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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

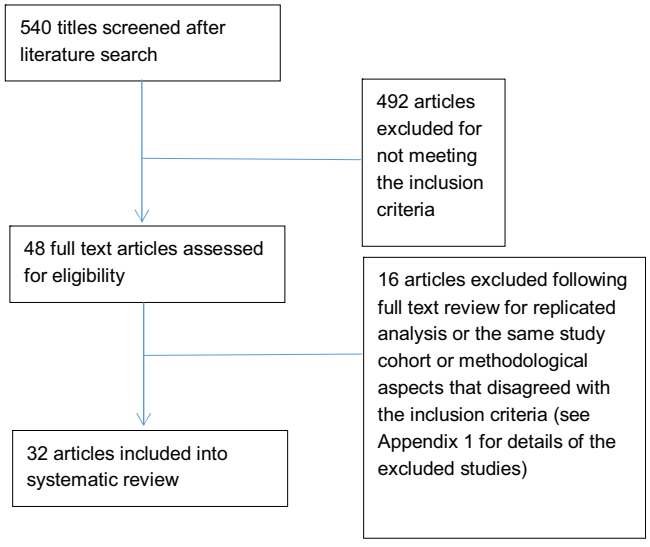

Fig. 1. Study Selection.

Table 1
Pre-dialysis Patients.

