

**Clinical implications of geriatric
impairments in chronic kidney disease:**

Frailty, falls, fractures, and functional decline

Namiko A. Goto

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Clinical implications of geriatric impairments in chronic kidney disease: Frailty, falls, fractures and functional decline

Klinische implicaties van geriatrische problemen bij patiënten
met chronische nierinsufficiëntie

Kwetsbaarheid, vallen, fracturen en functionele achteruitgang
(met een samenvatting in het Nederlands)

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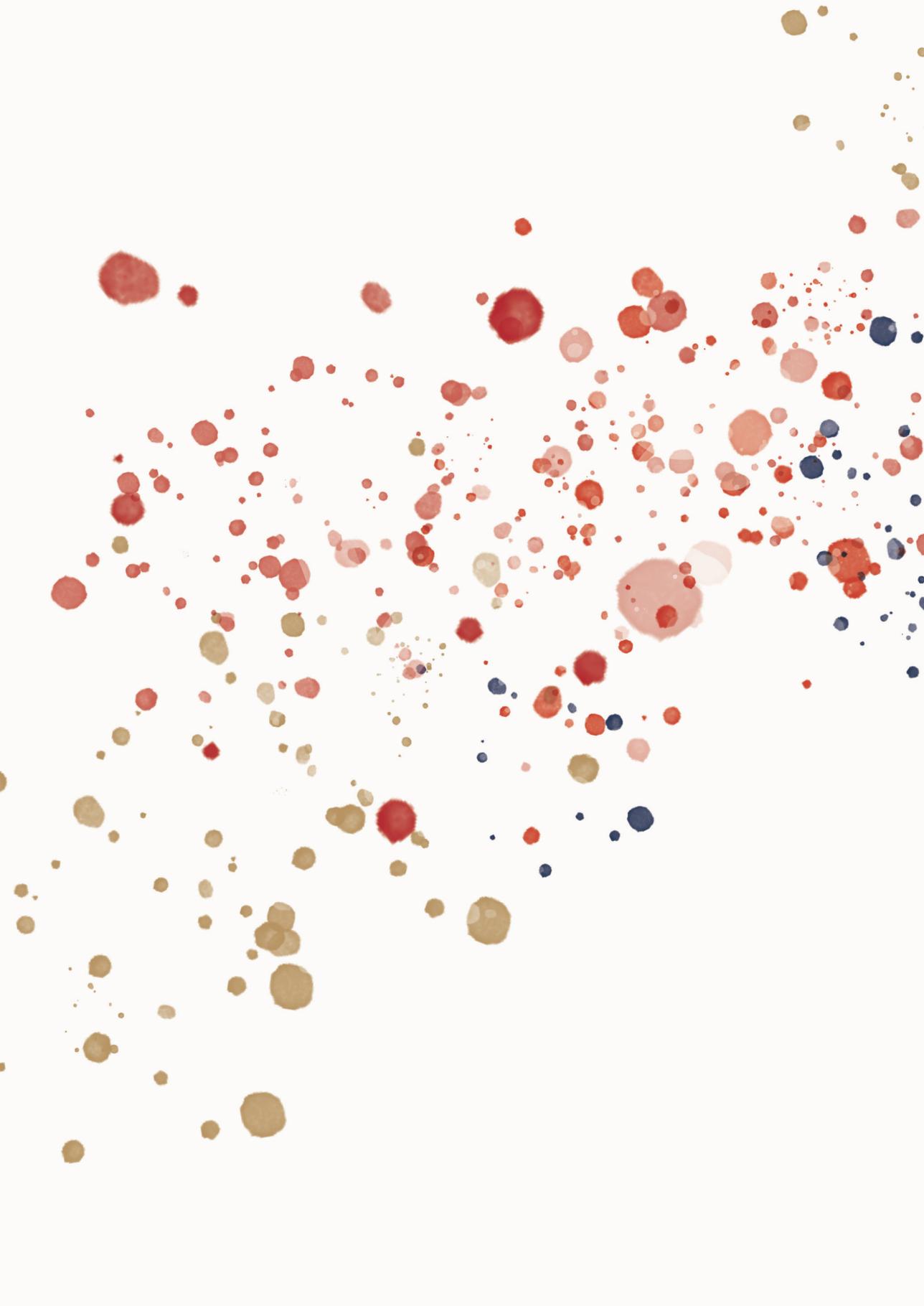
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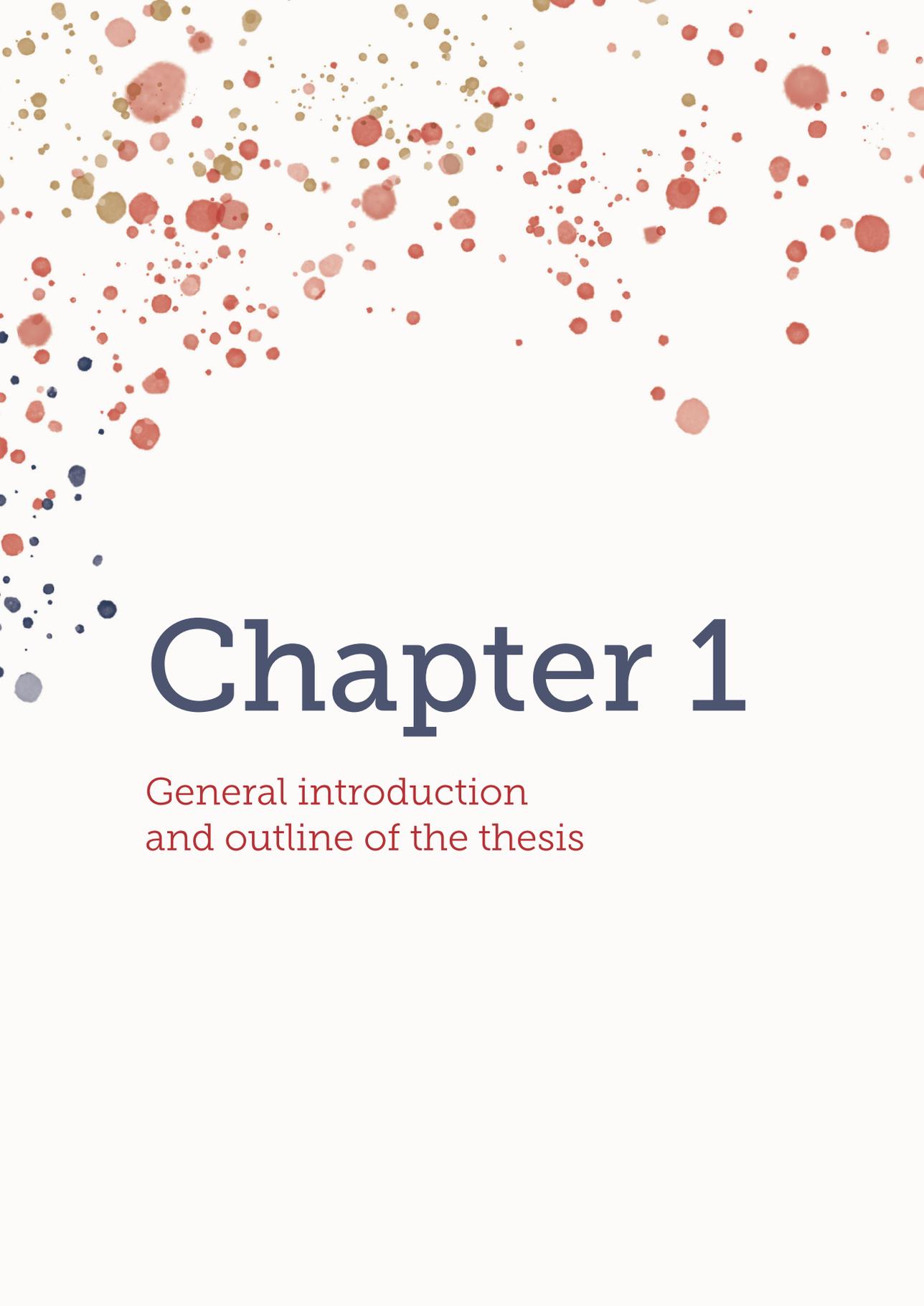
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Table of contents

Chapter 1	General introduction and outline of the thesis	7
<hr/>		
Part 1	Frailty	
<hr/>		
Chapter 2	Geriatric assessment in patients with end-stage kidney disease	21
Chapter 3	Frailty screening tools for elderly patients incident to dialysis	49
Chapter 4	Geriatric assessment and the relation with mortality and hospitalizations in older patients starting dialysis	75
<hr/>		
Part 2	Falls & Fractures	
<hr/>		
Chapter 5	The association between chronic kidney disease, falls and fractures: a systematic review	97
Chapter 6	Accidental falling in community dwelling elderly with chronic kidney disease	131
Chapter 7	Thoracic vertebral fractures and hyperkyphosis in elderly patients with end-stage kidney disease; do these patients have different clinical outcomes?	155
Chapter 8	The prevalence and incidence of vertebral fractures in end-stage kidney disease and the role of parathyroid hormone	177
<hr/>		
Part 3	Functional outcome, quality of life and caregiver burden	
<hr/>		
Chapter 9	Association of initiation of maintenance dialysis with functional status and caregiver burden	213
Chapter 10	Quality of life after the initiation of dialysis or maximal conservative management in elderly patients	235
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Part 4	Clinical implications of geriatric impairments in chronic kidney disease	
<hr/>		
Chapter 11	Geriatric considerations in elderly patients with end-stage kidney disease	257
Chapter 12	General discussion and conclusions	273
<hr/>		
Addendum		
<hr/>		
	Summary	291
	Nederlandse samenvatting	297
	List of authors with affiliations	305
	Acknowledgments	309
	Dankwoord	311
	List of publications	317
	Curriculum Vitae	321





Chapter 1

General introduction
and outline of the thesis

General introduction

The general population is aging rapidly; at this moment approximately 8% of the population in the Netherlands is older than 75 years and it is estimated to increase to almost 15% in 2040.¹ As patients age, illnesses such as chronic kidney disease become more prevalent.² Several studies estimated that between 23% and 36% of patients 65 years and older have chronic kidney disease.³ The Kidney Disease Improving Global Outcomes (KDIGO) workgroup defines chronic kidney disease as “abnormalities of kidney structure or function, present for more than 3 months, with implications for health”.⁴

Although chronic kidney disease in early stages is mostly asymptomatic, it can eventually lead to a broad range of complications that affect multiple organ systems. Important sequelae are anemia, chronic inflammation, abnormalities in calcium, phosphorus and mineral-regulating hormones, and abnormalities in sodium, potassium, water and acid-base homeostasis.⁵ Only part of patients with chronic kidney disease will eventually progress to end-stage kidney disease (ESKD).⁶ This is a state where the accumulation of toxins, fluid, and electrolytes lead to the uremic syndrome and if not treated, eventually death. While kidney dysfunction progresses to ESKD, patients can develop a wide range of symptoms, such as fatigue, pruritus, anorexia, and symptoms of fluid overload.⁷ To treat these symptoms, to maintain quality of life and to prolong life, there are several options for renal replacement therapy (RRT): hemodialysis (in center or at home), peritoneal dialysis and kidney transplantation. Although kidney transplantation is certainly an option, due to shortage of transplants and health requirements, by far most elderly will start dialysis therapy⁸ and remain on this therapy for the rest of their life. Both hemodialysis and peritoneal dialysis are very intensive treatments with high therapy burden.⁹

Besides RRT, patients can also choose for maximal conservative management, which is dedicated to symptom management to maintain quality of life as much as possible. Previous retrospective studies showed that dialysis treatment in patients of 80 years and older did not offer survival benefit over maximal conservative management.¹⁰⁻¹² A similar lack of survival benefit was seen for the comorbid patients of 75 years and older.¹¹ Given the burden of dialysis therapy, this raises questions if dialysis is the best treatment for elderly patients with ESKD. However, some elderly patients do benefit, and age itself does not seem a good indicator of lack of benefit, as biological age can differ significantly from calendar age. The elderly population is very heterogeneous, with high variability in comorbidity burden, medication use and presence of geriatric impairments. In various study populations, awareness of the presence of geriatric impairments improved outcome

by adjusting treatment decisions and creating a personalized treatment plan for the elderly patient.¹³⁻¹⁵ Therefore, more knowledge on specific geriatric impairments, such as frailty, falls, fractures and functional status, and their relation with outcome may help to better select patients who may benefit from dialysis treatment. In addition, it is not life prolongation that elderly value most: most elderly with advanced chronic kidney disease prioritize maintaining independence over life prolongation.¹³ Subsequently, more information on the course of functional status could potentially help patients, caregivers and healthcare providers in their discussion whether to start dialysis.

Frailty

A frequently used concept to identify patients with high risk of poor health outcomes is frailty. This can be defined as “a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, thereby causing vulnerability to adverse outcomes.”¹⁷ Consequently, frail patients have a decreased ability to cope with daily or acute stressors. This can be illustrated by the following example: in non-frail patients a mild urinary tract infection frequently presents with dysuria. In very frail patients, this mild urinary tract infection can have a disproportionate effect, leading to a delirium, accidental fall or increased functional dependency. In non-ESKD study populations, frail patients were at higher risk of mortality, hospitalizations, falls and functional decline.^{13,18,19} Therefore, the assessment of frailty could provide an opportunity to improve decision-making in elderly patients with end-stage kidney disease.

The geriatric assessment is the most accepted method to diagnose frailty.^{20,21} This is a systematic method that uses the domains somatic, psychologic, physical function and social activity/support to assess the health status of patients. In various study populations, the use of a geriatric assessment led to an improved survival, independence, treatment tolerance and treatment completion.^{13-15,18} Therefore, by distinguishing frail from fit patients, this method could potentially help to select patients that are likely to benefit from dialysis treatment and on the other hand select patients in whom maximal conservative management might be a more appropriate option.

One important disadvantage of the geriatric assessment is that it is time-consuming; a full geriatric assessment takes approximately one hour. As the ESKD population is aging, not every clinic may have enough time to perform a complete geriatric assessment in every elderly patient. A possible solution could be the use of a frailty screening tool to select patients that are likely to benefit from the geriatric assessment, provided that the frailty screening tool is sensitive enough.

Falls & Fractures

Falls are a major health issue in the elderly population. The World Health organization defined a fall as “an event which results in a person coming to rest inadvertently on the ground or floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects”.²² Previous research estimated that approximately a third of people aged 65 years and older fall each year.²³ This rate is even higher in the institutionalized elderly.²⁴ Falls can lead to serious complications and even to death. In a study that assessed elderly patients with chronic kidney disease, 13% experienced a serious fall-related injury. Of the patients that experienced a serious fall-related injury, almost one in five patients died within one year.²⁵ Moreover, falls can lead to severe fear of falling, which can subsequently cause avoidance of mobilization²⁶ and loss of independence. In addition, falls place a substantial economic burden on society.²⁷

In the elderly population, accidental falls are the most frequent cause of fractures. Patients with chronic kidney disease are more prone to fractures due to chronic kidney disease-mineral bone disorder (CKD-MBD). This is defined as a “systemic disorder of mineral and bone metabolism due to chronic kidney disease, which is manifested by 1) abnormalities of calcium phosphorus, PTH, or vitamin D metabolism; 2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and 3) vascular or other soft-tissue calcification”.²⁸ One main component of CKD-MBD is renal osteodystrophy, which is characterized by abnormal bone remodeling,^{29,30} and is seen in a majority of patients with chronic kidney disease stage 3-5 and in all patients requiring dialysis.³¹ Several studies showed that patients on dialysis therapy had a four times higher risk of hip fractures compared to the general population.³²⁻³⁴ Whereas the prevalence and the consequences of hip fractures are well studied in the ESKD population, less is known about the prevalence of vertebral fractures. Because the presentation of vertebral fractures is mostly atypical, they are frequently undiagnosed.³⁵ Nevertheless, in the general population, vertebral fractures are associated with a more impaired mobility, functional limitation,³⁶ poorer quality of life,³⁷ more complaints of depression,³⁸ and a higher mortality³⁹ compared to age- and sex-matched controls.

Functional status & caregiver burden

In nephrology care, there is increasing focus on Patient Reported Outcome Measures (PROMs).⁴⁰ These are questionnaires that measure the patients’ view of their health status. An important example of a PROM is functional status. As mentioned earlier, primary health goals of most elderly patients focus on remaining independent¹⁶ in self-care tasks (such as bathing, dressing and continence, also called activities of daily living (ADL)) as well as more complex tasks that support independent living in a community (such as shopping, housecleaning and telephone use, also called instrumental activities of

daily living (IADL)).⁴¹ To perform these tasks, cognitive, motor and perceptual capacities are needed. Prior research showed that functional dependence in patients treated with dialysis is a strong predictor of mortality,^{42,43} as well as therapy withdrawal and time to first hospitalization.⁴³

Although functional status is a very important PROM, there are only few studies that focused on the trajectory of functional status after starting dialysis.^{44,45} Both reported a high rate of functional decline.^{44,45} However, these studies either focused on a very specific population (nursing home patients),⁴⁴ or were performed in a small single cohort,⁴⁵ and therefore do not inform us about the general elderly population. As one of the main goals of dialysis is to maintain or improve quality of life, this can also be seen as a quality measurement of therapy. Therefore, it is important to know in which patients functional status will improve after initiating dialysis (through improvement of uremic complaints) and in which it will decline (due to e.g. burden of dialysis therapy).

It is important to realize that patients are part of a much greater social network, consisting of maybe a spouse, children, friends and other family members. (Increasing) functional dependence can have a large impact on this social network and can put a strain on relationships. Furthermore, it can influence decision-making, as patients frequently do not want to become a burden for their loved-ones. Considering that we want to do best for both the patients as well as the caregivers, it is crucial to assess what impact decisions have on caregivers. Knowledge about caregiver burden also provides an opportunity to increase support adequately, to in the end, improve care for both.

The aim of this thesis is

- To assess the prevalence of geriatric impairments in patients with chronic kidney disease
- To assess the prevalence of early poor outcome in elderly patients initiating dialysis
- To assess the association between poor outcome and geriatric impairments

Outline of this thesis

The studies in this thesis are presented in four themes: frailty (**Part 1**), falls & fractures (**Part 2**), functional outcome, quality of life and caregiver burden (**Part 3**) and the clinical implications of geriatric impairments in chronic kidney disease (**Part 4**).

In **Part 1** the focus is on frailty. First, the prevalence of geriatric problems in a population with ESKD is presented (Chapter 2). Second, the value of the use of frailty screening tools as a way to select patients for a geriatric assessment is discussed (Chapter 3). Third, the prognostic value of frailty and geriatric impairments on mortality and hospitalizations in patients that just started dialysis is assessed (Chapter 4).

Part 2 focuses on falls and fractures. First, a systematic review is presented in which we assess whether, and to which degree, chronic kidney disease is associated with falls and fractures in adults (Chapter 5). Second, the results of a cross-sectional study that assesses the association between chronic kidney disease and falls in a large geriatric cohort are presented (Chapter 6). Third, the prevalence of vertebral fractures and hyperkyphosis in a cohort starting dialysis is provided. Furthermore, it assesses the association between vertebral fractures, hyperkyphosis and poor outcome (Chapter 7). Fourth, the results of a prospective study that assesses the prevalence of vertebral fractures in a cohort of chronic dialysis patients is presented (Chapter 8).

In **Part 3** the focus is on functional outcome, quality of life and caregiver burden. First, the trajectory of functional status after starting dialysis is presented. Furthermore, potential risk factors for poor outcome were explored. Additionally, the results of questionnaires answered by caregivers of these patients are presented (Chapter 9). In the second part of part 3, quality of life of both dialysis and patients on maximal conservative management are assessed (Chapter 10).

In **Part 4** the clinical implications of the presence of geriatric impairments will be discussed. First, different geriatric considerations are addressed that may be relevant in decision-making regarding treatment for ESKD (Chapter 11). Second, the main results and general discussion are presented. Furthermore, recommendations for clinical practice and further research are provided (Chapter 12).

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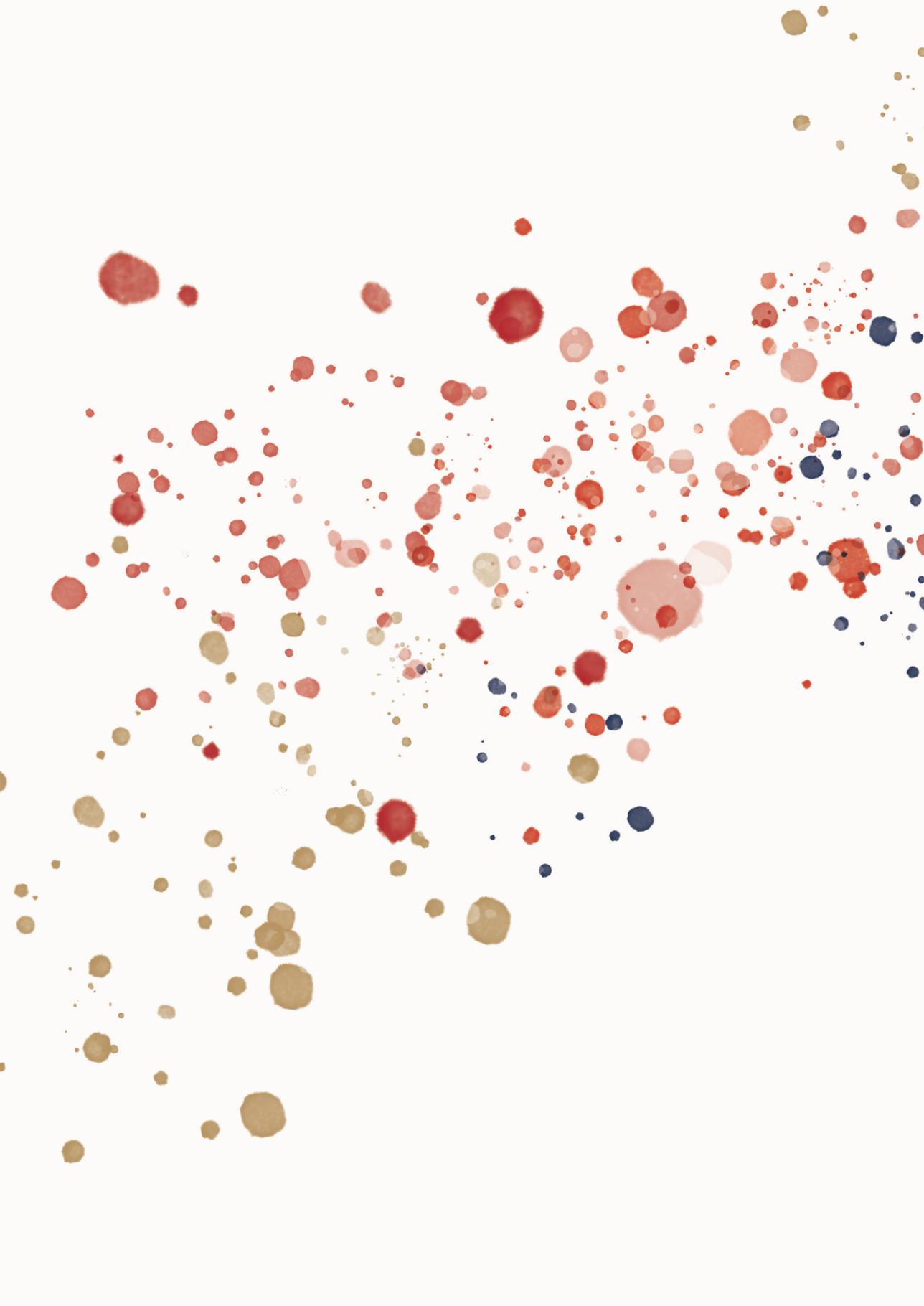
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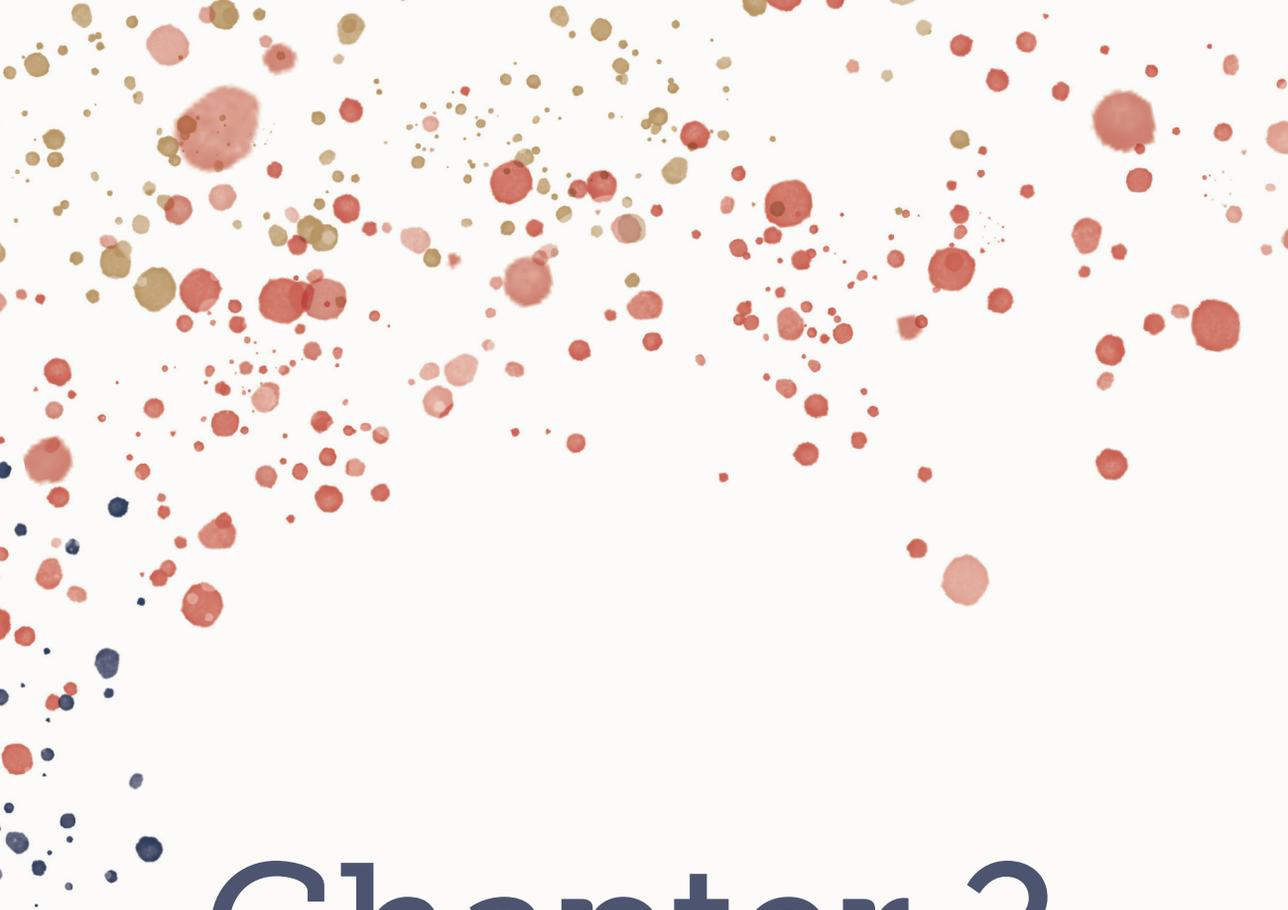


Part 1



Frailty





Chapter 2

Geriatric assessment in elderly patients with end-stage kidney disease

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Abstract

Background/Aims: Decision-making in elderly patients considering dialysis is highly complex. With the increasing number of elderly with end-stage kidney disease (ESKD) it may be important to assess geriatric impairments in this population. The aim of the Geriatric assessment in OLder patients starting Dialysis (GOLD) study was to assess the prevalence of geriatric impairments and frailty in the elderly ESKD population by means of a geriatric assessment (GA), which is a comprehensive tool for overall health assessment.

Methods: This study included 285 patients ≥ 65 years: 196 patients at the time of dialysis initiation and 89 patients who chose maximal conservative management (MCM). The GA assessed cognition, mood, nutritional status, (instrumental) activities of daily living, mobility, comorbidity burden, quality of life and overall frailty.

Results: Mean age of the participants was 78 years and 36% were women. Of the incident dialysis patients 77% started hemodialysis and 23% started peritoneal dialysis. Geriatric impairments were highly prevalent in both dialysis and MCM patients. Most frequently impaired geriatric domains in the dialysis group were functional performance (ADL 29%, IADL 79%), cognition (67%) and comorbidity (41%). According to the GA, 77% of the dialysis group was frail. In the MCM group, functional impairment (ADL 45%, IADL 85%) and frailty (88%) were highly prevalent.

Conclusions: Geriatric impairments and frailty are highly prevalent in the elderly ESKD population. Since impairments can be missed when not searched for in regular (pre) dialysis care, the first step of improving nephrology care is awareness of the extensiveness of geriatric impairment.

Introduction

The number of elderly patients initiating dialysis has increased considerably over the past decade.¹ This is the result of aging of the population, an increase in the prevalence of chronic kidney disease, earlier initiation of dialysis, and more liberal acceptance of elderly into dialysis programs.² In the elderly ESKD population, frailty is common.³⁻⁵ Frailty is a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and thereby causing vulnerability to adverse outcomes.⁶

There is general consensus that a geriatric assessment (GA) is the best approach for the identification of frailty in clinical practice.⁷ A GA is a systematic procedure that is designed to assess the health of the elderly population by focusing on somatic, functional, social and psychosomatic domains. It reveals deficits that are not routinely captured in standard history and examination⁸ and has been proven to be valuable for improving survival and functional outcomes in different categories of elderly patients.⁹⁻¹¹

The high prevalence of frailty in elderly patients with end-stage kidney disease (ESKD) makes the decision-making process with regard to dialysis highly complex. Many patients experience high disease burden due to dialysis^{12,13} and several studies did not show any benefit on survival and quality of life in the comorbid and elderly population for dialysis compared to conservative management.^{14,15} Nevertheless, elderly patients may benefit from dialysis, and age on itself is not a good selection criterion. Previous studies in the ESKD population showed that frailty is related to mortality, hospitalizations and falls.^{3,16} Therefore, understanding the burden of geriatric impairments could provide an opportunity to direct treatment decisions and to start preventive interventions. However, data on the prevalence of geriatric impairments and frailty in the ESKD population are limited. Also limited data is available on the degree of impairment in elderly at the initiation of dialysis.¹⁷⁻¹⁹

Therefore, the aim of this study is to assess the prevalence of geriatric impairments and frailty through a GA in a population with ESKD at the time of initiating dialysis and in a population choosing for maximal conservative management (MCM).

Materials and methods

Study participants

To describe the prevalence of geriatric impairments in older ESKD patients, baseline data were used from the Geriatric assessment in OLder patients starting Dialysis (GOLD) study. This is a prospective, multicenter inception cohort study assessing the relationship of geriatric assessment with outcome in ESKD patients. Participants were enrolled from 17 centers across the Netherlands in the period from August 2014 to September 2017 (Appendix 1). Patients were recruited from the pre-dialysis outpatients clinics by their treating nephrologists. If inclusion criteria were met patients were contacted by one of the researchers or research nurses to make an appointment for inclusion. Both dialysis (peritoneal dialysis (PD) and hemodialysis (HD)) and conservative patients who were ≥ 65 years were included. The aim was to include patients eligible for dialysis between 3 weeks before and 2 weeks after dialysis initiation. Well informed patients opting for MCM were included when estimated glomerular filtration (eGFR) was ≤ 15 ml/min per 1.73m^2 . Patients were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language, or if they suffered from a terminal nonrenal-related condition. The study was conducted in accordance with the declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients before enrollment.

Data collection

An overview of used test instruments, source of information and cut-off points is shown in Appendix 2.

Geriatric assessment

For the GA, participants were either visited at home or in the dialysis center. For patients that had already started dialysis, assessment was performed on a nondialysis day or just prior to starting a HD session. The assessments were performed by one of the two investigators or one of the two trained research nurses. For the GA, seven domains were assessed (Appendix 2): comorbidity burden (Cumulative Illness Rating Scale-Geriatric (CIRS-G)²⁰), activities of daily living (Katz-6²¹), instrumental activities of daily living (IADL) (Lawton and Brody²²), depressive symptoms (GDS-15^{23,24}), nutrition (Mini nutritional assessment (MNA)²⁵), mobility (Timed up and Go test, TUG²⁶) and cognition. Cognition was assessed with the Mini Mental State Examination (MMSE²⁷), semantic fluency test²⁸, clock drawing test²⁹ and enhanced cued recall test (ECR³⁰). An impaired cognition was defined as one or more impaired cognitive tests.

Impairments in cognition, mood, functional performance (ADL and IADL), mobility, comorbidity burden and nutritional status were counted. If data about specific impairments were missing, only these impairments were not counted.

Caregiver

For all patients a relevant caregiver was approached (if available) and when participating, informed consent was asked. Questionnaires for caregivers were either obtained during the visit to the patient or sent by mail. Questionnaires for caregivers were preferably filled out within two weeks of enrolment of the patient. Caregivers were asked to fill out three questionnaires that are related to cognition; the informant questionnaire on cognitive decline (IQCODE)³¹, the neuropsychological inventory (NPI)³², and the interview of deterioration in daily life dementia (IDDD)³³. Furthermore, caregiver burden was measured by the SPPIC (Self-Perceived Pressure Informal Care)³⁴.

Additional data

Baseline demographic data included age, sex, education level, alcohol use, smoking status, living situation, type of dialysis and polypharmacy (defined as the use of ten or more medications³⁵). Clinical characteristics obtained from medical charts included cause of kidney failure, blood pressure, body mass index and lab results (eGFR). Furthermore, patients were asked about accidental falling in the previous six months and the use of a walking aid and an additional balance test (four test balance scale, FTBS) was performed. Health related quality of life was measured by the EuroQol-5D³⁶, which includes self-rated problems with mobility, self-care, usual activities, pain/discomfort and anxiety and depression. In addition, two frailty screening tools were used: the Fried Frailty Index⁶ and Groningen Frailty Index (GFI)³⁷.

Statistical analysis

Categorical variables were reported as proportions, continuous variables were reported as means with standard deviations (SD) or medians with interquartile range for non-parametric data. Data were analyzed using SPSS software (IBM SPSS statistics version 21).

Results

Data are presented for the 196 dialysis (77% HD, 23% PD) and 89 MCM patients who consented to participate in the GOLD study. Details on recruitment are shown in Appendix 3. The majority of the dialysis group was included after start of dialysis (median 8 days, interquartile range (IQR) 12 days). Baseline characteristics are shown in Table 1. The mean age of the population was 78 years (SD 7) and 36% were women. Most patients were living at home (94%). The main cause of ESKD was vascular disease (51%) and diabetes (17%). In the overall group 63% of the patients had polypharmacy with a median number of 8 medications (IQR 5).

Table 1. Baseline demographics

	Dialysis (n=196)	Conservative (n=89)
Age (mean \pm SD)	75 (7)	82 (6)
Female (n, %)	64 (33%)	39 (44%)
Single/widow	83 (42%)	50 (56%)
Living at home	186 (95%)	82 (92%)
Higher education level (n, %)*	42 (21%)	16 (18%)
Intoxications		
- Smoker (n, %)**	144 (77%)	57 (70%)
- Current alcohol use (n, %)	76 (41%)	31 (40%)
Laboratory values (mean \pm SD)		
- eGFR CKD-EPI in ml/min per 1.73m ²	8 (3)	11 (4)
Underlying kidney disease (n, %)		
- Diabetes	30 (15%)	17 (19%)
- Vascular	99 (51%)	45 (51%)
- Other/unknown	67 (34%)	27 (30%)
Measurements (mean \pm SD)		
- Systole in mmHg	150 (22)	151 (26)
- Diastole in mmHg	75 (14)	75 (13)
- BMI	27 (5)	26 (5)
Number of medications (median, IQR)	11 (8)	8 (2)
Type of renal replacement therapy		
- Hemodialysis	150 (77%)	-
- Peritoneal dialysis	46 (23%)	-

IQR, interquartile range; SD, standard deviation; eGFR, estimated glomerular filtration rate.

* University education, higher professional education

** Smoker; if the participant has smoked but stopped, or is still smoking.

The following variables had missing data: Smoker (5.6%), Current alcohol use (7.4%), Systole (1.1%), Diastole (1.1%), BMI (0.4%).

