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Review

Frailty and chronic kidney disease: A systematic review

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ABSTRACT

Objective: Frailty is associated with increased vulnerability to poor health. There is growing interest in understanding the association between frailty and chronic kidney disease (CKD). This systematic review explored how frailty is measured in patients with CKD and the association between frailty and adverse outcomes across different stages of renal impairment.
Study design: Systematic analysis of peer reviewed articles.
Data sources: Pubmed, Medline, Web of Science and Cochrane were used to identify the articles.
Data synthesis: Articles published before the 17th of September 2016, that measured frailty in patients with CKD was eligible for the systematic review. Two independent researchers assessed the eligibility of the articles. Quality of the articles was assessed using the Epidemiological Appraisal Instrument.
Results: The literature search yielded 540 articles, of which 32 met the study criteria and were included in the review (n = 36,076, age range: 50–83 years). Twenty-three (72%) studies used or adapted the Fried phenotype to measure frailty. The prevalence of frailty ranged from 7% in community-dwellers (CKD Stages 1–4) to 73% in a cohort of patients on haemodialysis. The incidence of frailty increased with reduced glomerular filtration rate. Frailty was associated with an increased risk of mortality and hospitalization.
Conclusion: Frailty is prevalent in patients with CKD and it is associated with an increased risk of adverse health outcomes. There are differences in the methods used to assess frailty and this hinders comparisons between studies.

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1. Introduction

Frailty describes a state of increased vulnerability to health problems. There are two acknowledged conceptualisations of the term, which have resulted in different approaches to its measurement (McMillan & Hubbard, 2012). Firstly, frailty can be thought of as a syndrome with sarcopenia as the key pathophysiological feature (Fried, Tangen, & Walston, 2001): this facilitates the measurement of frailty using a specific set of signs and symptoms. This approach, developed by Linda Fried, defines five criteria that establish a phenotype for frailty: slowness, weakness, low physical activity, exhaustion and shrinkage (Fried et al., 2001).

The second approach, known as the frailty index approach, views frailty as a state of deficit accumulation that begins at the cellular level and leads to a loss of redundancy in organ systems (Jeffery, Shum, & Hubbard, 2013; Rockwood & Mitnitski, 2007; Ensrud, Ewing, & Taylor, 2007); here, frailty is quantified by counting deficits across multiple systems.

Patients who are frail, regardless of how it is measured, experience a decline in physical function and are at an increased risk of adverse health outcomes. Although there is a strong positive correlation between frailty and chronological age, patients with chronic disease also appear to be predisposed to frailty (Weiss, 2011).

The relationship between chronic kidney disease (CKD) and frailty is not completely understood. Studies have shown that inflammation is associated with frailty in many chronic diseases and this suggests a 'shared pathophysiology' of frailty (Jeffery et al., 2013). In particular, the pro-inflammatory cytokines interleukin-6 and tumour necrosis factor alpha may have a role in age-related muscle atrophy and sarcopenia, which are key features of frailty (Hubbard & Woodhouse, 2010). Shlipak et al. (Shlipak, Fried, & Crump, 2003) demonstrated that there are raised levels of pro-inflammatory cytokines in CKD patients. However, further research is needed to investigate the causal relationship between inflammation and frailty specifically in patients with CKD.

A previous systematic review (studies published to 2012) explored frailty in pre-dialysis patients and showed an association between frailty and CKD (Walker, Gill, & Macdonald, 2013). Here, we update and expand this evidence, by including patients on dialysis as well as in kidney transplant recipients. The aims of the systematic review were to explore how frailty is measured in patients with CKD, evaluate the relationship between frailty and severity of kidney failure and assess whether it predicts outcomes such as mortality and hospitalization.

2. Method

2.1. Search strategy

The following search terms were used to identify articles that assessed frailty in patients with CKD: 'Chronic kidney disease' OR 'kidney disease' OR 'Renal Insufficiency' OR 'dialysis' OR 'kidney failure' OR 'renal failure' AND 'frailty'.

The focus of this review was on assessment of frailty status. Thus, we did not broaden the search criteria for frailty to include geriatric or functional assessments. The literature search was conducted using online databases including Pubmed, Medline, Web of science and Cochrane libraries. The reference lists of key papers were also examined for articles of relevance.

2.2. Selection criteria

Inclusion criteria for the systematic review were primary research articles that analysed the prevalence of, or relationship between, frailty and CKD. All studies investigating frailty in dialysis, pre-dialysis and kidney transplant recipients published before 17th September 2016 were eligible for inclusion. Articles were excluded if they were not available in the English language. Where there were articles that involved different analyses on the same study population, the article that best answered the aims of the systematic review was selected for analysis.

3. Data analysis

Two independent reviewers examined the abstracts for relevance to the study criteria. Where there was a difference of opinion about inclusion of the study, a third reviewer was consulted.

A data extraction table was created which included information about the demographics of the study population, the sample size, method of frailty assessment, CKD measurement and outcome variables such as mortality rates and hospitalization.

Each article in the systematic review was assessed for quality using the Epidemiological Appraisal Instrument (EAI). The EAI, developed by Genaidy and colleagues, provides a systematic appraisal of study quality across the domains of sample selection, exposures and outcomes, statistical analysis and adjustment for co-variates and confounders (Genaidy, Lemasters, & Lockey, 2007) Each domain was scored out of 2, and the average across the domains was expressed as the overall EAI score. The closer the score to 2 the better the article.

Due to the significant heterogeneity in the sample populations, method of frailty assessment, and CKD measurement a meta-analysis was not performed.

4. Results

The literature search yielded 540 articles. Forty-eight articles met the inclusion criteria and were selected for full text review. After the full text review a further 16 studies were excluded from further analysis for the following reasons: article did not measure frailty in the study population (n = 3); not available in English (n = 2); did not measure frailty in a CKD population (n = 3); repeated analyses on the same study population (n = 8); and one article whose results were not available for the systematic review. This resulted in 32 studies that were included as part of the systematic review (Fig. 1). Overall, there were 18 studies (56%) which were designed as primary prospective analyses of frailty in

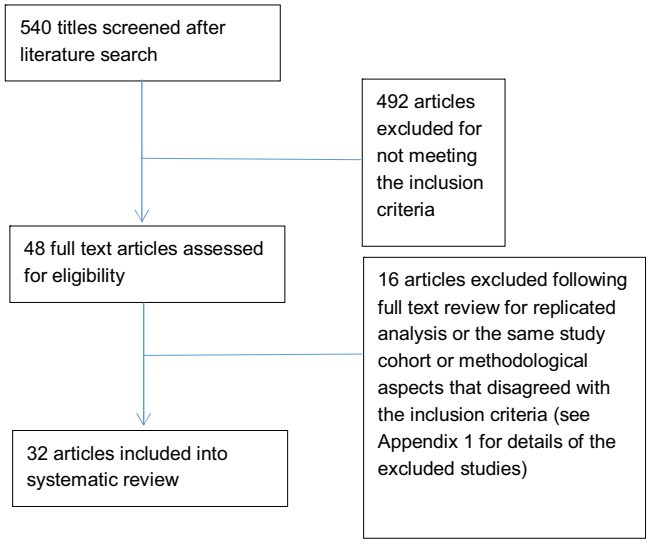

Fig. 1. Study Selection.