Reference	Study Characteristics	Study Population	Primary Outcome	Study Design	EAI	Frailty assessment	GFR estimation and Average GFR	Frailty Prevalence
Shlipak, Stehman-Breen, & Fried (2004)	N = 648 %female = 39 Mean age = 76 years	Cardiovascular Health Study (enrolment) *USA*	Investigate the prevalence and association of CKD with frailty and disability	Secondary analysis of an established cohort.	1.57	Fried	CrCl 41 mLs/min	15%
Dalrymple et al. (2013)	N = 4150 %female = 59 Mean age = 75 years	Cardiovascular Health Study (3 year review) *USA*	Examined the prevalence and development of frailty in patients with incident CKD	Secondary analysis of an established cohort	1.67	Fried	Cystatin C/ CrCl 73 mLs/min (median GFR)	9.7%
Roshanravan et al. (2012)	N = 336 %female = 19 Mean age = 59 years (+/− 13)	Pre-dialysis CKD stages 1-4–Outpatients *USA*	Prevalence and association of CKD with frailty. Measured outcomes including mortality and progression to dialysis	Primary prospective study	1.76	Fried	Cystatin C 51 mLs/min	14%
Wilhelm-Leen et al. (2009)	N = 10 256 %female = 53 Mean age = 50 years (+/− 1.3)	National Health and Nutrition Evaluation Survey *USA*	Correlation of frailty with CKD and mediators of this interaction	Secondary analysis of an established cohort.	1.81	Fried	CrCl 106.21 mLs/min (includes controls)	7.9%
Hart et al. (2013)	N = 1602 %female = 0 Mean age = 74 years (+/− 5.9)	Osteoporotic fractures in men Study *USA*	Association of frailty with CKD	Secondary analysis of an established cohort	1.67	Fried	Cystatin C/ CrCl Mean GFR not published	Not published
Mansur et al. (2014)	N = 61 %female = 41 Mean age = 61 years (+/− 11.5)	Pre dialysis CKD patients *Brazil*	Association between frailty, CKD and QOL in pre-dialysis patients.	Primary prospective study	1.19	Modified Fried	CrCl 27 mLs/min	42.6%
Reese et al. (2013)	N = 1111 %female = 47 Median age = 65 years (+/− 8)	Chronic renal insufficiency cohort *USA*	Association between CKD severity and frailty and risk factors for frailty.	Secondary analysis of an established cohort	1.86	Fried	CrCl 49 mLs/min (median GFR)	7%
Yamada et al. (2013)	N = 8063 %female = 62 Mean age = 81 years (+/− 7.4)	J-MACC study – Community dwelling individuals *Japan*	Risk of requiring long-term care insurance in frail patients with CKD	Secondary analysis of an established cohort	1.52	Frailty Check List	CrCl Not published	Not published
McAdams-DeMarco, Suresh et al. (2013)	N = 383 %female = 40 Mean age = 54 years (+/− 13.9)	Renal transplant recipients *USA*	Frailty as a risk factor for early hospital readmission post kidney transplant	Primary prospective study	1.76	Fried	No GFR estimation	18.8%
Garonzik-Wang et al. (2012)	N = 183 %female = 36 Mean age = 53 years (+/−14)	Renal transplant recipients *USA*	Association between frailty and delayed graft function in renal transplant recipients	Primary prospective study	1.52	Fried	No GFR estimation	25%
McAdams-DeMarco, Isaacs et al. (2015)	N = 349 %female = 38.1 Mean age = 53.3 (+/− 14.2) years	Renal transplant recipients *USA*	The natural trajectory of frailty before and after kidney transplantation.	Primary prospective study	1.67	Fried	No GFR estimation	19.8% (at baseline)
Rodriguez Villarreal et al. (2014)	N = 56 %female = 48.2 Mean age = 79 (+/− 5) years	Pre-dialysis patients *Spain*	Exploring factors that influenced the decision for conservative care versus dialysis in older patients with Stage 4-5 CKD.	Primary prospective study	1.57	Fried	CrCl 16 mLs/min	0%
Lee et al. (2015)	N = 168 %female = 37 Mean age = 65.9 years	Pre-dialysis patients *Korea*	Examine the prevalence of frailty and its influence on quality of life	Primary prospective study	1.67	Fried	CrCl 41.1 mLs/min	37.5%
Montesanto et al. (2014)	N = 1038 %female = 53.2 Mean age = 83.4 years	Pre-dialysis patients *Italy*	The relationship between frailty, GFR estimating using BIS1 equation and mortality.	Secondary analysis of an established cohort	1.86	Population based approach	CrCl 53 mLs/min	48.3%
Meulendijks et al. (2015)	N = 63 %female = 35 Median age = 75 years	Pre-dialysis patients *Netherlands*	Evaluation of whether the Groningen Frailty Index can distinguish between fitter patients who may benefit from dialysis from frailer patients in need of geriatric assessment.	Primary prospective study	1.48	Groningen Frailty Index	CrCl 16 mLs/min	32%
	N = 110 %female = 46.4		Pilot study investigating the feasibility of using the frailty index in patients with pre-dialysis chronic		1.76	Frailty index	NA	Mean FI = 0.25

Table 1 (*Continued*)

Reference	Study Characteristics	Study Population	Primary Outcome	Study Design	EAI	Frailty assessment	GFR estimation and Average GFR	Frailty Prevalence
Hubbard et al. (2015)	Mean age = 65.2 (+/− 14.6) years	Pre-dialysis patients *Australia*	kidney disease. Cross sectional analysis of frailty	Primary prospective study.				
Delgado, Grimes et al. (2015)	N = 812 %female = 39.5 Median age = 52 years (42-61 years IQR)	MDRD Pre-dialysis patients *USA*	Investigation of self-reported frailty and its association with GFR and mortality Prospective cohort study	Secondary analysis of an established cohort	1.67	Modified Fried	CrCl Iodine 145-iothalamate clearance 33.1 mLs/min	16%
Pugh et al. (2016)	N = 283 %female = 44% Median age = 74 (63–81 years IQR)	Pre-dialysis patients *UK*	Relationship between frailty and co-morbidity with the risk of mortality in elderly patients referred to an outpatient chronic kidney disease clinic.	Primary prospective study	1.48	Clinical Frailty Scale	CrCl 16 mLs/min	33%

CKD. The remaining 14 studies (44%) were secondary analysis of established cohorts not originally sampled for examining frailty.

