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Frailty in Chronic Kidney Disease

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ABSTRACT

Frailty is regarded as the most problematic consequence of aging. Whilst there is no precise definition for frailty, most clinicians agree that patients who are frail are vulnerable to poor health. Frailty can be conceptualised as a syndrome with a set of symptoms and signs that are measured to give a categorical classification of frailty as described by Fried and colleagues. Alternatively, frailty can be considered as a state, where deficits in health across multiple organ systems accumulate over time. These deficits are summated to give a continuous measure of frailty called the frailty index (FI).

Patients with chronic kidney disease (CKD) are at risk of frailty. CKD has effects in multiple systems and it leads to accelerated manifestation of frailty, especially in those who are on dialysis. The Fried approach to frailty assessment has been applied in numerous settings of patients with CKD. However, there are limitations of the Fried approach especially when the prevalence of frailty is high, and a more precise measure is needed of the severity of frailty in an individual.

The thesis begins with a systematic review of frailty in patients with CKD. It focuses on how frailty is assessed, including the Fried approach and other assessment methods; differences in frailty between dialysis and pre-dialysis patients; and how frailty changes across the spectrum of severity in kidney function. The systematic review yielded 37 articles encompassing 53,000 patients with CKD. The most common method of frailty assessment was the Fried approach (n=27 articles, 73%). The prevalence of frailty ranged between 7% in a population of pre-dialysis patients with CKD to 73% in patients on dialysis. There was considerable heterogeneity in how the studies defined the Fried phenotype and this impacted on the reported prevalence of frailty. Regardless of the method of assessment, frailty was associated with an increased risk of mortality and hospitalization.

The systematic review highlighted gaps in the current evidence, especially in better delineating risk amongst patients on dialysis where the prevalence of frailty may be high. This leads to the next chapter of the thesis, a prospective study of the Frailty Index in CKD (FI-CKD). The aim of the study was to investigate the frailty index (FI) in outpatients with pre-dialysis and dialysis dependent CKD. Associations between FI and kidney function were explored as well as the relationship between FI and change in kidney function, mortality and hospitalization after twelve months of follow up. Amongst 314 patients, the mean FI was 0.29 (SD 0.13) corresponding to a clinical description of mild to moderate frailty. FI was associated with an increased risk of mortality (OR: 1.8; 95% CI 1.77 – 2.44) and hospitalization (OR 1.3 95% CI 1.06-1.5). Patients with a higher CKD stage were significantly more likely to have a higher FI. However, there was no significant

differences in the average FI between dialysis and pre-dialysis patients, perhaps due to the limited number of patients on dialysis (n=86, 27%) or due to selection bias.

The final chapter reviews the implications of the prospective study for clinical practice. FI may be incorporated into electronic medical records to provide more contemporaneous support for clinical decision making. The studies described in this thesis have provided the basis for a longitudinal investigation of frailty in patients with end stage kidney disease and exploring changes in FI with dialysis initiation versus conservative management.

Declaration by author

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Publications during candidature

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2. Dr Nancye M Peel
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5. Mr Sebastian Senff
 - a. Assisted with data recording and compiling the database. Aided with data collection
6. Mr Kevin Chan
 - a. Helped with compiling the database and its internal consistency.

Statement of parts of the thesis submitted to qualify for the award of another degree

No part of the thesis is submitted to qualify for another degree.

Research Involving Human or Animal Subjects

No animal or human subjects were involved in this research

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List of Abbreviations used in the thesis

Abbreviation	Full Term
CI	Confidence interval
CKD	Chronic kidney disease
EAI	Epidemiological appraisal instrument
eGFR	Estimated glomerular filtration rate
FI	Frailty index
HR	Hazard Ratio
IL-6	Interleukin 6
K/DOQI	National kidney disease outcome quality initiative.
OR	Odds ratio
RR	Relative risk
SD	Standard deviation
SF-36	Short form 36 questionnaire
TNF-a	Tumour necrosis factor alpha

CHAPTER 1: INTRODUCTION

1.1 Defining Frailty

Frailty is 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 (1). Firstly, frailty can be thought of as a syndrome with sarcopenia as the key pathophysiological feature (2): this facilitates the measurement of frailty using a specific set of signs and symptoms that are measured to classify patients who are frail or not. The second 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 (3-5); here, frailty is quantified by counting deficits across multiple systems. This provides a continuous variable that not only describes if a patient is frail or not but also the severity of the frailty. 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 diseases also appear to be predisposed to frailty (6). Patients with chronic kidney disease (CKD) are at a higher risk of frailty and subsequent adverse health outcomes.

1.2 Demographics

The assessment of frailty is increasingly becoming important because population aging means more primary and tertiary health care providers are involved in geriatric care. Recent data from the Australian Bureau of Statistics demonstrate that the proportion of patients aged above 65 years has increased from 12% to 15.3% between the period of 1996 to 2016 (7). In the same period, the proportion of patients aged above 85 years has almost doubled from 1.1% to 2.0% (7). Due to decrease in fertility rates and improved survival rates, the rate of population aging in Australia is projected to increase further into the future (7). This has implications for the provision of health care, housing, the size of the working population and the need for skilled labour (7). New Zealand and other developed nations including Japan, Canada and the United States, are experiencing similar changes in population aging.

CKD is prevalent amongst older Australians with 42.2% of individuals above 75 years of age having an indicator of CKD (8). The AusDiab study, conducted in 42 randomly selected census localities across Australia, showed that increasing age was the strongest risk factor for the presence of CKD even after multi-variate analysis (9). The prevalence of end stage kidney disease requiring treatment is projected to increase to 31, 589 individuals by 2020 with the greatest rise occurring in those above 75 years of age (10). Furthermore, the survival of patients on dialysis is improving

(11). A recent observational study showed a 25% reduction in adjusted mortality rate with dialysis inception in Australia and New Zealand between years 2008-2012 compared to 1998-2002 (11). Patients on dialysis are living longer and the age of commencement of dialysis is increasing. Thus, the care of older individuals with CKD will become increasingly important. The most common aetiology of CKD requiring renal replacement therapy in Australia is diabetes followed by primary glomerulonephritis and hypertension (12). There is a similar spectrum of CKD in patients in New Zealand, however, primary glomerulonephritis is more common (12).

1.3 Pathophysiology

Aging can be viewed as the accumulation of damage to multiple systems at the cellular and molecular level (13). This is dependent on the maintenance and repair systems which are influenced by genetics and epigenetics and ultimately results in the phenotype of aging. Many organ systems have redundancy that confers a certain resilience against insults such as disease. However, in patients who are frail, there is loss of redundancy, meaning that even trivial insults such as a change in medication, urinary tract infection or admission to hospital can result in instability and falls, delirium and disability (13). The accumulation of deficits in multiple systems leads to a reduction in redundancy and leads to the phenotype of the frail patient.

Frailty has been studied in relation to changes in multiple organ systems including the brain, immune system, skeletal system and hormonal control. In the brain, aging is associated with loss of function of hippocampal neurons, which are involved in memory and potentiation of microglial cells which may cause neuronal injury and are implicated in delirium (13). There are changes to the innate and adaptive immune system resulting in a blunting of response to an acute stimulus (13). However, following a stimulus there is persistence of a low grade inflammatory response even after removal of the stimulus. This is mitigated by multiple cytokines including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha), which contribute to muscle catabolism, loss of adiposity and anorexia (13). Changes to the endocrine system in frailty include a decrease in IGF-1 levels, decrease in the sex hormones including testosterone and oestrogen and a rise in cortisol levels (13). The net effect of the hormonal changes and pro-inflammatory cytokine milieu is that there is a change in the balance between muscle formation and destruction towards catabolism. This is thought to result in the manifestation of sarcopenia, which is a key contributor to frailty (13).

Aging also affects kidney function. Firstly, after the age of 30, there is progressive replacement of glomeruli with fibrous tissue, known as glomerulosclerosis (14). In the afferent and efferent arterioles of the nephrons there is intimal thickening, but the tunica media atrophy, which means

there is blunting of the response to autonomic stimuli (such as changes in blood pressure) (14). Loss of juxtamedullary nephrons results in direct channels being formed between afferent and efferent arterioles resulting in aglomerular circulation (bypassing the glomerulus) (14). Renal tubules undergo fatty degeneration and there is thickening of the glomerular basement membrane (14). Therefore, there is a decline in glomerular filtration with age and a reduction in the ability to reabsorb sodium in the distal tubules (14).

Senile changes in renal function are inevitable with ageing. However, there are differences between patients with CKD and these senile changes. Healthy older individuals have intact proximal tubular function, no changes to erythropoietin levels, a normal urine analysis and intact fractional excretion of urea, calcium, magnesium, phosphorus and potassium (14).

The relationship between kidney disease and frailty is not completely understood. Studies show that inflammation is associated with frailty in many chronic diseases and this suggests a 'shared pathophysiology' of frailty (3). Shilpkap et al demonstrated that there are raised levels of pro-inflammatory cytokines in CKD patients (15). However, further research is needed to investigate the causal relationship between inflammation and frailty specifically in patients with CKD.

1.4 Relationship between Frailty and CKD

The prevalence of frailty ranges between 7% in patients with pre-dialysis CKD to 73% in a cohort of patients on haemodialysis (16, 17). Frailty is associated with an increased risk of death, hospitalization and falls in patients with CKD (18). The relationship between frailty and CKD depends on the severity of kidney failure, demographics and co-morbidities of the patient. The close association of frailty and adverse health outcome reinforces why frailty assessment is an important consideration in the care of patients with CKD. The following systematic review will explore the relationship between frailty and CKD in more detail.

1.5 Frailty Assessment

This section addresses the question of how frailty can be identified and assessed in patients with CKD. Fried et al described a phenotype for frailty based on a secondary analysis of patients in the Cardiovascular health study (2). The Fried approach proposes that frailty is a syndrome with sarcopenia and age-related decline in physical function as the key pathophysiological features (2). It describes a phenotype of frailty based on the presence of three or more of the following criteria: slowness measured with gait speed; weakness measured with grip strength; weight loss of more

than 10 pounds in 12 months; low physical activity and exhaustion measured using questionnaires (2). The Fried approach is well validated in a number of different settings of patients with chronic diseases including the CKD population (6). It is a useful method of screening for frailty and it has been shown to be predictive of health outcomes (13).