Patients at the time of initiating dialysis

Results for the geriatric assessment in the incident dialysis population are shown in Table 2. Data provided by caregivers are shown in Table 3. The distribution of geriatric impairments is shown in figure 1a and 1b. Most patients had between 1-4 geriatric impairments. Only 12 patients (6%) had no geriatric impairments in any of the major domains (cognition, mood, mobility, functional performance (ADL and IADL), comorbidity burden and nutritional status). According to the GFI and the Fried Frailty index 62% and 46% of the patients in the dialysis group were frail respectively. No differences were seen in the prevalence of geriatric impairments in different age categories (Appendix 4, tables 5 and 6).

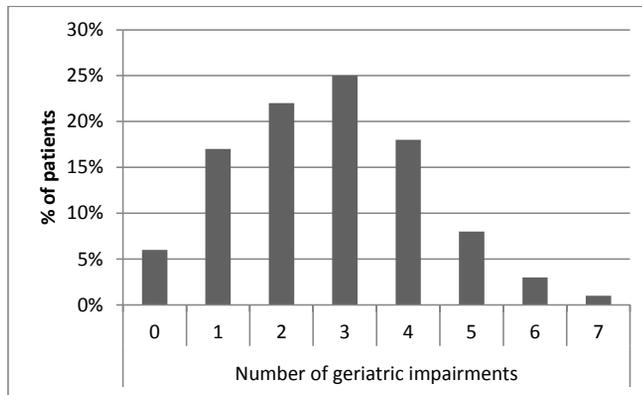


Figure 1a. Number of geriatric impairments in patients initiating dialysis

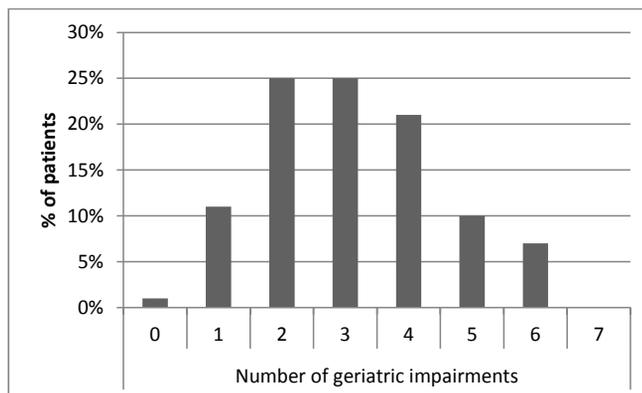


Figure 1b. Number of geriatric impairments in patients opting for maximal conservative management (MCM)

Functional performance was the most commonly affected geriatric domain: IADL was impaired in 79% and ADL in 29%. Most common difficulty in ADL was bathing. For IADL most patients needed help with cooking, doing groceries and laundry, and almost half of the patients needed help with medication use.

Sixty-seven percent of the patients in the dialysis group had one or more impaired cognitive tests. Most frequently impaired was the clock drawing test (50%). Of the 114 included caregivers, more than half reported that their relative had shown deterioration in daily functioning and/or neuropsychological symptoms. Moreover, 17% reported symptoms of cognitive decline. Most common neuropsychological symptoms were a changed appetite (32%), depression/dysphoria (24%) and irritability/lability (19%). The rate of depression/dysphoria experienced by the caregiver corresponds to the GDS filled out by the patients, in which 31% of the patients had symptoms of depression. Almost one third of the caregivers (28%) experienced the care for the patient with ESKD as burdensome. Of these caregivers, 8% felt overburdened.

Table 3. Results of caregiver questionnaires

	Caregiver dialysis (n=114, 58%)	Caregiver MCM (n=64, 73%)
Additional subjective cognition tests, n (%)		
IDDD	64 (56%)	40 (63%)
IQCODE	19 (17%)	14 (22%)
NPI	65 (59%)	46 (73%)
Perceived caregiver burden, n (%)		
Moderate burden caregiver	22 (20%)	15 (24%)
Overburden caregiver (SPPIC ≥ 4)	9 (8%)	5 (8%)

IDDD, Interview for deterioration in daily life dementia; IQCODE, Informant question on cognitive decline; NPI, neuropsychological inventory; SPPIC, Self-Perceived Pressure Informal Care'.

The following variables had missing data: IQCODE (0.6%), NPI (2.2%), SPIC (2.8%).

A severe comorbidity burden, defined as two or more illnesses with a score of 3 or at least one score of 4, was seen in 41% of the patients. Most frequently impaired organ systems were the hematopoietic (27%), vascular (23%), heart (22%), and respiratory system (22%).

Mobility was tested by the Timed up and Go test (TUG). This test evaluates the time it takes for the patient to rise from a chair, walk 3 meters, turn around, walk back to the chair and sit down. Only 32% of the patients completed the TUG-test in normal time (<11 seconds) and 19% of the patients had a severely impaired mobility according to the

TUG-test. An impaired balance on the four balance test was seen in 62% of the patients; 28% of the patients experienced a fall in the past half year. Moreover, 35% of the patients required a walking aid.

According to the MNA, only 4% of the patients were malnourished. However, almost half (47%) of the patients were at risk for malnutrition. Many patients suffered from weight loss and 45% had weight loss greater than 3 kilograms despite being potentially fluid overloaded. Almost 25% of the patients experienced pressure sores or skin ulcers at time of inclusion.

Seventy-seven percent of the patients had a reduced quality of life according to the EuroQol-5D. Most frequent reported were problems with mobility (58%), problems with daily activities (59%) and pain or other physical complaints (51%). Patients graded their state of health with a mean score of 6 out of 10 (SD 1).

Patients choosing maximal conservative management

The 89 patients in the conservative group were mostly included at the beginning of stage 5 kidney failure (when the decision to forego dialysis was made). In contrast, patients in the dialysis group were included at the time of initiating dialysis, and therefore at a more advanced stage 5. Thus, patients in the conservative group had a higher eGFR at inclusion (11 vs 8 ml/min/1.73m²) compared to dialysis patients. Given this difference in the timing of the GA and stage of ESKD, a statistical comparison between these two groups was not considered meaningful.

The mean age in the conservative group was 82 (SD 6) years and more than half (56%) of the patients were single/widowed (Table 1). The prevalence of impairment in cognition, symptoms of depression, malnutrition, severe comorbidity and caregiver burden were similar to the dialysis group. Patients in the conservative group were frequently care dependent (ADL 45%, IADL 85%) and had a reduced mobility: one-third had a severely impaired TUG (33%) and 69% was dependent on the use of a walking aid. According to the GFI and Fried Frailty index 64% and 40% respectively were frail in the MCM group. Results are shown in Table 2.

Table 2. Results of geriatric assessment in dialysis and patients on conservative management

	Dialysis (n=196)	MCM (n=89)
Cognition		
Cognitive tests (n, %)		
- Impaired MMSE	27 (14%)	16 (18%)
- Impaired fluency	58 (30%)	23 (26%)
- Impaired enhanced cued recall	34 (18%)	15 (17%)
- Impaired clock drawing test	98 (50%)	48 (55%)
Impairment of ≥ 1 cognitive test	132 (67%)	62 (70%)
Mood		
Symptoms of depression, GDS (n, %)	60 (31%)	31 (35%)
Nutritional status		
MNA (n,%)		
- At risk for malnutrition	93 (47%)	33 (37%)
- Malnutrition	10 (5%)	1 (1%)
Functional performance		
Dependent in ADL (n,%)	57 (29%)	40 (45%)
Dependent in IADL (n,%)	154 (79%)	76 (85%)
Mobility		
Immobile (n,%)	12 (14%)	6 (14%)
Impaired Time up and go* (n,%)		
- Mildly impaired	91 (49%)	40 (48%)
- Severely impaired	36 (19%)	28 (33%)
Comorbidity burden		
Comorbidity severe (n,%)	81 (41%)	39 (44%)
Frailty		
Frail according to Fried Frailty Index (n,%)	85 (46%)	32 (40%)
Frail according to GFI (n,%)	121 (62%)	57 (64%)
Other		
Impaired health related quality of life (EuroQol-5D) (n,%)	151 (77%)	76 (85%)
≥ 1 fall in the past half year (n,%)	50 (28%)	24 (31%)
Impaired four balance test* (n,%)	110 (62%)	55 (72%)
Polypharmacy (n,%)	128 (65%)	50 (56%)

MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; GDS, Geriatric Depression Scale; ADL, activities of daily living, IADL, instrumental activities of daily living; GFI, Groningen Frailty Index.

* TUG and four balance test; if immobile test is scored as impaired

The following variables had missing data: Enhanced cued recall (3.2%), Clock drawing test (4.6%), Timed Up and Go (5.3%), Fried Frailty Index (6.0%), Fall in the past half year (9.8%), Four balance test (10.5%).

Discussion

In this analysis of 196 elderly ESKD patients incident to dialysis, the prevalence of geriatric impairments was very high; 77% of the patients had two or more geriatric impairments. Most frequent impairments were seen in functional performance, cognition and severe comorbidity. In the group of 89 patients who chose conservative management the prevalence of geriatric impairments was even higher; 88% had two or more geriatric impairments.

To our best knowledge, this is one of the largest studies that used a very extensive GA to study multiple geriatric domains in patients with ESKD. The prevalence of geriatric impairment in this study is difficult to compare with other similar studies because every study using a GA in this population addressed a different selection of geriatric domains, using various tests and varying cut-off points. Despite this, all studies reported a high prevalence of different geriatric impairments^{18,19,38,39} and the prevalence of individual domains is mostly comparable to our study findings.^{40,41} However, compared to some of these studies we found a relatively high rate of functional dependency (79% IADL dependency in our study population vs 60% and 26% in other studies)^{18,38} and cognitive impairment (14% impaired MMSE in our study population vs 7%). A possible explanation could be that in the initiation period of dialysis, patients are in worse metabolic condition compared to patients stable on dialysis. In addition, assessing patients on stable dialysis resulted in a different patient selection compared to incident dialysis patients. As the dialysis initiation period had the highest mortality rate⁴², those patients in the poorest condition may already be deceased.

In elderly ESKD patients, a GA is able to reveal a high prevalence of geriatric impairments^{18,19,38,39}. The prevalence of impairments across a range of domains is relevant because it provides information about frailty, and therefore the vulnerability of a patient to adverse outcomes. Furthermore, it reveals problems that are frequently unrecognized or inadequately addressed in older adults. Cognitive impairment, for example, is often undiagnosed in hemodialysis patients.⁴⁰ Awareness of how prevalent geriatric problems are can be the first step for the nephrologist to address these problems timely in their population. Other methods that are frequently used to identify vulnerability are frailty screening tools. In our study population 62% and 46% of the patients initiating dialysis were considered frail based on the GFI and Fried Frailty Index respectively. Although some frailty screening tools have a high sensitivity and positive predictive value for vulnerability as determined by a full GA, the negative predictive value is not higher than 60%.⁴³ Therefore, a negative frailty screening cannot be used in a clinical setting to direct treatment decisions, since many vulnerable patients will be missed.

The findings that are obtained by the GA can be used for multiple purposes. First, in studies focusing on one or more geriatric domains in patients on dialysis, a reduced functional performance, cognitive impairment, depression and immobility were all associated with negative outcomes, such as (early) mortality and hospitalizations.¹⁶ Furthermore, frailty in patients with ESKD is associated with worse quality of life, irrespective of dialysis or MCM.⁴⁴ Therefore, the recognition of geriatric impairments could potentially help to direct treatment decisions regarding start of dialysis and can also help to direct treatment goals with patients and family (e.g. decisions concerning the start of strict fluid restriction, start of new medication and diet).⁴⁵ Second, the identification of geriatric impairments may guide preventive interventions. For instance, when functional impairment, malnutrition or accidental falling are present, it could initiate rehabilitation, nutritional interventions and fall prevention programs which could potentially improve health outcomes and/or quality of life.⁴⁶⁻⁴⁹ Furthermore, early recognition of cognitive impairment allows for diagnosis and appropriate treatment, education, and psychosocial support. Third, the recognition of caregiver burden allows for starting or increasing professional care at home.

This study has several limitations. First, the MCM patients were included when eGFR fell below 15ml/min/1.73m² (mean 11±4), while the actual start dialysis was at a lower eGFR (8±3ml/min/1.73m²). Since the dialysis patients were included at a more advanced stage of kidney failure, this may have negatively affected metabolic state, geriatric impairment and comorbidity burden in dialysis patients. Therefore, these two groups are not fully comparable and no statistical analysis was performed. Second, the geriatric domains could have been influenced by uremia and dialysis. This could have led to an overestimation of number of geriatric problems. For example, previous research showed that patients had a poorer balance right after dialysis.⁵⁰ Therefore the four balance test could be performed worse by patients who did the test after dialysis. Furthermore, also the setting of the assessment could have influenced our study results. Third, as patients were referred to our study by their treating nephrologists, it is possible that sicker patients were less likely to be enrolled in the study, or on the other hand, that nephrologists would only include patients when they had doubts during the decision-making process. This could potentially limit the generalizability of our findings. Despite these limitations, major strengths of this study are the use of a large inception cohort of patients at the time of dialysis initiation and the use of a very extensive GA that used multiple sources to assess the different domains.

In conclusion, geriatric impairments and frailty are highly prevalent in the elderly ESKD population. Since impairments can be missed when not searched for in regular (pre)dialysis care, the first step of improving nephrology care for the elderly patients is awareness of the extensiveness of geriatric impairment. A GA could be implemented to detect and

address impairment, thereby improving regular care. Furthermore, understanding the burden of geriatric impairments provides an opportunity to direct treatment decisions for start of dialysis and guide preventive interventions. Further research should focus on geriatric conditions in relation to the decision-making process of starting dialysis, prognostication and improving clinical outcomes such as quality of life, survival and functional decline.

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Supplementary Data

Appendix 1. List of participating centers across The Netherlands

Albert Schweitzer Hospital, Dordrecht; Amsterdam University Hospital, Amsterdam; Bernhoven Hospital, Uden, Diakonessenhuis, Utrecht; Groene Hart Hospital, Gouda; Jeroen Bosch Hospital, 's Hertogenbosch; Spaarne Gasthuis, Hoofddorp, Haarlem; Maasstad Hospital, Rotterdam, St Antonius Hospital, Nieuwegein; St Elisabeth Hospital, Tilburg; Franciscus Gasthuis & Vlietland hospital, Rotterdam, Schiedam; Ter Gooi Hospital, Hilversum; University Medical Center Utrecht, Utrecht; Zaan Medical Center, Zaandam; Gelderse Vallei Hospital, Ede.

Appendix 2. Overview of testing methods used in the GOLD study

Geriatric condition	Testing method	Source
Geriatric assessment		Patient
Cognition	MMSE ¹	Patient
	Clock ²	Patient
	ECR ³	Patient
	Semantic fluency test ⁴	Patient
Comorbidity	CIRS-G ⁵ - Severe	Patient
Functional status	KATZ-6 (ADL) ⁶	Patient
	Lawton & Brody (IADL) ⁷	Patient
Mobility	TUG ⁸	Patient
	- Mildly impaired	
	- Severely impaired	
Mood	GDS ^{9,10}	Patient
Nutritional status	MNA ¹¹	Patient
	- At risk for malnutrition	
	- Malnourished	
Fried frailty index¹²		Patient
Malnutrition	1. Unintentionally weight loss ($\geq 4,5$ kg or $\geq 5\%$ of total body weight) in previous year	Patient
General health	2. Exhaustion	Patient
Physical performance	3. Physical activity: Last 3 months ≥ 4 hours sedentary lifestyle, no activities like cycling or running	Patient
	4. 4 meter walking test	Patient
	5. Handgrip strength ¹³	Patient

Range of score (Cut-off value)	Additional information	
	Baseline	Six-month follow-up
0-7 (≥ 2 Geriatric impairments*)	X	* Impairment in cognition, comorbidity, ADL, IADL, mobility, mood or malnourished
≥ 1 impaired test	X	
0-30 (<25)	X	
0-14 (<11)	X	
0-16 (<14)	X	
- (<5 th percentile)	X	Corrected for age and education level
$\geq 2x$ score 3 or $\geq 1x$ score 4	X	Renal comorbidity excluded
0-6 (≥ 1)	X	X
0-7 (≥ 1)	X	X
-	X	- If patients were immobile the TUG was scored as severely impaired.
10-20 seconds	X	- Average of three measurements
>20 seconds	X	
0-15 (≥ 5)	X	
0-30	X	
17-23.5	X	
<17	X	
0-5 (≥ 3)	X	
Yes=1, No=0	X	
Yes=1, No=0	X	
Yes=1, No=0	X	
≥ 6 seconds=1, <6 seconds=0	X	
<u>Men</u>	X	
≥ 70 years: 21.3kg (=1)		
<70 years: 28.2kg (=0)		
<u>Women</u>		
≥ 70 years: 14.7kg (=1)		
<70 years: 15.4kg (=0)		

Appendix 2. Continued

Geriatric condition	Testing method	Source
GFI¹⁴		
Physical performance	Are you able to carry out these tasks single-handedly and without any help? (The use of aids such as a walking stick, walking frame, wheelchair, is considered as independent). 1. Shopping 2. Walking around outside 3. Dressing and undressing 4. Going to the toilet	Patient
General health	5. What mark do you give yourself for physical fitness? (scale 0 to 10)	
Neurosensory deficits	6. Do you experience problems in daily life because of poor vision 7. Do you experience problems in daily life because of being hard hearing?	
Malnutrition	8. During the past 6 months have you lost a lot of weight unwillingly (3kg in 1 month or 6 kg in 2 months)	
Polypharmacy	9. Do you take 4 or more different types of medicine?	
Cognition	10. Do you have any complaints about your memory?	
Mood, psychosocial	11. Do you sometimes experience emptiness around you? 12. Do you sometimes miss people around you? 13. Do you sometimes feel abandoned? 14. In the past 4 weeks did you feel downhearted or sad? 15. In the past 4 weeks did you feel nervous or anxious?	
Surprise question	Would you be surprised if the patient would die within 6 months after dialysis initiation?	Nephrologist
Frailty Question	Please indicate how frail the patient is in your opinion	Nephrologist
Other		
Additional subjective cognitive tests		
	NPI ¹⁵	Caregiver
	IDDD ¹⁶	Caregiver
	IQCODE ¹⁷	Caregiver
Additional mobility tests/questionnaires		
	Falls	Patient
	FTBS ¹⁸	Patient

Range of score (Cut-off value)	Additional information	
	Baseline	Six-month follow-up
0-15 (≥ 4)	X	X
	X	X
Yes=0, No=1	X	X
0-6=1, 7-10=0	X	X
Yes=1, No=0	X	X
No=0, Sometimes=1, Yes=1	X	X
No=0, Sometimes=1, Yes=1	X	X
No=0, Sometimes=1, Yes=1	X	X
No=0, Sometimes=1, Yes=1	X	X
No=0, Sometimes=1, Yes=1	X	X
	X	
0-10 (≥ 5)	X	
0-12 (≥ 1 yes)	X	X
0-33 (≥ 1 yes)	X	X
0-5 (mean ≥ 3.38)	X	X
≥ 1 in previous 6 months	X	X
0-4 (≥ 1)	X	If patients were immobile the TUG was scored as severely impaired.

Appendix 2. Continued

Geriatric condition	Testing method	Source
Health related quality of life		
	EuroQol-5D ¹⁹	Patient
Caregiver burden		
	SPICC ²⁰	Caregiver

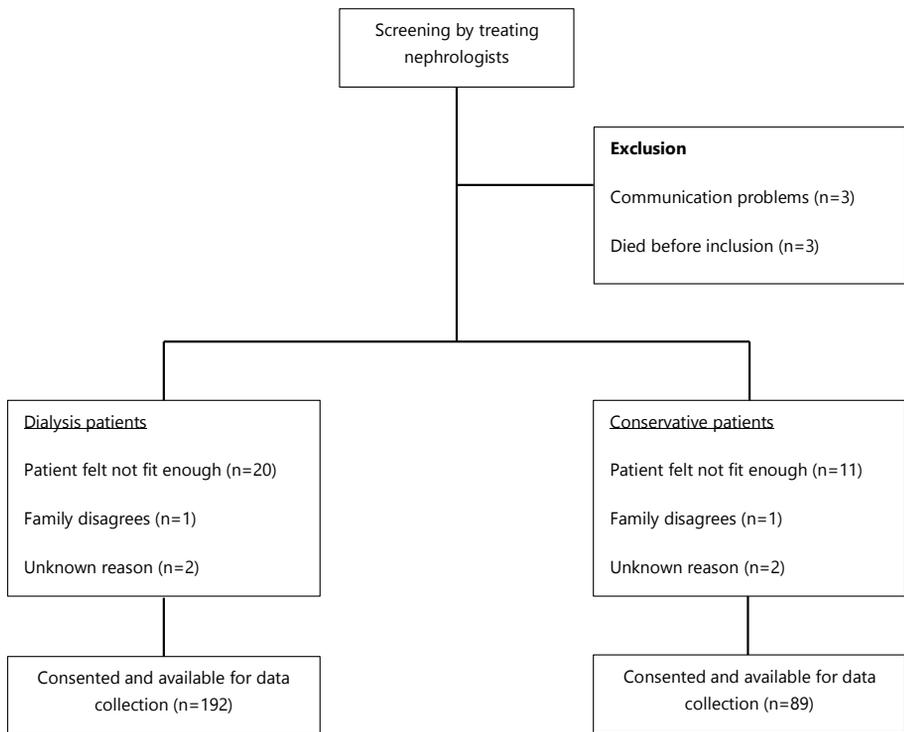
MMSE, Mini Mental State Examination; ECR, enhanced cued recall; CIRS-G, Cumulative Illness Rating Scale-Geriatric; ADL, activities of daily living, IADL, instrumental activities of daily living; TUG, timed up and go test; GDS, geriatric depression scale; MNA, Mini Nutritional Assessment;

Range of score (Cut-off value)	Baseline	Six-month follow-up	Additional information
0-5 (≥ 1)	X	X	
0-9 (≥ 4 moderate burden, ≥ 7 high burden)	X	X	The SPPIC scores were dichotomized and summed subsequently. Scores 1 and 2 were recorded into 0 (not perceiving pressure) and scores 3, 4 and 5 were recorded into 1 (perceiving pressure).

GFI, Groningen Frailty Index; NPI, neuropsychological inventory; IDDD, interview of deterioration in daily life dementia; IQCODE, informant questionnaire on cognitive decline; FTBS, Four test balance scale; SPPIC, Self-Perceived Pressure from Informal Care.

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Appendix 3. Flow chart recruitment

Appendix 4. Geriatric impairments per age category

Table 5. Geriatric impairments per age category in the group initiating dialysis

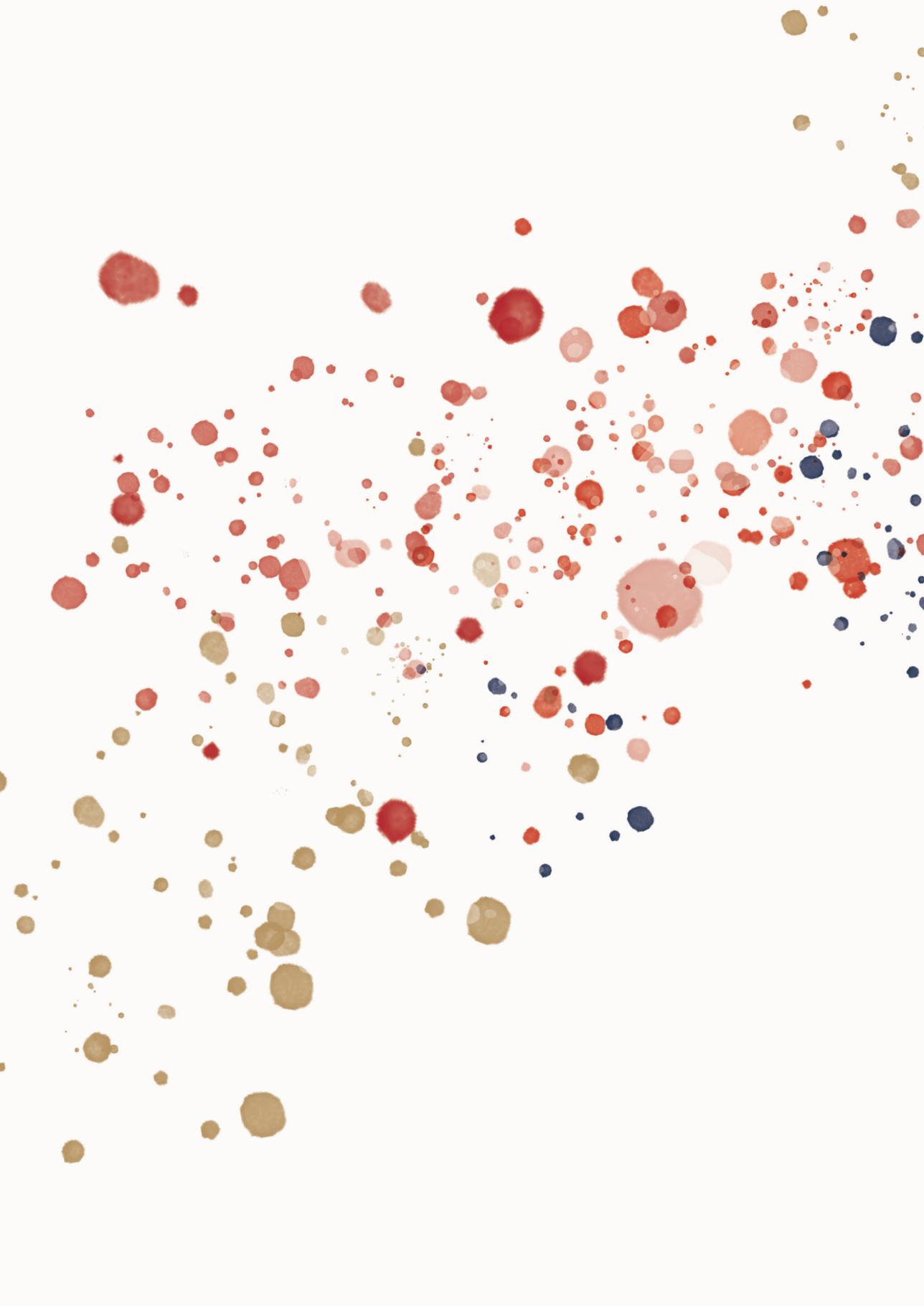
	Age category (in years)			P-value
	65-74 (n=94)	75-84 (n=82)	≥85 (n=20)	
Cognition	58 (62%)	61 (74%)	13 (65%)	0.20
Mood	25 (27%)	32 (39%)	3 (15%)	0.06
Functional status				
- ADL	24 (26%)	25 (31%)	8 (40%)	0.41
- IADL	70 (75%)	65 (79%)	19 (95%)	0.12
Mobility	15 (17%)	17 (22%)	4 (20%)	0.65
Nutritional status	6 (6%)	3 (4%)	1 (5%)	0.72
Severe comorbidity	41 (44%)	36 (44%)	4 (20%)	0.12
Frail according to GA	69 (73%)	66 (81%)	15 (75%)	0.54

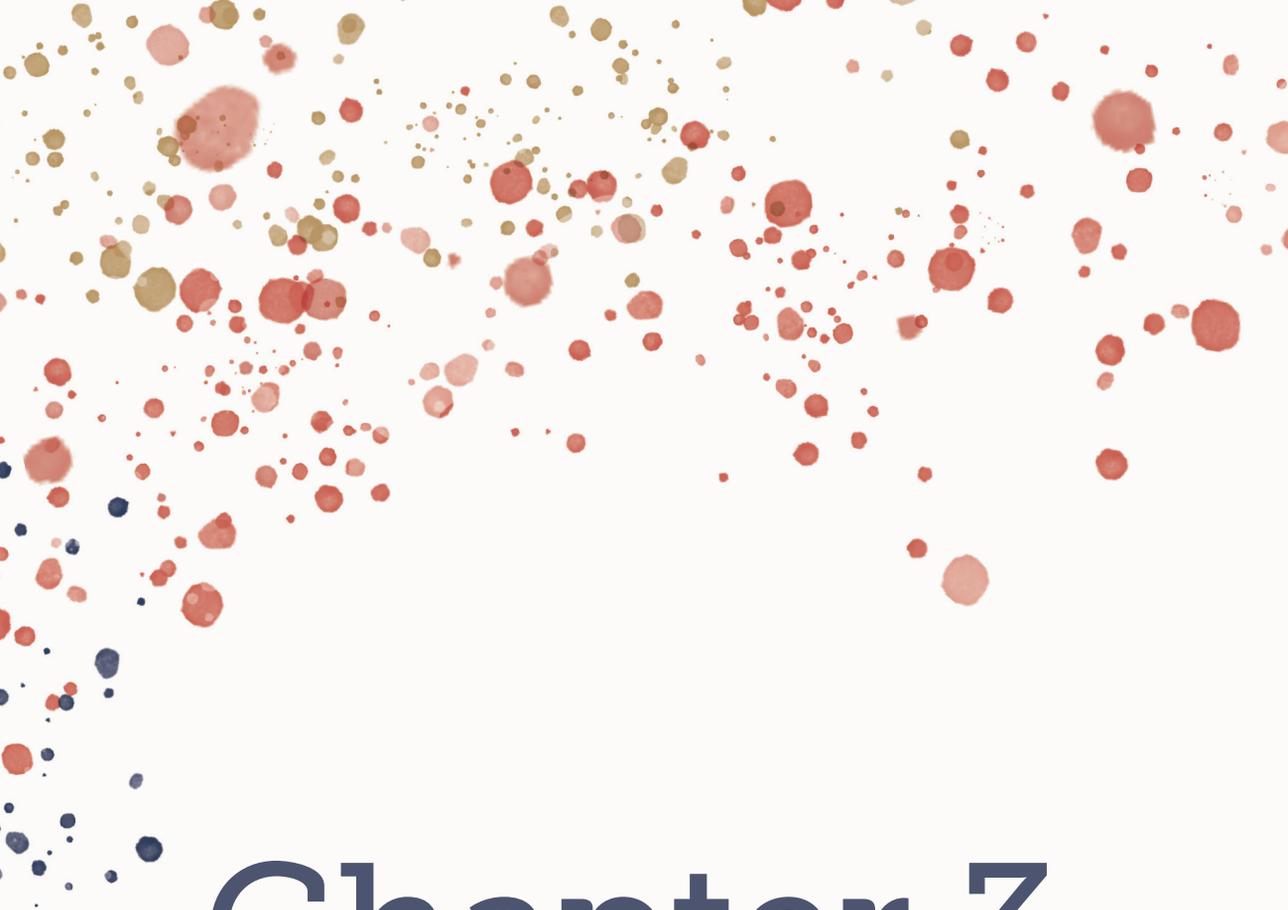
ADL, Activities for daily living; IADL, Instrumental activities of daily living; GA, Geriatric assessment.

Table 6. Geriatric impairments per age category in the group choosing for maximal conservative management

	Age category (in years)			P-value
	65-74 (n=11)	75-84 (n=47)	≥85 (n=31)	
Cognition	6 (55%)	34 (72%)	22 (71%)	0.50
Mood	2 (18%)	19 (40%)	10 (32%)	0.35
Functional status				
- ADL	4 (36%)	20 (43%)	16 (52%)	0.61
- IADL	8 (73%)	37 (79%)	31 (100%)	0.02
Mobility	2 (18%)	15 (34%)	11 (38%)	0.49
Nutritional status	0 (0%)	1 (2%)	0 (0%)	0.64
Severe comorbidity	7 (64%)	16 (34%)	16 (52%)	0.11
Frail according to GA	9 (82%)	40 (85%)	29 (94%)	0.44

ADL, Activities for daily living; IADL, Instrumental activities of daily living; GA, Geriatric assessment.





Chapter 3

Frailty screening tools for
elderly patients incident
to dialysis

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Abstract

Background: A geriatric assessment is an appropriate method for identifying frail elderly patients. In chronic kidney disease, it may contribute to optimize personalized care. However, a geriatric assessment is time consuming. The purpose of our study was to compare easy to apply frailty screening tools with the geriatric assessment in patients eligible for dialysis.

Methods: A total of 123 patients on incident dialysis ≥ 65 years old were included < 3 weeks before to ≤ 2 weeks after dialysis initiation, and all underwent a geriatric assessment. Patients with impairment in two or more geriatric domains on the geriatric assessment were considered frail. The diagnostic abilities of six frailty- screening tools were compared to the geriatric assessment: the Fried Frailty Index, the Groningen Frailty Indicator, Geriatric8, the Identification of Seniors At Risk, the Hospital Safety Program, and the clinical judgment of the nephrologist. Outcome measures were sensitivity, specificity, positive predictive value and negative predictive value.

Results: In total, 75% of patients were frail according to the geriatric assessment. Sensitivity of frailty screening tools ranged from 48% (Fried Frailty Index) to 88% (Geriatric8). The discriminating features of the clinical judgment were comparable with the other screening tools. The Identification of Seniors at Risk screening tool had the best discriminating abilities, with a sensitivity of 72%, a specificity of 79%, a positive predictive value of 91%, and a negative predictive value of 48%. The negative predictive value was poor for all tools, which means that almost one half of the patients screened as fit (nonfrail) had two or more geriatric impairments on the geriatric assessment.

Conclusion: All frailty screening tools are able to detect geriatric impairment in elderly patients eligible for dialysis. However, all applied screening tools, including the judgment of the nephrologist, lack the discriminating abilities to adequately rule out frailty as compared to a geriatric assessment.

Introduction

Worldwide, the incidence of end stage kidney disease (ESKD) in the elderly has risen in the past decades.¹ This has resulted in a growing number of elderly patients starting dialysis.² A substantial proportion of these patients exhibit functional and cognitive impairment^{3,4} or will experience loss of personal independence within the first months to years on dialysis.⁵ These aspects affect quality of life and may lead to higher hospitalization rates and mortality rates.⁶ Furthermore, retrospective research in the elderly population (≥ 75 years old) with multiple comorbidities has shown no survival benefit of dialysis compared with conservative care.^{7,8,9} It is difficult to estimate upfront which elderly patients will benefit from dialysis initiation and for which vulnerable patients existence on dialysis will be challenging.¹⁰

Emerging evidence exists on the role of frailty as a measurement for the heterogeneity of ageing in chronic kidney disease (CKD).^{11,12} The phenotype of frailty is characterized by generalized decline in multiple physiological systems, with exhaustion of functional reserves and vulnerability to a range of adverse outcomes including disability.¹³ In patients eligible for dialysis, frailty is associated with poor survival.^{14,15} A prognostic evaluation of frailty may improve patient-centered care and decision making in ESKD.¹⁶

There is general consensus that a geriatric assessment is the best systematic approach for the identification of frailty in clinical practice.^{17,18,19} The geriatric assessment is a multidimensional approach to evaluate the health status of elderly patients regarding somatic, functional and psychosocial domains in a systematic and evidenced-based way.²⁰ Components it should consist of are: (instrumental) activities of daily living; sensory deficits; mobility, including falls; mood and cognition; nutrition; comorbidity; polypharmacy; and social support. It can help to detect underlying geriatric impairment, which would otherwise be overlooked in seemingly fit patients. Additionally, it can form a starting point for personalized interventions to optimize the patients' independence.^{21,22} In other fields of medicine, a geriatric assessment has shown to optimize treatment decisions, thereby improving quality of life.^{20,23,24}

An evaluation of ESKD patients by means of a geriatric assessment has been suggested for improving informed decision making concerning dialysis initiation as well.²⁵ A disadvantage is that it can be time consuming, and many fit elderly may undergo a full evaluation unnecessarily. Applying a short frailty screening tool could form a first step in selecting patients who would benefit most from a more comprehensive geriatric evaluation.¹⁹ Several frailty screening tools exist, of which the clinical overt disability in

physical performance on the basis of the Fried criteria has been most frequently used in dialysis.²⁶ An ideal screening tool for geriatric impairment in this setting should have a high sensitivity, which ensures that actually frail patients will be screened as frail, and sufficient specificity, so that the time-consuming process of a full geriatric assessment is optimally utilized.

In this analysis of the Geriatric Assessment in Older Patients starting Dialysis (GOLD) study, we have assessed the discriminating abilities of several screening instruments for detecting frailty in elderly patients eligible for dialysis compared with a more comprehensive geriatric assessment. For this analysis, we use the baseline results of the GOLD study.