4.1. Demographics of the study population

Fifteen studies examined frailty in pre-dialysis patients with CKD, fourteen in the dialysis population and three in patients who had received kidney transplantation. These studies examined frailty in a total of 36,076 participants with CKD (82% in pre-dialysis patients and 18% in dialysis patients). The study characteristics and population demographics are reported in Tables 1 and 2.

4.2. Critical appraisal of quality

The average EAI score for the studies was 1.63 (Standard deviation—0.18). The individual scores for each article are reported in Tables 1 and 2. Overall, the articles performed well in describing the aims and defining the exposure and outcome variables. However, most articles did not publish sample size calculations, participation rates or account for subjects lost to follow up—these criteria were three lowest achieved amongst those of the EAI.

4.3. Method of frailty assessment

The majority of studies classified frailty using the Fried phenotype (n = 23, 72%). However, there were variations in the interpretation of the five characteristics of frailty compared to the original definitions stipulated by Fried et al. (Table 3) (Fried et al., 2001).

Estimation of physical activity and exhaustion showed the most heterogeneity between the studies. The most common methods of physical activity assessment were estimation of kilocalories (n = 9, 41%), patient self-report (n = 8) and questionnaire based assessment (n = 6). Exhaustion was determined most frequently by patient self-report (n = 11, 48%), Short-Form 36 vitality score (n = 6) and the Centre for Epidemiological Studies Depression Scale (n = 5). Grip strength was the most common method of assessing weakness (n = 14, 61%), whilst slowness was measured using timed gait speed (n = 17, 74%). Shrinkage was estimated by measuring weight loss over 12 months (n = 12, 52%).

There were seven studies (30%) that modified the Fried criteria for frailty and substituted the measurement of grip strength and gait speed for questionnaire based assessments of physical function. This method improves the feasibility of investigating frailty in large sample populations (Woods, LaCroix, & Gray, 2005). However, Painter and Kuskowski (2013) showed that using questionnaire based data over-estimated the reported prevalence of frailty in haemodialysis patients.

Ten studies (31%) employed a different measure to the Fried phenotype for frailty assessment. The most common of these, used in three studies, was the Clinical Frailty Scale. This is a clinical assessment of frailty developed from the Canadian Study of Health and Aging, which ranks fitness from a score of 1 (Very fit) to a score of 8 (severely frail and unlikely to recover from a minor illness) to a score of 9 (terminally ill) (Rockwood, Song, & MacKnight, 2005). Other scales used include the frailty index approach, which provides a quantitative assessment of frailty as the proportion of potential deficits in health (Rockwood & Mitnitski, 2007) This has been shown to be reproducible and be predictive of outcomes (Jones, Song, & Rockwood, 2004). Chao et al. uses the FRAIL scale (Fatigue, Resistance, Ambulation, Illness, Loss of weight), which is related to the criteria developed by Fried et al. but adds co-morbidity (illness) to self-reported assessment of the other criteria (Morley, Malmstrom, & Miller, 2012). Other measures used in the studies include the Groningen Frailty Indicator, Montensanto approach, Edmonton Frail Scale and a frailty check list (Meulendijks, Hamaker, & Boereboom, 2015; Orlandi & Gesualdo, 2014; Montesanto, De Rango, & Berardelli, 2014; Yamada, Arai, & Nishiguchi, 2013).

4.4. Prevalence of frailty

Frailty was prevalent in patients with CKD, particularly in those on dialysis. Amongst the pre-dialysis population the prevalence of frailty ranged from 7%, in a study of community dwellers with CKD (median estimated glomerular filtration rate (eGFR) = 49 mLs/min), to 42.6% in a smaller study of patients with more severe CKD (mean eGFR = 27 mLs/min) (Reese, Cappola, & Shults, 2013; Mansur, Colugnati, & Grincenkov, 2014). A study by Rodriguez et al. (Rodriguez Villarreal, Ortega, & Hinostroza, 2014) had no patients who were frail, despite the sample population having severe CKD (mean eGFR = 16). However, patients in this study were referred into the clinic for consideration for dialysis; as a consequence of this screening process, only those who were 'fit' were selected (Rodriguez Villarreal et al., 2014).