However, there are limitations to the Fried approach frailty assessment amongst CKD patients. Firstly, the Fried approach categorizes patients into those who are frail and those who are not. This can be problematic in populations where the prevalence of frailty is high because the dichotomous categorization of frailty using the Fried approach makes it less useful as a predictor of adverse outcomes in CKD patients. Furthermore, cognitive impairment and emotional well-being, important factors contributing to disability and functional status, are not assessed by the Fried phenotype (13). The criteria for frailty require performance-based measurements of gait speed and grip strength which may be difficult to apply in some clinical settings and larger cohorts of patients. Furthermore, the method by which the criteria are defined is subject to interpretation and this may alter the reported prevalence of frailty in a given study population (19).

The frailty index (FI) is an alternative method of frailty assessment. This approach conceptualises frailty as a state of deficit accumulation. These deficits originate at the cellular and molecular level and decrease redundancy in organ systems, which lead to an increased vulnerability to stressors. The FI approach identifies deficits in health which are equally weighted to calculate a score. Deficits are variables which are biologically sensible, accumulate with age and do not saturate too early (13). This typically includes the presence of disease, activities of daily living, disability, emotional state and cognition. It is not the type of deficit that is important but the number of deficits in determining the level of frailty (13). The FI has been shown to correlate with an increased risk of death and institutionalisation in the Canadian Study of Health and Aging (20). It is well validated and has been applied in many different settings.

Use of the FI has advantages over the Fried approach in CKD patients. Frailty can be quantified as a continuous variable, which is more useful in attributing risk especially amongst the dialysis population where the prevalence of frailty is high. Furthermore, FI does not rely on performance-based data, which is advantageous in the assessment of frailty in larger cohorts.

Disadvantages of FI are related to its complexity with some models having as many as 90 variables. Collecting the information to complete the FI takes time and resources, which may not be available in certain clinical settings. A categorical approach to frailty is also more easily understood by clinicians and patients rather than a continuous variable without context. Finally, the accuracy of

any diagnostic tool relies on the quality of data that is inserted into the tool. Recall bias and information bias has the potential to reduce the validity of the FI.

There are several approaches that have been applied to overcome the disadvantages of the FI. Firstly, an abbreviated version of the FI with 58 variables has been applied to an outpatient setting of patients with CKD in a prior feasibility study (21). This took on average 10 minutes to complete and showed good internal validity when compared with the Fried Approach. Furthermore, the FI-CKD assessment form used in the pilot study has predominantly binary variables that limit subjectivity and bias influencing the accuracy of the tool. The FI correlates well with the Clinical Frailty Scale ($r=0.8$) and the FI can be divided into categories with clinical descriptors (such as mild, moderate or severe frailty) according to prior work performed by Rockwood and colleagues (22). For instance, a cut-off score of 0.25 has been used as the border between fitness and mild frailty (22).

This thesis will continue with a systematic review that examines the current evidence surrounding frailty in patients with CKD. It explores the differences in frailty assessment; prevalence of frailty in patients with pre-dialysis and dialysis CKD; the relationship between frailty and changes in kidney function estimated with GFR; and the association of frailty in adverse health comes in patients with CKD. The systematic review leads to the prospective study of the Frailty Index in Chronic Kidney Disease. The aim of this study is to investigate the FI and the relationship with dialysis and changes in kidney function estimated with glomerular filtration rate (GFR). The methods of the prospective study including aims, settings, data collection, analysis and ethics will be presented. The thesis will present the results and critically analyse the findings in the discussion. Finally, the thesis concludes by examining how the research contributes to current and future practice.

CHAPTER 2: SYSTEMATIC REVIEW

2.1 Introduction

There has been great interest in exploring frailty in patients with CKD. Previous literature has shown that frailty correlates with adverse health outcomes including an increased risk of mortality, hospitalization and falls in patients with CKD (18). Frailty is also a predictor of adverse outcomes in patients with kidney transplantation (23).

A previous systematic review (studies published to 2012) explored frailty in pre-dialysis patients and showed an association between frailty and CKD (18). Here, we update and expand this evidence, by including patients on dialysis as well as 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. Potential gaps in the available literature and avenues for future research will be explored in the prospective study of the FI in patients with CKD (Chapter 3) and the conclusions (Chapter 4).

The systematic review has been published in the journal *Geriatrics and Gerontology* (24). The full review can be found in Appendix 1. For the purposes of the thesis, the systematic review has been up dated to include articles published till the 1st November 2017.

2.2 Methods

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.

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 1st November 2017 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.

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 (25). 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.

2.3 Results

The literature search yielded 586 articles. Sixty articles met the inclusion criteria and were selected for full text review. After the full text review a further 23 studies were excluded from further analysis for the following reasons: article did not measure frailty in the study population (n=4); not available in English (n=3); did not measure frailty in a CKD population (n=4); repeated analyses on the same study population (n=9); two article whose results were not available for the systematic review; one further article was excluded because of insufficient quality and lack of generalizability

of the results to populations outside that study setting. This resulted in 37 studies that were included as part of the systematic review (Figure 1). Overall, there were 19 studies (51%) which were designed as primary prospective analyses of frailty in CKD. The remaining 18 studies (49%) were secondary analyses of established cohorts not originally sampled for examining frailty.

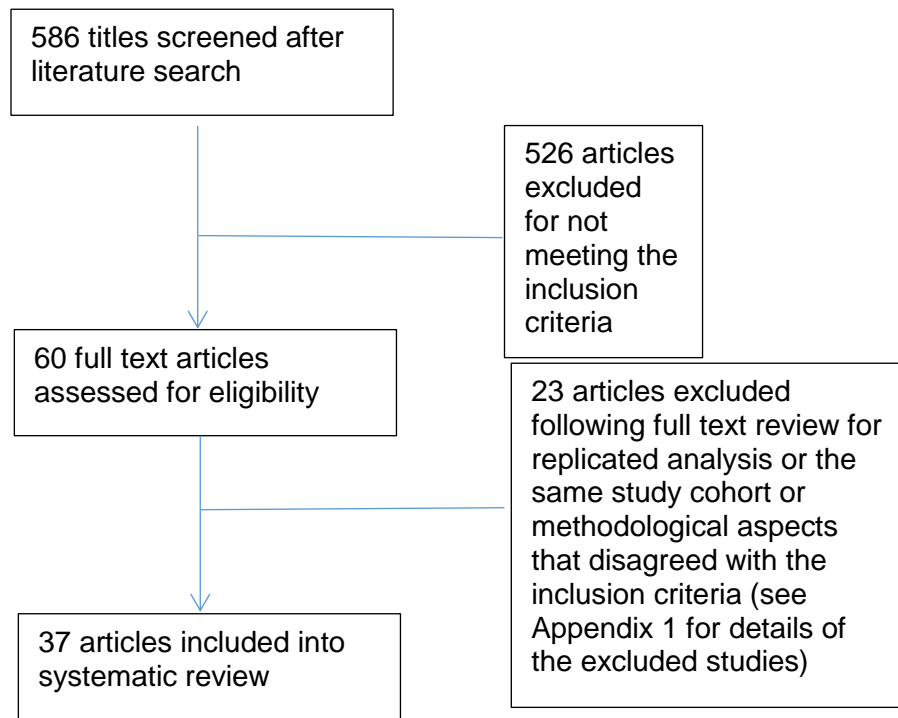


Figure 1 Systematic Review: Study selection

Demographics of the Study Population

There were an equal number of studies included in this systematic review that explored frailty in dialysis and pre-dialysis patients with CKD (n=17, 46%), whilst three studies were performed in patients who had received kidney transplantation. These studies examined frailty in a total of 52 798 participants with CKD (84% in pre-dialysis patients and 16% in dialysis patients). The study characteristics and population demographics are reported in Tables 1 and 2.

Table 1 Systematic Review: Pre-dialysis Patients

Reference	Study Characteristics	Study Population	Primary Outcome	Study Design	EAI	Frailty assessment	GFR estimation and Average GFR	Frailty Prevalence
Shlipak et al 2004 (26)	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 41mLs/min	15%
Dalrymple et al 2013 (27)	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 73mLs/min (median GFR)	9.7%
Roshanravan et al 2012 (28)	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 51mLs/min	14%
Wilhelm-Leen et al 2009 (29)	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 106.21mLs/min (includes controls)	7.9%
Hart et al 2013 (30)	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 (31)	N = 61 %female = 41	Pre dialysis CKD patients Brazil	Association between frailty, CKD and QOL in pre-dialysis patients.	Primary prospective study	1.19	Modified Fried	CrCl 27mLs/min	42.6%

	Mean age = 61 years (+/- 11.5)							
Reese RP et al 2013 (16)	N = 1111 %female = 47 Median age = 65 years (+/- 8)	Chronic renal insufficiency cohort <i>USA</i>	Association between CKD severity and frailty and risk factors for frailty.	Secondary analysis of an established cohort	1.86	Fried	CrCl 49mLs/min (median GFR)	7%
Yamada et al 2013 (32)	N = 8063 %female = 62 Mean age = 81 years (+/- 7.4)	J-MACC study – Community dwelling individuals <i>Japan</i>	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 De-Marco et al 2013 (23)	N = 383 %female = 40 Mean age = 54 years (+/- 13.9)	Renal transplant recipients <i>USA</i>	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 (33)	N = 183 %female = 36 Mean age = 53 years (+/-14)	Renal transplant recipients <i>USA</i>	Association between frailty and delayed graft function in renal transplant recipients	Primary prospective study	1.52	Fried	No GFR estimation	25%
McAdams De-Marco et al 2015 (34)	N = 349 %female = 38.1 Mean age = 53.3 (+/- 14.2) years	Renal transplant recipients <i>USA</i>	The natural trajectory of frailty before and after kidney transplantation.	Primary prospective study	1.67	Fried	No GFR estimation	19.8% (at baseline)

