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Frailty in the Critically Ill Patient

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This review explores current definitions of frailty, methods available to diagnose it, and its application to perioperative and critically ill patients.

Frailty is increasingly recognised as a potential contributor to patient outcome during an episode of critical illness. However, there is currently no consensus definition or assessment tool. Two main models exist to conceptualise frailty —the "frailty phenotype" and the "deficit model". Both models have been validated in the community setting to be predictive of patient outcomes. However, they are limited in critical care by their applicability at the bedside. In the community, a diagnosis of frailty is associated with increased risk of falls, hospitalisation, institutionalisation and death. The direct pathophysiological pathway that results in a frail state is currently unknown, despite considerable research in this area. Frail patients have disordered homeostasis of many systems, including the inflammatory, coagulation, and neuro-endocrinal systems. The prevalence of frailty is approximately 1 in 5 elderly patients, and is increased in patients undergoing major surgery. Frail surgical patients are at higher risk of morbidity and mortality than non-frail patients. The role of frailty in the critical care environment is less clear. Thus far, the small number of studies has produced conflicting results. It appears that frailty has a higher prevalence than in thecommunity and may be associated with poorer ICU outcomes. However, further research intothe application of frailty assessment tools in the ICU is required.

Recently there has been increased recognition of the importance of functional status for patient outcome following Intensive Care Unit (ICU) admission. This includes patient functional status both upon ICU admission and discharge. Similarly, frailty is one determinant of a patient's functional state and its impact upon outcomes is being increasingly recognised (McDermid et al. 2011; McDermid and Bagshaw 2014). Previous literature on this topic has focused on geriatric and perioperative patients, in whom frailty has been shown to be associated with an increased risk of hospital admission, institutionalisation, postoperative complications and mortality (Song et al. 2010; Graham et al. 2009; Fried et al. 2001; Woods et al. 2005; Rockwood et al. 2005; Xue 2011; Partridge et al. 2012). However, the lack of a consensus definition and uncertainty on how to best assess frailty have resulted in limited research in the critically ill. There is increasing evidence suggesting that the consideration of frailty in critically ill patients may provide additional prognostic information.

What is Frailty?

There is currently no consensus definition of frailty nor a single definitive assessment tool, despite recent international attempts at consensus (Fried et al. 2001; Xue 2011). However, frailty is commonly conceptualised as a " multidimensional geriatric syndrome characterised by an increased vulnerability, resulting from an ageassociated decline in reserve and function, such that the ability to cope with everyday or acute stressors is compromised" (Xue 2011). The precise pathophysiology of frailty is incompletely understood. Frailty appears to be differentiated from normal ageing by the accumulation of multiple pathological abnormalities that contribute to frailty's characteristic clinical manifestations of sarcopenia, malnutrition, and decreased energy expenditure (Hubbard and Woodhouse 2010) **(Figure 1).**

The primary pathological process has been postulated to be chronic inflammation (Hubbard and Woodhouse 2010). Other significant pathological contributors are likely to include disordered coagulation, as well as dysfunction of the immune and neuro-endocrinal systems (Hubbard et al. 2009a; Waltson et al. 2002; Hunt et al. 2010). These suppositions are supported by research revealing that frail patients have significantly altered levels of C-reactive protein, interleukin-6, tumour necrosis-factor, as well as elevated clotting factor VIII, fibrinogen and D-dimer levels. Additionally, frail patients are more likely to have a disordered hypothalamicpituitary axis, disordered glucose metabolism and lower vitamin D levels (Hunt et al. 2010; Bayliss et al. 2013; Ensrud et al. 2011; Leng et al. 2004).

How these biological abnormalities contribute to frailty is also poorly understood. It is known that there exists a strong association between chronically elevated inflammatory cytokines and decreased physical performance, muscle weakness, atrophy, and the progression of disability in elderly patients (Cesari et al. 2004; Ferruci et al. 1999). However, elderly patients often have altered biochemical markers as a result of other concurrent chronic illnesses such as renal failure and cardiovascular disease (Waltson et al. 2002).

Thus it appears that a critical mass of abnormalities in a patient's homeostatic systems is required before a frail state develops (Hubbard and Woodhouse 2010). Further confounding current pathophysiological models is the find- ing that these observed biological abnormalities might not entirely account for the pathology underlying a

frail state. The psychosocial environment of a patient may also impact on the genesis of frailty. This is supported by research demonstrating frailty's association with smoking, lower socio-economic status and lack of physical exercise (Hubbard et al. 2009b; Lang et al. 2009).