Frailty was more prevalent amongst patients on haemodialysis with the range being from 14% to 73% (Bao, Dalrymple, & Chertow, 2012; Kutner, Zhang, Allman, & Bowling, 2014). There was no statistical comparison performed of the prevalence between dialysis and pre-dialysis patients because of the differences in the methods used to assess frailty.

Table 2
Dialysis Patients.

Study	Study Characteristics	Study Population	Primary Outcome	Study Design	EAI	Frailty Assessment	Prevalence of frailty
Bao et al. (2012)	N = 1576 %female = 45 Mean age = 59.6 years	Comprehensive Dialysis Study HD% = 89.3 *USA*	Frailty prevalence dialysis cohort. GFR at dialysis initiation and its relationship with frailty	Secondary analysis of an established cohort	1.62	Modified Fried	73%
McAdams-DeMarco et al. (2013a)	N = 146 %female = 47 Mean age = 61 years (+/− 13.6)	Single haemodialysis centre HD% = 100 *USA*	Prevalence of frailty and outcome assessment	Primary prospective study	1.67	Fried	41.8%
Delgado et al. (2013)	N = 80 %female = 37 Mean age = 55 years (+/− 13)	Nandrolone and Exercise Study HD% = 100 *USA*	A comparison of function based frailty assessment and performance based tests. Body composition and frailty status.	Secondary analysis of an established cohort	1.19	Modified Fried: Performance based and Function Based Criteria	59% (performance based)
Painter and Kuskowski (2013)	N = 188 %female = 56 Mean age = 54.4 (+/− 16) years	Renal Exercise Demonstration Study HD% = 100 *USA*	Analysis of two methods of applying the Fried phenotype for frailty: questionnaire based physical function vs measurement	Secondary analysis of an established cohort	1.81	Fried	24% (measured physical function)
Johansen et al. (2007)	N = 2275 %female = 47 Mean age = 58 years (+/− 16)	Dialysis Morbidity/ Mortality Study HD% = 51.9 *USA*	Investigation of the prevalence and predictors of frailty amongst dialysis patients and correlation with adverse health outcomes. Prospective cohort study	Secondary analysis of an established cohort	1.71	Modified Fried	68%
Kutner et al. (2014)	N = 742 %female = 40.6 Mean age = 57 years (+/− 14.1)	ACTIVE/ADIPOSE Study HD% = 100 *USA*	Frailty and its association with ADL difficulties	Secondary analysis of an established cohort	1.71	Fried	14%
McAdams-DeMarco et al. (2013b)	N = 95 %female = 46 Mean age = 61 years (+/− 12.6)	Single dialysis centre HD% = 100 *USA*	Association of frailty with risk of falls in patients with ESKD	Primary prospective study	1.71	Fried	46.3%
Orlandi and Gesualdo (2014)	N = 60 %female = 30 Mean age = 71 years (+/− 6.9)	Single dialysis centre HD% = 100 *Brazil*	Assessment of frailty in elderly patients undergoing dialysis	Primary prospective study	1.10	Edmonton Frailty scale	38%
Salter, Gupta, & Massie (2015)	N = 146 %female = 46.6 Mean age = 61 years	Single dialysis centre HD% = 100 *USA*	Comparison between measured frailty and clinician perceived frailty	Primary prospective study	1.71	Fried	41.7%
Chao, Hsu, & Chang (2015)	N = 46 %female = 53 Mean age = 67.3 (+/− 11.9) years	Single dialysis centre HD% = 100 *Taiwan*	Exploring frailty in a rural dialysis centre in Taipei and comparison between different self-reported measures of Frailty.	Primary prospective study	1.52	FRAIL scale amongst others.	19.6%
Alfaadhel et al. (2015)	N = 390 %female = 33 Mean age = 63 years (+/− 15)	Single dialysis centre HD% = 100 *USA*	Assessed whether the clinicians perception of frailty correlated with outcomes in a population of patients on dialysis.	Primary prospective study	1.81	Clinical frailty scale	26%
Iyasere, Brown, & Johansson (2016)	N = 251 %female = 40.7 Median age = 76 (70-81 years IQR)	Single Dialysis Centre HD% = 48.6 *UK*	Comparison of frailty and quality of life between patients on haemodialysis with those on peritoneal dialysis. Cross sectional analysis	Primary prospective study	1.57	Clinical frailty scale	47.4% (overall)
McAdams-DeMarco, Tan, & Salter (2015)	N = 324 %female = 43.5 Mean age = 54.8 years (+/− 13.3)	Predictors of arrhythmic and cardiovascular risk in ESKD Study. HD% = 100 *USA*	Investigated the relationship between frailty and cognition both at base line and at one year of follow up. Prospective cohort study	Secondary analysis of an established cohort	1.76	Fried	34%
Drost, Kalf, Vogtlander, & van Munster (2016)	N = 95 %female = 43 Mean age = 65.2 years (+/− 12)	Single dialysis centre HD% = 44 *Netherlands*	Comparison between prevalence of frailty assessed using the frailty index versus the Fried Frailty Phenotype. Cross sectional analysis	Primary prospective Study	1.76	Fried and Frailty Index	36.8% (measured using FI)

