability that is gaining adoption in routine practice. Although useful as a prognostic factor, decisions about admission to critical care and life-sustaining treatments should not ordinarily be made on the basis of frailty alone, but as part of a holistic assessment of the patient and the context of the critical illness, as part of shared decision making in full partnership with patients and their families.

Take-Home Messages

- Frailty is a condition characterised by loss of biological reserve, failure of homeostatic mechanisms and resultant increased vulnerability to stressors.
- Across Europe, the prevalence of frailty in critical care is lower in Western and Southern Europe. This likely reflects the differences in service models and emphasis on triage.
- The two most extensively validated models of frailty are the phenotype model (based on five physical characteristics) and the cumulative deficit model (based on the accumulation of a range of health deficits spanning clinical signs, symptoms, diseases, disabilities and impairments).
- Alternative simple instruments have been developed which are more feasible to complete in the time-pressured acute hospital environment and have fewer performance-based measures which may be confounded by acute illness. The Clinical Frailty Scale (CFS), a nine-item pictorial scale, has gained popularity given it is relatively simple to use and has shown good inter-rater reliability.
- Frailty is a strong prognostic factor regarding hospital and long-term mortality, severity of illness and morbidity after critical care admission. Frailty serves as a valuable component to the comprehensive assessment required for critical care decision making.

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