Methods

Study design and patient selection

These analyses include the baseline characteristics of the GOLD study, a multicenter, prospective, cohort study assessing the relation between a geriatric assessment and poor outcome in ESKD patients. All patients included in the GOLD study were included in these analyses, except for patients who received conservative therapy. Participants were enrolled from 17 different hospitals across the Netherlands (Chapter 2, Appendix 1) in the period from August of 2014 to August of 2016. Consecutive patients eligible for dialysis were included between 3 weeks before and 2 weeks after the first dialysis session. Patients were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language, or if they suffered from a terminal nonrenal-related condition. If applicable, the caregiver of each patient was asked to participate as well. The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients and participating caregivers before enrollment.

Data collection and analysis

Baseline demographic data collected from the medical charts and during the geriatric assessment included age, sex, education level, and living situation. Other clinical characteristics included cause of kidney failure, type of dialysis, acute or planned start of dialysis, blood pressure, body mass index (BMI) and smoking habit.

For the geriatric assessment, participants were either visited at home (on a nondialysis day for patients on hemodialysis) or in the dialysis center before starting the dialysis session. The assessments were performed by the primary investigator (I.N.v.L) or one of the trained research nurses. The geriatric assessment consisted of validated questionnaires or a structured assessment of the following seven domains (Chapter 2, Appendix 2): activities of daily living (Katz²⁷), instrumental activities of daily living (Lawton and Brody²⁸), mobility (Timed- Up-and-Go²⁹; the average of three measurements was recorded), depressive symptoms (the Geriatric Depression Scale³⁰), nutrition (the Mini Nutritional Assessment³¹), comorbidity burden (the Cumulative Illness Rating Scale- Geriatrics³²) and cognition. The cognitive test battery consists of four tests: the Mini Mental State Examination³³, the Enhanced Cued Recall³⁴, the Clock drawing test³⁵ and fluency³⁶. Cognitive impairment was defined as one or more abnormal cognitive test scores.

The outcome of the geriatric assessment was composed by the sum of impairment in the seven geriatric domains: thus, a minimum score of zero points and a maximum of seven points could be obtained. Patients with impairment in two or more domains were considered frail.²⁴

In addition to the geriatric assessment, six different frailty screening tools were applied: the Groningen Frailty Indicator³⁷, the Fried Frailty Index, Geriatric 8³⁸, the Identification of Seniors at Risk-Hospitalized Patients screening³⁹, the Hospital Safety Program criteria (Veiligheidsmanagementsysteem; the elderly-specific component of the nationally implemented safety program)⁴⁰ and the clinical judgment of the nephrologist (frailty question). Since there is no consensus on the definition of frailty, we included several frailty screening tools that incorporate different aspects of frailty.

For the clinical judgment, the treating physician was asked to indicate how frail the patients was in his/her opinion on a scale from zero to ten, where zero was fit and ten was frail. A score of ≥ 5 was a priori defined as frail. For the Fried Frailty Index, maximal grip strength (best of three measurements) was measured in the dominant hand using an electronic hand dynamometer (Model EH101), and walking speed was measured as the fastest time of two measurements. Four screening tools were included in the initial data collection (the Groningen Frailty Indicator, the Fried Frailty Index, Geriatric8, and the frailty question) (Chapter 2, Appendix 2), whereas two screening tools were constructed based on the collected data (the Hospital Safety Program and the Identification of Seniors at Risk-Hospitalized Patients screening) (Appendix 1).

Statistical analysis

The discriminative value of the six frailty screening modalities was assessed by comparing them to the outcome of the geriatric assessment. Differences between fit and frail patients on the basis of the geriatric assessment were assessed with chi squared test for categorical variables and student's t test for continuous variables, if normally distributed or Mann-Whitney U test in non-normally distributed variables. Sensitivity, specificity, and predictive values were calculated using the outcome of two or more impaired domains of the geriatric assessment as the reference test. Data analysis was performed with SPSS version 22 software.¹⁵ A two-tailed $p < 0.05$ was considered statistically significant.

Results

The analysis included 123 consecutive elderly patients starting dialysis. The 54 patients treated with conservative care were not included. Table 1 shows the baseline characteristics. Mean age was 76 (± 7) years old, and 64% of the patients were men; 76% of patients started hemodialysis, and 24% started peritoneal dialysis.

Table 1: Baseline characteristics of elderly on incident dialysis (the GOLD Study)

	All (n=123)	Frail (n=92, 75%)	Fit (n=31, 25%)	P-value
Demographics				
Age (years)	76 (± 7)	76 (± 7)	74 (± 7)	0.28
Sex (male)	64%	60%	77%	0.08
Single status/widow(er) %	37%	40%	29%	0.26
Living in nursing home facility %	6%	8%	0%	0.11
University level of education %	21%	19%	29%	0.22
Cause of kidney failure %				
				0.16
Vascular	50%	53%	39%	
Diabetes	19%	20%	16%	
Glomerulonephritis	3%	2%	7%	
Interstitial nephropathy	3%	3%	3%	
Polycystic	2%	0%	10%	
Other	11%	11%	12%	
Unknown	11%	11%	13%	
Clinical parameters				
Treatment modality hemodialysis %	76%	79%	68%	0.10
Acute start dialysis %	23%	28%	6%	0.01
Systole (mmHg)	149 (± 22)	148 (± 23)	149 (± 19)	0.70
Diastole (mmHg)	74 (± 14)	74 (± 15)	76 (± 10)	0.57
Body mass index	(± 6)	27 (± 6)	27 (± 3)	0.90
Current or former smoker %	75%	73%	79%	0.58
Mean (\pm SD)				

Geriatric impairment

Table 2 shows the proportion of patients experiencing impairment across each of the geriatric domains as identified with the geriatric assessment. In this population, functional impairment was high: 78% needed help with instrumental activities of daily life, 34% needed help with basic activities of daily living and in 25% of patients mobility was severely impaired. Cognitive impairment (impairment of one or more cognitive domains) was present in 66% of patients. Severe comorbidity burden (in addition to kidney failure) was found in 35% of patients. The risk of severe malnutrition or prevalence of severe depressive symptoms was low, 6% and 4% respectively. However, risk of malnutrition reached 50%, and 27% of patients showed mild depressive symptoms.

Of all patients, 75% (n=92) had impairment in two or more domains and were considered frail. As shown in Table 1, frail patients did not differ from fit patients in age and treatment modality. In the frail group, more patients started acutely with dialysis (instead of planned) compared to the fit group (28% vs. 6%; p=0.01).

Screening instruments

The prevalence of frailty differed widely according to the different frailty screening tools as shown in Table 3. The lowest percentage of frailty was found with the Fried Frailty Index (48%), and highest percentage with the Geriatric8 (88%).

As can be seen in Table 4, the different tools focus on different aspects of frailty and allocate a different weight to the various items. Some additional items, such as age, general health, polypharmacy, educational level, and neurosensory impairment, are incorporated in one or more screening tools, whereas they are not part of the geriatric assessment. The Fried Frailty Index is the only screening tool using objective measurements (handgrip strength and walking speed); the other tools use only self-reported items.

Sensitivity, specificity, positive predictive value, and negative predictive value of each of the six frailty screening tools for impaired geriatric assessment (two or more impaired domains) are listed in Table 3, and the absolute numbers can be found in Appendix 2. Sensitivity for impaired geriatric assessment was highest for the Geriatric8 (92%). However, only 12% of all patients were scored as fit, which resulted in low specificity (26%).

Table 2. Domains incorporated in the geriatric assessment and prevalence of impaired domains

Domain	Test	Category	Range	Cut-off	Source	Impairment ^a	
ADL	Katz-scale		1-6	(≥1)	Patient	34% (n=42)	
IADL	Lawton & Brody		1-7	(≥1) ^b	Patient	78% (n=96)	
Mobility	Timed up and go	<i>No impairment</i>		(< 10 s)	Patient	37% (n=45)	
		<i>Moderate</i>		(10-20 s)		39% (n=48)	
		<i>Severe</i>		(> 20 s)		25% (n=30)	
Cognitive impairment	MMSE		0-30	(<25)	Patient	12% (n=15)	
				0-14	(≤10)		45% (n=55)
				0-16	(<14)		13% (n=16)
				0-40	(<15) ^c		39% (n=48)
							66% ^d (n=81)
Depressive symptoms	GDS	<i>No impairment</i>	0-15	(<5)	Patient	69% (n=85)	
		<i>Mild symptoms</i>		(5-10)		27% (n=33)	
		<i>Severe symptoms</i>		(>10)		4% ^d (n=5)	
Malnutrition	MNA	<i>No malnutrition</i>	0-30	(24-30)	Patient	45% (n=55)	
		<i>Risk of malnutrition</i>		(17-23.5)		50% (n=62)	
		<i>Malnutrition</i>		(0-17)		6% ^d (n=7)	
Comorbidities	CIRS-G	Severe ^e	0-12		Chart	35% (n=43)	
Frailty							
Geriatric Assessment	≥2 Geriatric impairments ^f		0-7	(≥2)		75% (n=92)	

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; ECR, Enhanced Cued Recall; GDS, Geriatric Depression Scale; MNA, Mini Nutritional Assessment; CIRS-G, Cumulative Illness Rating Scale-Geriatric.

^aImpairment: percentage of patients who scored below/above the cutoff value. ^bOne or more impairment in IADL.

^cLess than 15 words. ^dCategory used to calculate frailty. ^eCIRS-G₂≥2xscore 3 or ≥1xscore 4. ^fImpairment in (I)ADL, severe mobility impairment, impairment in greater than or equal to cognitive domain, severe depressive symptoms, malnutrition, and severe comorbidity score.

Table 3. Discriminating test characteristics of all frailty measurements used in the GOLD study and the prevalence of frailty according the tests

Screening modality	Cut-off value	Prevalence of frailty	Sensitivity	
Fried Frailty Index	≥3	48%	59%	(48-70%)
GFI	≥4	67%	74%	(64-83%)
G8	≤ 14	88%	92%	(85-97%)
ISAR-HP	≥2	60%	72%	(61-81%)
VMS	≥2	82%	90%	(79-96%)
Frailty question (Q)	≥5	63%	72%	(61-82%)

PPV, positive predictive value; NPV, negative predictive value; GFI, Groningen Frailty Indicator; G8, Geriatric8; ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program criteria); frailty question, clinical judgment of the nephrologist.

Figure 1 shows the relationship between sensitivity and false-positives (1 - specificity). Optimal test characteristics of a screening instrument would be a 0% false positive score (100% specificity; x-axis) and a 100% sensitivity; y-axis), represented by the ▲ in Figure 1. The diagonal line represents a random guess (i.e., 50:50 chance), which would not be discriminative at all. The Identification of Seniors at Risk most closely approximates the left upper corner, with a high specificity (79%) and a fairly good sensitivity (72%). The positive predictive value of the Identification of Seniors at Risk was high (91%). This resulted in 6 of 68 patients being incorrectly screened as potentially frail. However, the negative predictive value was low for this tools (48%), meaning that 24 out of 46 patients were misidentified and considered fit while having two or more impaired geriatric domains. The differences between the tools were small, and none of the tests scored >60% for their negative predictive value. The discriminating abilities of the tools did not improve when we compared them with three or more impairments on the geriatric assessment (Appendix 3a).

Specificity		PPV		NPV	
85%	(66-96%)	92%	(83-97%)	41%	(34-49%)
52%	(33-70%)	82%	(76-87%)	40%	(29-52%)
26%	(12-45%)	79%	(75-82%)	53%	(31-74%)
79%	(59-92%)	91%	(83-96%)	48%	(38-58%)
38%	(19-59%)	78%	(72-83%)	60%	(37-79%)
67%	(45-84%)	88%	(80-93%)	42%	(32-53%)

Table 4. Similarities between frailty screening instruments and Geriatric Assessment: percentage of questions addressing a geriatric issue

	GA	Fried	GFI	G8	ISAR-HP	VMS
ADL	14%	-	13%	-	-	25%
IADL	14%	-	7%	-	50%	-
Mobility/physical performance/falls	14%	60%	7%	12%	25%	25%
Cognition	14%	-	7%	12% ^a	-	25%
Mood	14%	-	33%	12% ^a	-	-
Malnutrition	14%	20%	7%	47%	-	25%
Comorbidity	14%	-	-	-	-	-
Other items of the frailty measurements						
Neurosensory Impairment ^b	-	-	13%	-	-	-
General Health	-	20%	7%	12%	-	-
Polypharmacy ^c	-	-	7%	6%	-	-
Age ^d	-	-	-	12%	-	-
Low educational level					25%	

GA, Geriatric Assessment; Fried, Fried Frailty Index; GFI, Groningen Frailty Indicator; G8, Geriatric8; ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program criteria); ADL, activities of daily living; —, no similarity; IADL, instrumental activities of daily living.

^aCognitive impairment or mood disturbances. ^bHearing or vision loss. ^c>3 medications. ^d<80, 80-85, >85.

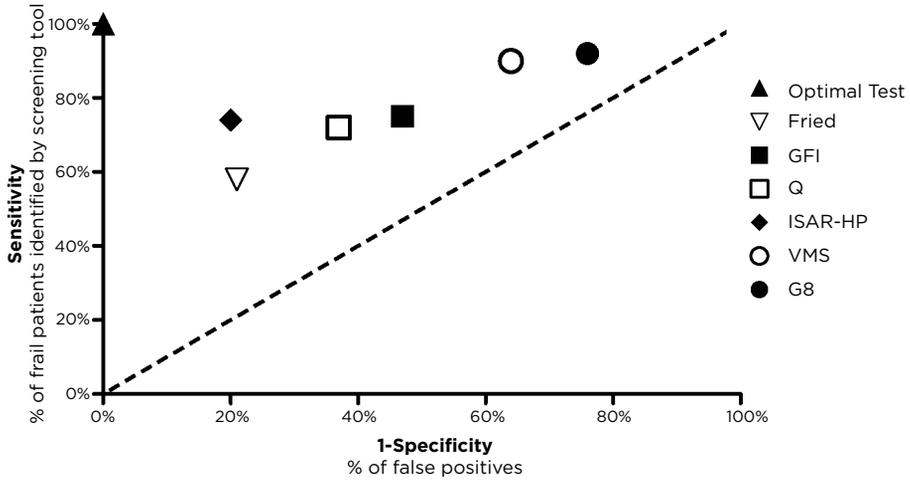


Figure 1. Frailty screening tools compared with the geriatric assessment (two or more impairments). Diagonal represents a random guess (i.e., 50-50 chance). Fried, Fried Frailty Index; G8, Geriatric 8; GFI, Groningen Frailty Indicator; ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; Q, Frailty Question; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program Criteria).

The clinical judgment of the nephrologist, the frailty question, had moderate discriminating ability for geriatric impairment when compared with the five frailty screening tools (Appendix 3b and 3c).

Discussion

This cross-sectional analysis of elderly patients enrolled in the GOLD study shows that geriatric impairment is highly prevalent at the time of dialysis initiation, with 78% of patients showing functional dependency (impairment in instrumental activities of daily living) and 66% showing cognitive impairment. Three quarters of the study population (75%) had significant impairment in two or more geriatric domains and was considered frail. As a geriatric assessment can be time consuming, we set out to compare frailty screening tools that can select those patients who could benefit from a more comprehensive geriatric assessment in the context of decision making concerning dialysis initiation. High sensitivity is important for this approach, which ensures that frail patients will accurately be screened as frail. In addition, specificity should be adequate, because an overinclusive measure will not save time. Only the Geriatric8 and the Hospital Safety Program criteria (VMS vulnerable elderly) stand out for having a good sensitivity, but both lack discriminative abilities; using the Geriatric8 as an initial screening tool would select 88% of all patients for a time-consuming geriatric assessment, whereas in only 75% of patients, two or more impaired domains will be found. Because the Geriatric8 is not sufficiently discriminative here, using this tool is not sensible when there is scarcity of resources to perform a geriatric assessment. Of the frailty screening tools, the Identification of Seniors At Risk has the best discriminating abilities in the ESKD population, showing the highest specificity and a fairly good sensitivity, and 91% of patients with a positive Identification of Seniors at Risk (ISAR-HP) are frail according to the geriatric assessment (high positive predictive value). However, the negative predictive value is poor (48%). Consequently, more than half of the patients who are screened as fit, will in fact, have two or more impairments on the geriatric assessment, and a negative frailty screening cannot be used to adequately rule out frailty. In conclusion, frailty screening instruments do not appear to be particularly helpful in preselecting frail patients who may benefit from an additional geriatric evaluation process.

Another observation that arises from these data is that the discriminating features of clinical judgment (frailty question) are comparable with the screening tools. Thus, the gut feeling of the nephrologist seems to be as useful as a screening tool to detect geriatric impairment. How valuable the clinical judgment is in detecting vulnerable patients at risk for poor outcome was illustrated before by the surprise question: “would I be surprised if this patient died in the next year?”. The odds of dying were 3.5 if the answer was no (95% confidence interval, 1.36 to 9.07) compared with yes.⁴¹ Nonetheless, as can be observed from the low negative predictive value, clinical judgment detects vulnerable patients, but will still overlook a large population in whom geriatric impairment exists.

With the increase of the elderly ESKD population, the need for evidence to support the decision-making process increases. Several studies assessed the potential of screening instruments for distinguishing between fit patients eligible for dialysis and patients in whom the burdens of dialysis may not outweigh the benefits and for whom conservative care should be discussed more extensively as an alternative option. Multiple risk stratification algorithms have been developed for (short-term) mortality, incorporating laboratory data and comorbidity burden.^{25,42,43,44} Presence of functional impairment is scored as well but only to a limited extent. Because functional impairment together with impairment in other geriatric domains influences quality of life, these mortality risk models may not suffice as a screening tool for identifying high-risk patients, because they lack sufficient information to support shared decision making concerning dialysis initiation.¹⁰ An advantage of an initial frailty screening may be that it does not only detect patients at risk for poor outcome¹⁴ but it additionally identifies patients with potential geriatric impairment who may benefit from a subsequent comprehensive assessment and geriatric rehabilitation.

The work-up of a frailty-screening instrument followed by a geriatric assessment in the process of shared decision-making in elderly patients is increasingly used in daily practice.⁴⁵ However, reports on comparison of different frailty tools in dialysis patients are sparse. To our knowledge, this is the first study to assess the discriminating abilities of frailty screening tools in the incident dialysis population. Johansen et al⁴⁶ compared two frailty definitions, performance based and self-reported function, based in prevalent hemodialysis patients from the US Renal Data System. Frailty was prevalent in 31% according to the performance-based definition and in 52% according to the self-reported definition, and 27% of patients were frail according to both definitions. Both frailty tests were associated with mortality, with patients who met both definitions having the highest mortality risk (hazard ratio, 2.46; 95% confidence interval, 1.51 to 4.01). No comparison was made with a more comprehensive geriatric assessment. In one small report, the Groningen Frailty Indicator was applied in patients with ESKD (n=65), and frail patients (Groningen Frailty Indicator ≥ 4) were referred to a geriatrician for additional assessment. Over half of geriatric problems detected by the geriatrician were not reported in the nephrologists' notes. The problems that were overlooked mainly concerned mental health, cognition and neurosensory deficits. No sensitivity/specificity analysis could be performed.⁴⁷ Another report comparing the Groningen Frailty Indicator, the Identification of Seniors At Risk, and the Hospital Safety Program criteria with an extended Fried Frailty Index as a gold standard showed a comparable performance for the Groningen Frailty Indicator and the Identification of Seniors At Risk in a heterogeneous group (n=95) of pre-dialysis patients and patients established on dialysis.⁴⁵ In geriatric oncology, the use of screening tools to assess functional

reserves before the start of chemotherapy is more common practice. However, in this population, screening tools lacked the discriminating abilities to select oncology patients for further geriatric evaluation as well.¹⁹

Although its importance has been recognized in chronic kidney disease,^{14,15} thus far, no consensus exists of the definition of frailty and the components of which it consists.⁴⁸ Assessment of frailty in ESKD mainly focuses on overt clinical disability, based on the Fried criteria, which includes poor endurance, muscle weakness and malnutrition. However, because frailty is a phenotype of decreased physiological reserve and multisystem dysregulation associated with increased vulnerability to stressors,¹³ cognitive and psychosocial issues may contribute as well and should not be ignored.⁴⁸

In addition, the cut-off value of two or more geriatric impairments of the geriatric assessment is arbitrary. However, previous research showed that the risk of disability and mortality was higher in patients meeting a cut-off score of two or more geriatric impairments.^{49,50} If we change the cut-off value for frailty in our study to three or more impairments, the prevalence of frailty would decrease to 44%. Overall, the discriminating abilities of the tests do not improve. In addition, using a combination of two frailty screening tools does not lead to better discriminating abilities, because sensitivity increases but specificity decreases (Appendix 3c). Future research should focus on establishing greater uniformity in the cut-off values and the content of a geriatric assessment to allow for a better comparison.

Predictive values are related to the prevalence of the outcome. Consequently, in a population in which frailty would be less prevalent, the screening tools would have a lower positive predictive value. The prevalence of frailty in our study is comparable with that in two other studies in patients on incident dialysis (68% and 73%).^{14,15} Both studies used a modified definition of the Fried Frailty Index. Even in young patients, the prevalence of frailty was found to be high (40%).¹⁵ Therefore, the generalizability of the predictive values of the screening tests in general is good. Because in our study impairment in instrumental activities of daily living is the most frequently encountered geriatric impairment (78%), the Identification of Seniors at Risk, which has a particular focus on instrumental activities of daily living, has the best positive predictive value of all tools. Because the Fried Frailty Index focuses on the physical performance phenotype exclusively, it is not surprisingly that sensitivity for frailty according to the multidimensional geriatric assessment is poor. However, tools that incorporate a wider range of geriatric impairments (Table 4) lack specificity.

This is a unique cohort of incident dialysis patients undergoing a geriatric assessment. However, there are some limitations. First, it is a selected cohort, in which the decision to start dialysis has already been made. Although it is likely that the discriminating abilities of the frailty screening tools for geriatric impairment are comparable for elderly patients who choose conservative therapy and who may exhibit a higher burden of geriatric impairment, data are currently lacking. Second, the frailty question is not a validated test but merely a Visual Analog Scale to objectify the clinical judgment of the physician on frailty. The cut-off value was predefined, but this was not based on available evidence, because this approach has not been used before. Thus, such a screening method should be used with caution in clinical practice. Third, a geriatric assessment such as used in this study is not a replacement of a consultation of a geriatrician, and detection of depressive symptoms with the geriatric depression scale is not comparable with a full psychological examination. Also, there is a great deal of variation in the way that geriatric assessments are conducted. Several combinations of tools and various models are available for implementation of geriatric assessment; in oncology practice, an expert panel could not endorse one over another.²⁰ The use of a uniform assessment would enhance comparability in clinical research. Fourth, although emerging evidence exists on the predictive value of a geriatric assessment in decision making in elderly patients in other fields of medicine,^{24,20} the relation between a geriatric assessment and poor outcome after dialysis initiation has not been fully established yet. However, physical, cognitive and psychosocial geriatric impairment were shown to be related to mortality and hospitalizations.⁶ This will be subject of the longitudinal analysis of the GOLD study.

Conclusion

A geriatric assessment may fill a knowledge gap in optimizing personalized care in elderly patients, but a large disadvantage is that it can be time consuming. A screening tool preceding a geriatric assessment, identifying the potentially frail patients who would actually benefit from this comprehensive assessment, would be useful. We have shown that screening tools are able to detect geriatric impairment in patients eligible for dialysis. The vast majority of the appointed patients are genuinely frail and could benefit from a long-term care plan and additional attention to help improve or maintain functional and psychosocial abilities. However, all applied screening tools lack the discriminating abilities to adequately rule out frailty compared with a geriatric assessment. Although the clinical judgment of the nephrologist performs similarly to the screening tools, it does not adequately select patients with or without geriatric impairment. Almost half of the patients screened as fit did have a considerable number of geriatric impairments. Frailty screening tools could be used as a first step to detect frailty, but future research should focus on establishing a more reliable preselection method for elderly patients who could benefit from a more comprehensive geriatric assessment.

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Supplementary data

Appendix 1. Frailty screening tools

VMS Vulnerable Elderly ¹		
Components	Description/cut-off	Score
Delirium*	1. Do you have memory problems?	Yes=1
	2. In the last 24 hours did you need help with daily self-care?	Impairment domain: ≥ 1
	3. During previous hospitalization or illness were there periods that you were confused?	
Falls	4. In the last 6 months did you fall?	Yes=1 Impairment domain: ≥ 1
Physical impairment	Do you need help with:	Yes=1
	5. Bathing	Impairment domain: ≥ 2
	6. Dressing	
	7. Toileting	
	8. Transferring from/to chair	
	9. Feeding	
10. Do you use incontinence material?		
Malnutrition	11. Have you lost weight unintentionally?	
	- More than 3 kg in the last month	Yes=2
	- More than 6 kg in the last 6 months	Yes=3
	12. Did you experience a decreased appetite over the last month?	Yes=1
	13. Did you use supplemental drinks or tube feeding over the last month?	Yes=1 Impairment domain: ≥ 2
	Frailty: Impairment ≥ 1 domain	
ISAR-HP ²		
Components	Description/cut-off	Score
IADL	- Before hospital admission, did you need assistance for IADL (e.g. assistance in the housekeeping, preparing meals, shopping etc.) on a regular basis?	Yes=1
	- Do you need assistance for traveling?	Yes=1
Mobility	Do you use a walking device (e.g. cane, walking frame, crutches etc.)?	Yes=2
Other	Did you pursue education after age 14?	Yes=1
Frailty: ≥ 2 points		

Appendix 1. Continued

G8 ⁸		
Components	Description/cut-off	Score
Malnutrition	- Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0=Severe decrease in food intake 1=Moderate decrease in food intake
	- Weight loss during the last 3 months	0=Weight loss >3kg 1=Does not know 2=Weight loss between 1 and 3 kg 3=No weight loss
	- Body Mass Index (BMI)(weight in kilograms/ height in square meters)	0=BMI<19 1=BMI 19 to <21 2=BMI 21 to <23 3=BMI ≥23
Mobility	Mobility?	0=Bed or chair bound 1=Able to get out of bed/chair but does not go out 2=Goes out
Cognition/mood	Neuropsychological problems?	0=Severe dementia or depression 1=Mild dementia 2=No psychological problems
Polypharmacy	Takes more than three prescription drugs per day?	0=Yes 1=No
General health	In comparison with other people of the same age, how does the patient consider his/her health status?	0.0= Not as good 0.5= Does not know 1.0= As good 2.0= Better
Age	Age	0=>85 1=80-85 2=<80

Total score 17, Frailty: ≤14

VMS, Veiligheidsmanagementsysteem (Hospital Safety Program Criteria); ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; G8, Geriatric8.

* Caregivers were asked to fill in a form with additional questionnaires on cognition and behavior of the patient (neuropsychiatric inventory, NPI). Impairments in the NPI which was used to calculate the delirium score of the VMS score

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Appendix 2. Absolute numbers of positive and negative scores for the different frailty screening tools

Frailty screening modality		GA score (n)			Total
Test	Score	-	+	<i>total</i>	
Fried Frailty Index	-	23	33	56	
	+	6	46	52	
	<i>total</i>	29	79		108
Groningen Frailty Indicator	-	18	22	40	
	+	16	67	83	
	<i>total</i>	34	89		123
G8	-	8	7	15	
	+	26	82	108	
	<i>total</i>	34	89		123
ISAR-HP	-	24	22	46	
	+	6	62	68	
	<i>total</i>	30	84		114
VMS-vulnerable elderly	-	9	6	15	
	+	16	52	68	
	<i>total</i>	25	58		83
Frailty Question	-	17	21	38	
	+	10	55	65	
	<i>total</i>	27	76		103

G8, Geriatric 8; ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program Criteria); Frailty Question, Clinical Judgement of the nephrologist.

Appendix 3a. Prevalence and discriminating test characteristics frailty measurements– Geriatric Assessment minimum of 3 impairments

Screening modality	Cut-off value	Prevalence of frailty	Sensitivity
Fried Frailty Index	≥3	48%	59% (48-70%)
GFI	≥4	67%	74% (64-83%)
G8	≤ 14	88%	92% (85-97%)
ISAR-HP	≥2	60%	72% (61-81%)
VMS-vulnerable elderly	≥2	82%	90% (79-69%)
Frailty Question (Q)	≥5	63%	72% (61-82%)

PPV, positive predictive value; NPV, negative predictive value; LHR+, positive likelihood ratio; LHR-, negative likelihood ratio; GFI, Groningen Frailty Indicator; G8, Geriatric8;

Appendix 3b. Prevalence and discriminating test characteristics frailty measurements - Frailty Question compared to the other tests

Screening modality	Cut-off value	Prevalence of frailty	Sensitivity
Fried Frailty Index	≥3	51%	64% (50-76%)
GFI	≥4	69%	69% (57-80%)
G8	≤ 14	87%	91% (81-97%)
ISAR-HP	≥2	63%	68% (55-80%)
VMS	≥2	84%	83% (68-93%)

PPV, positive predictive value; NPV, negative predictive value; LHR+, positive likelihood ratio; LHR-, negative likelihood ratio; GFI, Groningen Frailty Indicator; G8, Geriatric8;

Appendix 3c. Frailty Question and one of the other tests compared to the Geriatric Assessment

Screening modality	Cut-off value	Prevalence of frailty	Sensitivity
Q & Fried Frailty Index	≥5 or ≥3	67%	78% (68-86%)
Q & GFI	≥5 or ≥4	84%	91% (84-96%)
Q & G8	≥5 or ≤ 14	93%	97% (91-99%)
Q & ISAR-HP	≥5 or ≥2	75%	87% (78-93%)
Q & VMS	≥5 or ≥2	83%	87% (78-93%)

PPV, positive predictive value; NPV, negative predictive value; LHR+, positive likelihood ratio; LHR-, negative likelihood ratio; GFI, Groningen Frailty Indicator; G8, Geriatric8;

Specificity		PPV		NPV		LHR+	LHR-
85%	(66-96%)	92%	(83-97%)	41%	(34-49%)	4.00 (1.59-10.06)	0.48 (0.35-0.65)
52%	(33-70%)	82%	(76-87%)	40%	(29-52%)	1.53 (1.04-2.24)	0.51 (0.31-0.82)
26%	(12-45%)	79%	(75-82%)	53%	(31-74%)	1.25 (1.00-1.55)	0.29 (0.12-0.75)
79%	(59-92%)	91%	(83-96%)	48%	(38-58%)	3.36 (1.64-6.92)	0.36 (0.24-0.58)
38%	(19-59%)	78%	(72-83%)	60%	(37-79%)	1.44 (1.05-1.98)	0.27 (0.11-0.68)
67%	(45-84%)	88%	(80-93%)	42%	(32-53%)	2.16 (1.21-3.87)	0.42 (0.27-0.66)

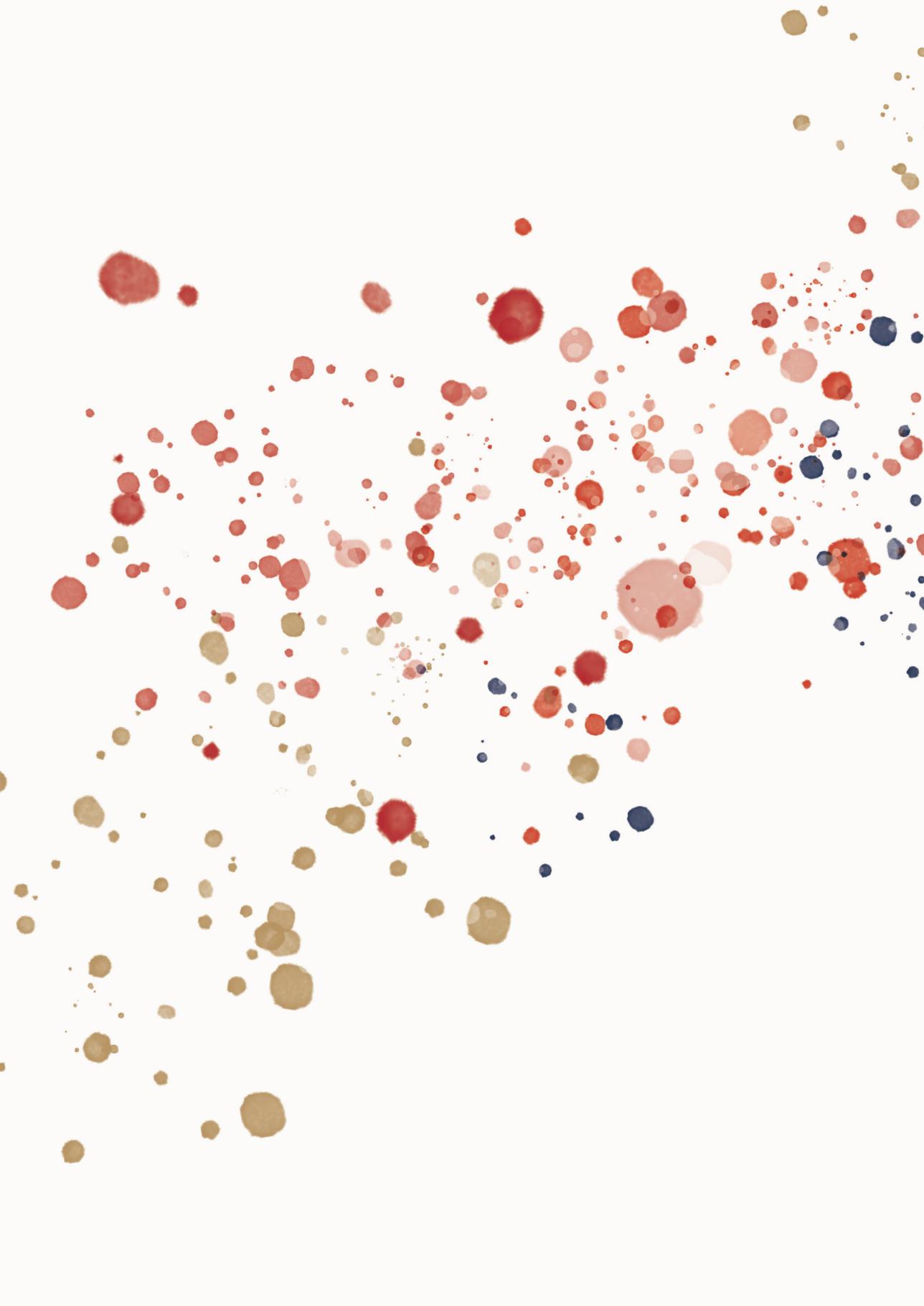
ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program criteria); frailty question, clinical judgment of the nephrologist.

Specificity		PPV		NPV		LHR+	LHR-
71%	(53-85%)	78%	(67-86%)	55%	(44-64%)	2.16 (1.24-3.78)	0.52 (0.34-0.78)
32%	(18-49%)	63%	(57-69%)	38%	(25-52%)	1.01 (0.77-1.35)	0.97 (0.54-1.76)
18%	(8-34%)	66%	(62-69%)	54%	(30-76%)	1.11 (0.94-1.32)	0.50 (0.18-1.38)
46%	(29-63%)	68%	(60-75%)	46%	(33-59%)	1.26 (0.89-1.79)	0.69 (0.41-1.16)
15%	(4-35%)	61%	(55-66%)	36%	(16-64%)	0.98 (0.79-1.21)	1.11 (0.36-3.42)

ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program criteria).

Specificity		PPV		NVP		LHR+	LHR-
64%	(45-81%)	87%	(80-91%)	50%	(39-61%)	2.20 (1.35-3.84)	0.34 (0.21-0.54)
39%	(20-58%)	82%	(77-85%)	60%	(40-77%)	1.49 (1.12-1.89)	0.22 (0.10-0.50)
19%	(7-37%)	75%	(66-82%)	78%	(75-81%)	1.20 (1.01-1.43)	0.17 (0.04-0.63)
58%	(39-75%)	86%	(80-90%)	60%	(45-73%)	2.07 (1.36-3.16)	0.23 (0.12-0.42)
28%	(13-47%)	79%	(76-83%)	40%	(23-60%)	1.20 (0.94-1.52)	0.48 (0.22-1.07)

ISAR-HP, Identification of Seniors at Risk-Hospitalized Patients; VMS, Veiligheidsmanagementsysteem (Hospital Safety Program criteria). Q, Frailty Question: clinical judgment of the nephrologist.