4.5. Glomerular filtration rate and frailty

Six studies demonstrated a negative correlation between eGFR and the risk of frailty in pre-dialysis patients with CKD (Reese et al., 2013; Roshanravan, Khatri, & Robinson-Cohen, 2012; Wilhelm-Leen, Hall, Tamura, & Chertow, 2009; Dalrymple, Katz, & Rifkin, 2013; Hart, Paudel, & Taylor, 2013; Delgado, Grimes, & Glidden, 2015). Three of the six studies used cystatin C to estimate eGFR,

Table 3
Fried Frailty Assessment.

Original Definition of the Fried Phenotype by Fried et al (5)	Interpretation of Fried Phenotype (n = 23)
Slowness	Gait speed (n = 17, 74%)
Gait speed	Questionnaire based assessment of physical function (n = 5)
	Subjective perception of gait speed (n = 1)
Weakness	Dyno metre measurement of grip strength (n = 14, 61%)
Grip Strength	Questionnaire based assessment of physical function (n = 5)
	Timed sit-to-stand (n = 2)
	Self-report (n = 2)
Exhaustion	Patient self-report (n = 11, 48%)
Centre for epidemiological studies depression scale	Centre for Epidemiological Studies depression scale (n = 5)
	Short form 36 Questionnaire (n = 6)
	Short form 12 Questionnaire (n = 1)
Shrinkage	Weight loss of 10 pounds over 12 months (n = 12, 52%)
>10 pounds of unintentional weight loss in 12 months	Other measures of weight loss (BMI, 5% loss in total weight, lean appendicular mass, cachexia) (n = 9, 39%)
	Not measured (n = 2)
Low Physical Activity	Estimation of kilocalories (n = 9, 39%)
Estimated kilocalories per week	Patient self-report (n = 8)
	Questionnaire based physical activities scale (n = 6)

two used creatinine and one use iodine 145-iothalamate clearance. A study by Roshanravan et al. (Roshanravan et al., 2012) found that the relationship between frailty and CKD was attenuated when using creatinine instead of Cystatin C to estimate GFR. In five studies, there was significant increase in the risk of frailty with eGFR less than 45mLs per minute (Reese et al., 2013; Roshanravan et al., 2012; Wilhelm-Leen et al., 2009; Dalrymple et al., 2013; Hart et al., 2013). In the remaining study, only patients with an eGFR less than 30mLs per minute were at a statistically significant increased risk of frailty because those with an eGFR >45 was used as the reference population (Delgado, Grimes et al., 2015).