Rodriguez et al 2014 (35)	N = 56 %female = 48.2 Mean age = 79 (+/- 5) years	Pre-dialysis patients <i>Spain</i>	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 16mLs/min	0%
Lee et al 2015 (36)	N = 168 %female = 37 Mean age = 65.9 years	Pre-dialysis patients <i>Korea</i>	Examine the prevalence of frailty and its influence on quality of life	Primary prospective study	1.67	Fried	CrCl 41.1mLs/min	37.5%
Montesanto et al 2014 (37)	N = 1038 %female = 53.2 Mean age = 83.4 years	Pre-dialysis patients <i>Italy</i>	The relationship between frailty, GFR estimating using BIS1 equation and mortality.	Secondary analysis of an established cohort	1.86	Population based approach	CrCl 53mLs/min	48.3%
Meulendijks et al 2015 (38)	N = 63 %female = 35 Median age = 75 years	Pre-dialysis patients <i>Netherlands</i>	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 16mLs/min	32%
Hubbard et al 2015 (39)	N = 110 %female = 46.4 Mean age = 65.2 (+/- 14.6) years	Pre-dialysis patients <i>Australia</i>	Pilot study investigating the feasibility of using the frailty index in patients with pre-dialysis chronic kidney disease. Cross sectional analysis of frailty	Primary prospective study.	1.76	Frailty index	NA	Mean FI = 0.25
Delgado et al 2015 (40)	N = 812 %female = 39.5 Median age = 52 years (42-61 years IQR)	MDRD Pre-dialysis patients <i>USA</i>	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 33.1mLs/min	16%

Pugh et al 2016 (41)	N = 283 %female = 44 Median age = 74 (63-81 years IQR)	Pre-dialysis patients <i>UK</i>	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 16mLs/min	33%
Ballew et al 2017 (42)	N = 4987 %female = 56 Mean age = 75.6 years	Pre-dialysis patients (ARIC study) <i>USA</i>	Evaluate the relationship between frailty, kidney function estimated with cystatin C and polypharmacy	Secondary analysis of an established cohort	1.81	Fried phenotype	Cystatin C 61mLs/min	6.8%
Lee et al 2016 (43)	N = 9606 %female = 52.4 Mean age = 73.6 (+/- 5.5) years	Pre-dialysis patients <i>Japan</i>	Investigate the association between frailty, kidney function, diabetes and hypertension in pre-dialysis patients in a Japanese community.	Secondary analysis of an established cohort	1.62	Modified Fried Phenotype	CrCl 67.4 mls/min	9.2%

Table 2 Systematic Review: Dialysis Patients

Study	Study Characteristics	Study Population	Primary Outcome	Study Design	EAI	Frailty Assessment	Prevalence of frailty
Bao 2012 et al (17)	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 2013 (44)	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 (45)	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 et al 2013 (19)	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 (46)	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 (47)	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 2013 (48)	N = 95 %female = 46 Mean age = 61 years (+/- 12.6)	Single dialysis centre HD% = 100 <i>USA</i>	Association of frailty with risk of falls in patients with ESKD	Primary prospective study	1.71	Fried	46.3%
Orlandi et al 2014 (49)	N = 60 %female = 30 Mean age = 71 years (+/- 6.9)	Single dialysis centre HD% = 100 <i>Brazil</i>	Assessment of frailty in elderly patients undergoing dialysis	Primary prospective study	1.10	Edmonton Frailty scale	38%
Salter et al 2015 (50)	N = 146 %female = 46.6 Mean age = 61 years	Single dialysis centre HD% = 100 <i>USA</i>	Comparison between measured frailty and clinician perceived frailty	Primary prospective study	1.71	Fried	41.7%
Chao et al 2015 (51)	N = 46 %female = 53 Mean age = 67.3 (+/- 11.9) years	Single dialysis centre HD% = 100 <i>Taiwan</i>	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 (52)	N = 390 %female = 33 Mean age = 63 years (+/- 15)	Single dialysis centre HD% = 100 <i>USA</i>	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 et al 2016 (53)	N = 251 %female = 40.7 Median age = 76 (70-81 years IQR)	Single Dialysis Centre HD% = 48.6 <i>UK</i>	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 et al 2015 (54)	N = 324 %female = 43.5 Mean age = 54.8 years (+/- 13.3)	Predictors of arrhythmic and cardiovascular risk in ESKD Study. HD% = 100 <i>USA</i>	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 et al 2016 (55)	N = 95 %female = 43 Mean age = 65.2 years (+/- 12)	Single dialysis centre HD% = 44 <i>Netherlands</i>	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)
Ng et al 2016 (56)	N = 193 %female = 49.7 Mean age = 60.6 years (+/- 12.1)	Single centre HD% = 0 PD% = 100 <i>China</i>	Investigating frailty in patients on PD and its relationship with outcomes including mortality, hospitalization and technique survival	Prospective Study	1.71	Frailty questionnaire	69.4%
Bancu et al 2017 (57)	N = 320 %female = 40.6 Mean age = 70.3 years (+/- 14 years)	Three dialysis centres HD% = 100 <i>Spain</i>	Pattern of frailty amongst dialysis patients, predictors of frailty and outcomes including mortality and hospitalization	Retrospective observational study	1.76	Fried phenotype	39%
Kang et al 2017 (58)	N = 1616 %female = 44.1 Mean age = 55.9 years	Multicentre HD% = 77.4 <i>Korea</i>	Evaluating differences between frailty, quality of life and disability between patients on haemodialysis and peritoneal dialysis.	Retrospective analysis of an established cohort	1.76	Modified Fried phenotype	34.6% (no difference PD vs HD)

Critical Appraisal of Quality

The average EAI score for the studies was 1.64 (Standard deviation – 0.18). The individual scores for each article are reported in Table 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.

Method of Frailty Assessment

Most of the studies classified frailty using the Fried phenotype (n=27, 73%). 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) (2).

Estimation of physical activity and exhaustion showed the most heterogeneity between the studies. The most common methods of physical activity assessment were patient self-report (n=11, 41%), estimation of kilocalories (n=9, 33%), and questionnaire based assessment (n=7). Exhaustion was determined most frequently by patient self-report (n=13, 48%), Short-Form 36 (SF-36) vitality score (n=7) and the Centre for Epidemiological Studies Depression Scale (n=6). Grip strength was the most common method of assessing weakness (n=16, 59%), whilst slowness was measured using timed gait speed (n=19, 70%). Shrinkage was estimated by measuring weight loss over 12 months (n=15, 55%).

There were eight 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 (59). However, Painter et al showed that using questionnaire based data over-estimated the reported prevalence of frailty in haemodialysis patients (19).

Eleven studies (30%) 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) (22). Other scales used include the FI approach, which provides a quantitative assessment of frailty as the proportion of potential deficits in health (4). This

has been shown to be reproducible and be predictive of outcomes (60). 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 (61). Other measures used in the studies include the Groningen Frailty Indicator, Montasanto approach, Edmonton Frail Scale and a frailty check list (32, 37, 38, 49).

Table 3 Systematic Review: Fried Frailty Assessment

Original Definition of the Fried Phenotype by Fried et al (2)	Interpretation of Fried Phenotype (n=27)
Slowness <i>Gait speed</i>	Gait speed (n=19, 70%) Questionnaire based assessment of physical function (n=7) Subjective perception of gait speed (n=1)
Weakness <i>Grip Strength</i>	Dyno metre measurement of grip strength (n=16, 59%) Questionnaire based assessment of physical function (n=6) Timed sit-to-stand (n=2) Self-report (n=2) Not state (n=1)
Exhaustion <i>Centre for epidemiological studies depression scale</i>	Patient self-report (n=13, 48%) Centre for Epidemiological Studies depression scale (n=6) Short form 36 Questionnaire (n=7) Short form 12 Questionnaire (n=1)
Shrinkage <i>>10 pounds of unintentional weight loss in 12 months</i>	Weight loss of 10 pounds over 12 months (n=15, 55%) Other measures of weight loss (BMI, 5% loss in total weight, lean appendicular mass, cachexia) (n=10, 40%) Not measured (n=2)
Low Physical Activity <i>Estimated kilocalories per week</i>	Patient self-report (n=11, 41%) Estimation of kilocalories (n=9, 33%) Questionnaire based physical activities scale (n=7)

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) = 49mLs/min), to 42.6% in a smaller study of patients with more severe CKD (mean eGFR = 27mLs/min) (16, 31). A study by Rodriguez et al had no patients who were frail, despite the sample population having severe CKD (mean eGFR =16) (35). 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 (35).

Frailty was more prevalent amongst patients on haemodialysis with the range being from 14% to 73% (17, 47). 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.

Glomerular Filtration Rate and Frailty

Seven studies demonstrated a negative correlation between eGFR and the risk of frailty in pre-dialysis patients with CKD (16, 27-30, 40, 42). Four of the seven studies used cystatin C to estimate eGFR, two used creatinine and one use iodine 145-iothalamate clearance. A study by Roshanravan et al found that the relationship between frailty and CKD was attenuated when using creatinine instead of Cystatin C to estimate GFR (28). This was supported by a more recent retrospective analysis by Ballew et al of 4987 community dwellers comparing cystatin C and creatinine clearance and the relationship with frailty (42). In five studies, there was significant increase in the risk of frailty with eGFR less than 45mLs per minute (16, 27-30). 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 (40). The study by Ballew et al demonstrated a significant relationship between odds of frailty with kidney function estimated with cystatin C, with the more severe the kidney disease the greater the odds of frailty (42).

A study by Dalrymple et al in the Cardiovascular Health Study cohort showed that CKD was associated with an increased risk of incident frailty (27). 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 (27). 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 (27).

Mortality, Hospitalization and Falls

Eleven studies assessed adverse health outcomes in frail patients with CKD: seven in dialysis populations and four in pre-dialysis cohorts. Johansen et al 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) (46). Similarly, Bao et al and McAdams De-Marco et al reported a significant risk of mortality associated with frailty amongst the dialysis population (17, 44). 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 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) (52). Bao et al and McAdams De-Marco et al also demonstrated that frailty correlated with an increased risk of hospitalization in dialysis patients (17, 44).