Chapter 4

Geriatric assessment and the relation with mortality and hospitalizations in older patients starting dialysis

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Abstract

Background and objectives: A Geriatric Assessment (GA) is a structural method for identifying frail patients. The relation of GA findings and risk of death in end-stage kidney disease (ESKD) is not known. The objective of the GOLD (GA in OLder patients starting Dialysis) Study was to assess the association of GA at dialysis initiation with poor outcome.

Design, Setting, Participants, and measurements: Patients ≥ 65 years old were included just prior to dialysis initiation. All participants underwent a GA, including assessment of (instrumental) ADL, mobility, cognition, mood, nutrition, and comorbidity. In addition a frailty screening (Fried Frailty Index, FFI) was applied. Outcome measures were 6- and 12-month mortality, and 6-month hospitalization. Associations with mortality were assessed with cox-regression adjusting for age, sex, comorbidity burden, smoking, residual kidney function and dialysis modality. Associations with hospitalization were assessed with logistic regression, adjusting for relevant confounders.

Results: 192 patients were included, mean age 75 ± 7 years, of whom 48% had ≥ 3 geriatric impairments and were considered frail. The FFI screening resulted in 46% frail patients. Mortality rate was 8% and 15% at 6- and 12-months after enrollment, and transplantation rate was 2% and 4%, respectively. Twelve-month mortality risk was higher in patients with ≥ 3 impairments (HR 2.97, 95%CI 1.19-7.45) compared to less impaired patients. FFI frail patients had a higher risk of 12-month mortality (HR 7.22, 95%CI 2.47-21.13) and hospitalization (OR 1.93, 95%CI 1.00-3.72) compared to non-frail patients. Malnutrition was associated with 12-months mortality, while impaired ADL and depressive symptoms were associated with 12-months mortality and hospitalization.

Conclusions: Frailty as assessed by a GA is related to mortality in elderly patients with ESKD. Individual components of the GA are related to both mortality and hospitalization. As the GA allows for distinguishing between frail and fit patients initiating dialysis, it is potentially of added value in the decision-making process concerning dialysis initiation.

Introduction

The chronic kidney disease (CKD) population is ageing and an increasing number of older patients start with dialysis.¹ Over the past decade the number of octogenarians on dialysis has almost doubled.² Approximately half of the octogenarians and nonagenarians starting dialysis will die within one year after initiating dialysis and dropout is particularly high early after initiation.^{2,3} As the burden of dialysis can be high in the elderly, nephrologists increasingly face the dilemma whether initiation of dialysis would be appropriate. Older patients with end-stage kidney disease (ESKD) often exhibit impairments across various geriatric domains, such as dependency in activities of daily living (ADLs), mobility impairment, cognitive impairment, depression and malnutrition.⁴ Accumulation and interaction of impairment of multiple domains may contribute to increased vulnerability to external stressors, also referred to as the frailty phenotype.⁵

Although emerging evidence exists on the relation between frailty and poor outcome, there is no consensus on the definition. While there are many operationalizations of frailty, most stem from two major frailty models: the phenotypic frailty model where frailty is seen as the final common pathway of ageing⁶ and the cumulative deficits model.⁷ In nephrology, the first model using the Fried Frailty criteria, is most often used to assess frailty; this screening tool measures physical reserves, malnutrition and exhaustion, and is associated with increased hospitalizations and mortality after dialysis initiation.^{6,8-10} A broader concept of frailty is the cumulative deficits model that includes impairment across various geriatric domains, such somatic, functional and psychosocial impairment.¹¹ By systematically assessing geriatric domains, a Geriatric Assessment (GA) is an evidenced based approach to assess this cumulative deficits construct of frailty. In other fields of medicine, GA improves treatment decision-making and contributes to improved function and survival in older patients.^{12,13} In ESKD, although a myriad of studies showed various geriatric impairments are related to poor outcome, no data are available on whether a GA at initiation of dialysis is related to outcome.⁴ Whether a GA is capable of distinguishing between fit patients and frail patients, in whom the benefits of dialysis do not offset the burden, is not known yet.

The GOLD (Geriatric assessment in OLder patients starting Dialysis) Study was conducted to assess the relation between GA and early mortality and hospitalization in older patients incident to dialysis. In addition, the relation between the individual geriatric impairments and poor outcome was assessed. Finally, we looked at other frailty instruments and poor outcome.

Methods

Study design and patient selection

The GOLD (Geriatric Assessment in OLder patients starting Dialysis) study is a multicenter, prospective, cohort study assessing the relation between a GA and poor outcome in ESKD patients. The GOLD study included both patients starting dialysis and patients choosing conservative care. For this analysis we only included the dialysis patients. Participants were enrolled from 17 different hospitals across the Netherlands (Chapter 2, Appendix 1) in the period from August 2014 to September 2017. Consecutive patients eligible for dialysis were included between 3 weeks before and 2 weeks after the first dialysis session. Patients were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language or if they suffered from a terminal non-renal related condition. Patients were followed from start of dialysis until kidney transplantation, death or censoring (recovery kidney function or loss to follow-up). The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients and participating caregivers prior to enrollment.

Data collection and analysis

Baseline demographic data collected from medical charts included age, sex, educational level and living situation, cause of kidney failure, residual renal function, acute start of dialysis, type of dialysis, dialysis access, blood pressure, body mass index (BMI) and smoking habit.

For the GA, participants were either visited at home (on a non-dialysis day for hemodialysis patients) or in the dialysis center, before starting the dialysis session. The assessments were performed by the investigators (IL or NG) or by one of the trained research nurses. The GA consisted of validated questionnaires or structured assessments of seven domains (Chapter 2, Appendix 2): activities of daily living (ADL, Katz²²), instrumental activities of daily living (IADL, Lawton and Brody²³), mobility (Timed-Up-and-Go²⁴), depressive symptoms (Geriatric Depression Scale²⁵), nutrition (Mini Nutritional Assessment²⁶), comorbidity burden (the Cumulative Illness Rating Scale-Geriatric (CIRS-G)^{27,28} and cognition (Mini Mental State Examination (MMSE),¹⁹ Clock drawing test,²⁰ fluency test²¹ and enhanced cued recall test).²² Impaired cognition was defined as one or more impaired cognitive tests. The time needed to apply a GA was approximately 1-1.5 hour. The outcome of the GA was composed by the sum of impairment in the seven geriatric domains.²³ Patients were defined as being frail when they had impairments in ≥ 2 domains (GA2+)²³, all patients with < 2 impairments were considered fit. Results of the structured GA were not communicated with the treating physician and therefore did not influence treatment decisions.

In addition four frailty screening methods were applied: Fried Frailty Index (FFI)⁶, Groningen Frailty Indicator (GFI)²⁴ (Chapter 2, Appendix 2), the clinical judgment of the nephrologist by means of the “Surprise Question” and the nephrologists’ estimation of the level of frailty. For the Surprise Question, clinicians were asked whether *they would be surprised if the patients would die within 6 months after dialysis initiation*.²⁵ For the estimation of frailty, the treating nephrologist was asked to indicate how frail the patients was in his/her opinion on a scale from 0-10, where 0 was fit and 10 was frail. A score of ≥ 5 was a priori defined as frail.

For follow-up, data on 6- and 12-month mortality and 6-month hospitalizations were collected from each center. The patients who were alive after 6 months were contacted by telephone and asked whether the dialysis therapy was according to (or above) or below their initial expectations.

Statistical analysis

Data is summarized using means with standard deviation (SD), or proportions when appropriate. All domains were dichotomized into impaired and not impaired according to the pre-defined cut-off values (Chapter 2, Appendix 2). Differences between groups were assessed using chi-squared tests for dichotomous variables and t-tests for normally distributed continuous variables.

The relation of the GA and frailty screening methods with mortality was assessed with log rank tests. Factors significantly associated with 12-months mortality (or with a p value ≤ 0.10) were analysed with a cox proportional hazards model, adjusting for age, sex and high comorbidity as defined by the CIRS-G (model 1) and additionally for current smoking, residual renal function and dialysis modality (model 2). Frailty as measured with the GA was a priori defined as having impairments in ≥ 2 domains (GA2+).²³ As none of the patients screened as fit by this definition died, the relation between GA2+ and mortality could not be analysed with a cox-regression model. Thus, we further used ≥ 3 impairments (GA3+) for the definition of frailty, and analyzed this accordingly.²³ Due to a low number of deaths, multivariate analysis for 6-month mortality was not performed. Proportional hazards assumptions were assessed using a log-minus-log plot.

A logistic regression analysis was performed for the relation of geriatric impairment with hospitalization (yes/no), adjusted for age, sex and comorbidity burden. A two-tailed p < 0.05 was considered statistically significant. Data analysis was performed with SPSS version 22 software.

Results

Baseline characteristics

A total of 196 incident dialysis patients were included in the GOLD Study. Another 28 patients were screened, but excluded because of terminal illness (n=3), language barrier (n=3) or refusal to participate (n=22). The majority of the patients were included just after the start of dialysis (median 8 days, interquartile range (IQR) 1-13). Four patients were excluded from the prospective analysis because they did not meet the inclusion criteria regarding the interval between time of inclusion and start of dialysis. No patients were lost to follow up. The mean age was 75 (± 7) years and 67% of patients were male (Table 1).

Impairment across all geriatric domains was common (Table 2). Of all patients, 76% suffered from ≥ 2 impairments (GA2+) and 48% from ≥ 3 impairments (GA3+). When frailty-screening tools were applied, the prevalence of frailty ranged from 46% (FFI) to 66% (clinical impression nephrologist).

Of all patients, 77% started hemodialysis (HD) and 23% peritoneal dialysis (PD). The mean age was lower in the PD group compared to the HD group (73 ± 6 vs. 76 ± 7 , $p=0.04$) and PD patients were less likely to live alone (27% vs. 47% of the HD patients, $p=0.02$). In general, the PD group was less impaired than the HD group, although this did not reach statistical significance (Data not shown).

Follow-up

Follow-up was complete for all patients. The 6-month mortality rate was 8% (n=15, of whom 6 patients (40%) withdrew from dialysis prior to death), and transplantation rate 2% (n=3), while 12-month mortality rate was 15% (n=29) and transplantation rate 4% (n=7). Patients who died within 12 months were older at baseline (mean age 79 ± 7 vs. 75 ± 6 years, $p < 0.01$). Other baseline characteristics did not differ significantly between patients who died and who did not.

Table 1. Baseline characteristics

	N=192
Demographics	
Age, years, mean \pm SD	75 \pm 7
Sex (% male)	67%
Medical history (%)	
Hypertension	89%
Diabetes Mellitus	39%
Myocardial infarction	33%
Peripheral vascular disease	17%
Cerebrovascular event	17%
Clinical parameters	
Cause of kidney failure	
Renal vascular	50%
Diabetes	16%
Glomerulonephritis	7%
Other	27%
Dialysis modality (% PD)	23%
Acute start of dialysis	16%
Access: Central venous line (% of HD)	38%
BMI (kg/m ²), mean (\pm SD)	26 \pm 5
Systolic blood pressure (mmHg) ^a	150 \pm 22
Diastolic blood pressure (mmHg) ^a	74 \pm 14
eGFR (ml/min/1.73m ² CKD-EPI)	8.0 \pm 3.0
Hemoglobin (mmol/L)	6.3 \pm 0.9
Albumin (g/L)	34 \pm 6
Smoking (current) n (%)	14%
Social setting	
Living alone	42%
Living in a nursing home facility	5%
University	22%
Polypharmacy	
Mean no of drugs \pm SD	11 \pm 5

PD, Peritoneal dialysis; HD, Hemodialysis; BMI, Body Mass Index.

^aPre-dialysis

Geriatric impairment and mortality

Geriatric impairments were associated with 6- and 12-month mortality (Table 3). Six-month mortality was higher among patients with impairment in IADL (10% vs. 0%, $p=0.03$), cognitive impairment, as measured with the MMSE, (20% vs. 6%, $p=0.01$), depressive symptoms (14% vs. 5%, $p=0.04$) and malnutrition (30% vs. 7%, $p<0.01$). Twelve-month mortality was higher among patients with (functional) impairment compared to patients without impairment. In the multivariate analysis, ADL (hazard ratio (HR) 3.20, 95% confidence interval (CI) 1.45-7.06), depressive symptoms (HR 2.30, 95%CI 1.06-5.02) and malnutrition (HR 4.52, 95%CI 1.40-14.61) were associated with 12-month mortality (Table 4a, model 2). For IADL no events occurred in the fit group, therefore a log rank test was applied instead of a cox regression. IADL was significantly associated with 12-month mortality, when stratified for age (< 80 and ≥ 80 years) $p<0.01$.

Relation between frailty and mortality

GA. Twelve-month mortality rate was 21% among patients with ≥ 3 impairments (GA3+) and 8% among patients with less impairment ($p=0.02$). After correcting for potential confounders age and sex, GA3+ was associated with mortality, HR 2.97 (95%CI 1.19-7.45) (Table 4a, Model 2). In this model, age was not significantly associated with mortality (HR 1.06, 95%CI 1.00-1.12, $p=0.055$).

Frailty screening methods. Frail patients as measured with the FFI had a higher mortality risk compared to non-frail patients, with an adjusted HR 7.22 (95%CI 2.47-21.33) (Table 4a). In addition, the clinical impression of the nephrologist concerning frailty was related to mortality (HR 4.10, 95%CI 2.47-21.13). The Groningen Frailty Indicator and the Surprise Question were not related to mortality.

Hospitalization in the first 6 months after dialysis initiation

During the first 6 months of follow-up, approximately half of the patients (49%) were hospitalized. Patients with impairments in the following geriatric domains were more likely to be hospitalized compared to non-impaired patients when adjusted for potential confounders: ADL (Odds Ratio (OR) 2.88, 95%CI 1.46-5.70), IADL (OR 2.25, 95%CI 1.07-4.76), and depressive symptoms (OR 2.29, 95% CI 1.21-4.36). FFI (OR 2.35, 95%CI 1.28-4.30) and the clinical judgement of frailty by the nephrologist (OR 2.21, 95% CI 1.09-4.46) were both associated with hospitalization. GA2+, GA3+ and GFI were not. One out of six patients reported that the dialysis treatment in the first six months after dialysis turned out to be worse than initially expected, while the others reported it to be according to or above expectations. The difference in coping was more pronounced among frail patients: 23% of the FFI based frail patients reported the treatment to be worse than expected vs. 10% among fit patients, $p=0.03$.

Table 2. Geriatric Impairment at baseline

Geriatric impairment	N=192
Functional impairment, n (%)	
ADL: ≥ 1 impairment	29%
IADL: ≥ 1 impairment	78%
Mobility: severely impaired ^a	18%
Cognition, n (%)	
MMSE ^a	13%
Cognitive test battery ^{#a}	72%
Mood, n (%)	
Depressive symptoms	30%
Nutrition, n (%)	
Malnutrition [§]	5%
Comorbidities, n (%)	
Severe comorbidity burden [*]	42%
Frailty: GA	
GA ≥ 2 impairments	76%
GA ≥ 3 impairments	48%
Frailty: screening methods	
Fried Frailty Index (FFI) ^a	46%
Groningen Frailty Indicator (≥ 4)	61%
Surprise Question ("not surprised") ^b	23%
Clinical impression nephrologist ^c	66%

ADL, Activities of daily living; IADL, Instrumental activities of daily living; MMSE, Mini Mental State Examination; GA, Geriatric Assessment.

[#]One or more impaired cognitive tests: Mini Mental State Examination, Clock drawing test, fluency test, enhanced cued recall test [§]As defined by the Mini Nutritional Assessment ^{*}CIRS-G score $\geq 2 \times$ score 3 or $\geq 1 \times$ score

^a<5% missing, ^b21% missing, ^c22% missing

Table 3. Geriatric domains and association with 6- and 12-month mortality

Geriatric impairment	6-month mortality				P-value
	Impaired		Not impaired		
	N	%	N	%	
Functional impairment, n (%)					
ADL: ≥ 1 impairment	7/57	12	8/135	6	0.13
IADL: ≥ 1 impairment	15/150	10	0/42	0	0.03
Mobility: severely impaired ^a	3/35	8	10/148	7	0.71
Cognition, n (%)					
MMSE ^a	5/24	20	10/163	6	0.01
Cognitive test battery ^a	12/135	9	3/53	6	0.46
Mood, n (%)					
Depressive symptoms	8/57	14	7/135	5	0.04
Nutrition, n (%)					
Malnutrition	3/10	30	12/182	7	<0.01
Comorbidities, n (%)					
CIRS-G	7/81	9	8/111	7	0.71
Frailty: GA					
GA ≥ 2 impairments	15/150	10	0/42	0	0.03
GA ≥ 3 impairments	11/107	10	4/85	6	0.15
Frailty: screening modalities					
Fried frailty Index ^a	12/84	14	3/99	3	<0.01
Groningen Frailty Indicator (≥ 4)	10/117	9	5/75	7	0.64
Surprise question nephrologist ^b	3/35	9	8/117	7	0.73
Frailty according to nephrologist ^c	8/98	8	3/51	6	0.61

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; CIRS-G, Cumulative Illness Rating Scale-Geriatric; GA, Geriatric Assessment.

^a<5% missing, ^b21% missing, ^c22% missing

		<i>12-month mortality</i>		P-value
Impaired	Not impaired	N	%	
N	%	N	%	
16/57	28	13/135	10	<0.01
29/150	19	0/42	0	<0.01
9/35	26	18/148	12	0.04
6/24	25	22/136	14	0.14
21/135	16	7/53	13	0.68
23/99	23	6/93	7	<0.01
4/10	40	25/182	14	0.02
15/81	19	14/111	13	0.26
29/150	19	0/42	0	<0.01
22/107	21	7/85	8	0.02
24/84	29	4/99	4	<0.01
21/117	18	8/75	11	0.17
5/35	14	19/117	16	0.78
21/98	21	3/51	6	0.01

Table 4a. Geriatric domains and association with 12-month mortality

	Crude		
	HR	95%CI	P-value
Functional impairment			
ADL: ≥ 1 impairment	3.00	1.44-6.23	<0.01
IADL: ≥ 1 impairment	n/a*		
Mobility: severely impaired	2.16	0.97-4.81	0.06
Cognition			
Test battery	1.26	0.53-2.96	0.60
MMSE	2.13	0.86-5.25	0.10
Depressive symptoms			
	2.39	1.15-4.94	0.02
Malnutrition			
	3.45	1.20-9.91	0.02
Severe comorbidity burden			
	1.05	0.78-1.40	0.77
Frailty			
GA ≥ 3 impairments*	2.63	1.13-6.17	0.03
Fried frailty	8.03	2.78-23.16	<0.01
GFI (≥ 4)	1.71	0.76-3.86	0.20
Surprise question	0.89	0.33-2.39	0.82
Frailty according nephrologist	3.97	1.18-13.32	0.03

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; CIRS-G, Cumulative Illness Rating Scale-Geriatric; GA, Geriatric Assessment; GFI, Groningen Frailty Indicator.

Adjusted					
HR	Model 1 ¹		Model 2 ²		
	95%CI	P-value	HR	95%CI	P-value
3.10	1.43-6.71	<0.01	3.20	1.45-7.06	0.04
2.04	0.87-4.77	0.10	1.97	0.80-4.85	0.14
2.09	0.83-5.24	0.11	2.18	0.85-5.57	0.10
2.30	1.09-4.84	0.03	2.30	1.06-5.02	0.04
4.51	1.45-14.04	0.01	4.52	1.40-14.61	0.01
2.36	1.12-6.21	0.04	2.97	1.19-7.45	0.02
7.49	2.57-21.83	<0.01	7.22	2.47-21.13	<0.01
3.88	1.15-13.11	0.03	4.10	1.19-14.14	0.03

¹Adjusted for age, sex, CIRS-G comorbidity burden; ²Adjusted for age, sex, CIRS-G comorbidity burden, smoking, residual renal function and dialysis modality; ³Adjusted for age, sex, CIRS-G comorbidity burden, residual renal function and dialysis modality *For the relation with the GA comorbidity was not included in the model, as comorbidity was already captured in the GA analysis not applicable, as no events occurred in the non-impaired group.

Table 4b. Geriatric domains and association with 6-month hospitalizations

	Crude			Adjusted ³		
	OR	95%CI	P-value	OR	95%CI	P-value
Functional impairment						
ADL: ≥ 1 impairment	2.61	1.37-4.96	<0.01	2.63	1.31-5.34	<0.01
IADL: ≥ 1 impairment	2.23	1.09-4.56	0.03	2.10	0.99-4.45	0.05
Mobility: severely impaired	1.90	0.89-4.08	0.10	1.97	0.86-4.50	0.11
Cognition						
Test battery	0.65	0.34-1.23	0.19			
MMSE	1.86	0.77-4.50	0.17			
Depressive symptoms	2.35	1.24-4.44	<0.01	2.01	1.05-3.85	0.04
Malnutrition	1.52	0.41-5.56	0.53			
Severe comorbidity burden	1.24	1.00-1.59	0.09	1.23	0.95-1.59	0.12
Frailty						
GA ≥ 3 impairments [*]	1.50	0.84-2.65	0.17			
Fried frailty	2.26	1.15-4.10	<0.01	2.31	1.24-4.32	<0.01
GFI (≥4)	1.27	0.71-2.67	0.43			
Frailty according nephrologist	2.25	1.12-4.53	0.02	2.35	1.14-4.86	0.02

ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; CIRS-G, Cumulative Illness Rating Score-Geriatric; GA, Geriatric Assessment; GFI, Groningen Frailty Indicator.

¹Adjusted for age, sex, CIRS-G comorbidity burden; ²Adjusted for age, sex, CIRS-G comorbidity burden, smoking, residual renal function and dialysis modality; ³Adjusted for age, sex, CIRS-G comorbidity burden, residual renal function and dialysis modality ^{*}For the relation with the GA comorbidity was not included in the model, as comorbidity was already captured in the GA [†]analysis not applicable, as no events occurred in the non-impaired group.

Discussion

In the GOLD Study, we assessed geriatric impairment and frailty in older patients incident to dialysis and their relation with poor outcome. Impairment of the individual geriatric domains activities of daily living (ADL), depressive symptoms and malnutrition at the start of dialysis were associated with one-year mortality. In addition the cumulative deficits model using the Geriatric Assessment was associated with poor outcome. Frail elderly incident dialysis patients with an accumulation of deficits (≥ 3 geriatric impairments on a GA) were almost 3 times as likely to die within the first year compared to patients with less impairment. In addition, frail patients according to the Fried Frailty Index (FFI) were more than 7 times as likely to die within the first year compared to non-frail patients, and more than 2 times as likely to be hospitalized.

A GA is recognized as the best clinical practice standard test for the identification of frailty and has been widely adopted in routine elderly care.²³ As far as we know, the relation between GA and mortality has not been established before in elderly dialysis patients. This prognostic information further emphasizes the benefits of using a comprehensive GA (CGA) in nephrology care. Besides identifying geriatric problems that may inform us on mortality risk, a CGA focuses on a multidisciplinary approach and creating an overall plan for treatment and follow-up.²⁶⁻²⁸ In other fields of medicine, a GA contributes to tailor-made care in the elderly. A recent systematic review in geriatric oncology showed that after geriatric evaluation, the initial oncologic treatment plan was altered in 28% of patients, mainly towards less invasive treatment, and additional non-oncologic interventions were recommended in the majority of patients. A positive effect was found on treatment completion and less treatment-related toxicity.²⁹ Although a CGA has proven beneficial in non-ESKD patients, we do not know yet what effect the CGA has on outcome in patients initiating dialysis.³⁰

The main disadvantage of a GA is that it is time-consuming. Besides, the experience with GA in nephrology care is sparse so far and it is unclear how, when in the illness trajectory, and how frequently it should be used. Furthermore, several combinations of tools and various models are available for implementation of a GA.^{23,31} As an example, an expert panel of the European Renal Association-European Dialysis Transplant Association (ERA-EDTA) and the European Union Geriatric Medicine Society (EUGMS) could not endorse one physical functioning test over another.³² For the assessment of functional status of older patients, the guideline recommended using a simple score to assess functional status, including a self-reported scale and a field test (i.e. sit to stand, gait speed, six minute walk test). Clinical practice and cross-study comparison would benefit from agreement on uniformity of a certain subset of tests and cutoff

values in the nephrology population. The next step would be to assess how to identify patients that would benefit from a GA as a guide for treatment decision-making, or for identifying targets to improve overall quality of life. Whether implementation of a GA in the (pre)dialysis phase could be (cost-) effective in ESKD patients has to be established as well.

Compared to the cumulative deficits model of frailty, the FFI screening for frailty had a stronger relation with mortality and was associated with hospitalization risk and worse coping. In addition, the FFI is an easy to apply screening instrument in clinical practice. The most elaborate aspects are measuring handgrip strength and walking speed, which can be performed within a few minutes if the right tools are available. However, the physical frailty phenotype is not static, but may fluctuate over time.³³ Therefore, it should be used with care and conclusions on poor risk should not be made on a single frailty measurement. It may be useful to perform repeated measurements as kidney function declines. While very specific to physical frailty, the sensitivity of FFI to other geriatric impairments that may be relevant to decision making, such as the psychosocial and cognitive domains is poor.³⁴ Thus, in the context of optimizing personalized care, the FFI provides very limited additional information on the overall health status. Consequently, the role of FFI in the process of decision-making appears limited to screening patients with poor prognosis.

Several clinical scores have been developed to predict short-term mortality, with a moderate to good predictive value.^{25,35-37} Some of these models included geriatric impairment, such as immobility and dementia,^{25,35} and assistance with daily living³⁶ but these impairments were collected registry data and International Statistical Classification of Diseases and Related Health Problems codes. Geriatric impairments usually falls outside traditional disease-oriented care, and as a result are frequently overlooked and not well documented.^{26,28,38} For example, in a cohort of hemodialysis patients, a cognitive test battery revealed severe cognitive impairment in 31% of patients and moderate impairment in 36%, while in less than 3% the diagnosis cognitive impairment was actually documented in the medical chart.³⁸ In our study, we found that prospectively assessed impairment in ADL, depressive symptoms and malnutrition at the start of dialysis were associated with 1-year mortality. This is in line with the outcome of previous studies assessing the association between specific geriatric impairments and poor outcome in this population.⁴ Interestingly, impairments in these domains can potentially improve with applying interventions.^{30,39} In our study cognitive impairment was not related to mortality after correction for confounders. This may be explained by the low number patients and by the fact that we have included mild cognitive impairment instead of (severe) dementia. As our study shows there is a strong

relation between geriatric impairments and poor outcome, we advocate expanding the prospective assessment of geriatric impairments in a larger population and assessing the predictive value of geriatric impairment. These factors may be adopted into a more accurate prediction model.

This is the first longitudinal study that focuses on the prognostic value of the cumulative deficits model by means of a GA in incident older dialysis patients. However, some limitations exist. The number of patients was not sufficient to apply a standard multivariate analysis on 6-month mortality, and for 12-month mortality, the model could be adjusted for only a few variables leaving a potential risk of residual confounding. This was due to the fact that overall mortality was lower than expected based on mortality rates reported in other cohorts.^{35,37} Furthermore, this is a selected cohort, in which the decision to start dialysis has already been made. Thus, the results cannot directly be extrapolated to the predialysis phase. In addition, as we included mainly Caucasian patients with a relatively low rate of diabetes, our findings may not be fully generalizable to all elderly incident dialysis patients. Although it is likely that the GA is related to mortality at the moment of decision-making as well, data are currently lacking. In addition, the cut-off values of the GA for the definition frailty are arbitrary, although patients with ≥ 2 or ≥ 3 geriatric impairments are generally considered impaired.²³

Conclusion

This prospective analysis of the GOLD study shows that frailty at the time of dialysis initiation demonstrates a good prognostic value for poor outcome in the elderly, both the cumulative deficits model of frailty, measured with a GA, and the physical frailty model, measured with the Fried Frailty Index, are related to mortality. A GA is capable to distinguish between frail and fit patients initiating dialysis, but can also identify potential targets for intervention. Consequently, a GA may be of added value in decision-making in ESKD. Whether the findings of our study can be extrapolated to the pre-dialysis population and whether the actions derived from a GA may improve outcome

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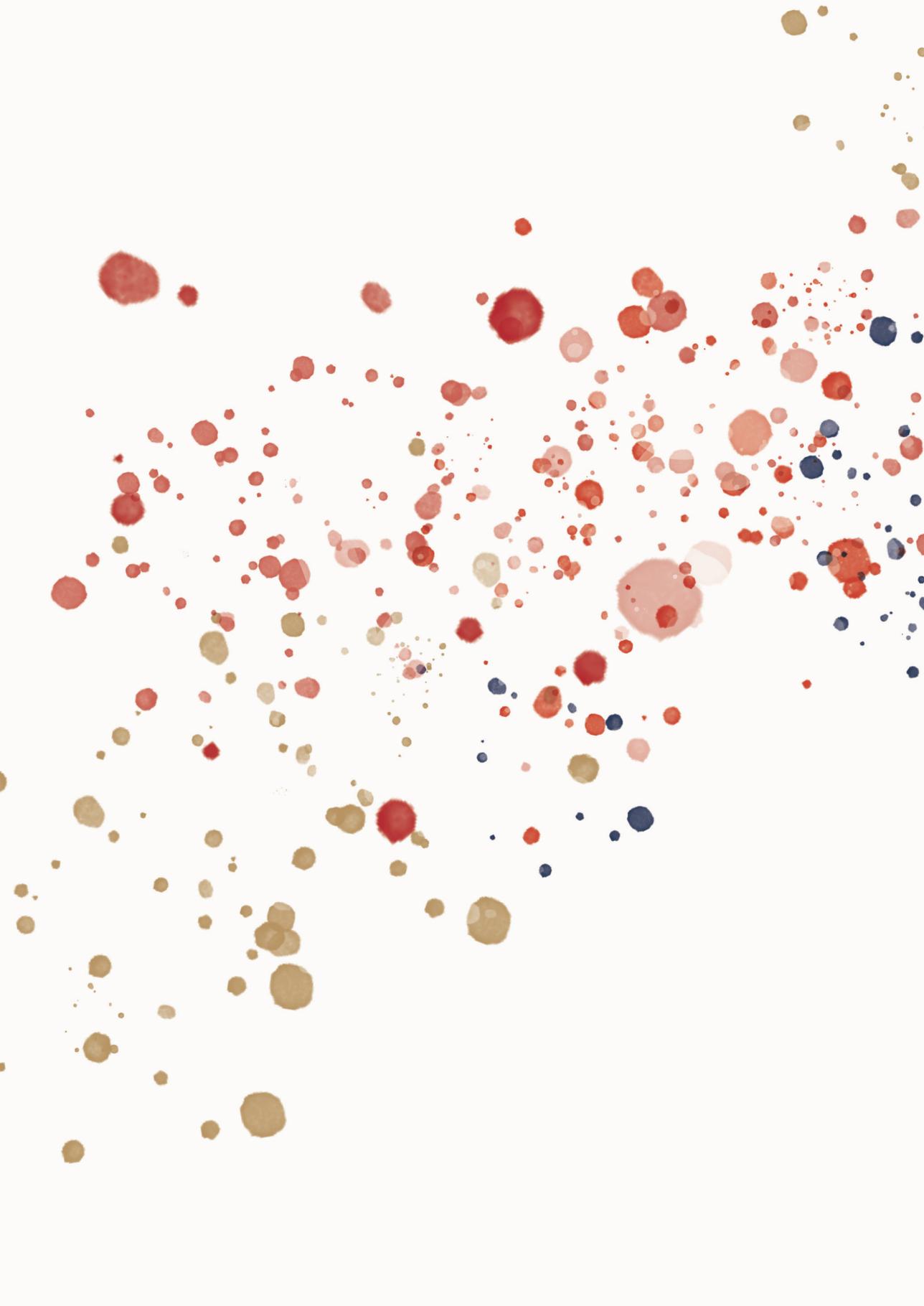
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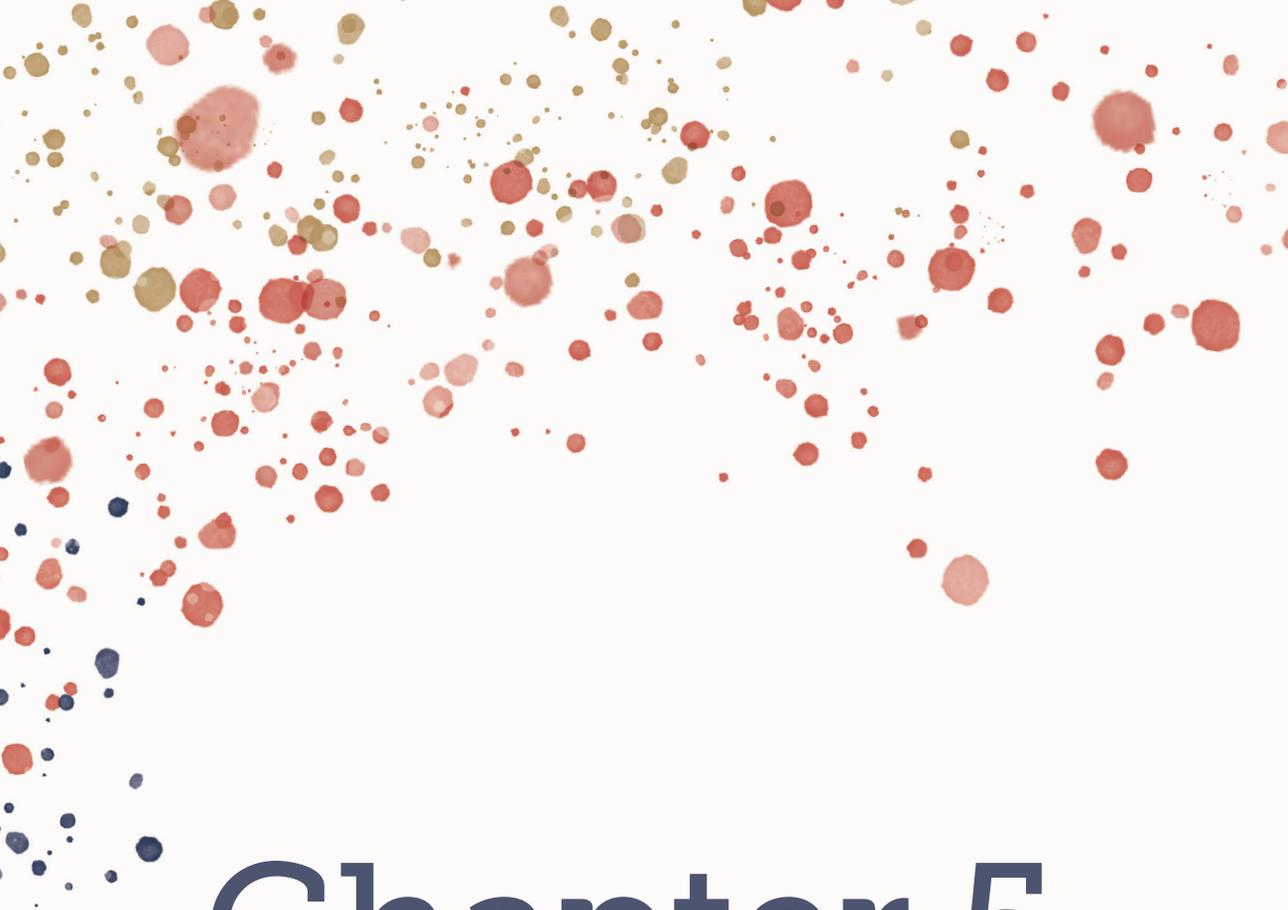


Part 2



Falls & Fractures





Chapter 5

The association between chronic kidney disease, falls and fractures: a systematic review

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Under revision

Abstract

Purpose: Patients with chronic kidney disease (CKD) are more likely to experience falls and fractures due to renal osteodystrophy and the high prevalence of risk factors for falls. However, it is not well established how great the risk is for falls and fractures for the different stages of CKD compared to the general population. The objective of this systematic review was to assess whether, and in which degree, CKD was associated with falls and fractures in adults.

Methods: A systematic search in PubMed, Embase, CINAHL and The Cochrane Library was performed on the 7th of September, 2018. All retrospective, cross-sectional and longitudinal studies of adults (18 years of older), that studied the association between CKD, fractures and falls were included. Additional studies were identified by cross-referencing.