How to Diagnose and Measure Frailty

To date, several methods have been developed to diagnose and measure frailty (Whitson et al. 2007). A recent review identified 27 published tools for the assessment of frailty that range from isolated biochemical abnormalities or physiological parameters to detailed multidisciplinary team assessments (Bouillon et al. 2013; Sternberg et al. 2011). However, frailty research and debate is driven by two distinct but validated frailty models. The first model views frailty as a physical syndrome or 'phenotype'. The second model views frailty as a collection of deficits in measurable health domains, (the 'deficit' model) (Sternberg et al. 2011). A recent review revealed that 83% of published literature on frailty used either of these models (Bouillon et al. 2013).

Phenotype Model

The phenotype model is based on the pioneering work of Fried et al. in North America. Fried et al. followed more than 5300 elderly patients for seven years, and found the presence of greater than three of the following features: unintentional weight loss, weakness, low energy levels, slowness, and decreased physical activity characterized a frail state (Fried et al. 2001). In this study a frail state was predictive of falls, hospitalisation, and death with adjusted hazard ratios of 1.29 (CI 1-1.68), 1.29 (CI 1.09-1.54), and 2.24 (CI 1.51-3.33) at 3 years respectively. This was the first study to show that, although age and co-morbidity were associated with frailty, they did not define frailty itself and frailty exists as a distinct clinical entity. Additionally this study was the first to assess patients in the community, as opposed to patients already admitted to hospital or other healthcare institutions.

Frailty Model

The alternative approach considers frailty as the accumulation of numerous health deficits. The greater the number of deficits a patient acquires, the higher risk of a frail state (Mitnitski et al. 2001; Rockwood and Mitnitski 2011). The Canadian Health Study of Aging is the largest study utilising this approach. This study looked at over 10,000 elderly patients, and after integrating patient co-morbidities, clinical examinations findings and an assessment of activities of daily living, developed a 70-point frailty index. The frailty index was shown to be predictive of death and institutiona lisation at 70 months, with hazard ratios of 1.26 (CI 1.24–1.29) and 1.56 (CI 1.48–1.65), respectively (Rockwood et al. 2007). It may be contended that the frailty index approach is consistent with the concept that development of frailty is a gradual process rather than an absent or present phenomenon. Rockwood et al. have suggested that the frailty index may be a more robust and sensitive measure of frailty-associated outcomes than the frailty phenotype (Rockwood et al. 2007). However, Bouillon et al. have suggested that the two models of frailty have similar predictive and discriminative ability to detect frailty (Bouillon et al. 2013).

Limitations

A major limitation of many frailty assessment tools is their impracticality in many clinical contexts. Many tools are not suitable for use at the bedside, time-consuming to perform, require specially trained clinicians, or the performance of specialised biochemical and physical investigations. Tools Newer tools have been developed that may overcome some of these barriers and increase their practicality, especially in critical care.

• **Clinical Frailty Scale:** The Clinical Frailty Scale (CFS) has been derived from the frailty index developed in the Canadian Health Study of Aging. The CFS is a simple visual analogue 9-point scale ranging from very fit (1) to terminally ill (9), with a score greater than 4 indicating frailty (**Figure 2**). In a cohort of over 2,300 patients, the CFS was shown to be predictive of six-month mortality and institutionalisation, with hazard ratios of 1.30 (CI 1.27–1.33) and 1.46 (CI 1.39–1.53) respectively. Furthermore, it has been validated against the frailty index showing a high degree of correlation, with a Pearson correlation coefficient of 0.80, $p < 0.01$ (Rockwood et al. 2005). The greatest benefit of the CFS is its ease of use, lack of required ancillary testing, and its ability to be applied at the bedside.

• **Edmonton Frailty Scale:** Another simple but validated tool is the Edmonton Frailty Scale (EFS). The EFS incorporates a brief 10-point assessment of specific health domains, including cognition, medication usage, nutrition and social supports. Functional status is assessed via the 'timed up and go' or TUG test. The EFS has

been validated for use by primary care physicians and geriatricians (Hilmer et al. 2009), and also has been shown to be predictive of outcome in acute general medical in-patients and patients admitted with acute coronary syndromes (Hilmer et al. 2009; Graham et al. 2013). Rolfson et al. (2006) demonstrated the ease of EFS usage in 158 elderly patients. Using a non-medical assessor and a trained geriatrician to assess frailty, Rolfson et al. found a high level of agreement between the EFS values obtained by both assessors (Pearson correlation coefficient 0.64, $p < 0.01$) and importantly that the EFS took less than 5 minutes to administer (Rolfson et al. 2006). Although a simple and validated tool, the EFS is potentially limited in its assessment in the critically ill by the need for a practical functional assessment.