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) (46).

Roshanravan et al 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) (28). In a study by Wilhelm-Leen et al, 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]) (29). Studies by Delgado et al and Pugh et al also demonstrated an increased risk of mortality in patients with pre-dialysis CKD who were frail (41, 62).

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 demonstrated that frailty increased the risk of falls by three times compared to those who were not frail (Relative risk [RR]=3.09, 95% CI 1.38 – 6.90) (48).

Frailty and the Kidney Transplant Recipient

Three studies have investigated frailty in kidney transplant recipients. McAdams De-Marco et al demonstrated that incident frailty increased the risk of hospital readmission amongst kidney transplant recipients (RR= 1.61, 95% CI 1.18-2.19) (23). This risk persisted after adjustment for age, gender, co-morbidity, time spent on dialysis and donor factors. Another study by Garonzik-Wang et al showed that frailty was an independent risk factor for delayed graft function (RR=1.94,

95% CI 1.13-3.36) (33). A second study by McAdams De-Marco investigated the change in frailty status after kidney transplantation (34). 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]) (34).

2.4 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=27, 73%). This is a well validated method of frailty assessment that classifies patients as frail, pre-frail or not frail categories (2). However, the Fried phenotype is less useful in grading the severity of frailty in populations where the prevalence of frailty is high (13). This is particularly problematic in patients on dialysis with one study demonstrating the prevalence of frailty be as high as 73% (17). Other methods, such as the FI, provide a continuous variable that may improve the discrimination of those patients at high risk, especially in patients on dialysis (39).

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, involves replacing performance based tests with questionnaire based data to grade loss of physical function (59). 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) (59). There were eight studies that modified the Fried phenotype and used the approach of using questionnaire data to replace the measured variables (17, 19, 31, 36, 39, 45, 46, 58). Subsequently, Painter et al conducted a comparison of measuring gait speed and grip strength versus questionnaire data in quantifying the prevalence of frailty in haemodialysis patients (19). The study found the prevalence of frailty was 24% in the performance based group and 78% in the group using questionnaire data (19). Thus, the method by which the characteristics of the Fried 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 14 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. Six studies demonstrated that eGFR less than 45mLs/min was associated with increased odds of frailty (16, 27-30, 40, 42). 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 (16, 31). Amongst dialysis patients, the highest prevalence of frailty in the studies analysed was 73% (17). 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 (17, 28, 29, 40, 41, 44, 46, 52, 56-58). Frailty also predicted an increased risk of falls in patients with CKD (48, 62). In the kidney transplant recipient, frailty was associated with an increased risk of early hospital readmission and delayed graft function (23, 33). Patients who were frail prior to transplantation were also more likely to have improvement in frailty after transplantation (34). A previous systematic review by Walker et al found similar associations between frailty and adverse health outcome in patients with non-dialysis CKD (18). The association of frailty with mortality risk is consistent with other studies in community dwellers with normal renal function (5, 59).

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 (34).

Whilst several 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 FI, demonstrated that a frailty assessment is feasible in an outpatient CKD clinic and could be conducted in approximately 10 minutes using a questionnaire (39). 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 (63). 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 and kidney transplant recipients. The total sample size is large with 53 000 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=18, 49%) 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.

2.5 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.

However, there is a need to better understand causality and why frailty is associated with adverse health outcomes in patients with CKD. There were no comparisons between patients with CKD and

patients with other chronic diseases, to establish whether CKD patients were unique in their higher likelihood of developing frailty. CKD may represent the cumulative consequences of deficits in health, such as hypertension, diabetes or chronic glomerulonephritis that result in the phenotypic expression of frailty. The fact that worse kidney function increases the likelihood of frailty is suggestive that kidney disease itself correlates with frailty. It is difficult, however, to definitively establish the contribution of kidney disease to frailty versus the diseases that caused the kidney disease in the first place.

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. A categorical description of frailty is useful in describing frailty in large populations. A continuous variable would accurately define the severity of frailty, particularly in patients with more severe CKD where the prevalence of frailty is high. Consistency in how frailty is defined is important in comparisons between cohorts of patients with CKD.

Following is a prospective study of investigated the use of the frailty index in patients with dialysis and pre-dialysis CKD.

CHAPTER 3: PROSPECTIVE STUDY OF FRAILTY IN CHRONIC KIDNEY DISEASE3.1

3.1 Introduction

The systematic review highlighted potential avenues for further research into frailty in patients with CKD. Firstly, there is a need to explore other frailty assessment methods that better delineate risk, particularly amongst dialysis patients, where the prevalence of frailty may be high. The FI is one such method that provides a continuous variable to better define frailty in a population. Much of the research into frailty in patients with CKD is based on populations outside Australia and New Zealand. An FI-CKD pilot study provided evidence that an FI could be a feasible means of frailty quantification in patients with CKD (39). However, there is a need to expand this data set to patients on dialysis as well. Finally, we need a greater understanding of how interventions modify frailty over time. Examples specific to patients with CKD include the effects of dialysis or kidney transplantation.

3.2 Methods

Aims

The aims of the FI-CKD study were:

1. Assess the relationship between FI and kidney function.
2. Examine the effects of dialysis on FI
3. Investigate if baseline frailty is associated with increased risk of mortality and hospitalization.

Hypotheses

1. Patients with reduced kidney function would have a greater FI.
2. FI would be greater in those on dialysis
3. Baseline frailty would be associated with increased risk of adverse outcomes at 12 months follow-up

Study Design and Settings

The FI-CKD project was a prospective, multi-centre longitudinal study of the FI in patients with CKD. Recruitment began with a pilot study in August 2013 at the Princess Alexandra Hospital, Brisbane, Australia. The second phase of recruitment commenced on July 2014 and continued to

January 2015 and included patients recruited from Whangarei Dialysis Centre, North Island, New Zealand.

The Princess Alexandra Hospital is a 780 bed tertiary hospital in the metropolitan centre of Brisbane Australia. It has one of the largest CKD services in Australia and includes outpatient haemodialysis centre, outpatient clinic and facilities to support patients on peritoneal dialysis and home haemodialysis. The Princess Alexandra Hospital is the centre for kidney transplantation in the state of Queensland.

The Whangarei Dialysis Unit is the largest dialysis unit in the Northland of New Zealand. It caters for 58 patients on haemodialysis and works in association with Whangarei Hospital.

There were four data collectors involved in interviewing patients at the two recruitment sites. The three data collectors at the Princess Alexandra Hospital include the principle study investigator (Rakin Chowdhury), Mr Mitchel Krosch (Medical Student) and Sebastian Senff (Medical Student). There was a fourth data collector in Whangarei Dialysis centre, Ari (Medical Student).

Internal validity was achieved by training of the data collectors and by consistency with frailty assessment form. Furthermore, the frailty assessment form counts the majority of deficits as dichotomous variables which minimizes subjectivity in the assessment.

Statistical Power

The target sample size for the study was 250 patients. Assuming adverse outcomes (mortality and hospitalization as a composite outcome over one year) occur in 25% of older people in the frailest quartile and 5% of older people in the fittest quartile, and setting alpha at 5% and power at 80%, the sample size estimate would be 50 per quartile.

Eligibility Criteria and Recruitment

Outpatients in nephrology clinics and dialysis centres at the two centres for data collection were invited to participate in the study. Patients who agreed to participate were provided with written information about the project and consent was attained (Appendix 2).

Participants were eligible for inclusion if they were older than 18 years of age and had CKD. However, participants were excluded if they were not able to speak the English language and no interpreter was available.

Measures

Frailty measures utilized

Frailty was measured using the FI-CKD (Frailty Index in CKD). The FI-CKD was previously developed in a pilot study and showed feasibility in the setting of outpatients with CKD (39). The FI-CKD involves using the frailty assessment form (Appendix 3), which includes 58 coded items which represent potential deficits in health. Deficits can be a symptom, sign, disease, disability or laboratory measure that corresponds with adverse health outcome (4). For a variable to be a deficit it must satisfy five criteria (64):

- The variable must be associated with health status
- The chosen variables should cover a range of health status. For instance, the FI-CKD covers deficits in perceived health status co-morbidity, cognition, polypharmacy, mental well-being, sleep, activities of daily living, mobility and communication.
- The prevalence of the deficit should increase with age
- The deficit should not completely saturate with age. An example of a variable that does saturate with age is presbyopia (so presbyopia cannot be used as a deficit)
- If the FI is re-applied to the same individual over time, then the same set of variables should be used

The deficits were ascertained predominantly by patient self-report. Sometimes patients with complex histories do not have a complete recollection of all their medical problems or their medications. Furthermore, cognitive impairment would impair the recall of some this information. For this reason, deficits surrounding co-morbidity and medications were cross checked with the patient's electronic medical record to ensure accuracy. The FI-CKD was calculated as number of deficits in health divided by the total number of deficits measured as per previous methodology (4, 64).

There were other frailty assessment tools that were considered for the prospective study. One method involves using interRAI (Resident Assessment Instrument) which is a comprehensive assessment of patients' physical, cognitive and psycho-social functioning (65). The data is derived from a variety of different sources including the patient, medical records, family and health care providers involved in the patient's treatment (65). A FI can be derived from the detailed information provided by interRAI and this has previously been demonstrated in an acute care setting (65). However, interRAI would not be feasible in an outpatient setting predominantly because of time

constraints. Patients were often opportunistically approached whilst waiting for an outpatient clinic appointment and so the time with the patient would be 20 minutes at most. Furthermore, much of the information provided by interRAI requires care giver assessment (65). Most patients presenting to the outpatient clinic came alone and so again this was not deemed as feasible for the study.

Other approaches to frailty assessment such as the Fried phenotype were considered. As mentioned in the systematic review, the disadvantage of using the Fried phenotype include the feasibility of the performance based test and the categorical classification of frailty in the population. This may be less useful in populations where the prevalence of frailty is high, such as patients with CKD. The other tools available such as the Clinical Frail Scale, FRAIL scale and Montesaño tool all provide a categorical classification of frailty and have similar limitations.