A study by Dalrymple et al. (Dalrymple et al., 2013) in the Cardiovascular Health Study cohort showed that CKD was associated with an increased risk of incident frailty. Patients with CKD who did not have baseline frailty were followed for four years. The risk of developing frailty was inversely related to baseline eGFR (Dalrymple et al., 2013) Patients with a eGFR between 15 and 45 mLs/min were twice as likely to develop frailty over four years when compared with patients with normal eGFR (Dalrymple et al., 2013).

4.6. Mortality, hospitalization and falls

Eight studies assessed adverse health outcomes in frail patients with CKD: four in dialysis populations and four in pre-dialysis cohorts. Johansen et al. (Johansen, Chertow, Jin, & Kutner, 2007) examined frailty in dialysis patients and found an increased risk of death associated with frailty after one year of follow-up (Hazard Ratio [HR] 2.24, 95% CI 1.6–3.15). Similarly, Bao et al. (Bao et al., 2012) and McAdams De-Marco et al. (McAdams-DeMarco, Law, & Salter, 2013a) reported a significant risk of mortality associated with frailty amongst the dialysis population. The relationship between frailty and risk of death persisted after multivariate adjustment for age, sex and co-morbidities in all three studies. Alfaadhel et al. (Alfaadhel, Soroka, & Kiberd, 2015) demonstrated that each one point increase in the Clinical Frailty Scale was associated with an increased risk of mortality in haemodialysis patients (HR 1.22 [95% CI 1.04–1.13]; median follow-up: 1.7 years). Bao et al. (Bao et al., 2012) and McAdams De-Marco et al. (McAdams-DeMarco et al., 2013a) also demonstrated that frailty correlated with an increased risk of hospitalization in dialysis patients. An analysis of a composite end-point of death or hospitalization reached statistical significance in the study by Johansen et al. (HR 1.56 95% CI 1.36–1.79) (Johansen et al., 2007).

Roshanravan et al. (Roshanravan et al., 2012) conducted a study in patients with CKD stages 1–4 and demonstrated that frailty was an independent risk factor for death or progression to dialysis (HR: 2.5 [95% CI 1.4–4.4]; median follow-up: 2.6 years). In a study by Wilhelm-Leen et al. (Wilhelm-Leen et al., 2009), frailty increased the risk of death in patients with CKD and the risk was only partly attenuated in a multivariate model that adjusted for co-morbidities, inflammation and sarcopenia (HR 2.0 [95% CI 1.5–2.7]). Studies by Delgado et al. (Delgado, Grimes et al., 2015) and Pugh et al. (Pugh, Aggett, & Goodland, 2016) also demonstrated an increased risk of mortality in patients with pre-dialysis CKD who were frail.

Frailty is a risk factor for falls in patients with end stage kidney disease In a cohort of haemodialysis patients, McAdams De-Marco et al. (McAdams-DeMarco, Suresh, & Law, 2013) demonstrated that frailty increased the risk of falls by three times compared to those who were not frail (RR = 3.09, 95% CI 1.38–6.90).

5. Frailty and the kidney transplant recipient

Three studies have investigated frailty in kidney transplant recipients. McAdams De-Marco et al. (McAdams-DeMarco, Law, & Salter, 2013b) demonstrated that incident frailty increased the risk of hospital readmission amongst kidney transplant recipients (Relative Risk = 1.61, 95% CI 1.18–2.19). This risk persisted after adjustment for age, gender, co-morbidity, time spent on dialysis and donor factors. Another study by Garonzik-Wang et al. (Garonzik-Wang, Govindan, & Grinnan, 2012) showed that frailty was an independent risk factor for delayed graft function (RR = 1.94, 95% CI 1.13–3.36). A second study by McAdams De-Marco et al. (McAdams-DeMarco, Isaacs, & Darko, 2015) investigated the change in frailty status after kidney transplantation. It found that the prevalence of frailty in the cohort decreased at 3 months of follow up and that patients who were frail before transplantation were twice as likely to have improvement in frailty score after transplantation (HR: 2.55 [95% CI: 1.71–3.82]) (McAdams-DeMarco, Isaacs et al., 2015).