Results: A total of 39 publications were included, of which two publications assessed three types of outcome and four publications assessed two types of outcome. Ten studies focused on accidental falling, seventeen studies focused on hip, femur and pelvis fractures, seven studies on vertebral fractures and thirteen studies focused on any type of fracture without further specification. Generally, the risk of fractures increased when kidney function worsened, with the highest risks in the patients with stage 5 CKD or dialysis. This effect was most pronounced for hip fractures and any type of fractures. Furthermore, results on the association between CKD and accidental falling were contradictory.

Conclusions: Compared to the general population, falls and fractures are highly prevalent in patients with CKD. Besides more awareness of timely fracture risk assessment, there also should be more focus on fall prevention.

Introduction

Worldwide, chronic kidney disease (CKD) is highly prevalent, with an estimated prevalence of 7% in stages 3 to 5 and with even higher rates in the elderly population.¹ Patients with CKD are prone to fractures due to renal osteodystrophy. This is a complex disease which is caused by a disturbance in metabolic and hormone levels (e.g. altered levels of calcium, phosphorus, parathyroid hormone and vitamin D) that impairs bone quality and is characterized by abnormal bone remodeling.^{2,3} These bone abnormalities are seen in a majority of patients with CKD stage 3-5 and in all patients requiring dialysis.⁴ Therefore, it is likely that patients with mild to moderate CKD already have a higher risk of fractures and that risk of fracture increases when kidney function decreases. Fractures in patients with CKD are a serious complication and are associated with a high morbidity, mortality⁵ and economic burden.^{6,7}

An important risk factor for fractures are falls.⁸ Falls are a result of a complex interaction of factors such as muscle weakness, neuropathy, polypharmacy, chronic illnesses, cognitive decline, impaired mobility and frailty,⁹ of which are all highly prevalent in patients with CKD.¹⁰ Therefore, it is likely that patients with CKD are also more prone to falls than patients without CKD. In addition to a high morbidity, mortality and economic burden, falls can also lead to fear of falling, which can cause a decrease in physical activity and social isolation¹¹ and could thereby even further increase the risk of falling. Hence, although both falls and fractures seem to be important problems for patients with CKD, it is not well established how great the risk is for falls and fractures for the different stages of CKD compared to the general population.

More knowledge about the risk of falls and fractures could lead to better risk stratification, which could lead to better prevention strategies. Therefore, the objective of this systematic review is to assess whether, and in what degree, chronic kidney disease is associated with falls and fractures in adults.

Methods

Search strategy and selection criteria

We aimed to identify cross-sectional or cohort studies that investigated the association between chronic kidney disease, falls and fractures, through a comprehensive search (from conception to September 7th, 2018) of PubMed, Embase, CINAHL and The Cochrane Library. We used the search terms *chronic kidney disease (dialysis patients included)*, *fracture* and *falling*, with relevant synonyms. The complete search strategy is shown in Appendix 1. No limits were applied in the search.

Two authors (NG, GW) independently screened title and abstract, removed duplicate publications, and selected studies that assessed the association of CKD and fractures or falling. Studies were also included if relative risk could be calculated from prevalence/incidence from a CKD-population compared to a non-CKD population. Animal studies, studies in children, studies in very specific populations (e.g. only patients with systemic lupus erythematosus, aluminum related bone disease), therapeutic studies, case reports, systematic reviews, conference abstracts, opinion papers, and studies not published in English were excluded. The publication retrieval was completed by cross-reference checking in Web of Science for selected articles; citations of retrieved reviews, meta-analysis, and guidelines were also screened for potentially omitted studies. A similar selection procedure as described above was followed to check for eligibility of articles that were thereby retrieved. Initial disagreements on eligibility and selection of articles were resolved by discussion and their inclusion is based on full consensus.

Data extraction

Data regarding study design and results were independently extracted by two investigators (NG and FO) for each eligible study. Items that were extracted are study design, patient selection, number of participants (dialysis, CKD), demographics (age, sex), method for estimated glomerular filtration rate (eGFR) calculation, as well as the outcomes in terms of association between CKD falling and fractures. If a study provided various measurements of eGFR, first choice was to extract data of the CKD-EPI based on serum creatinine. When this was not available, second choice was the MDRD based on serum creatinine, followed by the Cockcroft Gault (CG) (based on serum creatinine) and other measurements. Measurements of eGFR based on urinary creatinine were not included, as these made our studies less comparable. Furthermore, baseline characteristics were extracted for the whole population.

Quality assessment

The methodological quality of each of the studies was assessed independently by two reviewers (NG and FO), using the Newcastle-Ottawa quality assessment scale. This scale was adapted to create one scale for quality assessment of longitudinal studies, case-control studies and cross-sectional studies (Appendix 2). Disagreements among the reviewers were discussed during a consensus meeting and in case of persisting disagreement, the assistance of a third reviewer (MH) was enlisted.

Data synthesis and analysis

If baseline characteristics were not available for the whole population, these were calculated when possible. To increase comparability, risk ratios, rate ratios or odds ratios were calculated whenever possible by dividing the incidence/prevalence of the CKD group by the incidence/prevalence of patients. When multiple incidences were provided in the course of the study, the most recent incidence was used to calculate a relative risk. Furthermore, to keep the studies as comparable as possible, when data was stratified by age, only data of all age categories of ≥ 65 years were included (n=2).^{12,13} To visualize the risks of falls and the various fracture types, the calculated and given risk ratios, odds ratios or rate ratios were visualized in a graph. Due to the heterogeneity in the study populations, a formal meta-analysis was not considered feasible.

Results

Characteristics of included studies

Our search identified 12,149 potential publications (6,023 from Embase, 5,490 from Pubmed, 348 from CINAHL and 288 from Cochrane). After removing 1,890 duplicates and 10,220 studies for other reasons (Figure 1), a total of 37 unique publications were included in this review. Cross reference checking yielded two additional publications.

The characteristics of the 39 included studies are summarized in Table 1. The first publication is from 2000 and the most recent from 2018. Most studies were conducted in the United States. The size of the study populations ranged from 173 to 4,099,342 (median 5,601). Most studies included elderly patients, with a median age over 65 years in most studies. Eight studies included only dialysis patients,¹³⁻²⁰ all other studies included various stages of CKD. Ten studies focused on accidental falling,^{19,21-29} seventeen studies focused on hip, femur and pelvis fractures,^{12-14,17,18,20,24,30-39} seven studies on vertebral fractures^{12,15,22,24,40-42} and thirteen studies focused on any type of fracture without further specification.^{12,16,22,29,43-51}

Quality assessment

Results of quality assessment can be found in Figure 2 and Table 1. Reviewer agreement was over 95% for all aspects. The overall quality of included articles was good with a mean score of 6.0 out of 9 (standard deviation (SD) 1.3). Many studies did not specify if they included or excluded patients with a previous fall or fracture,^{13-18,22,26,28,29,34-37,41,42,46,47,49-51} and so risk of bias was often unclear regarding the definition of controls. This was also a concern with the non-response rate and rate of lost to follow-up: almost half of the studies did not report data on this. Full details of the quality assessment can be found in Appendix 3.

Accidental falling

Results for accidental falling are shown in Table 2 (studies that used $\geq 60/65$ as reference category), Figure 3a and Appendix 4 (studies that used different reference categories). Ten studies assessed the association between CKD and accidental falling.^{19,21-29} Of these, five studies used an eGFR ≥ 60 as a reference category,^{19,21,25,28} two studies an eGFR ≥ 65 ,^{23,24} one study an eGFR >90 ,²⁷ one study the highest quartile (eGFR ≥ 74),²² and one study compared used self-reported medical history of CKD.²⁶ Half of the included studies did not find an association between CKD and accidental falling,^{21,22,25,27,28} irrespective of CKD stage, reference category and/or adjustment for potential confounders. The two studies that used an eGFR of ≥ 65 as reference both showed a significant association between a lower eGFR and falls with adjusted odds

ratios ranging from 1.69 to 4.01.^{23,24} An increasing risk of accidental falling was seen with decreasing kidney function in the two studies where risk ratios were calculated from prevalence/incidence (stage 3a RR 1.55, stage 3b RR 2.00, stage 4 RR 2.39, stage 5 RR 3.45²⁹ and hemodialysis RR 4.7¹⁹, Figure 3a). In addition, one study addressed the association between self-reported medical history of CKD and falls and found a significant association (OR_{adj} 1.26, 95% CI 1.13-1.47).²⁶

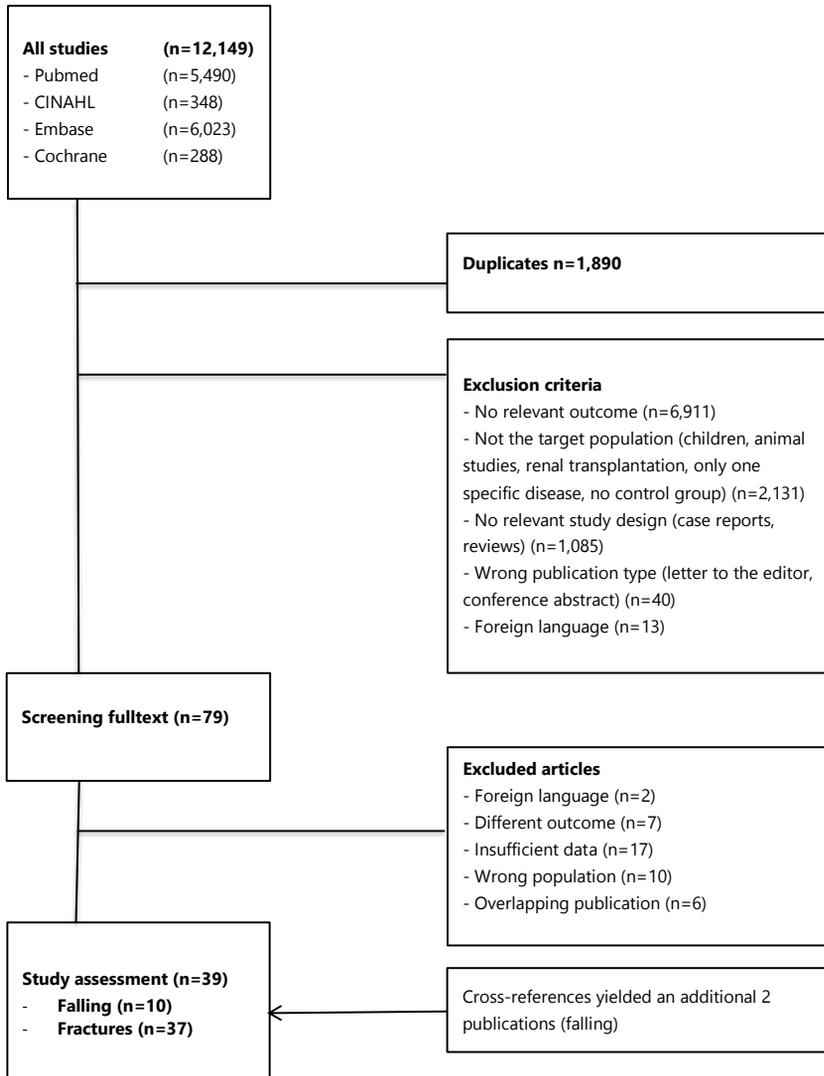


Figure 1. Flow diagram of study selection

Table 1. Characteristics of the included studies

Study	Study design	Patient selection
Alem, 2000 ¹⁴	RCS	United states renal data system (USRDS)
Arneson, 2013 ¹³	RCS	Medicare, USA
Atteritano, 2017 ¹⁵	CS	Population based cohort, USA
Bowling, 2016 ²¹	PCS	Populations based cohort, USA (REGARDS)
Chen, 2018 ²²	PCS	Population based cohort, The Netherlands (LASA)
Coco, 2000 ¹⁸	RCS	Outpatient dialysis unit (monocenter)
Daya, 2016 ⁴³	PCS	Population based (ARIC), USA
Dooley, 2008 ³⁰	RCS	Multicenter Veteran clinic, USA
Dukas, 2005 ²³	PCS	Multicenter study, Germany
Dukas, 2005 ²⁴	CS	Post hoc subanalysis of RCT
Elliott, 2013 ¹²	PCS	Population based cohort, Canada
Ensrud, 2007 ⁴⁰	CC	Population based cohort, USA (SOF)
Ensrud, 2012 ⁴⁴	CC	Multicenter cohort study, USA (WHI-OS)
Ensrud, 2014 ³²	CC	Population based cohort, USA (MrOS)
Fried, 2007 ³³	PCS	Population based cohort, USA
Hall, 2015 ²⁵	RCS	Multiple nursing homes, USA (RCT CONNECT for quality)
Hall, 2018 ⁴⁵	PCS	Multicenter Veteran clinic, USA
Hansen, 2016 ¹⁶	RCS	Danish population + all patients receiving dialysis in Denmark
Iwagami, 2018 ³⁴	RCS	Population based cohort, England
Kaji, 2010 ⁴¹	CS	Outpatient clinic for metabolic bone disorders, Japan
Kim, 2016 ³⁵	RCS	Multicenter cohort, USA (NIS)
Kinsella, 2010 ⁴⁶	CS	Monocenter study, Ireland
Kistler, 2018 ²⁶	CS	Behavioral risk factor surveillance system (BRFSS), USA
Kurajoh, 2018 ⁴⁷	CS	Multicenter study, Japan
LaCroix, 2008 ³⁹	CC	Multicenter cohort study, USA (WHI-OS)
Liao, 2016 ⁴⁸	RCS	Population based cohort, Taiwan (LHID2005)
Maravic, 2014 ¹⁷	RCS	French national database
McCarthy, 2008 ⁵¹	PCS	Multicenter cohort + population based cohort, USA
Mishima, 2015 ⁴²	CS	Tertiary center, Japan

Number of participants	Number of patients with eGFR <60/ dialysis**	Age (me(dia)n (±range)	% male	Overall score quality assessment (././9)	Outcome			
					Accidental falls	Hip/femur +pelvis fractures	Vertebral fracture	Any type of fracture
?	326,464**	NR	56%	4		X		
1,267,416*	101,995**	≥65	46%*	7		X		
192	92**	65,9*	78%*	8			X	
8,744	1,604	≥65	51%	7	X			
1,477	560*	75.8 ±6.6	48%	8	X		X	X
NR	1,272	58 ±0.4	49%	7		X		
10,955	693	63.3*	44%*	7				X
33,091	13,632	67.5 (?)	100%	8		X		
186	NR	75.0 ±4.1	48%*	6	X			
5,313	NR	74.0 (?)	20%	6	X	X	X	
1,815,943	128,957	≥65	44%	8		X	X	
396	186	≥65	0%	6		X	X	
2,190	NR	64.3*	0%	8				X
1,602	388	73.8*	100%	8		X		
5,888	1190*	74.8*	42%*	7		X		
510	179*	77.2 ±11.5	73%	7	X			
712,918	356,459	73.0*	100%	6				X
4,099,342	7,566**	46*	49%	6				X
484,698	242,349	75.4 ±9.7	39%	7		X		
659	85	64.5 ±8.2	0%	5			X	
278,018	38,932	NR	31%*	5		X		
1,702	347	61.7 ±10.8	0%	4				X
157,753	9,116	≥65	44%	6	X			
555	181	76.8*	0%	5				X
794	144	71 (?)	0%	9		X		
11,312	1,427	≥40	68%	6				X
68,953	29,487**	82.1*	24%*	4		X		
427	85	68 ±13.5	0%	7				X
173	68	62.3 ±12.2	57%	4			X	

Table 1. Continued

Study	Study design	Patient selection
Naylor, 2014 ²⁹	PCS	Population based cohort, Canada
Naylor, 2015 ⁵⁰	PCS	Population based cohort, Canada (CaMos)
Nickolas, 2006 ³⁶	CS	Population based cohort, USA (NHANES III)
Pérez-Sáez, 2015 ³⁷	RCS	Population based cohort, Spain (SIDIAPO)
Račić, 2015 ¹⁹	CS	Multiple HD centers, Bosnia and Herzegovina and Serbia + primary care center
Rafiq, 2014 ²⁷	RS	Multiple GP databases, UK (QICKD)
Robertson, 2018 ³⁸	PCS	Single health region Scotland
Rothenbacher, 2014 ²⁸	RCS	Population based cohort, Ulm + Germany (ActiFE)
Wakasugi, 2013 ²⁰	RCS	All dialysis facilities in Japan
Yenchek, 2012 ⁴⁹	PCS	Population based cohort, USA (Health, aging, and body composition study)

PCS, prospective cohort study; CS, cross-sectional study; RCS, retrospective study; CC, case-control study; NR, not reported.

*Calculated

Number of participants	Number of patients with eGFR <60/dialysis**	Age (me(d)ian (±range)	% male	Overall score quality assessment (.../9)	Outcome			
					Accidental falls	Hip/femur +pelvis fractures	Vertebral fracture	Any type of fracture
679,114	107,841	62.1*	45%*	7				X
2,107	320	67.2*	29%	4				X
6,270	875	64.9*	48%*	6		X		
873,073	32,934	67.6	47%	6		X		
406	106**	77.6*	61%	4	X			
135,433	NR	75.4 ±7.6	44%	6	X			X
39,630	19,882	63.3*	41%*	7		X		
1,385	196	75.6 ±6.5	57%	8	X			
NR	128,141	64.2*	62%	4		X		
2,754	587	73.6 ±2.9	49%*	7				X

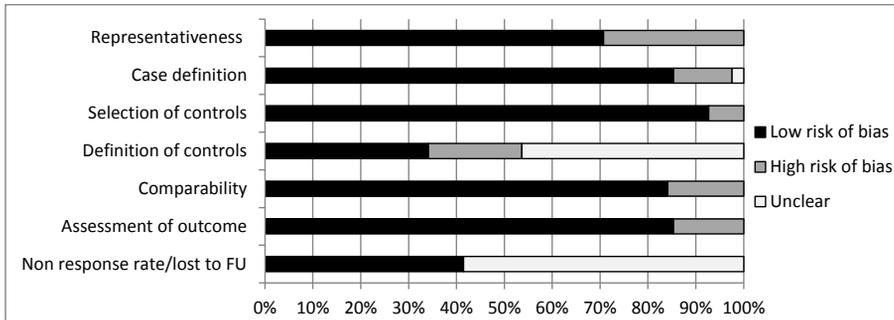


Figure 2. Quality assessment

Hip fractures

Results for hip fractures are shown in Table 3 (studies that used $\geq 60/65$ as reference category), Figure 3b and Appendix 4 (studies that used different reference categories). Seventeen studies reported on the association between CKD and hip fractures.^{12–14,17,18,20,24,30–39} Fifteen studies used an eGFR ≥ 60 as a reference category,^{12–14,17,18,20,30–38} one study an eGFR ≥ 65 ²⁴ and one study an eGFR >90 .³⁹ Eleven out of seventeen studies found a higher risk of hip fractures for the different stages of CKD.^{12–14,17,18,20,34–38} Three studies found an association for only the higher stages of CKD (eGFR <30 ³⁰, eGFR <45 ³¹ and <60 ³⁹) and hip fractures. Furthermore, three out of seventeen studies did not find an association between CKD and hip fractures,^{12,32,33} although one study did show an increasing relative risk when kidney function decreases, no association was seen between CKD and hip fracture when adjusted for potential confounders.¹² Generally, risks were increased when kidney function decreased,^{12,31,38} with the highest fracture risks in stage 5/dialysis (Figure 3b).^{13,14,17,18,20,35}

Vertebral fractures

Results for vertebral fractures are shown in Table 3 (studies that used $\geq 60/65$ as reference category), Figure 3c and Appendix 4 (studies that used different reference categories). Seven studies reported on vertebral fractures and CKD.^{12,15,22,24,40–42} Four out of seven studies found a higher risk of patients with CKD of developing vertebral fractures, compared to the non-CKD population.^{15,24,41,42} Furthermore, two other studies found a higher risk of vertebral fractures for patients with CKD, but when adjusted for potential confounders this risk was fully attenuated.^{12,31} This effect was not seen in the remaining study that did not find an association at all.²²

Any type of fracture

Results for any type of fracture are shown in Table 3 (studies that used $\geq 60/65$ as reference category), Figure 3d and Appendix 4 (studies that used different reference categories). Thirteen studies reported on incident fractures of any type and CKD.^{12,16,22,29,43-51} Eight studies used an eGFR ≥ 60 as reference category,^{12,16,22,29,43,45,49,50} two studies a reference category of ≥ 90 ,^{44,51} one study a reference category of 75-89,⁴⁶ one study did not specify their reference category⁴⁸ and one study assessed the association between fractures in a continuous way.⁴⁷ Eight out of thirteen studies found a higher risk of fractures when eGFR decreased $< 60 \text{ ml/min/1.73 m}^2$.^{16,22,29,44-46,49,50} Two studies found an increasing relative risk, but when adjusted for potential confounders this was fully attenuated.^{12,43} The three remaining studies that did not find an association studied very mild CKD (eGFR 60-90),⁵¹ assessed eGFR in a continuous way⁴⁷ or did not specify their reference group⁴⁸. In all included studies where multiple CKD-stages were included, the risk of fractures increased when eGFR worsens (Figure 3d).^{12,22,29,44-46}

Table 2. Study results for the association between accidental falling and chronic kidney disease (reference category $\geq 60/65\text{ml}/\text{min}/1.73\text{m}^2$)

Accidental falls		Degree of kidney impairment		
Study	eGFR method	<15	15-29	30-44
		Bowling, 2016 ²¹	CKD-EPI (creatinine)	
Dukas, 2005 ²³	CG (creatinine)			
Dukas, 2005 ²⁴	CG (creatinine)			
Hall, 2015 ²⁵	MDRD (creatinine)			
Naylor, 2014 ²⁹	CKD-EPI (creatinine)	♀ Risk Ratio 3.45*	♀ Risk Ratio 2.39*	♀ Risk Ratio 2.00*
Račić, 2015 ¹⁹	Hemodialysis	Risk Ratio 4.70*		
Rothenbacher, 2014 ²⁸	CKD-EPI (cystatin C)			

CG, Cockcroft Gault formula; CKD-EPI, Chronic kidney disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; HR, Hazard Ratio; OR, Odds Ratio.

Degree of kidney impairment			Adjusted (+/-)
<45	45-59	<60	
HR 1.09 (0.86-1.37)‡	HR 0.91 (0.76-1.09)		+
		OR 4.01 (1.48-10.89)†	+
		OR 1.69 (1.50-1.91)†	+
Rate Ratio 1.06 (0.85-1.32)	Rate Ratio 0.97 (0.76-1.23)		+
	♀Risk Ratio 1.55*		+
			-
		HR 1.03 (0.71-1.49)	+

*Calculated, †eGFR <65ml/min/1.73m³, ‡ dialysis excluded

Table 3. Study results for the association between fractures and chronic kidney disease (reference category $\geq 60/65\text{ml}/\text{min}/1.73\text{m}^2$)

Hip/femur fractures		Degree of kidney impairment	
Study	eGFR method	<15	15-29
		Alem, 2000 ¹⁴	Dialysis
Arneson, 2013 ¹³	Hemodialysis	Rate Ratio 4.0*	
Coco, 2000 ¹⁸	Dialysis	Rate Ratio 17.4 (12.4-34.0)	
Dooley, 2008 ³⁰	MDRD (creatinine)	♂HR 3.65 (1.87-7.13)‡	
Dukas, 2005 ²⁴	CG (creatinine)		
Elliott, 2013 ¹²	CKD-EPI (creatinine)	Rate Ratio 3.46 (3.13-3.83)*	
Ensrud, 2007 ⁴⁰	CG (creatinine)		
Ensrud, 2014 ³²	CKD-EPI (creatinine)		
Fried, 2007 ³³	MDRD (creatinine)		
Iwagami, 2018 ³⁴	CKD-EPI (creatinine)		
Kim, 2016 ³⁵	ICD	Rate Ratio 3.30*	
Maravic, 2014 ¹⁷	Dialysis	Rate Ratio 4.1*	
Nickolas, 2006 ³⁶	MDRD (creatinine)		
Pérez-Sáez, 2015 ³⁷	ICD		
Robertson, 2018 ³⁸	MDRD (creatinine)	Rate Ratio 1.74 (1.30-2.33)	
Wakasugi, 2013 ²⁰	Dialysis	♂ Rate Ratio 6.2 (5.7-6.8) ♀ Rate Ratio 4.9 (4.6-5.3)	

30-44	Degree of kidney impairment			Adjusted (+/-)
	<45	45-59	<60	
				+
				-
				-
				+
			OR 1.57 (1.18-2.09)†	+
Rate Ratio 2.53 (2.38-2.69)*		Rate Ratio 1.62 (1.54-1.71)*		-
	♀HR 2.32 (1.15-4.68)	♀HR 1.57 (0.89-2.76)		+
			♂HR 0.92 (0.58-1.47)	+
			♂ HR 0.97 (0.58-1.62) ♀ HR 1.38 (0.99-1.94)	+
HR 1.29 (1.24-1.36)‡		HR 1.04 (1.00-1.08) ‡	HR 1.11 (1.07-1.15)‡	+
			Rate Ratio 1.53*‡	-
				-
			OR 2.32 (1.13-4.74)‡	+
			HR 1.16 (1.06-1.27)	+
Rate Ratio 1.70 (1.38-2.09)		Rate Ratio 1.40 (1.16-1.70)	Rate Ratio 1.49 (1.24-1.79)	+
				+

Table 3. Continued

Vertebral fractures		Degree of kidney impairment	
Study	eGFR method	<15	15-29
Atteritano, 2017 ¹⁵	Hemodialysis	OR 6.33 (2.92-13.73)*	
Chen, 2018 ²²	MDRD (creatinine)		
Dukas, 2005 ²⁴	CG (creatinine)		
Elliott, 2013 ¹²	CKD-EPI (creatinine)	Rate Ratio 1.61 (1.37-1.89)*	
Ensrud, 2007 ⁴⁰	MDRD (creatinine)		
Kaji, 2010 ⁴¹	MDRD (creatinine)		
Mishima, 2015 ⁴²	Formula proposed by the Japanese Society of Nephrology		
Any type of fracture			
Chen, 2018 ²²	MDRD + CKD-EPI (creatinine)		
Elliott, 2013 ¹²	CKD-EPI (creatinine)	Rate Ratio 2.16 (2.00-2.34)*	
Hall, 2018 ⁴⁵	MDRD	♂ HR 1.91 (1.45-2.50)	♂HR 1.32 (1.16-1.49)
Hansen, 2016 ¹⁶	Dialysis	HR 1.85 (1.75-1.95)	
Naylor, 2014 ²⁹	CKD-EPI	♂ Rate Ratio 4.3 (3.70-5.00) ♀Rate Ratio 3.1 (2.80-3.50)	♂Rate Ratio 2.7 (2.20-3.30) ♀Rate Ratio 2.1 (1.90-2.30)
Naylor, 2015 ⁵⁰	CKD-EPI (creatinine)		
Yenchek, 2012 ⁴⁹	MDRD (creatinine)		

CG, Cockcroft Gault formula; CKD-EPI, Chronic kidney disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; HR, Hazard Rate; OR, Odds Ratio

Degree of kidney impairment			Adjusted (+/-)
30-44	<45	>45-59 <60	
			+
OR 0.63 (0.53-1.24)		OR 0.86 (0.56-1.32)	+
		OR 1.31 (1.10-1.55)†	+
Rate Ratio 1.67 (1.54-1.81)*		Rate Ratio 1.35 (1.27-1.44)*	-
	♀ OR 0.73 (0.24-2.24)	♀ OR 0.75 (0.45-1.23)	+
		♀ OR 2.32 (1.45-3.71)*	-
		OR 2.48 (1.20-5.12)* °	-
HR 1.46 (1.12-1.91)		HR 1.28 (1.12-1.46)	+
Rate Ratio 1.80 (1.72-1.88)*		Rate Ratio 1.38 (1.33-1.42)*	-
			+
			+
♂Rate Ratio 1.8 (1.60-2.00)		♂Rate Ratio 1.3 (1.20-1.40)	-
♀Rate Ratio 1.6 (1.50-1.70)		♀Rate Ratio 1.40 (1.30-1.50)	-
		Risk Ratio 1.86 (1.07-3.24)*	-
		Risk Ratio 1.26 (1.02-1.56)*	-

*Calculated, † eGFR <65ml/min/1.73m², ‡dialysis patients excluded, §Stage 5 CKD excluded

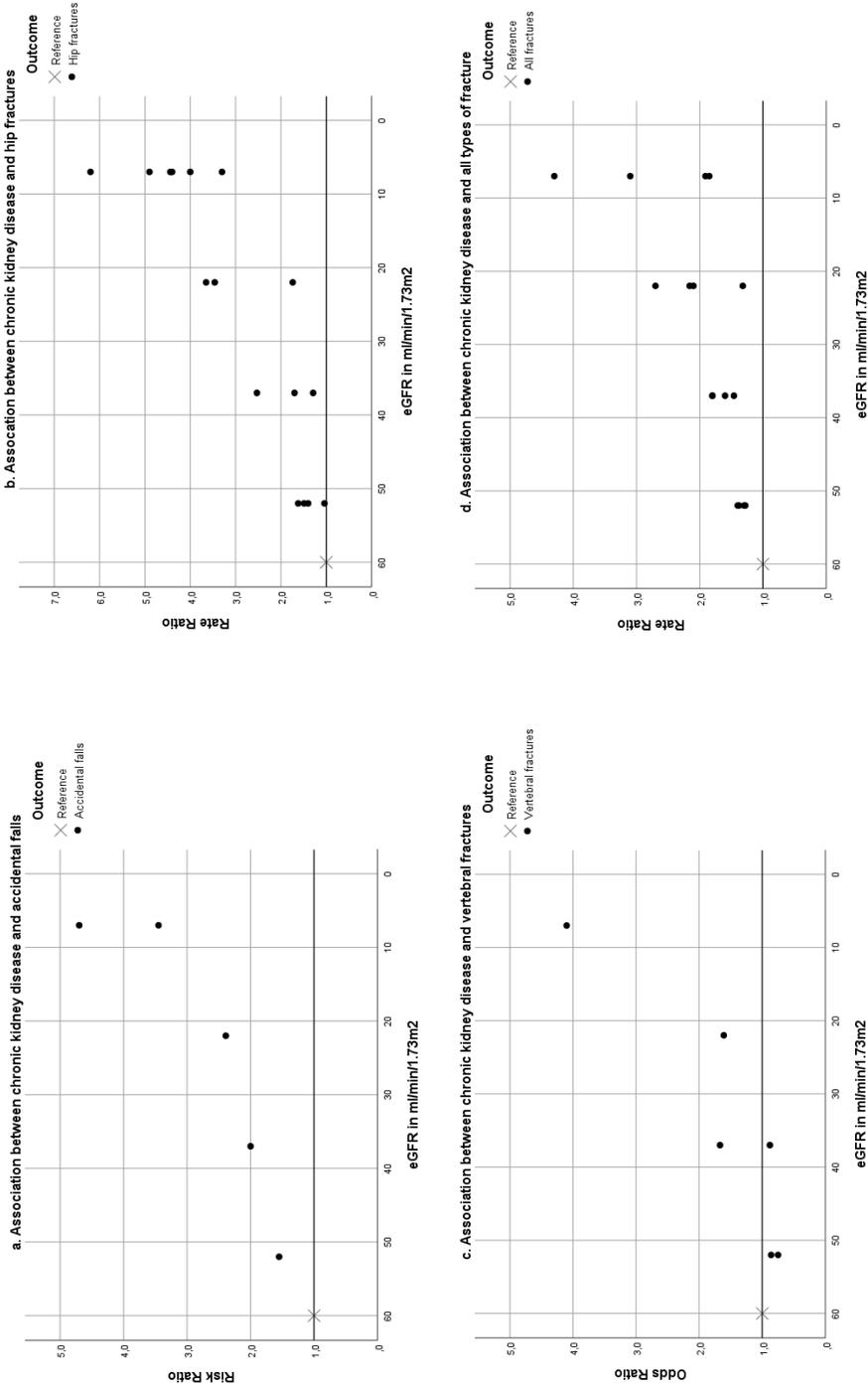


Figure 3 a,b,c and d. Association between chronic kidney disease, accidental falls (a), hip fractures (b), vertebral fractures (c) and all fractures (d)

Discussion

In this systematic review, we found that a lower eGFR is associated with a higher fracture risk. This effect was the most pronounced for the hip fractures and the any type of fracture group. Furthermore, the risk is higher when kidney function worsens, and starts approximately at an eGFR of <60 (Figure 3 a,b,c,d). For the association between a decreased eGFR and accidental falling the evidence is contradictory.

The findings that we report on fractures support our hypothesis that a decreasing eGFR is associated with a higher fracture risk. Moreover, almost all studies that assessed patients with stage 5 found that CKD is an independent risk factor for fractures. This is in line with previous studies that showed that even in early stages of CKD, and in almost all patients with stage 5 an abnormal bone histology was found.⁵² Although there were only a limited number of studies that assessed vertebral fractures, it is interesting that this risk seems to be lower compared to the hip and any type of fracture group. One possible explanation for these lower relative risks could be that half of the studies used ICD-codes or medical history to diagnose vertebral fractures.^{12,24,40} Prior research showed that approximately two-thirds of vertebral fractures remain unnoticed as they are frequently asymptomatic.⁵³ Thus, it is likely that fractures are missed in studies that used ICD-codes and/or medical history to diagnose vertebral fractures, and therefore a potential difference between vertebral fractures in patients with CKD and patients without CKD.

In general there was a graded risk for falls when kidney function worsens (Figure 3a). However, half of our studies did not find an association between CKD and accidental falling. One possible reason that some studies did not find an association between falls and CKD is that they adjusted their results for multiple confounders. There are several reasons why patients with CKD could fall more often compared to patients without CKD. First, CKD is frequently caused by hypertension and diabetes, which are both associated with falls.^{54,55} Second, CKD and treatment for optimization of CKD can lead to risk factors of falling. For example, due to inflammation and malnutrition, patients with CKD are more prone for muscle degeneration,⁵⁶ which could lead to instability and falls. Furthermore, medication (e.g. ACE-inhibitors) that are frequently administered to patients with CKD could lead to postural hypotension, which is also a risk factor for falls. Third, CKD is more common in the elderly population, which is also an important risk factor.⁹ Subsequently, this could mean that patients with CKD fall more often because of their risk profile, and not primarily because they have CKD.

Risks could also have been influenced by the type of measurement of eGFR. To keep our study results as comparable as possible, we chose to use the most frequently used measurements to estimate GFR (CKD-EPI, MDRD and CG based on serum creatinine). However, serum creatinine is dependent on muscle mass, which could lead to a false-negatively low serum creatinine due to low muscle mass and therefore relatively 'good' eGFR in the frail elderly.⁴³ This could potentially have led to a higher fracture rate in the better eGFR ranges. Another method to estimate eGFR in this population could be the use of Cystatin C which is independent of muscle mass. For example, two studies did not find an association for eGFR based on creatinine, but did find an association between eGFR based on Cystatin C and any type of fracture.^{43,47} On the other hand, another study that compared both methods did not find any difference for the association between CKD and hip fractures.³² More research is needed to explore the differences in outcome when using Cystatin C compared with serum creatinine.

As patients with CKD have much higher rates of falls and fractures compared to the non-CKD population, it is very important to screen these patients timely for potential risk factors. Prior research has shown that most patients who experienced a fall did not mention this to their healthcare provider,⁵⁷ therefore it is necessary for nephrologists and general practitioners to actively ask about previous falls in patients with CKD. For fractures, the updated Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends "BMD testing to assess fracture risk in patients with CKD stage 3a to 5 with evidence of CKD-BMD and/or risk factors for osteoporosis, if results will impact treatment decisions".⁵⁸ This could mean that in clinical practice, much more frequent BMD measurements should be done in patients with CKD, especially in the elderly with previous falls. Furthermore, as treatment of renal osteodystrophy is very complicated in the advanced stages of CKD, due to the heterogeneity of the illness and the limited experience with different treatments, it is also very important to prevent and lower the risks of falling as much as possible. At this moment, there is no clear recommendation from the KDIGO-guidelines to screen for accidental falling or to start interventions in patients with high risk of fracture (or falls). This could be important as it can potentially prevent morbidity and even mortality, as various studies showed that multiple interventions are able to lower the risk of falling in patients with CKD.⁵⁹⁻⁶¹

This systematic review provides valuable information about the fracture and fall risk of patients with CKD, but it has several limitations. Included studies were heterogeneous, assessing different CKD-stages, different eGFR methods, and different definitions for falls and fractures. Therefore, a meta-analysis could not be performed. Second, most studies were performed in elderly patients. Although we also presented

some evidence for the younger patients, this evidence was scarce and our findings can possibly not be fully extrapolated to the younger CKD population. However, considering falls and fractures, elderly are most at risk and therefore identification in this population could lead to the highest benefit. Third, considering non-English manuscripts were excluded this could potentially have led to publication bias.