Estimation of kidney function

GFR was estimated using the Modification of Diet in Renal Disease (MDRD) equation and serum creatinine (66). Estimated GFR with this approach was used because of its ease of availability and its widespread use in clinical practice in the study settings. Alternative measures include Cystatin C, which has advantages particularly in the assessment of kidney function in patients who are frail. Serum creatinine is produced by muscle breakdown and theoretically a frail patient with reduced muscle mass would have a lower production of creatinine thus resulting in overestimation of kidney function (28). Cystatin C is not dependent on muscle mass and previous studies have shown a stronger negative correlation between GFR estimated with cystatin C and frailty when compared with serum creatinine and frailty (28). However, Cystatin C is not widely utilized in clinical practice in Australia or New Zealand and it was not routinely available at the time of data collection.

GFR was also stratified into CKD stage according to the K/DOQI guidelines (National Kidney Disease Outcome Quality Initiative) (67). The most recent blood test to the date of assessment and the date of follow up was chosen to estimate GFR.

Outcomes

A review of health records was conducted at 12 months post study recruitment by the principal study investigator (RC). At this time, outcome data including mortality, hospitalization data and change in eGFR from baseline was attained from electronic medical records.

Statistical Analysis

Frailty indices for each participant were calculated as the sum of deficits divided by the total number of deficits measured (58 items). Information about patient demographics and co-morbidities were presented as frequencies and compared between dialysis and pre-dialysis patients using t-test for continuous variables with normal distributions and non-parametric tests for those not normally distributed. The Chi-squared test was used in comparisons of categorical data.

In the analysis of kidney function and FI, patients on dialysis were excluded because dialysis itself would be a confounding variable. Univariate association between FI and eGFR was tested using Pearson correlation coefficient. Further analyses were conducted between FI and CKD stage using ordinal regression analysis with adjustments for age and gender.

The outcomes of mortality and hospitalization were treated as dichotomous variables and analysed with logistic regression with adjustments for age, gender and dialysis status. The FI was multiplied by 10 to provide more meaningful reporting of risk when calculating odds ratios (68). Results were expressed as the odds of the outcome occurring per unit (0.1) increase in frailty and this follows a similar outcome analysis using the FI in a previous study (68).

Statistical analysis of data was conducted with IBM SPSS (Version 23.0).

Ethics

The FI-CKD study was approved by the respective Ethics Boards at the Princess Alexandra Hospital, Brisbane, and Whangarei Dialysis Centre, New Zealand. A copy of the ethics approval at the Princess Alexandra Hospital is provided in Appendix 4. Participants were given written information and signed informed consent forms were completed (see Appendix 3). Patients were de-identified at the time of analysis. All data was kept in a secure location and databases password protected.

3.3 Results

Demographics

There were 314 participants recruited into the FI-CKD study and 42% (n=132) were female.

The majority of the sample were pre-dialysis patients (n=228, 73%). Of those on dialysis (n=86, 27%), the most common type of dialysis was haemodialysis (n= 76, 88%) (Figure 2). Average age across the cohort was 64 years (SD 13.4 years) and the mean number of co-morbidities was 7 (SD 3). The most common aetiology causing CKD in the cohort was diabetic nephropathy (n= 102, n=32.5%), followed by renovascular nephrosclerosis (n=35, 11.1%), hypertensive nephrosclerosis (n=19, 6.1%) and focal segmental glomerulosclerosis (n=19, 6.1%) (Table 4).

Mean FI was 0.29 (SD 0.13), which corresponds to the Clinical Frailty Scale category of mild (FI 0.22) to moderate (FI 0.36) (22).

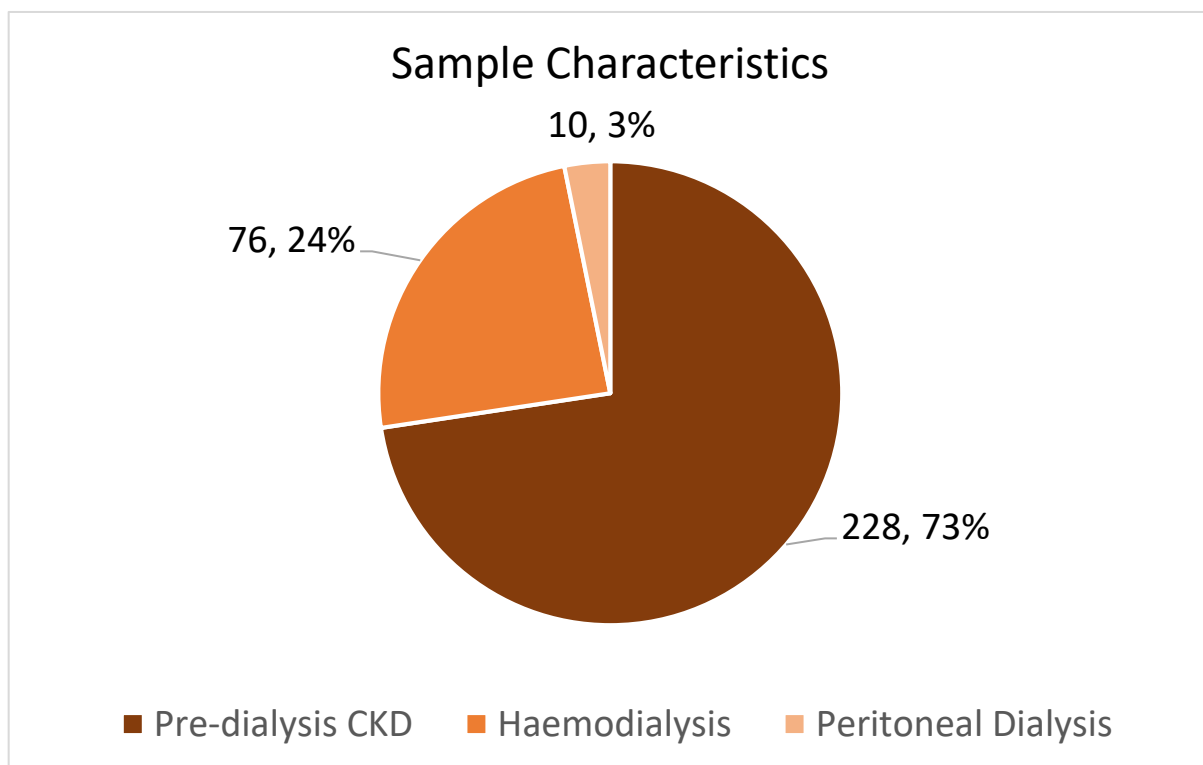


Figure 2 FI-CKD study: Demographics

Table 4 FI-CKD study: Aetiology of CKD in the cohort

Aetiology	Number (%)
Diabetic nephropathy	102 (32.5)
Renovascular nephrosclerosis	35 (11.1)
Hypertensive nephrosclerosis	19 (6.1)
Focal segmental glomerulosclerosis	19 (6.1)
Autosomal dominant polycystic kidney disease	17 (5.4)
Unknown aetiology	17 (5.4)
Other aetiologies	17 (5.4)
IgA Nephropathy	9 (2.9)
Obstructive Uropathy	9 (2.9)
Lupus nephritis	8 (2.5)
Mesangioproliferative glomerulonephritis	7 (2.2)
Reflux nephropathy	7 (2.2)
Analgesic nephropathy	6 (1.9)
Presumed chronic glomerulonephritis	6 (1.9)
Other aetiologies	53 (17)

Dialysis and Pre-dialysis Patients

There was no significant difference in mean frailty between patients on dialysis with those pre-dialysis (p=0.519). The two cohorts had similar demographics with no significant differences in age, gender or number of co-morbidities or aetiology of CKD (Table 4).

Table 5 FI-CKD study: Comparison of the cohort between dialysis and pre-dialysis patients

	Pre-dialysis	Dialysis
Number	228	86
Age (Standard deviation)	62.9 years (SD 11.7)	64.6 years (SD 14.0)
Gender (% female)	36 (41.9)	96 (42.1)
Number of Co-morbidities (IQR)	6 (4-8)	7 (5-9)
Frailty Index (IQR)	0.25 (0.1843 – 0.3491)	0.27 (0.1940 – 0.3750)

Frailty Index and Kidney Function

FI amongst pre-dialysis patients was correlated to eGFR and CKD stage. The average eGFR amongst the pre-dialysis cohort was 34 mL/min/1.73m² which corresponds to CKD stage 3b.

The relationship between FI and eGFR was investigated using linear regression. There was inverse correlation between eGFR and FI (Pearson correlation: -0.3, p<0.01). However, this relationship was not significant when adjusted for age and gender.

Kidney function was also stratified into CKD stage. Analysis using ANOVA with Bonferroni post hoc tests, demonstrated that patients with CKD stage 5 were frailer compared to those with CKD stage 1, 3A or 3B (Table 6).

The relationship between FI and CKD stage remained significant after adjustment for age and using ordinal regression analysis (p<0.05).

Table 6 FI-CKD study: CKD stage and FI

	CKD Stage						p value
	1 n= 17 (7.6%)	2 n=12 (5.3%)	3A n=28 (12.4%)	3B n=50 (22.2%)	4 n=76 (33.8%)	5 n=42 (18.7%)	
Age mean (SD)	44 (37-52)	48 (39-58)	63 (58-68)	66 (62-69)	70 (67-72)	69 (66-73)	P<0.05 (vs CKD Stage 1 and 2)
FI median (IQR)	0.17 (0.16- 0.28)	0.22 (0.16- 0.42)	0.23 (0.15- 0.25)	0.23 (0.21- 0.27)	0.31 (0.29- 0.37)	0.31 (0.27- 0.44)	

FI was also compared to change in kidney function from baseline after 12 months of follow up. There was no significant correlation between FI at baseline to change in eGFR over 12 months (Spearman's correlation coefficient = -0.04; p = 0.56).