Tool Comparison

To date, there has been limited comparison between the different frailty tools to predict patient outcomes. A systematic review by De Vries et al. concluded that whilst many tools have construct validity, comparisons between them are limited and difficult due to the range of population groups assessed. The various combinations of clinical and investigation parameters used further limit comparison (de Vries et al. 2011). A 2008 editorial contended that different tools to assess frailty may be required in different situations and no one tool may be ideal, e.g. bedside clinician versus public health officers seeking to explore population-based trends and planning requirements (Martin and Brighton 2008).

Frailty in the Community

The prevalence of frailty in the community has been reported to be between 6.9% to 22.7%, depending on the population studied and the tool used (Collard et al. 2012). Frailty has been consistently shown to have a higher prevalence in women and increasing prevalence with advancing age (Song et al. 2010; Graham et al. 2009; Woods et al. 2005; Collard et al. 2012). Furthermore, it appears that it is more common in Southern Europe and South America, perhaps reflecting cultural differences in diagnosing frailty in these respective populations (Santos-Eggimann et al. 2009; Alvarado et al. 2008).

Frailty in the Perioperative Setting

Frailty is a significant predictor of outcome in elderly patients presenting for surgery, regardless of the frailty assessment tools employed (Partridge et al. 2012). The reported prevalence of perioperative frailty varies markedly between 4-50% (Makary et al. 2010; Sepeheri et al. 2014), but is generally higher than that in community-based studies, irrespective of the surgery type. This may be influenced by the underlying indication for surgery, as the common surgical indications of cardiovascular or malignant diseases are also associated with a frail state.

Current evidence suggests that frailty is associated with significant postoperative complications. In mixed general, vascular and orthopaedic surgical populations frailty has been associated with increased delirium, infection, thromboembolic disease and pressures areas (Partridge et al. 2012). It has also been associated with prolonged hospital length of stay and an increased risk of institutionalisation post discharge (Partridge et al. 2012). One study reported that one-third of patients aged >65 years assessed as frail pre-operatively were institutionalised at 6 months post major elective surgery (Robinson et al. 2011).

Frailty has a potentially significant influence upon outcomes in the cardiac surgery and transplantation populations. Frailty, assessed in a variety of ways and as a component of a comprehensive perioperative assessment, has been shown to be associated with increased morbidity and mortality following cardiac surgery (Sepeheri et al. 2014; Afilalo et al. 2010; Lee et al. 2010; Sundermann et al. 2011). One study revealed that frailty was a more reliable predictor of oneand twelve-month mortality when compared to the more commonly administered EuroScore (Sundermann et al. 2011). In addition, the Fried frailty phenotype has been shown to be a better predictor of both quality of life and mortality in liver transplantation candidates than the traditional Model for End-Stage Liver Disease (MELD) score (Derck et al. 2015; Lai et al. 2014).The high prevalence of frailty in perioperative patients and its association with adverse postoperative outcomes may offer a unique opportunity for multidisciplinary-focused patient assessment and postoperative planning.

Frailty and Critical Care

Frailty is increasingly recognised as a potential contributor to critically ill patient outcome. However, research has been limited by difficulty using frailty diagnostic tools, due to a lack of premorbid history, the presence of interceding acute critical illness and the impracticality of applying many of the tools at the bedside. Thus, existing evidence of the utility of frailty assessment in critically ill patients is derived from a relatively small

number of studies (**Table 1**). Bagshaw et al. conducted a multicentre study in Canadian Intensive Care Units' (ICU) looking at frailty in 421 patients. Bagshaw utilised trained assessors to apply the CFS to all patients aged over 50 years of age at the time of ICU admission. They found that frailty was present in one in three patients and was associated with an increased risk of both hospital, adjusted odds ratio 1.81, (CI 1.09– 3.01) and 12-month mortality, adjusted hazard ratio 1.82, (CI 1.28–2.60), when compared to non-frail patients (Bagshaw et al. 2014). A follow-up study indicated that frail patients had significantly lower quality of health scores at 6 and 12 months (Bagshaw et al. 2015). A major limitation of this study was that only one in three of all eligible patients was included, questioning the practical application of frailty assessment in critically ill patients.