In conclusion, falls and fractures are both very common in the CKD-population and the risk increases when kidney function worsens. Besides more awareness of timely fracture risk assessment, there also should be more focus on fall prevention.

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Supplementary data

Appendix 1. Search strategy

Search performed on the 7th of September 2018.

Pubmed

("Renal Insufficiency, Chronic"[Mesh] OR Chronic kidney disease OR Chronic renal disease OR Chronic renal insufficiency OR Chronic kidney insufficiency OR End stage renal disease OR End stage kidney disease OR ESRD OR ESKD OR "Renal Dialysis"[Mesh] OR Dialysis OR Renal replacement therapy OR Kidney replacement therapy OR Hemodialysis OR "Renal Replacement Therapy"[Mesh] OR end-stage renal disease OR end-stage kidney disease)

AND

("Accidental Falls"[Mesh] OR Falls OR Falling OR fall OR fallen OR Bone fracture OR fracture OR fractures OR "Bone fracture"[Mesh] OR Vertebral fracture OR Vertebral fractures OR Spine compression fracture OR Spinal compression fracture OR Vertebral compression fracture OR Spinal fracture)

Appendix 2. Quality assessment tool

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

Selection (Maximum 4 stars)

- 1) Representativeness of the cases
 - a) All eligible cases with outcome of interest over a defined period of time, or an appropriate sample of those cases (e.g. random sample, only men/women, specific Medicare)*
 - b) any selection criteria were applied to the study population (e.g. only osteoporosis, veterans)
 - ? No data on selection process
- 2) Is the case definition adequate?
 - a) Validated measurement tool, calculation of eGFR is available or described*
 - b) ICD-codes, self-report
 - ? No description of measurement tool/self-report

3) Selection of Controls

- a) Same population/same study*
- b) Same population/different study
- ? no description

4) Definition of Controls

- a) Controls with previous occurrences of outcome of interest should not be excluded for falls. For fractures in the previous year these should be excluded*
- b) Exclusion of patients that fell before or inclusion of patients with a fracture in the previous 5 years
- ? no mention of history of outcome

Comparability (Maximum 2 stars)1) Comparability of cases and controls on the basis of the design or analysis

- a) study controls for age*
- b) study controls for any additional factor*

Exposure (maximum 3 stars)1) Assessment of outcome

- a) Fall calendar or at least every 3-6 months fall interview. For fractures radiologic confirmation**
- b) Every 6 months fall interview. For fractures ICD code/medical charts.*
- c) Only once a year interview/ self-report.
- ? no description

2) Non-Response rate

- a) same rate for both groups, response rate is satisfactory (>80%)/For cohort studies complete follow-up (<5%)*
- b) non respondents described/subjects lost to follow up unlikely to introduce bias (5-15%)*
- c) High loss to follow up (>15%)
- ? no description of non-responders/lost to FU

Appendix 3. Quality assessment accidental falling and fractures

	Selection		Comparability			Outcome	Total Max 9.		
	Representativeness	Case definition	Selection of controls	Definition of controls	Study controls for age	Study controls for additional factors		Assessment outcome	Non response rate/ lost to follow-up
Alem, 2000	*	*		?	*		*	?	4
Arneson, 2013	*	*	*	?	*	*	*	?	6
Atteritano, 2017	*	*	*	?	*	*	**	?	7
Bowling, 2016	*	*	*	*	*	*	*	?	7
Chen, 2018, falls &	*	*	*	?	*	*	**	*	8
Chen, 2018, fracture &	*	*	*	?	*	*	*	*	7
Coco, 2000	*	*		?	*	*	**	*	7
Daya, 2016	*	*	*	*	*	*	*	?	7
Dooley, 2008		*	*	*	*	*	*	?	6
Dukas, 2005		*	*	*	*	*	**	?	7
Dukas, 2005 falls &		*	*	?	*	*	*	?	4
Dukas 2005, fractures &		*	*	?	*	*	*	?	5
Elliott, 2013	*	*	*	*	*	*	*	?	7
Ensrud, 2007	*	*	*		*	*	**	*	8
Ensrud, 2012	*	*	*		*	*	*	?	6
Ensrud, 2014	*	*	*		*	*	*	*	7
Fried, 2007	*	*	*	*	*	*	*	?	7
Hall, 2015		*	*	*	*	*	*	*	7
Hall, 2018		*	*	*		*	*	*	6
Hansen, 2016	*	*	*		*	*	*	?	6
Iwagami, 2018	*	*	*	?	*	*	*	?	7
Kaji, 2010		*	*	?		*	**	?	5
Kim, 2016	*		*	?	*		*	*	5
Kinsella, 2010		*	*		*	*		?	4
Kistler, 2018	*		*	*		*		*	5
Kurajoh, 2018		*	*	?	*	*	*	?	5
Lacroix, 2008	*	*	*	*	*	*	**	*	9
Liao, 2016		?	*	*	*	*	*	*	6
Maravic, 2014	*		*	?			*	*	4
McCarthy, 2008	*	*	*	?	*	*	**	?	7

Appendix 3. Continued

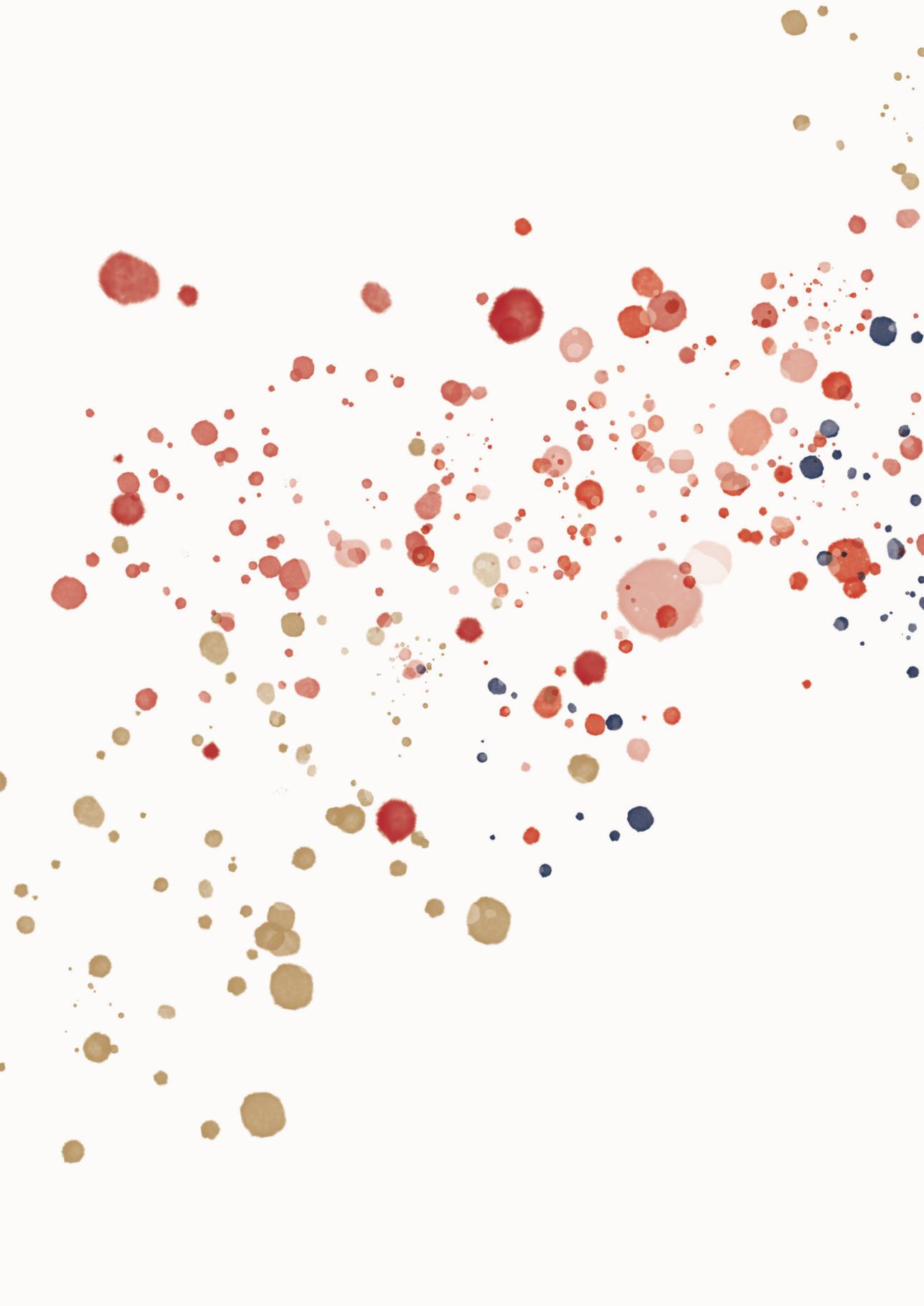
	Selection			Comparability		Outcome	Total		
	Representativeness	Case definition	Selection of controls	Definition of controls	Study controls for age	Study controls for additional factors	Assessment outcome	Non response rate/ lost to follow-up	Max 9.
Mishima, 2015		*	*	?			**	?	4
Naylor, 2014	*	*	*		*	*	*	*	7
Naylor, 2015	*	*	*				*	*	5
Nickolas, 2006	*	*	*	?	*	*		?	5
Pérez-Sáez, 2015	*		*	?	*	*	*	*	6
Račić, 2015	*	*	*	*				?	4
Rafiq, 2014	*		*	*	*	*	*	?	6
Robertson, 2018	*	*	*		*	*	*	?	6
Rothenbacher, 2014	*	*	*	?	*	*	**	*	8
Wakasugi, 2013	*	*		*	*	*		*	6
Yenchek, 2012		*	*	?	*	*	*	?	5

Appendix 4. Other cut-off points/reference groups

Study	eGFR method	Fall/type of fracture
Chen, 2018 ²²	MDRD + CKD-EPI (creatinine)	Falls
Kistler, 2018 ²⁶	Self-report ("ever had CKD?")	Falls
Rafiq, 2014 ²⁷	NHS codes	Falls
LaCroix, 2008 ³⁹	Cystatin C ⁻¹ *76.7.	Hip fracture
Daya, 2016 ⁴³		
Ensrud, 2012 ⁴⁴	CKD-EPI (cystatin C)	Any type of fracture
Kinsella, 2010 ⁴⁶	MDRD (creatinine)	Any type of fracture
Kurajoh, 2018 ⁴⁷	Japanese formula for eGFR _{cr}	Any type of fracture
Liao, 2016 ⁴⁸	?	Any type of fracture
McCarthy, 2008 ⁵¹	MDRD	Any type of fracture

CKD-EPI, Chronic kidney disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; CKD, chronic kidney disease; MDRD, NA, not applicable; HR, Hazard Ratio; OR, Odds Ratio

	Degree of kidney impairment					Reference group	Adjusted (+/-)
	<60	<70	<75	60-89	Unknown/other		
eGFR 9-57 HR 0.999 (0.995-1.002)						eGFR 74-254	+
					OR 1.26 (1.13-1.47)	No CKD in self report	+
OR 0.9 (0.9-0.9)				OR 1.1 (1.1-1.2)		≥90	-
♀OR 2.68 (1.41-5.08)				♀OR 1.10 (0.71-1.73)		≥90	+
HR 0.89 (0.56-1.41)						≥90	+
♀HR 2.46 (1.16-5.21)				♀HR 1.16 (0.85-1.58)		≥90	+
♀OR 1.37 (1.0-1.89)		♀OR 1.20 (0.93-1.55)				75-89	+
				Per 10 ml/ min/1.73m ² decrease: 0.96 (0.85-1.01)		NA	+
				1.10 (0.95-1.27)		No CKD	+
			♀HR 0.92 (0.84-1.01)			≥90	NR





Chapter 6

Accidental falling in community-dwelling elderly with chronic kidney disease

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Abstract

Purpose: The aim of the current study was to evaluate the association between a decreased eGFR and accidental falling in elderly patients who visited the day clinic of the department of geriatric medicine of the University of Medical Center Utrecht (UMCU).

Study design: A cross-sectional analysis with people aged ≥ 65 years of the Utrecht Cardiovascular Cohort was performed. Patients were stratified into different stages of kidney disease (<45 , $45-59$ and ≥ 60 ml/min per 1.73m^2). Logistic regression models were used to evaluate the association between chronic kidney disease and falling.

Results: Our analysis included 1,000 participants with a mean age 79.4 (± 6.6) years, of whom 38% had an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73m^2 and 17% <45 ml/min per 1.73m^2 . Univariate analysis showed a significant higher prevalence (odds ratio 1.75 (95% confidence interval 1.21-2.53; $P < 0.01$)) of falling in the population with an eGFR <45 ml/min per 1.73m^2 compared to patients with an eGFR ≥ 60 ml/min per 1.73m^2 . After correcting for multiple potential confounders in the multivariate analysis this association was no longer present.

Conclusions: In geriatric patients ≥ 65 years, patients with a decreased eGFR fall more often than patients with a preserved kidney function. This seems to be related with the risk profile of patients with CKD and not with a decreased eGFR itself, as after correcting for potential confounders no association remained. Nevertheless, accidental falling is a highly prevalent problem in the elderly CKD population. Therefore, nephrologists should actively ask about accidental falling, and thereby screen for high risk patients.

Introduction

Accidental falling is a common problem in the elderly population. Approximately one-third of people aged ≥ 65 years fall each year, increasing to around 40% for those ≥ 70 years of age.¹ These rates are even higher in institutionalized elderly.² A fall is defined by the World Health Organization (WHO) as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level.¹ Falls can result in serious injury, loss of independence, functional decline and death. Unintentional injuries are the fifth leading cause of death in older adults, and falls are responsible for two-thirds of these deaths.³ Among patients with chronic kidney disease (CKD) who experienced a serious fall incident, nearly one in five died within a year of the fall.⁴ Subsequently, falls place a substantial economic burden on society.⁵ The majority of falls have a multifactorial etiology. Important biological risk factors are age, gender, physical decline, cognitive impairment, depression, and co-morbidity. Important behavioral risk factors are the use of multiple medications, malnutrition and excess alcohol use.¹

In addition, CKD is a global public health issue and is associated with increasing age.^{6,7} Patients with CKD have a higher rate of cognitive impairment, depressive symptoms, exhaustion, impaired mobility, polypharmacy and frailty.⁸ Patients with CKD are also more vulnerable for fractures, due to renal osteodystrophy.⁹ The coexistence of factors such as polypharmacy, comorbidities, cognitive impairment and depression suggests that patients with different degrees of CKD are more likely to fall than the general population. However, it is not known if this potential effect on falling is the result of this high risk profile or also a direct result of a decreased estimated glomerular filtration rate (eGFR). Our hypothesis is that patients with a decreased eGFR fall more often as a result of the direct consequences of CKD on metabolic disturbances, such as anemia, low alfacalcidol levels, uremia and disturbances in electrolytes. It is important to understand whether the risk profile, the decreased eGFR or both are associated with falls, because it can help to better identify and treat high risk patients that need fall prevention and thereby prevent morbidity and mortality.

A few studies have focused on the association between falling and end-stage kidney disease (ESKD), mainly in the population with renal replacement therapy (RRT) (hemodialysis (HD), peritoneal dialysis (PD)).¹⁰⁻¹² Falls in elderly patients on RRT are highly prevalent, and associated with severe morbidity risks and high mortality.¹⁰⁻¹² However, a large part of the CKD-population will never progress to ESKD and therefore never need RRT. The few studies that assessed the association between falling and CKD found inconsistent findings.^{4,13-15} Two studies showed no association, but these studies focused on recurrent falling in nursing home residents only or on serious fall incidents.^{4,13} Other

studies that did show an association were post-hoc analysis of medication randomized controlled trials.^{14,15} No cross-sectional or prospective research is available on falling in community dwelling geriatric subjects with CKD.¹²

The aim of the current study was to evaluate the association between a decreased eGFR and accidental falling in elderly patients who visited the day clinic of the department of geriatric medicine of the University of Medical Center Utrecht (UMCU).

Materials and Methods

Study participants

A cross-sectional study was performed using the Utrecht cardiovascular cohort. This is a cohort study conducted at the UMCU. All patients that visited one of the geriatric outpatients clinics at the department of geriatric medicine in the UMCU (memory clinic, falls clinic and general geriatric day hospital) in the period from 1 January 2011 to 31 December 2014 were included. As part of usual care, all these patients underwent a comprehensive geriatric assessment consisting of a physical examination, cognitive and mobility tests and laboratory testing. In addition patients filled out a questionnaire concerning their general health and history of accidental falls. Data of these outpatients were collected in a database by the nurses and physicians working at the day clinic. The study protocol was approved by the Medical Ethics Committee of the UMCU.

For this analysis, patients were excluded if age was under 65 years, if no kidney function was available, when on RRT or if no questionnaire about accidental falls was available.

Data collection

The following data were extracted from the database: age, gender, living situation, medical history, intoxications, history of falls, number of medications, comorbidity, postural hypotension, body mass index, physical function, cognition, symptoms of depression, data of functional assessment (Katz-15 scale) and blood test results.

Falls were defined as a fall in the previous year. Frequent falls were defined as two or more falls in the past year. Comorbidity was scored by using the Charlson comorbidity index.¹⁶ This index is a widely used score to predict the risk of death from comorbid disease.

Cardiovascular disease was defined as a history of myocardial infarction, transient ischemic attack, stroke or peripheral artery disease. Postural hypotension was defined as a fall in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg when a person assumes a standing position after lying down for a period of at least 10 minutes. Blood pressure was measured after one and after three minutes after assuming standing position. Physical function was assessed by evaluating if the patient walked with the help of a walking aid. Functional assessment was assessed by the Katz-15 questionnaire.¹⁷ This is a combination of the Katz-6 ADL (assessing basic activities of daily living) and the IADL (9 items assessing everyday functional, or instrumental competence). A higher score indicates higher dependency in basic and instrumental daily living. Number of medications was dichotomized in polypharmacy or not using a cut-off point of ≥ 5 medications.

Cognition was based on the Mini Mental Examination (MMSE).¹⁸ This is a standardized and valid test with the purpose of screening for cognitive impairment. In this test orientation, attention, calculation, language, immediate and short-term recall, and visual construction are tested. The MMSE score ranges from 0 to 30 points. A higher score indicates better cognitive functioning. Impaired cognition was defined as an MMSE score <24 or a known diagnosis of Mild cognitive impairment (MCI) or dementia. When no MMSE was performed, because there was no indication, patients were considered to have a normal cognitive function.

Symptoms of depression were measured by the short version of the Geriatric depression Scale (GDS-15).¹⁹ If a patient had a score >5 patients were considered depressive.

Measures of kidney function

Measures of kidney function were calculated by the CKD epidemiology collaboration (CKD-EPI) equation (estimation of glomerular filtration rate based on creatinine, age and sex). For the equation Caucasian race was assumed. An impaired kidney function was defined as an eGFR <60ml/min per 1.73m². Kidney function was categorized into three groups according to the cut-off values recommended by the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative Guidelines (K/DOQI guidelines); ≥60, 45-59, and <45ml/min per 1.73m².²⁰ Because of the low number (n=38) of patients with an eGFR <30ml/min per 1.73m² no separate group was created for this kidney function.

Statistical analysis

Data were analyzed using SPSS software (IBM SPSS statistics version 21). Because the baseline data set showed some missing data (all variables <10% missing), we performed multiple imputation to replace missing data as implemented by SPSS, version 21. This procedure was repeated 10 times, resulting in ten different 'complete' datasets. The final results were averaged across these datasets and were used for logistic regression. Differences between group results were evaluated using the unpaired T-test for continuous parametric data, Kruskal-Wallis for non-parametric continuous data and Chi-square for categorized variables. For differences between continuous parametric data in the different kidney groups the One-Way Anova was used. Categorical variables were reported as proportions, continuous variables were reported as means with standard deviations or medians with interquartile range for non-parametric data.

To investigate the association between falling and the different stages of a decreased eGFR logistic regression analysis was performed. Potential risk factors were chosen a priori.²¹ Different models with potential confounders were used to calculate the adjusted odds ratio (OR). Model 1 is unadjusted. Model 2 adjusts for age and gender. Model 3

adjusts for model 1 and Katz-15, the use of a walking aid and polypharmacy, model 4 (final model) adjusts for model 3 and cardiovascular disease, GDS, cognitive impairment, postural hypotension and alcohol use. Adjusted OR were calculated for accidental falling and frequent falling. Because the patients visiting the geriatric outpatients clinic are a very heterogeneous population, additional subgroup analysis were performed for the different clinics (memory clinic, falls clinic, general geriatric day hospital). A two-sided probability of $p < 0,05$ was considered statistically significant. Outcomes were calculated with a 95% confidence interval (95% CI).

Results

This analysis includes all patients visiting the geriatric day clinic between 2011 and 2014, aged ≥ 65 years ($n=1,385$) who filled out the questionnaire about accidental falls ($n=1,012$). Patients with no available kidney function and patients on renal replacement therapy were excluded ($n=12$), leaving 1,000 participants for analysis. Patients that were excluded from analysis because of a missing questionnaire about accidental falls are shown in Appendix 1. In general, these excluded patients were comparable to our study population. Only differences were the need of professional help, more myocardial infarction and more impaired cognition. The characteristics of the included patients are shown in Table 1. The mean age of the population was 79.4 ± 6.6 years. The mean eGFR was 64.9 ± 19.3 ml/min per 1.73m^2 . Of the total population 38% of the patients had an eGFR < 60 ml/min per 1.73m^2 of whom 17% had a kidney function < 45 ml/min per 1.73m^2 . Compared to patients with a normal kidney function, patients in the group < 45 ml/min per 1.73m^2 were older (82.2 ± 6.6 vs. 78.0 ± 6.3), used more medication (84.8% vs. 65.6%) and had a higher comorbidity burden with more cardiovascular disease (47.0% vs. 27.7%) and diabetes (34.9% vs. 23.0%). They were also more dependent in ADL and IADL. Moreover, there was a higher use of a walking aid (70.2% vs. 48.8%) and postural hypotension (47.1% vs. 37.2%). Compared to the other day clinics, patients that were referred to the general geriatric day hospital had the highest rate of impaired kidney function (42.9%, 35.5% and 27.0%, in the 45-59 and ≥ 60 ml/min/ 1.73m^2 respectively, $p < 0.01$). On the other hand, patients that were referred to the memory clinic had a relatively low rate of impaired kidney function (49.4% in the preserved kidney group, 44.4% and 35.7% in the group with eGFR 45-59 and < 45 ml/min/ 1.73m^2 , $p < 0.01$). There were no significant differences in gender, smoking status, alcohol use, cognition and symptoms of depression between the different groups.

Overall, 617 (61.7%) patients had an accidental fall in the previous year. This rate was the highest in the < 45 ml/min group (70.8%). Frequent falling (≥ 2 falls in the past year) was also more common in the < 45 ml/min group (49.4% vs 41.8% in the population with a preserved kidney function) but this difference was not significant ($p=0.17$) (Table 1). Of all patients, 20.9% was referred to the falls clinic. If these patients were excluded from analysis, the fall rate was 54.8% in the main population and 68.3% in the population with an eGFR < 45 ml/min per 1.73m^2 .

Table 1. Baseline characteristics

Characteristic	CKD-EPI in ml/min per 1.73m ²			P-value
	<45 (n=168)	45-59 (n=214)	≥60 (n=618)	
Age, mean ± SD	82.2 (6.6)	81.4 (6.2)	78.0 (6.3)	<0.01
Female, n (%)	108 (64.3%)	144 (67.3%)	369 (59.7%)	0.12
Referred to:				
- Memory clinic	60 (35.7%)	95 (44.4%)	305 (49.4%)	<0.01
- Falls clinic	33 (19.6%)	39 (18.2%)	138 (22.3%)	0.40
- Geriatric assessment clinic	72 (42.9%)	76 (35.5%)	167 (27.0%)	<0.01
CCI, mean ±SD	7.0 (2.5)	5.6 (2.0)	4.8 (1.9)	<0.01
Diabetes, n (%)	58 (34.9%)	60 (28.0%)	142 (23.0%)	0.01
Cardiovascular disease, n (%)	79 (47.0%)	77 (36.0%)	171 (27.7%)	<0.01
Current smoker, n (%)	18 (11.6%)	27 (13.2%)	75 (12.8%)	0.90
Alcohol use, n (%)	62 (39.2%)	88 (43.3%)	271 (46.0%)	0.30
KATZ-15, median (IQR)	6.0 (6.0)	5.0 (6.0)	4.0 (5.0)	<0.01
Postural hypotension, n (%)	72 (47.1%)	103 (51.2%)	219 (37.2%)	<0.01
Walking aid, n (%)	113 (70.2%)	124 (61.1%)	295 (48.8%)	<0.01
Polypharmacy, n (%)	140 (84.8%)	149 (70.6%)	381 (65.6%)	<0.01
Cognitive impairment, n (%)	64 (38.1%)	82 (38.3%)	200 (32.4%)	0.17
Symptoms of depression, n(%)	36 (22.0%)	36 (17.1%)	119 (19.6%)	0.50
Accidental fall, n (%)	119 (70.8%)	134 (62.6%)	364 (58.9%)	0.02
Frequent falls, n (%)	79 (49.4%)	99 (46.5%)	253 (41.8%)	0.17

SD, Standard deviation; IQR, Interquartile range; CCI, Charlson Comorbidity Index; Accidental fall, fall in the previous year; Frequent falls, ≥2 falls in the previous year.

The following variables had missing data: Referred to (1.5%), Diabetes (0.2%), Current smoker (5.4%), Alcohol use (5.0%), KATZ-15 (7.6%), Postural hypotension (5.7%), Walking aid (3.1%), Polypharmacy (4.3%), Symptoms of depression (2.0%), Frequent falls (2.2%).

Table 2. Association between a decreased eGFR and falls

Accidental falls						
eGFR-group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	1.70	1.17-2.45	<0.01	1.37	0.94-2.02	0.10
45-59 vs. ≥60	1.17	0.85-1.61	0.34	0.97	0.69-1.35	0.83
Frequent falls						
eGFR group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	1.43	1.01-2.02	0.04	1.27	0.89-1.81	0.20
45-59 vs. ≥60	1.20	0.88-1.64	0.26	1.07	0.77-1.48	0.67

eGFR, estimated glomerular filtration rate in ml/min/1.72m²; Accidental fall, fall in the previous year; Frequent falls, ≥2 falls in the previous year. OR, odds ratio, CI (95%); 95% confidence interval.

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
1.12	0.75-1.67	0.60	1.08	0.72-1.62	0.72
0.90	0.64-1.27	0.54	0.87	0.61-1.23	0.42

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
0.98	0.67-1.44	0.93	0.94	0.64-1.38	0.75
0.98	0.70-1.38	0.91	0.94	0.67-1.33	0.74

Model 1 unadjusted, Model 2: adjusted for age and gender, Model 3: adjusted for model 2 KATZ-15, the use of a walking aid, polypharmacy. Model 4: adjusted for model 3 + diabetes, cardiovascular disease, alcohol, postural hypotension, cognitive impairment, symptoms of depression

Impaired kidney function and accidental falling

Odds ratios for the different models analyzing the association between decreased eGFR and falls are shown in Table 2. In the unadjusted model (model 1) an association was found between an eGFR <45ml/min and accidental falling (Odds ratio (OR) 1.70, 95% confidence interval (CI) 1.17-2.45). After correcting for potential confounders this association was no longer present (final model OR 1.08, 95% CI 0.72-1.62). A similar result was found for frequent falls: non-adjusted OR 1.43 (95% CI 1.01-2.02) and OR 0.94 (95% CI 0.64-1.38) in the fully adjusted model.

Additional subgroup analyses for the different geriatric outpatients are shown in Appendix 3a,b,c. An independent association between a decreased eGFR and falling (final model OR 2.08, 95% CI 1.06-4.08) was found in the group of patients visiting the general geriatric day hospital. No association was found for patients visiting the falls or memory clinic. Patients visiting the general geriatric day hospital were more frequently impaired in functional status (median 5.0 vs. 4.0 in both the memory and the fall clinic), had more polypharmacy (78.0% vs. 74.0% in the falls clinic and 62.5% in the memory clinic), had more symptoms of depression (26.0% vs. 17.3% in the memory clinic and 14.4% in the falls clinic) and had more frequently an eGFR <30ml/min/1.73m² (8.9% vs. 3.7% in the memory clinic and 2.4% in the falls clinic). More detailed baseline characteristics for the different outpatient clinics are shown in Appendix 2.

Discussion

In this cross-sectional study involving 1,000 community dwelling geriatric subjects aged 65 years and over, the prevalence of accidental falling was high (61,7%). Patients with an eGFR <45ml/min per 1.73m² had significantly higher rates of accidental falling (OR 1.70, 95% CI 1.17-2.45) compared to patients with a preserved kidney function. Patients in this group also fell more frequently (OR 1.43, 95% CI 1.01-2.02) than patients with a preserved kidney function. After correction for potential confounders there was no independent association between a decreased eGFR, accidental falling or frequency of falling in the overall group. However, in sub analysis, there was an independent association between an eGFR <45ml/min per 1.73m² and falling in the patients that were referred to the general geriatric day hospital (OR 2.08, 95% CI 1.06-4.08).

The rate of accidental falling in our population is high compared to other studies in the elderly population as well as in dialysis patients. A review about falling in community dwelling adults reported that 35-45% of persons over 65 years old fall every year, and up to 50% of those over 80 years old.²² A study performed in an elderly dialysis population found a percentage of 55%.²³ The high frequency of falling in our population is most likely due to the frail and elderly (mean age >80 years) population visiting the geriatric clinic. Also 1 in 5 patients was specifically referred to the falls clinic. However, if these patients are excluded from analysis, the fall rate remained high at a rate of 54.8% in the main population and 68.3% in the population with an eGFR <45ml/min per 1.73m².

Our results suggests that a decreased eGFR does not make a direct contribution on accidental falling in the overall geriatric population. There are several possible explanations why patients with a decreased eGFR in our study population fall more often. Firstly, CKD (and treatment for optimization of CKD) can lead to risk factors of falling. In our study population, patients with a decreased eGFR were older, used more medication, had a higher comorbidity burden, were more dependent in daily life, had more postural hypotension, and were more immobile. These are all risk factors for falling.^{1,21} Secondly, the main causes of CKD in the elderly population are cardiovascular risk factors, including hypertension and diabetes. These comorbidities are also associated with falling.^{21,24} Therefore, it is likely that patients with a decreased eGFR fall more often because of their risk profile and not by the direct consequences of a decreased eGFR.

Similar to our main finding, previous studies also did not find an association between accidental falling and a decreased eGFR. One large prospective cohort study in the United States in a population with patients of ≥65 years found no relationship between

a decreased eGFR (<45, 45-59, and ≥ 60 ml/min per 1.73m^2) and serious fall incidents. However, not only the serious fall incidents have consequences. Minor fall incidents can also lead to fear of falling, depression, social isolation and institutionalization. Patients in this study were also younger, and less frail than in our study population (less cognitive impairment, less depression and less immobility).⁴ In a retrospective study in nursing home patients with a history of falls, a decreased eGFR was not an (in)dependent risk factor for recurrent falling or injurious falls.¹³ The study population was comparable in age and kidney function (35% had a decreased eGFR vs. 38% in our study population), but had a higher use of a walking aid. Two studies that did find an association between a decreased eGFR and falling were sub analysis of double-blind placebo-controlled trials that studied the influence of calcitriol and estrogen on falling.^{14,15} These studies were performed in a healthier and younger population (severe chronic illness was excluded) and did not correct for most geriatric domains. Neither of these studies assessed the relationship between specifically stage 4 or stage 5 of CKD and accidental falling.

However, in the group that was referred to the general geriatric day hospital, we did find an independent association between a decreased eGFR and accidental falling. Our hypothesis is, that this association is a consequence of a higher frequency of a severely impaired kidney function (<30ml/min/ 1.73m^2) in the group of patients visiting the general geriatric day hospital. Since large population studies did find an independent association of mild to moderate CKD with gait disturbances and incident mobility,²⁵⁻²⁷ it could be possible that this effect on accidental falling is seen in a more advanced stage of CKD. Unfortunately, we could not perform an analysis on the association between falling and lower levels of eGFR because of the small groups (n=5 in <15ml/min per 1.73m^2 and n=33 in 15-29ml/min per 1.73m^2). Further research in patients with more severely impaired kidney function is needed to explore this hypothesis.

This study has several limitations. Due to the cross-sectional character of the study no falls incidence could be calculated. Furthermore, data on falls were self-reported by the patients and may be affected by recall bias (especially in patients visiting the memory clinic). As prior research has shown that elderly patients are often unable to recall falls over a longer period of time²⁸ it is possible that the fall prevalence may be even higher in our study population. There also was no information available on severity of a fall and the etiology of the fall. In our database, we did not specify type, dosage and duration of medication. Therefore we could not correct for the effect of fall-associated medication (sedatives, antidepressants). In addition, eGFR is not static and fluctuates over time. In our study population we only measured eGFR once (independently of moment of fall), and therefore these markers may not reflect true values of kidney function. Furthermore,

as levels of creatinine are affected by muscle mass, eGFR can be overestimated in the frail population. Despite these limitations, our study provides a large population of frail elderly with a high rate of accidental falling. Because a geriatric assessment was performed in every patient, much information was available on potential risk factors for falling.

The associations that we report in this study may have implications for the care of elderly patients with CKD. Previous research in the general population showed that less than half of the patients who experienced a fall reported this to a healthcare provider.²⁹ Therefore it is very important for the nephrologist (or general practitioner) to ask patients in this population about previous falls as most patients would not mention this problem by themselves. Several studies have also shown that fall prevention measures can significantly reduce the amount of falls and hospitalizations in elderly patients with CKD.³⁰⁻³² Therefore in patients with a previous fall, fall prevention should be performed to prevent morbidity and mortality.

In conclusion, patients with a decreased eGFR have more accidental falling and tend to fall more frequently than patients with normal kidney function. This is most likely due to the risk profile of the CKD patient, and not due to the decreased eGFR. Further research should focus on the relationship between lower levels of eGFR and falling and risk factors in the CKD population to improve patient selection.

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Supplementary data

Appendix 1: Characteristics of patients with missing questionnaires

Characteristic	Questionnaire available (n=1004)	Questionnaire missing (n=366)	P-value
Age, mean \pm SD	79.4 (6.6)	79.7 (7.1)	0.06
Female, n (%)	623 (62.1%)	225 (61.5%)	0.85
Living with professional help, n (%)	613 (61.2%)	235 (68.1%)	0.02
CCI, mean \pm SD	5.3 (2.2)	5.4 (2.1)	0.10
- Diabetes, n (%)	260 (25.9%)	96 (26.4%)	0.85
- CVA, n (%)	121 (12.1%)	49 (13.5%)	0.37
- TIA, n (%)	95 (9.6%)	35 (9.7%)	0.93
- Myocardial infarction, n (%)	119 (11.9%)	58 (16.0%)	0.05
- Peripheral arterial disease, n (%)	72 (7.2%)	25 (6.9%)	0.83
Current smoker, n (%)	120 (12.6%)	48 (15.5%)	0.19
Alcohol use, n (%)	421 (44.1%)	120 (39.0%)	0.11
Body mass index, mean \pm SD	26.2 (4.8)	25.3 (5.2)	0.07
Laboratory values			
- Albumin, mean \pm SD	39.7 (4.2)	38.7 (4.7)	0.02
- eGFR, mean \pm SD	71.5 (25.0)	69.0 (24.6)	0.93
Postural hypotension, n (%)	395 (41.7%)	121 (42.2%)	0.89
Walking aid, n (%)	535 (55.0%)	9 (60.0%)	0.70
Polypharmacy, n (%)	674 (70.1%)	244 (72.8%)	0.35
Impaired cognition, n (%)	295 (39.9%)	127 (52.3%)	<0.01
Symptoms of depression, n (%)	192 (19.5%)	65 (20.1%)	0.81
Katz-15, median (interquartile range)	4.0 (6.0)	3.5 (7.0)	0.40

SD, standard deviation; CCI, Charlson comorbidity index; eGFR, estimated glomerular filtration rate.