Frailty Index and Mortality

The relationship between FI and mortality at 12 months follow up was investigated with binary logistic regression. The statistical model included age, FI, gender and dialysis status to investigate which factors were associated with an increased risk of mortality. Higher FI correlated with an increased risk of mortality (p=0.001). For each 0.1 unit increase in FI, there was a 1.8 fold increased risk of death (OR: 1.8; 95% CI 1.77 – 2.44). The relationship between FI and mortality remained independent when adjusted for other variables.

Age and being on dialysis were also associated with an increased risk of mortality; gender was not significantly associated with mortality in this analysis.

Frailty Index and Hospitalization

FI was compared with the risk of hospitalization in 12 months of follow up after study recruitment. In binary logistic regression, FI correlated with an increased risk of hospitalization (OR 1.3 95% CI 1.06-1.5). In the statistical model, age and being on dialysis were also associated with an increased risk of hospitalization.

3.4 Discussion

There was a significant burden of frailty in this prospective study of 314 patients with CKD. The average FI was 0.29 (SD 0.13), representing a clinical description of mild to moderate frailty. Patients with poorer kidney function and a higher stage of CKD had significantly greater FI. Furthermore, FI was associated with an increased risk of mortality and hospitalization in patients with CKD; this risk was independent of age and gender.

FI inversely correlated with kidney function; the lower the eGFR the higher the FI. However, the relationship between FI and eGFR did not fit a linear or logarithmic model (Pearson correlation: 0.303, $p < 0.01$). The relationship between kidney function and CKD stage was significant on ordinal regression analysis after adjusting for age and gender.

There are limitations in correlating frailty with kidney function estimated with serum creatinine. Creatinine is a product of muscle breakdown and is both secreted and filtered in the nephron (69). Frail patients may have reduced muscle mass resulting in less creatinine produced and over estimation of GFR (30). Previous studies have used cystatin C to estimate GFR, which improves the correlation with frailty because it is not dependent on muscle mass (27, 28, 30). The relationship between frailty and kidney function may not be simple. Further research is needed to identify predictors of frailty in patients with CKD and why some patients with poor kidney function may not be frail.

FI was compared between patients on dialysis and those pre-dialysis from all CKD stages. There was no significant difference in FI between the two cohorts. In this study, patients on dialysis had similar characteristics to those pre-dialysis in terms of age, gender and number of co-morbidities. The results of this study contrast with the systematic review of frailty in CKD, which found studies investigating patients on dialysis had a higher prevalence of frailty. However, this is the first study to compare pre-dialysis and dialysis patients in the same prospective methodology with the same method of frailty assessment and in the same study setting. As acknowledged in the systematic review, it is difficult to compare the prevalence of frailty between studies because of the differences in how frailty is assessed in the dialysis and pre-dialysis populations.

We hypothesised several factors that may explain the similarity in frailty in dialysis and pre-dialysis patients in the FI-CKD study. Firstly, patients with stage 5 CKD who are frail and not fit for dialysis would be selected out of the dialysis cohort. Hence, selection bias would confound the relationship between frailty and dialysis status. The FI-CKD study had a limited proportion of patients in the dialysis cohort ($n=86$, 27%), which would limit the statistical power in the cohort

analysis. Using the FI would impact on direct comparisons to previous literature which commonly used the Fried frailty classification. However, there was good internal validity in that the same method of frailty assessment was used to assess frailty in the dialysis and pre-dialysis cohorts. Thus, the method of assessment should not impact on the ability to find a difference between the cohorts.

FI was independently associated with increased risk of mortality and hospitalization. For each 0.1 unit increase in the frailty index, the risk of mortality increased by 1.8 (95% CI 1.8 – 2.4). Other risk factors for mortality in this population were age and being on dialysis. This is consistent with previous literature, which finds frailty is associated with mortality in both pre-dialysis and dialysis patients with CKD (17, 28, 29, 40, 44, 46, 52). The association between FI and mortality was also comparable to previous literature in study populations other than CKD. One study, investigating adverse health outcomes in a tertiary rehabilitation facility found that for each 0.1 unit increase in the frailty index, the hazard ratio for mortality increased by 1.63 (95% CI 1.29-2.06) (68). The risk of hospitalization also correlated significantly with FI (OR 1.3 95% CI 1.06-1.5). In the statistical model, age and dialysis status were also associated with an increased risk of hospitalization.

Frailty has been associated with number of other co-morbidities. It is important to explore these associations because CKD is often a secondary manifestation especially diabetes and hypertension. Furthermore, a recent retrospective study in community dwellers with CKD showed that presence of hypertension or diabetes increased the risk of frailty in patients with an eGFR<30mLs/min (43).

Frailty and Hypertension

The relationship between frailty and hypertension is complex. Management of hypertension reduces the risk of disease progression in patients with CKD. However, a meta-analysis reviewing the treatment of hypertension in patients above 80 years of age showed a 14% increased risk of mortality in trials that were double-blinded (70). However, subsequent analysis of the HYVET (Hypertension in the Very Elderly) randomised controlled trial, which investigated BP control using an angiotensin converting enzyme inhibitor (ACEI) and thiazide diuretic combination, showed no relationship between frailty (measured with FI) and adverse health outcomes in patients above 80 years of age (71). Indeed, it was shown that mortality benefits and benefits in terms of stroke prevention and cardiovascular disease were retained even in those who were frail. It should be noted that patients in the HYVET study had less stringent BP targets (150/80 mmHg) compared with current guidelines for patients with proteinuria for instance (71). This indicates that blood

pressure control, at least with an ACEI or in combination with a thiazide, should not be denied to patients who are frail. Furthermore, further research is needed in those patients at risk of falls and those with dementia. The mean FI in the HYVET study was 0.19 indicating a fitter group of patients at least when compared to the FI-CKD study.

Frailty and Diabetes Mellitus

An interesting relationship exists between diabetes, frailty and sarcopenia. Diabetes is known to accelerate muscle loss which may be exacerbated by the presence of frailty (72). Insulin resistance results in an overall catabolic state within skeletal muscle resulting in muscle loss (72). Diabetes also promotes the pro-inflammatory milieu, and this again provides a link between diabetes and frailty (72). A prospective study in 1750 patients has shown an increased odds ratio of developing frailty (OR 2.18 95% CI 1.42 – 3.37) if the patient had diabetes at baseline (73). In patients with end-stage kidney disease, diabetes is associated with increased mortality risk. A multicentre cross-sectional study in one million participants with CKD showed that diabetes was associated with an increased risk of all-cause mortality and cardiovascular mortality (74). It is not known whether management of diabetes impacts on frailty in patients with CKD and this is certainly an avenue for future research.

Strengths of the FI-CKD study

The FI-CKD study has several strengths. It uses a repeatable, validated method of frailty assessment (frailty index), to investigate the spectrum of frailty in patients CKD. The FI has advantages over a classification system, in that it better delineates risk particularly in populations where the incidence of frailty is high. The FI also does not rely on performance-based data such as gait speed or hand strength, and this allows for easier adoption into clinical practice and to large populations. This is also one of the first studies that compares the prevalence of frailty between dialysis and pre-dialysis patients with the same method of frailty assessment. Furthermore, it provides more data about the spectrum of frailty in outpatients with CKD in Australia and New Zealand.

Limitations of the FI-CKD Study

There were limitations to the FI-CKD study. The number of patients in the dialysis cohort was small in proportion to the overall sample population and this reduced the statistical power in the cohort analysis. As acknowledged previously, measuring kidney function using serum creatinine in patients who are frail may over estimate kidney function because of reduced muscle mass. The average age of patients in this study was 64 years (SD 13.4 years) and so the FI in this population

would be different compared to older patients with CKD. FI was not directly compared with the Fried approach to classification of frailty. The previous pilot study did demonstrate that FI correlated with a modified Fried phenotype ($p < 0.001$) (39). The goals of the FI-CKD study were to investigate how FI changes with severity of kidney function and dialysis status and not to prove its diagnostic superiority over the Fried phenotype. It is thought that both models provide alternative and valid answers to the question of how best it is to measure frailty in patients with CKD.

CHAPTER 4: CONCLUSION

This thesis demonstrates that patients with CKD have a significant burden of frailty. The systematic review showed that frailty is highly prevalent in both dialysis and pre-dialysis patients with CKD and that frailty increases with increasing severity of kidney function. However, there was marked heterogeneity in the definition of the Fried criteria in the studies assessed in the systematic review. This was performed to assist feasibility in assessing frailty in large cohorts of patients or in retrospective studies.

The prospective study included in this thesis utilized a more precise assessment of frailty by using the FI. It again demonstrated that outpatients with CKD have a significant burden of frailty that changes with kidney function. The overall FI-CKD of the sample population was 0.29 corresponding to a clinical description of mild to moderate frailty. Kidney function measured by CKD stage correlated significantly with FI. However, the correlation between FI and eGFR was attenuated by the limitations of using serum creatinine to estimate GFR in a frail population. Interestingly, there was no significant difference in FI between pre-dialysis and dialysis patients. This perhaps reflects selection bias, in that patients on dialysis represent a fitter selection of patients with stage 5 CKD. FI correlated significantly with mortality and hospitalization and will prove to be a useful tool in delineating risk amongst patients with CKD.

4.1 Implications for policy and practice

The FI does not require performance based data, which lends itself to be integrated into electronic medical records. One recent study has validated an electronic FI which utilizes 30 deficits that have been derived from medical records in a population of 900,000 patients in the UK (75). This showed good internal validity and identified patients at risk of mortality, hospital admissions and nursing home admissions (75). A similar system could theoretically be employed in outpatient clinics of patients with CKD and could support decision making in real time, identify at risk individuals and direct community services to benefit these patients.

The effect of dialysis in older patients with stage 5 kidney disease and its impact on frailty is a subject of future research. Although several studies have shown that patients on dialysis are frail, the time course of this relationship between frailty and dialysis initiation needs to be better defined. One study has shown that earlier initiation of dialysis was associated with increased frailty and an increased risk of mortality (17). However, once this analysis was adjusted for frailty, the relationship between the early dialysis initiation and mortality became non-significant (17). A study

by Alfaadel et al further highlighted that frailty at dialysis initiation was independently associated with an increased risk of mortality (52). This indicates that the patient's frailty is the more important predictor of poor outcome from dialysis rather than the time when dialysis is initiated.