In France Le Maguet et al. performed a multicentre observational study of 196 patients aged greater than 65 years to investigate frailty, and employed both the Fried frailty phenotype and the CFS. This study permitted either the patient or their relatives to provide the necessary information to assign a frailty score. Frailty was found to be present in 41% and 23% of patients, using the Fried phenotype and the CFS, respectively. In this study, frailty, as defined by Fried's phenotype, was three times more likely to be associated with ICU mortality. In addition a CFS >4 was significantly associated with hospital and 6-month mortality (Le Maguet et al. 2014). However, the high number of patients with traumatic brain injury (20%) or admitted post cardiac arrest (8%) potentially confounded and reduced the generalisability of these findings.

Other research has focused on more specific sub-groups of critically ill patients with the CFS. Masud et al. assessed the correlation of frailty with outcome in elderly patients with severe burns. They found that frailty was associated with less surgery and higher mortality at 12 months (Masud et al. 2013).

Unfortunately, the correlation of frailty and adverse outcomes is not consistent in studies of the critically ill. In a retrospective assessment of over 100 patients aged greater than 80 years from the United Kingdom, Charles et al. (2011) found no correlation between the frailty score and adverse patient outcomes. Fisher et al. (2015) utilised the CFS in a single centre study of over 200 patients in an Australian tertiary hospital. They found that frailty, as defined by the CFS > 4 had a prevalence of 13%, was more common in chronic liver and chronic renal disease patients, and was significantly associated with increased hospital length of stay but not ICU or hospital mortality. In contrast to other studies Fisher et al. applied the CFS to all patients admitted to the ICU regardless of age and used a patient's next of kin, or senior nursing staff when next of kin were unavailable, to assign the CFS score. Consistent with other studies of frailty in the critically ill, only half of all eligible patients were able to be included in the study (Fisher et al. 2015).

Whilst current ICU predictive tools use age and co-morbidities in their models, they incorporate a very limited assessment of patients' pre-morbid function. Interestingly, within both Bagshaw's and Le Maguet's studies there appeared to be no significant difference in ICU illness severity scoring between frail and non-frail patients. This suggests that the assessment of frailty may potentially be an adjunct to existing predictive tools in quantifying a patient's pre-morbid reserve and post ICU discharge outcome.

Further confounding the role of frailty in the critically ill has been the suggestion that an episode of critical illness may rapidly accelerate a patient's pre-frail state or lead to the development of many of the characteristics of frailty. Baldwin et al. explored this in patients with respiratory failure who required ICU admission. Frailty was assessed immediately prior to hospital discharge via the Fried phenotype model. This study found frail patients had a 6-month mortality of 41%, and that with each increased Fried phenotype domain mortality increased three-fold (Baldwin et al. 2014). The application of frailty scoring at discharge may allow greater quantification of the physical, nutritional, cognitive and psychological disabilities of ICU survivors. This in turn may allow directed interventions to minimise long lasting sequelae.

Choice of Assessor

The ideal person needed to assess frailty in critical care is currently unknown. In the community, geriatricians have formal training and expertise in recognising and managing frail patients and accordingly are shown to have high inter-rater reliability (Rockwood et al. 2005; Rockwood et al. 2007). However, it is unclear whether this consistency exists outside this setting. In the studies performed in the critically ill, a variety of assessors have been used and there is no published data assessing their inter-rater reliability. Bagshaw et al. (2014;2015) utilised trained assessors to assign scores. Le Maguet (2014) and Fisher et al. (2015) utilised the patient's next of kin or, in their absence, a senior ICU nurse. Interestingly, in the latter study there was no statistical difference between the frailty scores assigned by these two methods. The problem of variability in inter-rater reliability was highlighted by Hii et al., who found that non-geriatrician clinicians were unable to accurately diagnose frailty and varied significantly in classifying frailty (Hii et al. 2015).

Conclusions

Frailty may be an important factor in predicting patient outcome in ICU and is being increasingly studied in different patient populations. Prevalence is approximately 1 in 5 of elderly patients in the community and is even higher in those undergoing major surgery or experiencing critical illness. Although evidence for a strong association between frailty and outcome exists in the community, current evidence suggests an inconsistent association between frailty and adverse patient outcomes in the critically ill. In addition, it remains unclear which tool is most appropriate to use for the assessment of frailty in ICU and who should be making such assessments. Further research is required into the assessment of frailty in the critically ill before its routine use can be recommended for prediction of outcome after ICU admission.

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