The interplay and interaction between frailty and acute kidney injury

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INTRODUCTION

Frailty is a medical syndrome manifested by an increased vulnerability to minor stressors caused by a reduction in a person’s homeostatic reserves [1]. It comprises domains such as nutritional status, energy expenditure, metabolic rate, cognitive function and sarcopenia. Frailty should be differentiated from ‘comorbidity’ or ‘disability’ [2]. Patients without comorbidities can still be frail, and although frailty leads to disability, a disabled person is not necessarily frail. Elderly people are particularly susceptible to developing frailty, but younger patients can be frail as well [3].

Frail patients are at a higher risk of death, become more dependent on others and more often end up being institutionalized, compared with non-frail patients of the same age and with a comparable number of comorbidities.

The relationship between chronic kidney disease (CKD) and frailty is well established, and the degree of frailty in CKD and end-stage kidney disease correlates with the quality of life and survival [4]. By contrast, the relationship between acute kidney injury (AKI) and frailty is less commonly studied. AKI and frailty share common pathways and there seems to exist a bidirectional relationship between the two conditions (Figure 1).

Predicted demographics show an increasing number of elderly people in parallel with an increasing number of patients at risk for AKI, CKD and frailty. Hence, the concept of frailty should be acknowledged in acute nephrology and included in clinical decision-making.

On a societal, ethical and health economics level, there is much to gain if frail patients could be identified for whom certain therapies could be considered futile and should be advised against, such as starting renal replacement therapy (RRT) for severe AKI.

THE BIDIRECTIONAL RELATIONSHIP BETWEEN AKI AND FRAILTY

AKI often complicates critical illness and is associated with high morbidity and mortality. AKI and frailty are likely to predispose to each other in a vicious circle, worsening a patient’s outcome [5] (Figure 1).

The association between age, frailty and kidney disease is unsurprising, considering the fact that the kidneys, like other organ systems, go through a process of normal senescence that includes both anatomical and physiological changes. These changes in a normal ageing kidney are distinct from kidney diseases, which are relatively common in the elderly. Elderly people are prone to developing AKI [6] because they have more comorbidities, are more often subjected to polypharmacy, which causes nephrotoxicity, and have decreased homeostatic reserves. Frail patients may be vulnerable to AKI through a common inflammatory response, sharing similar characteristics such as high white blood cell counts, low body mass index, and low haemoglobin and albumin levels [7]. Not only do elderly frail patients have a higher risk for AKI, but they also have less chances for recovery after an AKI episode, compared with younger patients [8]. Frailty is an independent predictor of AKI [7] and is associated with worse outcome. Frail patients are also more likely to be discharged to a nursing home [7]. Patients who are labelled as both having AKI and being frail have the poorest outcome 1 year after discharge [9]. An additional challenge in elderly frail patients lies in correctly diagnosing AKI. Serum creatinine (sCr) level becomes even less reliable in the presence of sarcopenia, and it is expected to decrease with age if the true glomerular filtration rate (GFR) is unchanged. The rate and magnitude of an increase in sCr levels may be blunted in the elderly because of lower muscle mass [10]. There also seems to be a J-shaped association between sCr levels and functional limitation in elderly adults, even after adjusting for muscle mass, demonstrating that sCr levels may be affected by factors other than GFR and muscle mass in elderly adults [11]. Creatinine may not simply be a product of muscle mass, but its level may also be influenced by muscle composition, activity, diet, health status and other factors.

The renal-specific contribution to frailty relates to factors such as volume overload, anaemia, potential cognitive deficits, medication toxicities and sarcopenia/muscle deconditioning. In critical illness (ICU) survivors, an episode of AKI versus no AKI predicted worse frailty scores at 3 and 12 months post-discharge, even after adjustment for severity of illness scores, chronic underlying comorbidities, baseline kidney function and baseline Clinical Frailty Scale (CFS) scores [12].
However, the underlying mechanisms explaining the relationship between AKI and frailty are still largely unknown, and future studies are needed to clarify whether the intersection of AKI and frailty results from the kidneys acting as a sensitive and easy-to-assess barometer of clinical status and/or from the deleterious effects of AKI itself on health.

**DISCUSSION**

The majority of patients surviving critical illness will experience reduced quality of life and/or greater dependency after hospital discharge. Most studies have shown that health-related quality of life is reduced in AKI versus no-AKI patients, at least in those treated with RRT [13, 14]. In one study [15], the majority of patients described their quality of life as being worse than death. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) study [16] demonstrated that overall, the estimated cost per quality-adjusted life year (QALY) saved by initiating dialysis and continuing aggressive care, rather than withholding dialysis and allowing death to occur, was $128 200. This is corroborated by most other studies, although Laukkanen et al. [17] found that the costutility ratio of acute RRT is poor, but acceptable, in patients with renal recovery who survive for >1 year. However, this is an unfair way to calculate QALYs, as the majority of frail patients treated with RRT will not survive the first year after hospital discharge [18, 19], and cost will thus be grossly underestimated. In a study by Wong et al. [20], patients aged >85 years who started dialysis as inpatients and underwent at least one other intensive care intervention had a median survival of 5 months, of which 2 months were spent in hospital.

Around 10% of critically ill patients with AKI treated with RRT will remain dialysis-dependent. This implies a risk factor for worsening frailty and can explain the vicious circle between frailty and kidney disease leading to increased dependency and poor quality of life, especially in the elderly population.