Appendix 2. Baseline characteristics for the different geriatric outpatients clinics

Characteristic	Referred to:			P-value
	Memory clinic	Falls clinic	Geriatric day hospital	
Age, mean ± SD	78,5 (6.7)	80,5 (6.3)	79.6 (6.6)	<0.01
Female, n (%)	55.0%	68.1%	68.3%	<0.01
eGFR:				
<30 ml/min/1.73m ²	3.7%	2.4%	8.9%	<0.01
30-44 ml/min/1.73m ²	9.3%	13.3%	14.0%	0.10
45-59 ml/min/1.73m ²	20.7%	18.6%	24.1%	0.28
≥60ml/min/1.73m ²	66.3%	65.7%	53.0%	<0.01
CCI, mean ±SD	5.2 (2.2)	5.4 (2.2)	5.5 (2.1)	0.10
Diabetes, n (%)	25.1%	26.3%	27.6%	0.73
Cardiovascular disease, n (%)	29.1%	35.7%	35.9%	0.08
Current smoker, n (%)	14.2%	7.3%	13.9%	0.04
Alcohol use, n (%)	51.8%	41.9%	35.2%	<0.01
Katz-15, median (IQR)	4.0 (6.0)	4.0 (5.0)	5.0 (7.0)	<0.01
Postural hypotension, n (%)	39.4%	39.3%	47.2%	0.08
Walking aid, n (%)	42.0%	71.3%	63.2%	<0.01
Polypharmacy, n (%)	62.5%	74.0%	78.0%	<0.01
Cognitive impairment, n (%)	48.7%	13.8%	26.7%	<0.01
Symptoms of depression, n(%)	17.3%	14.4%	26.0%	<0.01
Accidental fall, n (%)	49.6%	88.6%	60.0%	<0.01
Frequent falls, n (%)	30.0%	74.8%	43.1%	<0.01

SD, Standard deviation; IQR, Interquartile range; CCI, Charlson Comorbidity Index; Accidental fall, fall in the previous year; Frequent falls, ≥2 falls in the previous year

Appendix 3a. Association between a decreased eGFR and falls in patients visiting the memory clinic (n=460)

Accidental falls						
eGFR-group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	1.68	0.96-2.93	0.07	1.23	0.69-2.22	0.48
45-59 vs. ≥60	1.44	0.91-2.28	0.12	1.13	0.70-1.84	0.62
Frequent falls						
eGFR group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	1.30	0.73-2.32	0.37	1.13	0.62-2.07	0.69
45-59 vs. ≥60	1.34	0.83-2.16	0.24	1.16	0.70-1.93	0.56

eGFR, estimated glomerular filtration rate in ml/min/1.72m²; Accidental fall, fall in the previous year; Frequent falls, ≥2 falls in the previous year. OR, odds ratio, CI (95%); 95% confidence interval.

Appendix 3b. Association between a decreased eGFR and falls in patients visiting the falls clinic (n=210)

Accidental falls						
eGFR-group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	0.60	0.20-1.81	0.36	0.48	0.15-1.53	0.21
45-59 vs. ≥60	0.59	0.21-1.65	0.31	0.53	0.18-1.57	0.25
Frequent falls						
eGFR group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	0.89	0.37-2.18	0.80	0.87	0.35-2.16	0.76
45-59 vs. ≥60	0.80	0.36-1.78	0.58	0.81	0.35-1.85	0.61

eGFR, estimated glomerular filtration rate in ml/min/1.72m²; Accidental fall, fall in the previous year; Frequent falls, ≥2 falls in the previous year. OR, odds ratio, CI (95%); 95% confidence interval.

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
0.88	0.47-1.64	0.68	0.87	0.46-1.63	0.65
1.05	0.63-1.73	0.86	1.02	0.61-1.70	0.94

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
0.72	0.37-1.40	0.33	0.69	0.35-1.34	0.27
1.03	0.60-1.78	0.92	0.98	0.56-1.72	0.95

Model 1 unadjusted, Model 2: adjusted for age and gender, Model 3: adjusted for model 2 Katz-15, the use of a walking aid, polypharmacy. Model 4: adjusted for model 3 + diabetes, cardiovascular disease, alcohol, postural hypotension, cognitive impairment, symptoms of depression

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
0.39	0.12-1.32	0.13	0.39	0.11-1.45	0.16
0.49	0.16-1.48	0.21	0.33	0.10-1.10	0.07

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
0.85	0.33-2.18	0.74	0.79	0.30-2.12	0.64
0.85	0.36-1.97	0.70	0.74	0.31-1.79	0.51

Model 1 unadjusted, Model 2: adjusted for age and gender, Model 3: adjusted for model 2 Katz-15, the use of a walking aid, polypharmacy. Model 4: adjusted for model 3 + diabetes, cardiovascular disease, alcohol, postural hypotension, cognitive impairment, symptoms of depression

Appendix 3c. Association between a decreased eGFR and falls in patients visiting the geriatric assessment clinic (n=315)

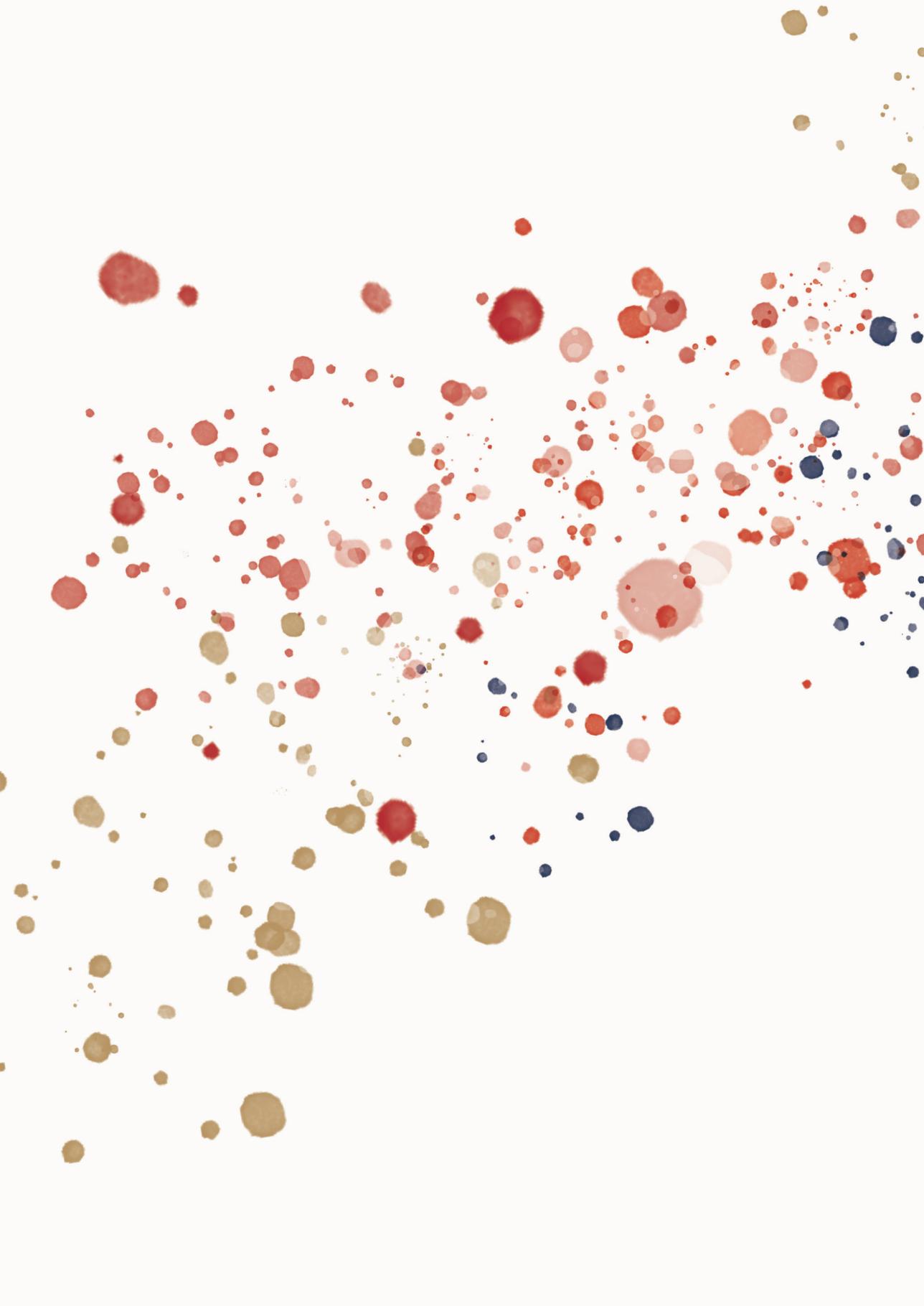
Accidental falls						
eGFR-group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	2.33	1.27-4.27	<0.01	2.30	1.23-4.30	<0.01
45-59 vs. ≥60	1.22	0.70-2.12	0.48	1.18	0.67-2.07	0.57
Frequent falls						
eGFR group	Model 1			Model 2		
	OR	CI (95%)	P-value	OR	CI (95%)	P-value
0-45 vs. >60	1.89	1.08-3.31	0.03	1.91	1.07-3.41	0.03
45-59 vs. ≥60	1.51	0.87-2.62	0.14	1.48	0.85-2.61	0.17

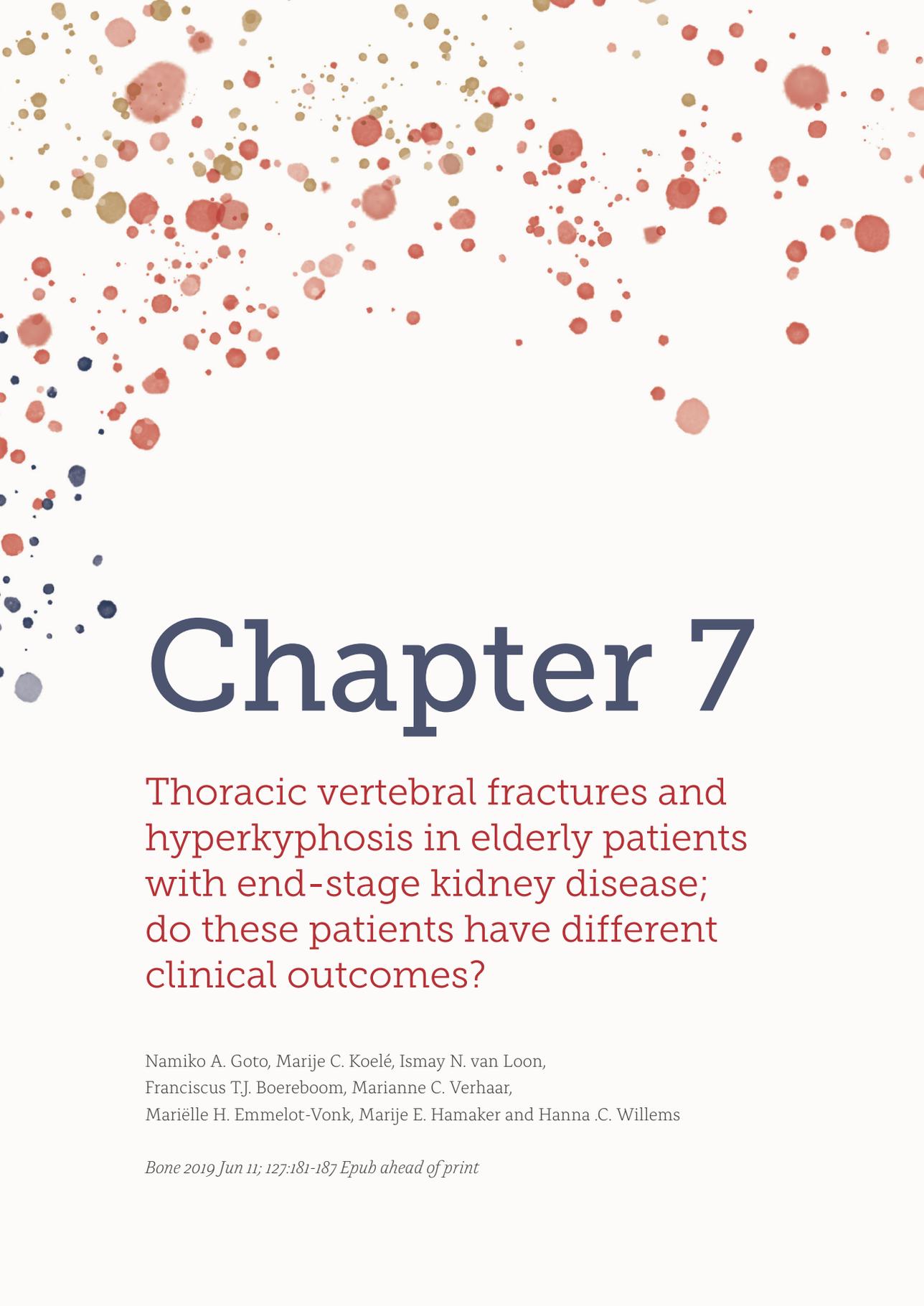
eGFR, estimated glomerular filtration rate in ml/min/1.72m²; Accidental fall, fall in the previous year; Frequent falls, ≥2 falls in the previous year. OR, odds ratio, CI (95%); 95% confidence interval.

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
2.20	1.13-4.27	0.02	2.08	1.06-4.08	0.03
1.07	0.59-1.94	0.82	0.92	0.50-1.70	0.80

Model 3			Model 4		
OR	CI (95%)	P-value	OR	CI (95%)	P-value
1.56	0.84-2.89	0.16	1.60	0.85-2.99	0.14
1.29	0.72-2.31	0.39	1.18	0.64-2.17	0.60

Model 1 unadjusted, Model 2: adjusted for age and gender, Model 3: adjusted for model 2 KATZ-15, the use of a walking aid, polypharmacy. Model 4: adjusted for model 3 + diabetes, cardiovascular disease, alcohol, postural hypotension, cognitive impairment, symptoms of depression





Chapter 7

Thoracic vertebral fractures and hyperkyphosis in elderly patients with end-stage kidney disease; do these patients have different clinical outcomes?

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Abstract

Background and objectives: Elderly patients with end-stage kidney disease (ESKD) are at high risk for fractures. However, the prevalence of vertebral fractures and hyperkyphosis is not studied well. This is relevant, because in the general population, both vertebral fractures and hyperkyphosis are associated with poor outcome. Therefore, the primary aim of our study was to assess the prevalence of vertebral fractures and hyperkyphosis in the ESKD population. The secondary aim was to assess if patients with vertebral fractures and/or hyperkyphosis more often have poor outcome after starting dialysis, such as accidental falling, functional decline and mortality compared to the patients without vertebral fractures and/or hyperkyphosis.

Design, setting, participants & measurements: This study included patients ≥ 65 years with ESKD who were enrolled in the Geriatric assessment in Older patients starting Dialysis (GOLD) study of whom a lateral chest radiograph was available. Chest radiographs were scored independently by two observers for vertebral fractures (Genant ≥ 1) and hyperkyphosis (≥ 50 degrees). The relation between vertebral fractures and hyperkyphosis with clinical outcomes (falls, decline in ADL and IADL, mortality) was studied using the Chi-square test.

Results: Of the 196 enrolled patients, chest radiographs were available for 160 patients. Mean age was 75.0 (SD ± 6.9), and 35% were female. The prevalence of vertebral fractures was 43% and of hyperkyphosis 22%. Patients with hyperkyphosis had a higher one-year mortality compared to patients without hyperkyphosis (20% vs. 8%, $p=0.04$). No differences were observed between patients with and without hyperkyphosis, vertebral fractures and the remaining outcomes after six months of follow-up.

Conclusions: In patients ≥ 65 years old with ESKD starting dialysis, vertebral fractures are highly prevalent. In contrast to the general population, patients with vertebral fractures did experience poor outcome as often as patients without vertebral fractures. Remarkably, patients with hyperkyphosis did have a higher one-year mortality. However, these patients did not experience more functional decline or accidental falls.

Introduction

In the Western world, approximately 40% of the population with end-stage kidney disease (ESKD) is older than 65 years.^{1,2} Both age and ESKD are associated with an increased risk of fractures.³ Elderly ESKD patients are more prone to falls, due to decreased postural reflexes,⁴ neurological and cardiovascular comorbidity and neurosensory impairment.⁵ Besides a higher risk of falls, osteodystrophy and osteoporosis increase the risk of fracture even further. For example, previous research showed a four times higher risk of hip fractures when patients were treated with dialysis compared to patients of the same age without ESKD.⁶⁻⁸ However, the prevalence of vertebral fractures in patients with ESKD has a broad range with prevalence ranging from 10-55%.⁹⁻¹⁵

In regular care of patients with ESKD, a chest radiograph is commonly performed. Besides amount of fluid retention and infection, these radiographs can also provide information about the condition of a large proportion of the vertebrae. Furthermore, these radiographs can be used to measure the kyphosis angle of the thoracic spine. Previous research in the non-ESKD population showed that vertebral fractures could lead to back pain,¹⁶ future fractures,¹⁷ reduced physical performance¹⁸ and an increased curvature of the thoracic spine in the sagittal plane (thoracic hyperkyphosis).¹⁹ Furthermore, both vertebral fractures and hyperkyphosis are associated with an increased mortality.^{16,20} Based on this information, it is possible that vertebral fractures and hyperkyphosis in elderly patients with ESKD who are initiating dialysis are also associated with poor outcome. If vertebral fractures and/or hyperkyphosis are associated with poor outcome, these could provide an opportunity to improve decision-making considering dialysis in the elderly patient with ESKD.

Therefore, the primary aim of the current study was to evaluate the prevalence of vertebral fractures and hyperkyphosis on lateral chest radiographs in a population with end-stage kidney disease initiating dialysis; the secondary aim was to assess if patients with vertebral fractures or hyperkyphosis more often experience poor outcome such as accidental falling, functional decline and mortality.

Materials and Methods

Study participants

Data were used from the Geriatric assessment in Older patients starting dialysis (GOLD) study. This is a multicenter, prospective cohort study assessing the relation between a geriatric assessment and outcome in patients with end-stage kidney disease (ESKD). The study was also designed to assess the prevalence of vertebral fractures, accidental falls and functional change in elderly patients initiating dialysis. Participants were enrolled from 17 centers across the Netherlands in the period from August 2014 to September 2017 (Chapter 2, Appendix 1). Patients initiating dialysis (peritoneal dialysis (PD) and hemodialysis (HD)) who were ≥ 65 years were included. Patients were recruited from the pre-dialysis outpatients clinics by their treating nephrologists. The aim was to include patients eligible for dialysis between 3 weeks before and 2 weeks after dialysis initiation. Patients were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language, or if they suffered from a terminal nonrenal-related condition. If inclusion criteria were met, patients were contacted by one of the researchers or research nurses to make an appointment for inclusion. After six months patients were contacted by telephone for follow up. Furthermore, data on six-month mortality was collected from each center. Because six-month mortality was lower than expected, we decided to extend the follow-up of mortality to one year.

The study was conducted in accordance with the declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients before enrollment.

Data collection

Baseline

For the geriatric assessment, participants were either visited at home (on a nondialysis day for patients on hemodialysis) or in the dialysis center before starting the dialysis session. The assessments were performed by one of the investigators (N.G., I.v.L.) or one of the trained research nurses. Baseline demographic data collected from the medical charts and during the geriatric assessment included age, sex, living situation and number of medications. Other clinical characteristics included cause of kidney failure, dialysis modality, body mass index (BMI), intoxications (alcohol use, smoking habit) and laboratory results (albumin, phosphate, PTH and calcium). Functional performance was assessed using the Katz-6 scale for basic activities of daily living (ADL)²¹ and the Lawton & Brody scale for instrumental activities of daily living (IADL).²² An impaired (I)ADL was defined as one or more impaired items. The cumulative incidence rating scale for geriatrics (CIRS-G) was assessed as a measure for co-morbidity burden based

on the patients' medical charts.²³ Severe comorbidity burden was defined as ≥ 2 score 3 or ≥ 1 score 4. Mobility was measured by the Timed Up and Go test (TUG). If the TUG was completed in less than 10 seconds, mobility was considered normal, 10 to 20 seconds was defined as mildly impaired and more than 20 seconds as severely impaired.²⁴ The cognitive function of the participants was assessed through the Mini Mental State Examination (MMSE).²⁵ Cognitive impairment was defined as an MMSE score lower than 25. For depression the Geriatric depression scale 15 'GDS-15' was used. Depression was defined as a score above 5.²⁶

To assess frailty the Fried Frailty Index was used.²⁷ This is a 5-item questionnaire that assesses malnutrition (unintentional weight loss ≥ 4.5 kg or $\geq 5\%$ body mass in the last year), exhaustion (self-report), weakness (reduced handgrip strength),²⁸ slow gait (≥ 6 seconds for 4 meters) and low physical activity (men < 393 kcal/week; women < 280 kcal/week). A score of 3 or more was considered as frail.²⁷

Follow-up

All patients alive six months after inclusion were interviewed by phone by a research nurse or investigator. During this interview, questionnaires about functional status (ADL, IADL) were completed. For baseline and follow-up, the number of functional dependencies in ADL and IADL were counted. If there were more dependencies (≥ 1) at follow-up in ADL or IADL, this was defined as functional decline.

Furthermore, patients were interviewed about accidental falls. Falls were defined according to the World Health Organization as 'an event which results in a person coming to rest inadvertently on the ground or floor or other lower level'.²⁹ Frequent falls were defined as two or more accidental falls. When patients had fallen, but no number of falls was available, this was scored as less than two falls.

Diagnosis of vertebral fractures

A lateral chest radiograph was taken in the period of six months before or six months after initiation of dialysis of each dialysis patient. Although this was part of the study design, most radiographs were already performed in regular care. In two centers (29 participants) there was no financial agreement on the costs of performing a chest radiograph. Therefore, in these centers, only chest radiographs that were performed in regular care were used for assessment. Every lateral chest radiograph was scored independently by two observers (NG, MK) for vertebral fractures. Chest radiographs were analyzed by using the semi-quantitative method of Genant.³⁰ All radiographs were re-read in consensus readings and verified by an expert geriatrician (HW). If case findings were different, defined as a different Genant score or a difference between the presence of vertebral fractures, the

diagnosis of the expert (HW) was considered as gold standard. In 42 out of 1775 assessable vertebrae (2%) the diagnosis of the third observer led to a different score. Fractures were categorized by severity: grade 1 (20-25% loss of height), grade 2 (25-40% loss of height) and grade 3 (>40% loss of height).

Based on Genant scores a summary number for the severity and the number of the vertebral fractures was calculated by dividing the sum of the abnormal grades by the number of vertebrae that could be assessed per patient. For example, a patient with a grade 2 and a grade 3, with 11 assessable vertebrae, gives a score of $((2+3)/11=0.45)$.

Kyphosis measurement

To quantify the thoracic kyphosis, the modified Cobb angle was used.³¹ This is the angle measured between the superior endplate of the 4th and the inferior endplate of the 12th thoracic vertebrae. Hyperkyphosis was defined as an angle of 50 degrees or higher. This is one of the most commonly used cut-off values in elderly patients.^{32,33}

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (version 25.0 for Windows, SPSS, Inc., Chicago IL.). Included patients were compared with excluded patients (patients in whom no chest radiograph was available) for baseline characteristics. Furthermore, we compared patients with vertebral fractures (grade ≥ 1) on the chest radiograph with patients with no vertebral fractures and patient with hyperkyphosis with patients with normal kyphosis angle for baseline characteristics and outcome (accidental falling, functional decline, mortality). Differences between groups were evaluated using the Chi-square test for categorical variables or the Fisher exact test in case of low number of events ($n \leq 5$), independent t-tests for continuous variables that were normally distributed and Wilcoxon rank sum test for non-parametric continuous data. The association between severity of vertebral fractures (summary score) and grade of kyphosis angle was assessed by using univariate linear regression. Categorical data were reported as proportions, continuous variables were reported as mean with standard deviation (SD) or median with interquartile range (IQR). A two-sided probability of $p < 0.05$ was considered statistically significant. Outcomes were calculated with a 95% confidence interval (95% CI).

Results

Baseline characteristics

This analysis includes all incident dialysis patients included in the GOLD-study (n=196) of whom a lateral chest radiograph was available (n=160). Baseline data of excluded incident dialysis patients (n=36) is shown in Appendix 1. No differences were found in baseline data between included and excluded patients. The mean age of the included patients was 75.3 (SD±6.9), and 35% were female. The majority of the patients was living at home (94%). The main cause of end-stage kidney disease was vascular disease (53%), followed by diabetes (14%). At baseline, 29% of the patients was dependent in ADL and 80% was dependent in IADL. Most frequently impaired domains in ADL were bathing (18%), incontinence (18%) and dressing (14%). Most frequently impaired domains in IADL were doing laundry (53%), medication use (46%) and housekeeping (44%) (Appendix 2). Regarding mobility, 63% was not able to perform the Timed up and Go test within 10 seconds (of whom 8 patients (5%) were immobile). Sixty-six percent of the patients was considered frail according to the Fried Frailty Index.

Prevalence of vertebral fractures

A mean of 11 (SD ±1.4) vertebrae could be analyzed per patient. Of all patients, 68 (43%) had one or more vertebral fractures (median 1.0, IQR 1.0). Highest grade of fracture per patient were Genant 1 in 36 patients (23%), Genant 2 in 25 patients (16%) and Genant 3 in 7 patients (4%). Of all fractures, most frequently fractured vertebrae were the 7th thoracic vertebra (16%), the 12th (9%) and the 8th thoracic vertebra (6%). Baseline data for the included patients are shown in Table 1. Patients with vertebral fractures were more impaired in ADL (40% vs. 21% in patients without vertebral fractures, p=0.01). No differences were seen in demographics, medical history, additional measurements (BMI, TUG, symptoms of depression, impaired cognition, impaired (I)ADL), laboratory results and frailty measurement. Baseline data for more severe fractures (Genant ≥2) are shown in Appendix 3.

Prevalence of hyperkyphosis

Baseline characteristics of participants with and without hyperkyphosis are shown in Table 1. Of all patients, 35 (22%) had hyperkyphosis (defined as a Cobbs angle of ≥50 degrees). Compared to the patients without hyperkyphosis, patients with hyperkyphosis were more frequently female (50% vs. 30%, p=0.02), had a lower BMI (median 24.1 (IQR 5.8) vs. median 26.3 (IQR 6.8), p=0.04) and more patients experienced accidental falls in the six months before inclusion (45% vs. 25%, p=0.03). Furthermore, patients were more impaired in ADL at baseline (46% vs. 24%, p=0.01) and were more frequently living in a nursing home (14% vs. 3%, p=0.01).

Table 1. Baseline characteristics (vertebral fractures (Genant ≥ 1) vs. no fractures) and hyperkyphosis vs. normal angle

	Vertebral fracture (n=68)	No/mild fractures (n=92)	P-value
Demographics			
Age, (mean, SD)	75.2 (6.9)	75.4 (6.9)	0.82
Female, n (%)	21 (31%)	35 (38%)	0.35
Single/widow	40 (59%)	50 (54%)	0.57
Living at nursing home	5 (7%)	4 (4%)	0.42
Intoxications			
- Smoker*	48 (75%)	66 (75%)	1.00
- Alcohol use	27 (43%)	34 (39%)	0.60
Medical history			
Severe comorbidity burden**	29 (43%)	41 (45%)	0.81
Number of medications (median, IQR)	11.5 (6.8)	11.5 (5.0)	0.24
Underlying kidney disease			
- Diabetes	8 (12%)	14 (15%)	0.42
- Vascular	35 (41%)	50 (54%)	
- Glomerulonephritis	6 (9%)	1 (1%)	
- Interstitial nephropathy	1 (2%)	2 (2%)	
- Polycystic kidney disease	3 (4%)	4 (4%)	
- Other/unknown	15 (22%)	21 (23%)	
Hemodialysis***	51 (75%)	69 (75%)	1.00
Additional measurements/tests/questionnaires			
BMI (median, IQR)	25.9 (6.0)	26.7 (7.5)	0.61
Timed-up-and-go-test (in seconds)			
- <10 (normal mobility)	21 (33%)	31 (35%)	0.37
- 10-20 (mildly impaired mobility)	27 (42%)	43 (49%)	
- >20 (severely impaired mobility/immobile)	16 (25%)	14 (16%)	
≥ 1 accidental falls (previous 6 months)	22 (37%)	20 (24%)	0.09
Symptoms of depression (GDS ≥ 5)	22 (32%)	25 (27%)	0.48
Impaired cognition (MMSE <25)	9 (13%)	13 (15%)	0.81
Impaired ADL at baseline (≥ 1)	27 (40%)	19 (21%)	0.01
Impaired IADL at baseline (≥ 1)	53 (78%)	75 (82%)	0.58
Laboratorium			
- Hemoglobin (mean, SD)	6.6 (0.9)	6.4 (1.0)	0.20
- Albumin (median, IQR)	34.3 (9.6)	34.0 (7.0)	0.33
- Bicarbonate (mean, SD)	20.3 (4.3)	20.7 (5.0)	0.69
- PTH (median, IQR)	25.6 (32.9)	27.4 (29.9)	0.74
- Calcium (mean, SD)	2.2 (0.2)	2.2 (0.2)	0.22
- Phosphate (mean, SD)	1.7 (0.6)	1.7 (0.6)	0.45
Frailty measurements			
Impaired Fried frailty index	26 (41%)	40 (46%)	0.61

ADL, Activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini mental state examination; GDS, Geriatric depression scale

Hyperkyphosis (n=35)	Normal kyphosis (n=125)	P-value
76.9 (7.3)	74.9 (6.7)	0.14
18 (50%)	38 (30%)	0.02
18 (51%)	72 (57%)	0.52
5 (14%)	4 (3%)	0.01
22 (67%)	92 (77%)	0.21
15 (46%)	46 (39%)	0.50
14 (40%)	56 (45%)	0.61
11.0 (7.0)	12.0 (6.0)	0.49
2 (6%)	20 (16%)	0.22
21 (60%)	64 (51%)	
0 (0%)	7 (6%)	
2 (6%)	1 (1%)	
2 (6%)	5 (4%)	
8 (22%)	28 (22%)	
27 (77%)	93 (74%)	0.74
24.1 (5.8)	26.3 (6.8)	0.04
12 (36%)	40 (34%)	0.14
11 (33%)	59 (50%)	
10 (30%)	20 (17%)	
14 (45%)	28 (25%)	0.03
9 (26%)	38 (30%)	0.59
7 (20%)	15 (13%)	0.26
16 (46%)	30 (24%)	0.01
28 (80%)	100 (80%)	1.00
6.5 (0.7)	6.5 (1.0)	0.71
34.0 (5.2)	34.4 (9.0)	0.60
19.9 (5.3)	20.7 (4.5)	0.40
26.1 (31.9)	27.7 (31.3)	0.89
2.3 (0.2)	2.2 (0.2)	0.04
1.6 (0.4)	1.8 (0.6)	0.07
19 (58%)	47 (40%)	0.07

* Smoker

** Cumulative Illness Rating Scale-Geriatric (CIRS-G) of ≥ 2 x score 3 or ≥ 1 x score 4

*** The other patients started peritoneal dialysis

Relation between severity of vertebral fractures and kyphosis

The mean severity score of vertebral fractures was 0.09 (SD 0.17) and the mean kyphosis angle 41.00 (SD 10.84). A higher vertebral severity score was associated with a larger kyphosis angle (B 21.35, 95% CI 12.1-30.6, $p \leq 0.001$). This explained 11.6% of the variance of the degree of kyphosis.

Outcome after six months and one year

Outcome data on mortality were available for all patients ($n=160$) and data on functional decline and accidental falling for 144 patients and are shown in Table 2. Six patients were lost to follow-up. After six months of follow-up, 10 of the included patients died and 3 patients received a kidney transplant. Of the patients still alive after six months, 27 (18%) declined in ADL and 65 (42%) patients declined in IADL. Domains that declined most were doing laundry (60% vs. 53% at baseline, $p=0.05$) and self-administering medications independently (57% vs. 46%, $p=0.02$) (Appendix 2). Forty-one patients (26%) experienced a fall in the six months after initiation of dialysis. Of these patients, 13 patients experienced ≥ 2 falls. After one year of follow-up another 7 patients had died (total of 17 patients).

Patients with hyperkyphosis had a higher one year mortality compared to patients without hyperkyphosis (20% vs. 8%, $p=0.04$). No differences were seen in outcome when comparing patients with vertebral fractures to patients without vertebral fractures.

Table 2. Outcomes for vertebral fractures (Genant ≥ 1) vs. no fractures and hyperkyphosis vs. normal angle

	Vertebral fracture (n=62)	No vertebral fracture (n=83)	P-value	Hyper-kyphosis (n=35)	Normal kyphosis (n=124)	P-value
Accidental falling	20 (32%)	21 (26%)	0.44	11 (34%)	30 (27%)	0.40
Decline in ADL	10 (16%)	52 (44%)	0.51	5 (16%)	22 (19%)	0.69
Decline in IADL	29 (47%)	36 (43%)	0.68	17 (55%)	48 (42%)	0.21
Mortality 6 months	5 (7%)	5 (5%)	0.62	4 (11%)	6 (5%)	0.15
Mortality 12 months	9 (13%)	8 (9%)	0.36	7 (20%)	10 (8%)	0.04

ADL, Activities of daily living; IADL, instrumental activities of daily living

P-value reflects the result of a Chi-Square test

Relation between vertebral fractures, hyperkyphosis and outcome variables (accidental falls, functional outcome and mortality)

Figure 1 shows the distribution of patients per outcome (accidental falling, functional decline, six-month and one-year mortality) the proportion of patients with hyperkyphosis, vertebral fractures or both. For patients that died within six months, no follow-up data was available on accidental falling and decline in ADL and IADL. Of the included patients, 24 (16%) patients had both hyperkyphosis and vertebral fractures and 81 patients (51%) had no vertebral fractures and no hyperkyphosis. Of the 24 patients with both hyperkyphosis and vertebral fractures 29% died within one year (compared to 0% for patients with only hyperkyphosis, 5% for patients with only vertebral fractures and 10% with no vertebral fractures and no hyperkyphosis, $p=0.02$). Data on one-year mortality, hyperkyphosis and vertebral fractures is shown in Table 3. Accidental falling and functional decline were not associated with the presence of hyperkyphosis or vertebral fractures.

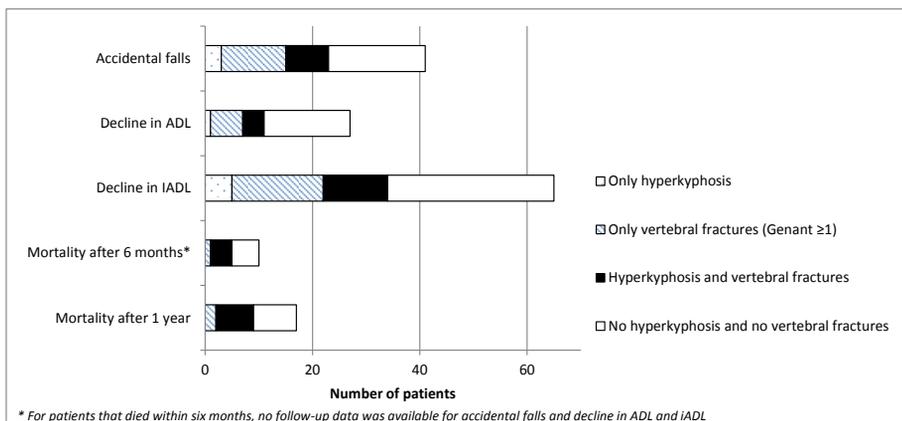


Figure 1. Distribution of patients according to vertebral fractures (Genant ≥ 1), hyperkyphosis, functional decline, accidental falls and mortality

Table 3. Relation between vertebral fractures, hyperkyphosis and one-year mortality

	Vertebral fracture and hyperkyphosis (n=24)	Only hyperkyphosis (n=11)	Only vertebral fractures (n=44)	No vertebral fractures and no hyperkyphosis (n=81)	P-value
Alive after one year (n,%)	17 (71%)	11 (100%)	42 (96%)	73 (90%)	0.02
Death within one year (n,%)	7 (29%)	0 (0%)	2 (5%)	8 (10%)	

P-value reflects the result of the Fisher's Exact Test.