6. Discussion

In this systematic review of frailty in patients with CKD, the prevalence of frailty increased with poorer kidney function and was highest in patients receiving dialysis. Frailty was a significant predictor of adverse health outcomes, particularly in those with severe CKD stages. However, we found differences in frailty assessment and estimation of GFR and this may have influenced the reported prevalence of frailty.

The Fried phenotype provided the basis for frailty assessment in the majority of the studies in this review (n = 23, 72%). This is a well validated method of frailty assessment that classifies patients as frail, pre-frail or not frail categories (Fried et al., 2001). However, the Fried phenotype is less useful in grading the severity of frailty in populations where the prevalence of frailty is high (Clegg, Young, & Iliffe, 2013). This is particularly problematic in patients on dialysis with one study demonstrating the prevalence of frailty be as high as 73% (Bao et al., 2012). Other methods, such as the frailty index, provide a continuous variable that may improve the discrimination of those patients at high risk, especially in patients on dialysis (Hubbard, Peel, & Smith, 2015).

The feasibility of using performance based tests of grip strength and slowness has proven to be problematic in retrospective studies that have used the Fried phenotype. One approach, proposed by Woods et al. (Woods et al., 2005), involves replacing performance based tests with questionnaire based data to grade loss of physical function. However, the correlation between measuring grip strength and slowness versus estimating physical function using the SF-36 questionnaire is poor (r = −0.34 for gait speed; r = 0.14 for grip strength) (Woods et al., 2005). There were seven studies that modified the Fried phenotype and used the approach of using questionnaire data to replace the measured variables (Painter & Kuskowski, 2013; Mansur et al., 2014; Bao et al., 2012; Hubbard et al., 2015; Johansen et al., 2007; Delgado, Doyle, & Johansen, 2013; Lee, Son, & Shin, 2015). Subsequently, Painter et al. (Painter & Kuskowski, 2013) conducted a comparison of measuring gait speed and grip strength versus questionnaire data in quantifying the prevalence of frailty in haemodialysis patients. The study found the prevalence of frailty was 24% in the performance based group and 78% in the group using questionnaire data (Painter & Kuskowski, 2013). Thus the methods by which the characteristics of Fried's phenotype of frailty are defined can considerably influence the prevalence of frailty in the population being investigated.

GFR estimation was different amongst the studies and this may influence the relationship between frailty and severity of CKD. The most common method of deriving an eGFR is by creatinine clearance, as reported in 12 studies. However since this relies on muscle mass, the eGFR of frail patients who have lost muscle mass may be over-estimated. Another method of estimating GFR is by using cystatin C which is not influenced by muscle mass and this was utilised in three studies. The strength of the association between frailty and eGFR appears to be increased by using cystatin C.

Regardless of the method of estimation, GFR seems to be an important mediator in the risk of frailty in patients with CKD. Five studies demonstrated that eGFR less than 45 mLs/min was associated with increased odds of frailty (Reese et al., 2013; Roshanravan et al., 2012; Wilhelm-Leen et al., 2009; Dalrymple et al., 2013; Hart et al., 2013). There were differences in the calculation of the odds ratios because of different definitions of the eGFR of the reference population. This influenced the value of the odds ratios and prevented comparisons between studies.

The prevalence of frailty ranged from 7% to 42.6% in pre-dialysis patients (Reese et al., 2013; Mansur et al., 2014). Amongst dialysis patients, the highest prevalence of frailty in the studies analysed was 73% (Bao et al., 2012). However, there was a wide range of frailty prevalence in the various CKD populations included in this review. Differences in the demographics of the study population, average eGFR, gender, co-morbidities and ethnicity may explain this difference. Furthermore, as demonstrated previously, the method of frailty assessment can considerably influence the proportion of patients classified as being frail.