Dialysis is a powerful modality which treats fluid overload and toxin accumulation and patients do experience a symptomatic benefit after dialysis intervention. Older patients who are fit should not be denied the opportunity to experience these benefits with dialysis initiation. The FI may provide useful information before dialysis initiation to identify those patients who are frail and may be better served by a conservative approach to their CKD management. Indeed, the challenges of initiating frailty in older patients with stage 5 CKD is the topic of a current research project by my colleagues at UQ. The aim of their study is to investigate the impact of dialysis or conservative management on frailty status and perceived quality of life.

More recent research is emerging on the impact of interventions other than dialysis on frailty status in patients with CKD. One study in Korea, has investigated the impact of exercise in patients with end stage kidney disease. Patients who were more active had significantly lower rates of frailty, reduced risk of falls and improved perceived health related quality of life (76).

FI has been applied outside patients with CKD and provides a way of predicting those vulnerable older patients who are more likely to have a detrimental impact to their level function after an insult. For instance, one study utilized the FI as part of a comprehensive geriatric assessment in patients presenting to hospital after hip fracture (77). In this setting, FI independently predicted adverse health outcomes in 178 patients with a mean FI of 0.34 (77). Patients who were classified as having high frailty ($FI > 0.4$) were significantly longer length of stay in hospital compared to those with low frailty ($FI < 0.25$). This is significant in the provision of services and identifying those patients who may need extensive rehabilitation if there are ever to return home at a reasonable level of function.

Although the topic of this thesis has been frailty, recent research has focused on identifying resilience factors in the elderly and the positive impact this has on survival. The American Psychological society defines resilience as: the process of adapting well in the face of adversity, trauma, tragedy, threats, or significant sources of stress," or "bouncing back" from difficult experiences. A recent systematic review of studies investigating resilience has found the following mental, physical and social factors that are associated with resilience (78):

Table 7 Conclusion: Resilience Factors

Mental	Social	Physical
Adaptive coping styles	Community involvement	ADL independence
Gratitude	Contact with family and friends	High mobility
Happiness	Self-rated successful aging	Physical health
Lack of cognitive failures	Sense of purpose	Self-rated successful aging
Mental health	Social support and connectedness	
Optimism/hopefulness	Social support seeking	
Positive emotions/regulation	Strong, positive relationships	

The presence of resilience is associated with positive health outcomes including longevity, better quality of life and mental well-being (78). Resilience research highlights the importance of recognising a patient’s assets in conjunction with frailty when considering their predicted response to an intervention such as starting dialysis.

4.2 Future Research

The FI-CKD study forms part of a programme of research that investigates the efficacy of the FI in identifying patients at risk of adverse health outcomes in patients with CKD. Future research will be directed into applying the FI to clinical practice as a potential decision-making tool. An example of this is the research being undertaken by Chen and colleagues which is examining the effects of dialysis initiation versus conservative management on frailty in older patients with CKD.

This study utilized the FI in a cross sectional prospective study. More longitudinal data is needed to establish the effects of dialysis initiation on frailty over time and the impacts this has on outcomes.

This leads to the question about what can be done to reverse the effects of frailty in patients with end stage kidney disease. Interventions that merit investigation include the impact of exercise. This may be a potential avenue to reverse the process of sarcopenia and frailty. The role of hypertension and diabetes on the development of frailty needs to be explored in greater detail. Frailty is associated with changes in body composition especially in patients on dialysis (79). Could changes in diet and changes to BMI have an impact on frailty in individuals with Stage 5 CKD?

4.3 Personal Reflection

I have been fortunate to be part of the renal unit at the Princess Alexandra Hospital as a medical student, an intern and registrar. I am in debt to the many patients who have volunteered their time to teach me about their experiences with living with CKD from the pre-dialysis stage to starting dialysis and receiving their first kidney transplant. I have witnessed the impact dialysis can have in reversing some of the effects of CKD, its limitations and the changes it has on the patient over time.

My research has taught me to look a little harder at the patient and think about their trajectory in healthcare. Sometimes, I like to look back at their presentations and identify potential opportunities where things could have been done differently to the benefit of the patient. I believe thinking about frailty is an important part of clinical practice and being more scientific and accurate in frailty assessment is crucial in improving my role as a medical registrar.

I have attained several new skills in completing this thesis and my MPhil. These include formulating a research question, preparing a study protocol, submitting an ethics application, data collection, managing a research team and a team of data collectors, completing a systematic review, publishing a paper to a peer reviewed journal and oral presentations at unit meetings and conferences.

I hope my research will be beneficial to the care of patients with CKD in the future and contribute to our understanding of frailty in general.

4.4 Publications Arising from the Thesis

A systematic review investigating frailty in CKD was conducted as part of literature review. This has been published in the Archives of Gerontology and Geriatrics 2017 (24). An abstract of the preliminary results has been presented to the Australia/New Zealand Geriatric Medicine Conference 2016. The results of the FI-CKD will be submitted for publishing in a peer reviewed journal (see Appendix 5 for a proposed abstract for the prospective study).

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APPENDICES

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Appendix 1: Frailty and Chronic Kidney Disease: A systematic review

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 were 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.

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.¹

Firstly, frailty can be thought of as a syndrome with sarcopenia as the key pathophysiological feature²: 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.²

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 systems³⁻⁵; 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.⁶

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.³ In particular, 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.⁷ Shlipak et al⁸ 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.⁹ 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.

Method

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.

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.

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-variables and confounders.¹⁰ 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.

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 (Figure 1). Overall, there were 18 studies (56%) which were designed as primary prospective analyses of frailty in CKD. The remaining 14 studies (44%) were secondary analysis of established cohorts not originally sampled for examining frailty.

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.

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 Table 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.

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).²

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.¹¹ However, Painter et al¹² 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).¹³ Other scales used include the frailty index approach, which provides a quantitative assessment of frailty as the proportion of potential deficits in health.⁴ This has been shown to be reproducible and be predictive of outcomes.¹⁴ 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.¹⁵ Other measures used in the studies include the Groningen Frailty Indicator, Montesaño approach, Edmonton Frail Scale and a frailty check list.¹⁶⁻¹⁹

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) = 49mLs/min), to 42.6% in a smaller

study of patients with more severe CKD (mean eGFR = 27mLs/min).^{20,21} A study by Rodriguez et al²² 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.²²

Frailty was more prevalent amongst patients on haemodialysis with the range being from 14% to 73%.^{23,24} 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.

Glomerular Filtration Rate and Frailty

Six studies demonstrated a negative correlation between eGFR and the risk of frailty in pre-dialysis patients with CKD.^{20,25-29} Three of the six studies used cystatin C to estimate eGFR, two used creatinine and one use iodine 145-iothalamate clearance. A study by Roshanravan et al²⁵ 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.^{20, 25-28} 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.²⁹

A study by Dalrymple et al²⁷ 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.²⁷ 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.²⁷

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 al³⁰ 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 al²³ and McAdams De-Marco et al³¹ 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 al³² 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 al²³ and McAdams De-Marco et al³¹ 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).³⁰

Roshanravan et al²⁵ 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 al²⁶, 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 al²⁹ and Pugh et al³³ 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 al³⁴ 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).

Frailty and the Kidney Transplant Recipient

Three studies have investigated frailty in kidney transplant recipients. McAdams De-Marco et al³⁵ 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 al³⁶ 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-Marco³⁷ 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]).³⁷

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.² However, the Fried phenotype is less useful in grading the severity of frailty in populations where the prevalence of frailty is high.³⁸ This is particularly problematic in patients on dialysis with one study demonstrating the prevalence of frailty be as high as 73%.²³ 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.³⁹

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 al¹¹, 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).¹¹ There were seven studies that modified the Fried phenotype and used the approach of using questionnaire data to replace the measured variables^{12,21,23,39,30,40,41}. Subsequently, Painter et al¹² 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.¹² 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 45mLs/min was

associated with increased odds of frailty.^{20, 25-28} 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.^{20,21} Amongst dialysis patients, the highest prevalence of frailty in the studies analysed was 73%.²³ 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.^{23,25,26,29-33} Frailty also predicted an increased risk of falls in patients with CKD.^{34,42} In the kidney transplant recipient, frailty was associated with an increased risk of early hospital readmission and delayed graft function.^{35,36} Patients who were frail prior to transplantation were also more likely to have improvement in frailty after transplantation.³⁷ A previous systematic review by Walker et al⁹ 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.^{5,11}

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.³⁷

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 minutes using a questionnaire.³⁹ 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.⁷ 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.

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.

Appendix 2: Participant Information

Non-Interventional Study

Princess Alexandra Hospital

Title	Clinical Utility of the Frailty Index in CKD patients
Short Title	Frailty in Chronic Kidney Disease
Protocol Number	Version 3 June 2014
Project Sponsor	Nil
Coordinating Principal Investigator/ Principal Investigator	Dr Ruth Hubbard
Associate Investigator(s)	Dr Nancye Peel Mr Rakin Chowdhury
Location	Nephrology Outpatient Department

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project, **Frailty Index in Chronic Kidney Disease**. We are investigating the measurement of frailty in outpatients with chronic kidney disease at the Princess Alexandra Hospital.

This Participant Information Sheet tells you about the research project. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read
- Consent to take part in the research project
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information to keep and the consent form can be made available to you should you request it.

2 What is the purpose of this research?

Many people with chronic kidney disease remain fit and active. Some people have other diseases and develop problems with their overall health. **Frail** is a term used in medicine to describe these vulnerable people. Frailty does not have a precise meaning but 'frail' patients have sometimes lost weight, become weaker and able to exercise less or have problems with their memory. Frailty is important because people who become frail often do less well than other people and need more care from relatives and medical services.

It is not known why some people become frail and others do not. It may be the result of a combination of changes in the body due to age or illness. For example, muscles tend to waste in frail people and they tend to lose muscle strength. Some things seem to slow down like the production of blood cells or the body's ability to break down medicines. It is likely to be a combination of all these factors.