Further research into what drives physicians to opt for aggressive versus supportive care is necessary [19]. Bagshaw et al. [18] demonstrated that there is a wide range of patient-specific factors and differing clinician perception of the benefits of each management approach, which would explain the heterogeneity in willingness to offer RRT or not, and the reasons supporting the decision-making. Frailty was more prevalent among older patients to whom clinicians were less willing to offer dialysis. One of the main conclusions of the study is that the most important risk faced by patients with severe AKI, irrespective of whether they undergo dialysis or not, is death. Advanced age in itself is rarely a reason for not starting dialysis. Unfortunately, a physician’s decision to start or forgo dialysis mostly is not the result of a shared decision-making process [18, 19].

The fact that frail patients with AKI have a poor outcome, regardless of the therapy given, is an issue that needs to be better addressed and discussed with patients. Informing patients about their prognosis can make them want to opt for supportive care and optimize their time with family and loved ones, rather than spend their last days in an intensive care environment in vain. This is important from an ethical point of view, as it allows personalized treatment, dignity in care and equitable use of resources. Customizing treatment of patients with severe AKI through shared decision-making is essential if we want to make the switch from a paternalistic type of medicine towards a patient-centred approach.

To avoid futile care and non-rewarding spending of healthcare budgets [21, 22], while preserving dignity in patient care, the following points merit some attention:

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**FIGURE 1:** Graphic illustration of the relationship between frailty and kidney disease, the underlying pathophysiological mechanisms that are likely involved and the overlap between the concepts of frailty, comorbidity and disability.
(i) Caregivers should be aware of the importance of the concept of frailty and acknowledge the important impact frailty has on short- and long-term outcomes. On admission into intensive care, the most appropriate tool with which to assess frailty is the CFS [23].

(ii) Supportive care should be offered as a valuable option to frail patients, e.g. the option of not starting RRT in severe AKI [24, 25]. Many patients now state they did not think that supportive therapy and forgoing dialysis was an option.

(iii) Caregivers need guidance on how to have an open, constructive conversation with patients and/or their next-of-kin about this topic. Proper communication (as always) is important, so that patients and their families understand why a certain treatment is better not offered. Often patients have unrealistic expectations about their health status after admission into intensive care, and this needs to be addressed. Specific tools should be developed to aid physicians in this task.

(iv) AKI should not be regarded as a benign condition that is easy reversible, especially in the frail patient [26]. This underlines the importance of a well-structured transition of care. It is important to acknowledge the special needs of frail patients and the advantages of a multidisciplinary approach and coordinated specialist services [27, 28]. Specific pharmacological and non-pharmacological interventions should be explored in frail patients, with a focus on rehabilitation, nutritional interventions and exercise [29].

In the ICU, physicians are faced with extra challenges when trying to comply with the above points. ICU patients are mostly severely ill and incapacitated, which hinders direct communication and often, a surrogate decision-maker will have to make the decisions. Regular re-evaluations should take place to assess whether the patients themselves are able to be involved in the decision-making process. For an intensivist who often has little or no insight into a patient’s background, assessing baseline frailty can be difficult and hence a multidisciplinary approach involving all caregivers is important. The role of the nursing team should not be underestimated. They also should be in agreement with the proposed line of action. Neglecting this aspect could lead to misunderstandings in communication with the patient, and it could also lead to moral distress and burn-out within the team [30].

Since there is mostly no specific treatment for AKI (except RRT), prevention of AKI is key. Prevention of frailty and/or its progression could have an impact on AKI incidence. Potential interventions that can reduce frailty mainly focus on exercise (endurance, flexibility, balance and resistance training with low-to-moderate intensity, in 30- to 45-min sessions, three times a week), nutrition, medication reconciliation and organization of social support systems. Several pharmacological and non-pharmacological interventions can be offered to frail patients, but so far there is no hard evidence for the benefit of any of these interventions.

Although prospective observational studies suggest a relationship between AKI and frailty, it is inherently impossible to infer the causality between AKI and frailty from this study type. There is a clear need for sufficiently powered randomized controlled trials (RCTs) on interventions that reduce frailty and subsequently AKI. Because AKI can occur due to multiple underlying aetiologies, and even as a result of multiple hits at the same time and across different settings, it is also possible that a potential benefit might only be present in certain settings. More research is needed to disentangle the complex relationship between AKI and frailty across these different settings and to further unravel the underlying pathophysiology.

Research in this domain is expected to enhance awareness of the concept of frailty and its relationship with AKI. There is a need for standardization of the definition of frailty, so that it can be used in a feasible way and across different settings such as primary care, ambulatory care, acute care, critical care and nursing home care. It is problematic that frail elderly patients are often excluded from research since they are likely to respond differently to interventions, compared with non-frail patients. High-quality evidence could eventually lead to the development of guidelines on how to organize a holistic approach in the care of frail patients at risk for AKI and in AKI patients at risk for frailty. This will hopefully lead to a customized approach, focusing on the special needs of this vulnerable group of patients. On a health economics level, the cost-effectiveness of such an approach in the long term should be evaluated.

CONCLUSION

Frailty, defined as exaggerated vulnerability to minor stressors, is an independent predictor for AKI whereas, on the other hand, non-frail patients who develop AKI are at risk for frailty. In both CKD and AKI, frailty is associated with both short-term and long-term adverse outcomes. Especially in the elderly, there is a need for evaluation of the frailty status on hospital admission, and the presence of frailty should be considered when making decisions on treatment such as whether or not to start RRT in frail patients with severe AKI. Patients and/or their surro- gate decision-makers should be informed about the concept of frailty and the impact it can have on survival, the degree of dependency and the quality of life overall, empowering them to make well-informed decisions about whether or not to opt for aggressive versus supportive care. From both an ethical and a health economics viewpoint, it is necessary to move away from an imperative and paternalistic form of medicine and more towards shared decision-making, which is crucial to every model based on a patient-centred approach.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES


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