Patients with CKD who were frail were at increased risk of mortality and hospitalization. The risk of mortality was significant in both dialysis and pre-dialysis patients with CKD (Bao et al., 2012; Roshanravan et al., 2012; Wilhelm-Leen et al., 2009; Delgado, Grimes et al., 2015; Johansen et al., 2007; McAdams-DeMarco et al., 2013a; Alfaadhel et al., 2015; Pugh et al., 2016). Frailty also predicted an increased risk of falls in patients with CKD (McAdams-DeMarco, Suresh et al., 2013; Delgado, Shieh, & Grimes, 2015). In the kidney transplant recipient, frailty was associated with an increased risk of early hospital readmission and delayed graft function (Garonzik-Wang et al., 2012; McAdams-DeMarco, Suresh et al., 2013). Patients who were frail prior to transplantation were also more likely to have improvement in frailty after transplantation (McAdams-DeMarco, Isaacs et al., 2015). A previous systematic review by Walker et al. (Walker et al., 2013) found similar associations between frailty and adverse health outcome in patients with non-dialysis CKD. The association of frailty with mortality risk is consistent with other studies in community dwellers with normal renal function (Ensrud et al., 2007; Woods et al., 2005).

The findings of this systematic review have multiple implications for clinical practice. Firstly, it highlights the prevalence of frailty particularly in those with Stage 5 CKD and those on dialysis. Identifying these patients is important because frailty is associated with poor health outcomes. Frailty is a useful marker of health status and can be used to monitor response to interventions; an example of this can be seen in the study by McAdams de Marco and colleagues who explored how frailty status changed before and after kidney transplantation (McAdams-DeMarco, Isaacs et al., 2015).

Whilst a number of the articles in this systematic review were primary prospective studies, there is little data commenting on the length of time to complete these frailty assessments or the resources needed. One study, investigating the frailty index, demonstrated that a frailty assessment is feasible in an outpatient CKD clinic and could be conducted in approximately 10 min using a questionnaire (Hubbard et al., 2015). However, there is a need to compare different frailty assessment methods to establish which is better suited in a clinical setting. With the exception of kidney transplantation, there is no evidence for interventions that can change a patient's frailty status if they have CKD. Frailty manifests when there is a critical number of deficits across multiple systems including those that regulate inflammation (Hubbard & Woodhouse, 2010). Thus, it is likely that multiple strategies will be needed in tackling this issue of frailty in patients with CKD.

There are strengths and limitations inherent in this systematic review. It encompasses a diverse range of populations with CKD including patients on dialysis, community dwellers who are not on dialysis and kidney transplant recipients. The total sample size is large with 36,000 patients. However, differences in the method of frailty assessment and estimation of GFR between the studies meant there was considerable heterogeneity between studies. For this reason, a meta-analysis and summation statistics could not be performed to take full advantage of the large sample size. A large proportion of studies (n = 14, 44%) used a secondary analysis in an existing cohort of patients to examine the relationship between frailty and CKD. This raises issues of external validity and whether the studies sufficiently addressed selection bias when presenting the findings. Unpublished results and a single article not available in the English language were excluded from this systematic review. Publication bias is a possibility because of exclusion of these studies.

7. Conclusion

Based on the number of studies, consistency and quality of the findings, there is strong evidence that frailty is associated with CKD and that patients with more severe CKD are more likely to be frail. Frailty predicts poor outcomes in patients with CKD including an

increased risk of mortality and hospitalization. There is a need to better understand causality and why frailty is associated with adverse health outcomes in patients with CKD. Further research should also explore different methods of frailty assessment that better delineate those who are most frail and who may benefit from targeted intervention.

Conflicts of interest

None.

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