We are carrying out a study in the Princess Alexandra Hospital, looking at how we can measure frailty in people with chronic kidney disease. We think that by asking questions about different aspects of health (medical problems, ability to look after yourself, mood, sleep, thinking) we can work out how frail a person is.

We would like to include you in the study. This does not mean that we think that you are frail. We are trying to test if the measurement instrument works so want to include a whole range of people – from those who are very fit to those who are very frail.

3 What does participation in this research involve?

If you consent to taking part in the study, we will ask you some questions about your medical history and medications. You will also be asked about your memory, quality of life and current level of functioning, for example whether you are able to wash and dress yourself independently. The questions take about **10 minutes** to answer. We would also like to contact you by telephone in **12 months** for a follow-up. We would like to ask you some questions about whether your level of functioning has changed and if you have had any admissions into hospital. These questions would take **5 minutes** to answer.

Please note there are no costs associated with participating in this research project, nor will you be paid. The research project has been designed so that the researchers interpret the results in a fair and appropriate way. We would also appreciate it if you provide a contact number for the follow up in 12 months. Your contact details will be kept confidential and will only be used for the purposes of this research.

4 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information. The Consent Form will be made available from the Centre for research in Geriatric Medicine should you wish to access it.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Princess Alexandra Hospital Nephrology Department.

5 What are the possible benefits and risks of taking part?

Whilst there will be no clear benefit to you from your participation in this research the information that you provide will help us show how frailty impacts the health of patients with chronic kidney disease. This research does not involve any interventional treatment you will be receiving routine medical care. As such we do not anticipate any risk to you from taking part in this interview.

6 What if I withdraw from this research project?

If you decide to withdraw from this research project, please notify a member of the research team before you withdraw.

If you do withdraw your consent during the research project, the study researcher and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. If you do not want them to do this, you must tell them before you join the research project.

7 What happens when the research project ends?

You will be provided with usual clinical care during the course of the research project and after it ends. The results of the project will be made available to you via the Centre for Research in Geriatric Medicine (University of Queensland).

Part 2 How is the research project being conducted?

8 What will happen to information about me?

By signing the consent form you consent to the study researcher collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All electronic data will be kept in a password protected database. Any identifiable material will be kept securely under lock and key. Your information will only be used for the purpose of this research project and future approved research projects and it will only be disclosed with your permission, except as required by law.

Any personal information will remain confidential and you will be de-identified as part of the analysis of this study. All data will be disposed of securely in seven years at the end of the storage period.

This research forms part of a larger investigation into frailty in different patient populations. The information you provide may be used in further studies for this purpose.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the research team accessing health records if they are relevant to your participation in this research project.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

In accordance with relevant Australian privacy laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

9 Who is organising and funding the research?

This research project is being conducted by The Centre for Research into Geriatric Medicine (University of Queensland) and the Princess Alexandra Hospital Nephrology Department.

10 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Princess Alexandra Hospital (Metro South). This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

11 Further information and who to contact

The person you may need to contact will depend on the nature of your query. If you have any concerns or complaints about the study please do not hesitate to contact the person listed below.

Study Contact person

Name	Dr Ruth Hubbard
Position	Consultant Geriatrician, Senior Lecturer (UQ), Principal Investigator
Telephone	3176 5530
Email	crgm@uq.edu.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	Metro South HREC
Telephone	3443 8049
Email	EthicsResearch.PAH@health.qld.gov.au

Consent Form - Adult providing own consent

Title Clinical Utility of the Frailty Index in CKD patients
Short Title Frailty in Chronic Kidney Disease
Protocol Number Version 3 June 2014
Project Sponsor Nil
**Coordinating Principal Investigator/
Principal Investigator** Dr Ruth Hubbard
Associate Investigator(s) Dr Nancye Peel
Mr Rakin Chowdhury
Location Nephrology Outpatient Department

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given access to this document if I should request it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The Centre for Research in Geriatric Medicine concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.

A member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

Name of Participant (please print) _____
Signature _____ Date _____

Declaration by Study Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Researcher (please print) _____
Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

Appendix 3 Frailty Assessment Form



Frailty Assessment Form

Completed by
 Date
 Interview time (mins).....

Declined interview: Yes No
 Reasons for declining
 interview.....
 Age.....
 Gender: Male Female

Patient ID

Motivation	circle one:	High	Usual	Low					
Self rated health	circle one:	Excellent	Good	Fair	Poor	Couldn't say			
Cognition	circle one:	Normal	Mild cognitive impairment	Dementia					
	circle all that apply:	Agitation/wandering	Delusions/hallucinations	Delirium					
Emotional	Normal OR circle all that apply:	Anxiety	Bereavement	Depression	Fatigue				
Sleep	Normal OR circle all that apply:	Poor or disrupted	Daytime drowsiness						
Communication	circle one for each								
	Speech	Normal	Impaired	Hearing	Normal	Impaired	Vision	Normal	Impaired
Strength	Grip strength	Normal	Weak	Proximal muscle strength	Normal	Weak			
	Hemiparesis:	Arm	Yes No	Leg	Yes No				
Mobility	Transfer Walking Aid used?	Ind	Asst	Dep	Slow ?	Yes No			
		Ind	Asst	Dep	Low levels of activity?	Yes No			
		Walking stick	Frame						
Balance	Balance Falls	Normal	Impaired						
		None	Yes						
Elimination	Bowel Bladder	Cont	Occas accident	Incont					
		Cont	Occas accident	Incont					
Nutrition	Weight change Appetite Weight	Stable Normal Normal	Loss Fair Under	Gain Poor Obese	Weight = Height = BMI =				
ADLs	Feeding Bathing Dressing Toileting	Ind	Asst	Dep					
		Ind	Asst	Dep					
		Ind	Asst	Dep					
		Ind	Asst	Dep					
IADLs	Cooking Cleaning Shopping Medications Driving Banking	Ind	Asst	Dep					
		Ind	Asst	Dep					
		Ind	Asst	Dep					
		Ind	Asst	Dep					
		Ind	Asst	Dep					
		Ind	Asst	Dep					

Medical history

- Hypertension
- COPD
- TIA/Stroke
- Angina/MI
- CCF
- Diabetes
- Cancer
- Alcohol excess
- Hip Fracture
- OA/RA
- Osteoporosis
- PVD
- Anaemia
- ↑cholesterol

Social Engagement

- Frequent
- Occasional
- Rarely

Problems	
1.	
2.	
3.	
4.	
5.	
6.	
7.	

**Number of different
 meds in 24 hours =**

Previous Transplant : Yes No
 Currently on Dialysis: Yes No
 Dialysis type: HD PD

eGFR =

CKD stage

1 2 3 4 5

Appendix 4: Ethics Approval Form

Submission Code Date: 01/05/2014 HREC Reference: Online Form
2:00:57

14.2. Authorisation by District CEO or delegate


Study Title (in full):	Clinical utility of the frailty index in patients with chronic kidney disease
HREC Reference Number	
Principal Investigator	Dr Ruth Hubbard
Associate investigator(s)	Dr Nancye Peel Mr Rakin Chowdhury

The Site Specific Assessment (SSA) form for the above research study has been completed (with all attachments).

This research is: Authorised
 Not authorised

Specify conditions applying to authorisation (if any) or reasons for not authorising:

My signature indicates that I authorise / do not authorise this research study to commence at this site on the condition that all the scientific and ethical aspects of the Human Research Ethics Committee approved protocol are met.

Name of District CEO or delegate:	Dr Stephen Ayre
Signature:	 PAH-QEIL HEALTH NETWORK
Date:	23/6/14
Executive Director	
Name of the QH site for the research to be conducted:	

For those sites without access to the Australia – Research Ethics Database (AU-RED) once authorisation is given, the District CEO / delegate should email a copy of the authorised SSA form to the Research Ethics and Governance Office, Office of Health and Medical Research, REGU@health.qld.gov.au for uploading onto AU-RED.

The Australia – Research Ethics Database (AU-RED) is an online research ethics and governance management tool used by Queensland Health (QH) which is also used to capture all research conducted within QH facilities.

Appendix 5: Abstract Prospective Study

Background: Frailty can be conceptualized as an accumulation of deficits across multiple systems in an approach known as the frailty index (FI). FI has been validated in a number of patient populations and it correlates with health outcomes including mortality and hospitalization. Previous literature has shown patients with chronic kidney disease (CKD) have a high prevalence of frailty. However, there is a need to better delineate risk amongst this population and understand how frailty changes with kidney function and dialysis status.

Aim: The aim of the FI-CKD study is to investigate the FI and its association with kidney function and dialysis status. Secondary outcomes include the association of frailty with mortality and hospitalization in patients with CKD.

Methods: Outpatients from nephrology clinics and dialysis centres were recruited in two study settings between August 2013 and January 2015. A previously validated method using a structured interview and frailty assessment form was used to collect data to calculate the FI. The patients' medical records provided information about co-morbidity and kidney function (estimated with serum creatinine). A follow up of health records was conducted 12 months after recruitment to record mortality and hospitalization data. Ethics boards at the corresponding recruitment sites approved the FI-CKD study.

Results: There were 314 participants recruited and 42% (n=132) were female. The average age was 64 years (SD 13 years) with the majority having pre-dialysis CKD (n=228, 73%). The average FI for the sample was 0.29 (SD 0.13), which corresponds to mild to moderate frailty. There was no significant difference in frailty between patients on dialysis to those pre-dialysis (p=0.52). FI correlated with CKD stage even after adjustments for age and co-morbidity on ordinal regression analysis (p<0.05). For each 0.1 unit increase in FI, there was a 1.8 fold increased risk of death (95% CI 1.77 – 2.44). FI also correlated with an increased risk of hospitalization (OR 1.3 95% CI 1.06-1.5).

Conclusion: Patients with CKD have a significant burden of frailty. Kidney function was associated with FI; patients with higher CKD stage were more likely to have a higher FI and be frailer. However, there was no significant difference in FI between pre-dialysis and dialysis patients, perhaps due to a lack of statistical power or due to selection bias. FI was strongly associated with an increased risk of mortality and hospitalization.