Discussion

In this prospective multicenter cohort study of 160 elderly incident dialysis patients, 43% of the patients had vertebral fractures, 22% had hyperkyphosis, and 16% had both vertebral fractures and hyperkyphosis. After six months of follow-up, patients with vertebral fractures and/or hyperkyphosis experienced functional decline, accidental falling and mortality as often as patients without vertebral fractures or hyperkyphosis. Remarkably, after one year of follow-up, 20% of the patients with hyperkyphosis had died compared to 8% of the patients without hyperkyphosis. This mainly concerns the 24 patients with both hyperkyphosis and vertebral fractures of whom 29% died within one year.

The prevalence of vertebral fractures in our study was in the upper range compared to previous studies in the elderly dialysis population (mean age ranging from 64-72 years) that have found a prevalence ranging from 10-55%.^{9-12,14,34} However, study results are difficult to compare because of the use of different methods to assess vertebral fractures, different cut-off values to define fractures (>20% vs. >25%), and the amount of vertebrae assessed. Interestingly, a Dutch population based cohort study with a comparable age (mean 75.8 years) has found a prevalence of vertebral fractures of 47%.³⁵ This is strikingly similar to the prevalence in our dialysis population (43%), particularly considering that only 1% of this population based cohort had stage 5 kidney disease³⁵ and 30% of had an eGFR <60ml/min.³⁵ As bone abnormalities worsen when eGFR decreases,³⁶ we expected a higher vertebral fracture prevalence in patients with ESKD initiating dialysis than in the general population. Our lower prevalence is probably caused by the use of only thoracic chest radiographs for assessing vertebral fractures whereas the population based study used both thoracic and lumbar radiographs. Therefore, our study may have underestimated the number of lumbar vertebral fractures. On the other hand, bone abnormalities of chronic kidney disease may be more severe in cortical bone.³⁷ As a large part of the vertebrae consist of trabecular bone, this may account for the similar prevalence of vertebral fractures at the initiation of dialysis.

Compared to the general elderly population, the prevalence of hyperkyphosis that we have found was also lower than expected. Prior research estimated the prevalence of hyperkyphosis in the elderly population between 20-55%,^{33,38-40} of which only the study of van der Jagt et al used a similar method to diagnose hyperkyphosis³³ No literature could be found on the prevalence of hyperkyphosis in patients with kidney disease. As severe hyperkyphosis can already be seen without additional imaging, it is possible that patients with severe hyperkyphosis are more frequently labeled as frail, and therefore less likely to initiate dialysis. Furthermore, as patients who have worse health may have been less likely

to participate in this study, this could have led to a relatively healthy ESKD population. Both could have led to a relatively low prevalence of hyperkyphosis.

To our best knowledge, no previous research assessed the association between vertebral fractures, falls and functional decline in the ESKD population. However, there were two studies that assessed the relation between vertebral fractures and mortality in patients treated by hemodialysis.^{10,34} One study found an association between vertebral fractures and a higher two-year mortality in women treated by hemodialysis³⁴ and the other study showed this for both women and men, but by only assessing lumbar vertebral fractures.¹⁰ In contrast to these studies and studies in the general population,¹⁸ we did not find an association between vertebral fractures and poor outcome. A possible explanation may be that the initiation of dialysis had such a big impact, that other risk factors (such as vertebral fractures) were less important for prognosis in the first year after start of dialysis. Furthermore, no follow-up data on accidental falls and functional decline was available for patients that died within six months. As elderly patients frequently deteriorate in physical function before death,⁴¹ it is well possible that these patients experienced a fall or showed functional decline before death. This could have led to an underestimation of falls and functional decline which could have obscured a potential association between vertebral fractures and poor outcome could have been missed.

Interestingly, despite the low event rate of death, we did find a higher one-year mortality after start of dialysis in patients with hyperkyphosis. Considering every patient that died with hyperkyphosis had also vertebral fractures, and only 12% of the variance of the degree of kyphosis was explained by severity of vertebral fractures, the combination of both vertebral fractures and hyperkyphosis seems to be important for predicting mortality. Unfortunately, because of no mortality events in the only hyperkyphosis group, no additional analysis could be performed to assess a possible interaction between hyperkyphosis and vertebral fractures. Our study findings are in agreement with a previous study in the general population that showed that in older women with vertebral fractures, hyperkyphosis was a risk factor for death.²⁰ A possible reason for this association could be that hyperkyphosis (possibly in combination with vertebral fractures) could be an indicator of physical dysfunction,⁴² such as a decrease in muscle mass and muscle strength, what could lead to frailty and subsequently poor outcome.⁴³ This was also observed in our study population as patients with hyperkyphosis tended to be more frail according to the Fried Frailty Index. Furthermore, they were more dependent on care and were more likely to experience accidental falls compared to patients without hyperkyphosis. These are all known risk factors for poor outcome in the ESKD-population.⁵ Therefore, it could be beneficial to perform additional frailty screening and optimization of physical performance in the patients with both hyperkyphosis and vertebral fractures.

The major strength of this study is a large multicenter cohort study where vertebral fractures were diagnosed by the use of radiographs, instead of using ICD-codes or medical history. Limitations are that we used a radiograph of the chest to diagnose vertebral fractures. Because this type of imaging only provides information on the first few lumbar vertebrae, this could have led to an underestimation of vertebral fractures. Second, due to low rate of events, and therefore lack of power in the study, it is possible that we have missed a potential association between vertebral fractures, hyperkyphosis and poor outcome. Furthermore, we could not perform regression analysis to adjust for potential confounders. Third, as patients with worse health were less likely to participate, the results that we have shown for the prevalence of vertebral fractures and hyperkyphosis are possibly not fully generalizable to all elderly initiating dialysis.

In conclusion, in patients ≥ 65 years with ESKD that are initiating dialysis, vertebral fractures are highly prevalent. In contrast to the general population, patients with vertebral fractures did not experience more often poor outcome. Remarkably, patients with hyperkyphosis did experience a higher one-year mortality. Considering these patients were also more frequently frail and dependent of care, especially in these patients additional frailty screening and optimization strategies of physical performance before initiation of dialysis could be beneficial. More research in larger cohorts is needed to better quantify the risk of poor outcome in ESKD patients with vertebral fractures and hyperkyphosis.

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Supplementary data

Appendix 1. Baseline characteristics of the excluded patients

	Chest radiograph available (n=160)	Chest radiograph unavailable (n=36)	P-value
Demographics			
Age, (median, IQR)	75.0 (10.0)	75.0 (11.0)	0.58
Female, n (%)	56 (35%)	8 (22%)	0.14
Single/widow (n, %)	70 (44%)	13 (36%)	0.40
Intoxications			
- Smoker (n, %)	114 (75%)	30 (86%)	0.17
- Alcohol (n, %)	61 (40%)	15 (43%)	0.79
Medical history			
Underlying kidney disease			0.23
- Diabetes (n, %)	22 (14%)	8 (22%)	
- Vascular (n%)	85 (53%)	14 (39%)	
Hemodialysis (n, %)	120 (75%)	30 (83%)	0.29
Severe comorbidity burden (n,%)	70 (44%)	11 (31%)	0.15
Number of medications (median, IQR)	11.5 (6.8)	11.0 (5.0)	0.42
Functional performance			
Impaired ADL at baseline (n, %)	46 (29%)	11 (31%)	0.83
Impaired IADL at baseline (n, %)	128 (80%)	26 (72%)	0.30
Malnutrition			
- Mild (n, %)	85 (53%)	18 (50%)	0.73
- Severe (n, %)	9 (6%)	1 (3%)	0.48
Mobility			
- Mildly impaired (n, %)	103 (68%)	24 (69%)	0.97
- Severely impaired (n, %)	30 (20%)	6 (17%)	0.71
Impaired four balance test (n, %)	94 (67%)	20 (65%)	0.78
Accidental falls (previous 6 months) (n, %)	42 (29%)	8 (24%)	0.53
Laboratorium			
- Hemoglobin (mean, SD)	6.5 (1.0)	6.3 (0.8)	0.30
- Albumin (median, IQR)	34.0 (7.4)	36.5 (8.4)	0.17
- Bicarbonate (mean, SD)	20.5 (4.7)	20.6 (7.0)	0.90
- PTH (median, IQR)	27.3 (31.3)	24.6 (28.4)	0.46
- Calcium (mean, SD)	2.2 (0.2)	2.3 (0.2)	0.14
- Phosphate (mean, SD)	1.7 (0.6)	1.8 (0.5)	0.58

Appendix 1. Continued

	Chest radiograph available (n=160)	Chest radiograph unavailable (n=36)	P-value
Other questionnaires/measurements			
Impaired cognition (MMSE<24)	24 (15%)	3 (8%)	0.29
Symptoms of depression (n, %)	47 (29%)	13 (36%)	0.43
Frailty measurements			
Impaired GFI (n, %)	98 (61%)	23 (64%)	0.77
Impaired Fried frailty index (n, %)	66 (43%)	19 (54%)	0.24

BMI, Body Mass Index; ADL, Activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini mental state examination; GDS, Geriatric depression scale; GFI, Groningen frailty indicator.

Appendix 2. Overview of impairments in (I)ADL at baseline and after six months of follow-up

	Baseline (n=160)	Follow-up (n=144)	P-value
Activities of daily living (patients with impairment, %)			
Bathing	29 (18%)	27 (19%)	0.65
Dressing	22 (14%)	19 (13%)	0.82
Toileting	5 (3%)	4 (3%)	1.00
Transferring indoors	4 (3%)	5 (4%)	0.69
Incontinence	28 (18%)	26 (18%)	0.65
Feeding	1 (1%)	1 (1%)	1.00
Instrumental activities of daily living (patients with impairment, %)			
Ability to use telephone	17 (11%)	22 (15%)	0.12
Shopping	81 (51%)	80 (56%)	0.24
Food preparation	63 (39%)	69 (48%)	0.09
Housekeeping	70 (44%)	66 (46%)	0.70
Laundry	84 (53%)	87 (60%)	0.05
Mode of transportation	61 (38%)	60 (42%)	0.38
Responsibility for own medications	73 (46%)	82 (57%)	0.02

P value reflects the result of a univariable model (McNemar test).

Appendix 3. Baseline characteristics for severe fractures (Genant ≥ 2) vs. no fractures/mild fractures

	Severe fracture (n=32)	No/mild fractures (n=128)	P-value
Demographics			
Age, (median, IQR)	76.0 (9.0)	74.5 (11.0)	0.71
Female, n (%)	13 (41%)	43 (34%)	0.46
Single/widow	18 (56%)	72 (56%)	1.0
Living at nursing home	1 (3%)	8 (6%)	0.49
Intoxications			
- Smoker*	20 (67%)	94 (77%)	0.24
- Alcohol use	8 (27%)	53 (44%)	0.09
Medical history			
Severe comorbidity burden**	12 (38%)	58 (45%)	0.43
Number of medications (median, IQR)	11.5 (7.5)	11.5 (6.5)	0.90
Underlying kidney disease			
- Diabetes	5 (16%)	17 (13%)	0.22
- Vascular	18 (56%)	67 (52%)	
- Glomerulonephritis	3 (9%)	4 (3%)	
- Interstitial nephropathy	1 (3%)	2 (2%)	
- Polycystic kidney disease	1 (3%)	6 (5%)	
- Other/unknown	4 (13%)	32 (25%)	
Hemodialysis***	23 (72%)	97 (76%)	0.65
Additional measurements/tests/questionnaires			
BMI (median, IQR)	26.3 (7.2)	25.8 (6.3)	0.95
Timed-up-and-go-test (in seconds)			
- <10 (normal mobility)	11 (37%)	41 (34%)	0.74
- 10-20 (mildly impaired mobility)	12 (40%)	58 (48%)	
- >20 (severely impaired mobility/ immobile)	7 (23%)	23 (19%)	
≥ 1 accidental falls (previous 6 months)	9 (31%)	33 (28%)	0.78
Symptoms of depression (GDS ≥ 5)	8 (25%)	39 (31%)	0.54
Impaired cognition (MMSE <25)	4 (13%)	18 (15%)	0.76
Impaired ADL at baseline (≥ 1)	13 (41%)	33 (26%)	0.10
Impaired IADL at baseline (≥ 1)	21 (66%)	107 (84%)	0.02

Appendix 3. Baseline characteristics for severe fractures (Genant ≥ 2) vs. no fractures/mild fractures

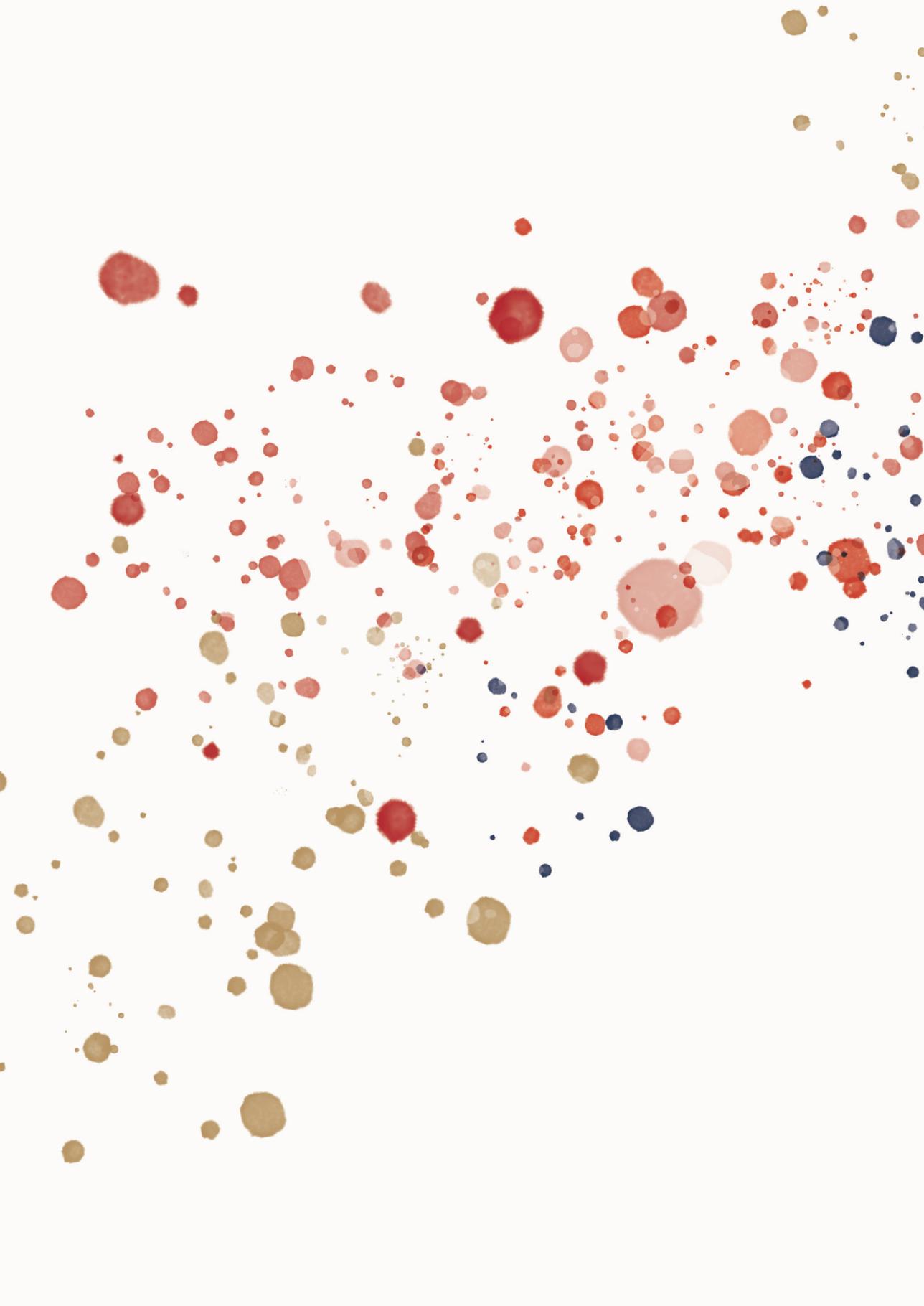
	Severe fracture (n=32)	No/mild fractures (n=128)	P-value
Laboratorium			
- Hemoglobin (mean, SD)	6.6 (0.9)	6.5 (1.0)	0.44
- Albumin (median, IQR)	33.8 (9.1)	34.1 (7.6)	0.71
- Bicarbonate (mean, SD)	19.9 (4.5)	20.7 (4.8)	0.39
- PTH (median, IQR)	26.4 (32.5)	27.3(32.8)	0.52
- Calcium (mean, SD)	2.2 (0.2)	2.2 (0.2)	0.86
- Phosphate (mean, SD)	1.7 (0.5)	1.7 (0.6)	0.68
Frailty measurements			
Impaired Fried frailty index	11 (38%)	55 (45%)	0.49

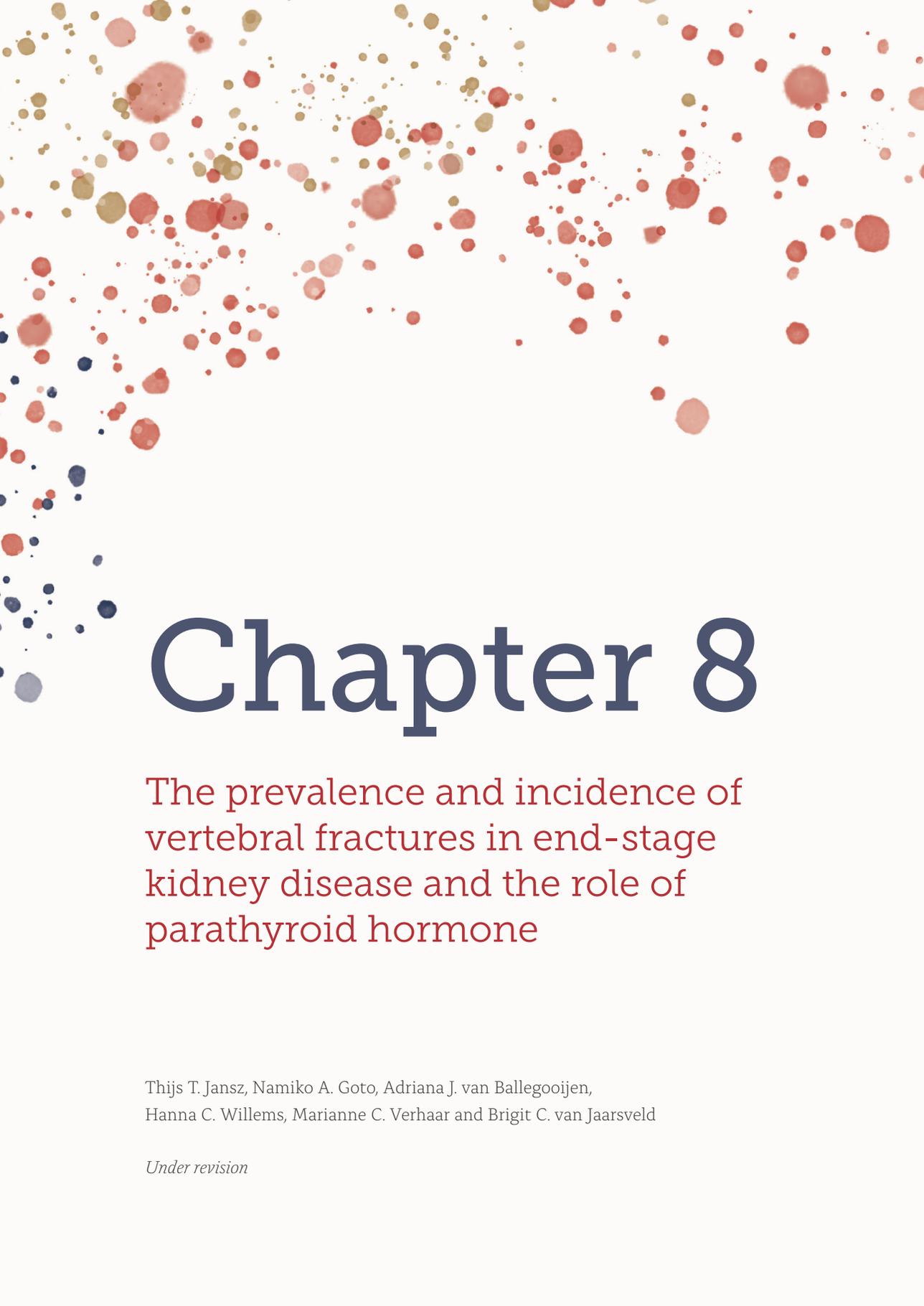
* Smoker

** Cumulative Illness Rating Scale- Geriatric (CIRS-G) of ≥ 2 x score 3 or ≥ 1 x score 4

*** The other patients started peritoneal dialysis

ADL, Activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini mental state examination; GDS, Geriatric depression scale





Chapter 8

The prevalence and incidence of vertebral fractures in end-stage kidney disease and the role of parathyroid hormone

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Under revision

Abstract

Introduction: Vertebral fractures are often overlooked, but even undiagnosed vertebral fractures negatively impact physical functioning, quality of life, and mortality. The risk of vertebral fractures in end-stage renal disease (ESRD) patients is unclear, and parathyroid hormone (PTH) might play a role in the development of vertebral fractures. We therefore determined vertebral fracture prevalence and incidence in ESRD patients and assessed associations of vertebral trabecular bone mineral density (BMD) and PTH with vertebral fracture.

Methods: In 146 transplantation-eligible patients on dialysis, we determined vertebral fractures on lateral chest radiographs, which image the thoracic and upper lumbar spine. We determined incident vertebral fractures in 70 patients with follow-up radiographs (23 received a kidney transplant) after median 1.8 years. Vertebral trabecular BMD was measured with computed tomography, and PTH measured with 2-site immunoassays, categorized in tertiles with the middle tertile as reference. We used Poisson regression to assess associations of vertebral trabecular BMD and PTH with vertebral fracture.

Results: Mean age of the study population was 52 ± 13 years, and 98 (67%) were male. Median dialysis duration was 26 (IQR 13–55) months. Vertebral fractures were present in 50/146 patients (34%) and incident vertebral fractures occurred in 20/70 patients (29%). Vertebral trabecular BMD was not associated with vertebral fracture prevalence (relative risk 0.97, 95% CI 0.89 to 1.04). For the lowest PTH tertile (<11 pmol/L), the relative risk of vertebral fracture was greater although not significant (2.28, 95% CI 0.97 to 5.97) and was significantly greater for the highest PTH tertile (≥ 30 pmol/L; 2.82, 95% CI 1.22 to 7.27) after adjustment for potential confounders.

Conclusions: The prevalence and incidence of vertebral fractures is high even in relatively young and healthy ESRD patients. Vertebral trabecular BMD is not associated with vertebral fracture, and the association of PTH with vertebral fracture risk appears U-shaped.

Introduction

Patients with end-stage renal disease (ESRD) have a high risk of fractures. The risk of hip fractures is four times higher in patients on dialysis compared to the general population.¹ While hip fractures are mostly clinically apparent, many vertebral fractures are presented atypically.² Vertebral fractures are easily missed on radiographs.³ Hence, they often remain undiagnosed, but even undiagnosed vertebral fractures negatively impact physical functioning,⁴ quality of life,⁵ and mortality risk.⁶ Nevertheless, due to poor documentation in cohorts and dialysis registries, the risk of vertebral fracture in ESRD remains largely unknown.⁷

Patients with ESRD have distinct risk factors for fracture beyond traditional risk factors due to chronic kidney disease-mineral and bone disorder.⁷ The disturbed bone metabolism, also known as renal osteodystrophy, comprises a spectrum of loss of bone mass due to high bone turnover, and microstructural abnormalities due to suppressed bone turnover.⁸ These specific types of renal osteodystrophy cannot be distinguished with conventional markers of bone fragility, such as bone mineral density (BMD).⁹ Clinicians commonly rely on parathyroid hormone (PTH) to estimate bone turnover in ESRD, however, the prognostic utility of BMD and PTH for fracture risk in ESRD is unclear.¹⁰ A recent meta-analysis indicated that lower BMD at the lumbar spine was associated with prevalent fractures among patients on dialysis, but not in age-adjusted analyses.¹¹ This suggests that vertebral BMD may not independently predict fracture risk in ESRD. Furthermore, studies observed that both low and high PTH values were associated with hip and vertebral fracture risk among patients with ESRD, but with various cut-off values.^{12–15} There is also an unclear relationship of PTH with BMD, with three studies of in total 289 patients on dialysis reporting negative associations of PTH with BMD at cortical sites (such as the distal radius), but inconsistent associations with BMD at trabecular sites (such as the spine).^{16–18}

In this study, we determined vertebral fracture prevalence in patients on dialysis using lateral chest radiographs and determined vertebral fracture incidence in patients with follow-up radiographs, who remained on dialysis or received a kidney transplant. We examined the relationships of vertebral trabecular BMD and PTH with the risk of vertebral fracture, and additionally the relationship of PTH with vertebral trabecular BMD.

Materials and methods

Study population

We used data from the NOCTx study, a prospective cohort that compared progression of coronary artery calcification between patients treated with different renal replacement therapies. Between December 2009 and February 2016, NOCTx recruited 181 patients from eight centers in the Netherlands, who were on chronic hemodialysis or peritoneal dialysis with a minimum dialysis duration of two months, who were on hemodialysis and switched to nocturnal hemodialysis, or who were on dialysis and received a kidney transplant. At inclusion, all dialysis patients were eligible for transplantation. NOCTx included patients between 18 and 75 years and excluded patients with a life expectancy <3 months or pre-emptive transplantation. All subjects gave written informed consent. NOCTx has been approved by the Medical Ethics Committee of the University Medical Center Utrecht and was conducted in accordance with the declaration of Helsinki.

Patients were treated according to the KDIGO guidelines by their attending nephrologist.¹⁰ Conventional hemodialysis was delivered 3 x 4–5 hours per week in-center with default 3.0 mEq/L dialysate calcium. Peritoneal dialysis was delivered as continuous ambulant peritoneal dialysis ($n=16$) or automated peritoneal dialysis ($n=8$) with default 2.5 mEq/L dialysate calcium. Nocturnal hemodialysis was delivered $\geq 4 \times 8$ hours per week at home with default 3.0 mEq/L dialysate calcium. Kidney transplant recipients received standard immunosuppressant regimens consisting of tacrolimus, mycophenolate mofetil, and prednisone in tapering doses (cumulative dose in first three months typically 1.0–1.4 g, maintenance dose 5–7.5 mg/day from three months post-transplantation). Acute rejections were treated with 3 x 1 g of methylprednisolone intravenously.

We studied vertebral fracture prevalence in patients that underwent a lateral chest radiograph as part of routine care within six months of inclusion in NOCTx ($n=148$). For kidney transplant recipients, this was the screening radiograph performed the day of transplantation. We excluded two patients because of poor quality radiographs leaving a sample of 146 patients. We studied associations of PTH in all patients with no history of parathyroidectomy and non-missing PTH values ($n=131$). We assessed the incidence of vertebral fractures in patients that underwent a second lateral chest radiograph as part of routine care >1 year after the first radiograph during maximum three years follow-up ($n=70$).

BMD measurements

In NOCTx, all patients underwent non-enhanced cardiac multi-slice computed tomography (CT) at inclusion, using a single iCT 256 scanner (Philips Medical Systems, Best, the Netherlands), which is checked for image quality and stability at least once every 2 weeks as part of our quality assurance system. The acquisition parameters were as follows: 120 kV, 40-50 mAs, rotation time 270 ms, and 128 x 0.625 mm collimation; table height was set by the attending medical physicist in order to position the patient in the isocenter of the gantry. A single reader (TJ) determined volumetric trabecular BMD of three consecutive thoracic vertebrae in the T7-T10 range.¹⁹ The reader placed a region of interest (ROI) at the center of the vertebra and changed its placement to exclude the cortical edge, bone islands, large veins, or calcified herniated disks, or excluded a vertebra entirely if it was fractured ($n=6$). We calculated BMD in mg/cm^3 by multiplying the mean CT value per patient (in Hounsfield units) with a calibration factor of 0.871 (calibration factor coefficient of variation 6.1%).²⁰ With this iCT 256 scanner-specific calibration factor, vertebral trabecular BMD can be measured accurately without a phantom, correlating highly with phantom-based BMD values ($r=0.987$).²⁰

In a random sample of 85 scan re-reads by the same reader, the 95% limits of agreement were -7.6 (95% CI -8.4 to -6.8) and 11.5 (95% CI 10.7 to 12.3) mg/cm^3 , and intra-observer reliability ($\text{ICC}_{\text{agreement}}$) was 0.99. In previous studies, the interscan variation has been shown to be low (2.8%).¹⁹

Parathyroid hormone

Parathyroid hormone was measured as part of routine care at clinical laboratories, with intact 2-site immunoassays (Beckman-Coulter, Fullerton, USA; Abbott Diagnostics, Abbott Park, USA; or Roche Diagnostics, Indianapolis, USA). Reference intervals of these assays are 1.3–9.3 pmol/L ; 1.6–7.2 pmol/L ; and 1.6–6.9 pmol/L , respectively. PTH values were averaged over measurements of the 3 months preceding the first lateral chest radiograph (mostly two measurements (60%), range 1–4 measurements).

Vertebral fracture assessment

Using lateral chest radiographs, which show the thoracic and upper lumbar spine, two trained physicians (TJ and NG) independently identified vertebral fractures and graded them according to Genant's semi-quantitative method.²¹ This method allows to exclude other possible causes of vertebral deformity, such as Scheuermann's disease, remodeling of vertebral bodies due to degenerative disk disease, or scoliosis. Lateral chest radiographs are reliable for the diagnosis of vertebral fractures, with excellent agreement and reliability compared to lateral spine radiographs (95–98% and 0.88–0.91 respectively).²² Fractures were graded by type (wedge, biconcave or crush deformity) and severity: grade

1 (20–25% height loss), grade 2 (25–40% height loss), or grade 3 (>40% height loss). All radiographs were re-read in consensus readings and verified by an expert geriatrician (HW). On average, we evaluated 10.8 ± 1.4 vertebrae per patient, which included the seventh thoracic vertebra in 145 (99%) patients and the first lumbar vertebra in 124 (85%) patients. The prevalence of vertebral fractures did not differ significantly between patients with ≤ 10 evaluable vertebrae (18/61 fractures) and patients with >10 evaluable vertebrae (32/85 fractures) ($p=0.40$).

We defined the incidence of a fracture as any new vertebral fracture not present on the first radiograph or deterioration of an existing fracture to a higher grade. We defined the follow-up time as the time between the first and second radiograph. We evaluated an average of 10.6 ± 1.3 vertebrae per patient, which included the seventh thoracic vertebra in all patients and the first lumbar vertebra in 53 (76%) patients.

Other study variables

At inclusion, study personnel recorded demographics at the University Medical Center Utrecht. Body mass index was calculated by dividing weight (kg) by height (m^2), based on chart review. Smoking status was self-reported and categorized as current and non-current smoking. Biochemical parameters (total calcium, albumin, phosphate, C-reactive protein, and total alkaline phosphatase) were measured in clinical laboratories in the 8 recruiting centers, and values were averaged over measurements of three months preceding inclusion (commonly 2-3 measurements). Medication use and medical history were assessed by chart review. We defined dialysis duration as the time between the first day of dialysis and the inclusion date, minus the time with a functioning kidney transplant, expressed in months.

Statistical analyses

We reported normally distributed variables as mean (\pm standard deviation), non-normally distributed variables as median (interquartile range, IQR), and categorical data as number (percentage). We tabulated patient characteristics according to vertebral fracture prevalence. We categorized PTH as tertiles, as we expected a U-shaped relationship with vertebral fracture.⁷

We evaluated associations of kidney transplantation versus dialysis with vertebral fracture incidence, of vertebral trabecular BMD with vertebral fracture prevalence, and lastly of PTH tertiles with both vertebral fracture prevalence and vertebral trabecular BMD. For vertebral fracture prevalence and incidence as outcome measure, we used Poisson regression due to the high event rate and reported relative risks (RR) with 95% confidence intervals (CI).²³ For vertebral fracture prevalence as outcome measure, we

adjusted for potential confounders age (years), sex, dialysis duration (months), and diabetes (type I or type II/absent). For vertebral fracture incidence as outcome measure, we adjusted for age (years), sex, and follow-up time (years), and stratified by dialysis or kidney transplantation, as we suspected distinct fracture etiologies. For vertebral trabecular BMD as outcome measure, we used linear regression and adjusted for potential confounders as described above.

To evaluate the continuous associations of PTH with vertebral fracture prevalence and vertebral trabecular BMD, we constructed P-splines adjusted for age (years) and sex.²⁴ We considered p-values ≤ 0.05 (two-tailed) statistically significant and used R 3.4.1 (R Foundation Statistical Computing) for all analyses.

Sensitivity analyses

To test the robustness of the associations, we repeated the analyses of the association of PTH with vertebral fracture prevalence stratified by age (<50 or ≥ 50 years); sex; history of diabetes, cardiovascular disease, current smoking, or transplantation; treatment with hemodialysis or peritoneal dialysis; use of prednisone; calcium-containing phosphate binders; vitamin D analogues; and cinacalcet.

Results

Study population

The mean age of the study population ($n=146$) was 52 ± 13 years, 98 (67%) were male, median dialysis duration was 26 (IQR 13–55) months, and 18 (12%) had diabetes. Eighteen patients (12%) were on long-term corticosteroids (low-dose up to 10 mg/day), while none used bisphosphonates and 23 (18%) used cinacalcet.

Patients that could not be evaluated for vertebral fractures ($n=35$) due to missing radiographs were similar in patient characteristics: mean age 51 ± 14 years, 23 (66%) were male, median dialysis duration was 31 (IQR 15–74) months, and eight (23%) had diabetes (Appendix 1).

Vertebral fracture prevalence and incidence

In total, 50 patients (34%) had 84 prevalent vertebral fractures. Patients with prevalent vertebral fractures were older, more often male, had longer dialysis durations, and more often used cinacalcet than patients without prevalent vertebral fractures (Table 1).

We assessed incident vertebral fractures in a subset of 70 patients: 47 who continued treatment with dialysis and 23 who received a kidney transplant at inclusion. The kidney transplant recipients ($n=23$) had a mean estimated glomerular filtration rate of 54 ± 19 mL/min/1.73m².

Patients that could not be evaluated for incident vertebral fractures ($n=76$) were similar in patient characteristics: mean age 51 ± 13 years, 23 (70%) were male, median dialysis duration was 31 (IQR 16–64) months, and 9 (12%) had diabetes. Furthermore, these patients were similar regarding treatment modality (38 patients on hemodialysis, 13 on peritoneal dialysis, 25 kidney transplant recipients versus 35, 12, and 23 respectively) and vertebral fracture prevalence (27/76 patients, 36% versus 23/70, 33%).

Table 1. Characteristics of the 146 patients with end-stage renal disease stratified by prevalence of a vertebral fracture on lateral chest radiograph.

	No vertebral fracture (<i>n</i> = 96)	Prevalent vertebral fracture (<i>n</i> = 50)
Demographics and medical history		
Age (years)	50 ±13	57 ±12
Male (%)	58 (60%)	40 (80%)
Body mass index (kg/m ²)	25.6 ±4.6	26.0 ±4.4
Diabetes mellitus (%)	13 (14%)	5 (10%)
Cardiovascular disease (%)	22 (23%)	12 (24%)
Current smoker (%)	7 (7%)	8 (16%)
History of kidney disease		
Dialysis duration (months)	21 (11–48)	38 (19–70)
Previous transplantation (%)	20 (21%)	16 (32%)
Parathyroidectomy (%)	4 (4%)	5 (10%)
Cause of end-stage renal disease (%)		
– Cystic kidney disease	16 (17%)	11 (22%)
– Interstitial nephritis	2 (2%)	2 (4%)
– Glomerulonephritis	27 (28%)	11 (22%)
– Vascular disease	18 (19%)	14 (28%)
– Diabetic nephropathy	6 (6%)	3 (6%)
– Other	13 (14%)	5 (10%)
– Unknown	14 (15%)	4 (8%)
Dialysis treatment (%)		
– Haemodialysis	68 (71%)	40 (80%)
– Peritoneal dialysis	28 (29%)	10 (20%)
Medication use at inclusion*		
Corticosteroids (%)	10 (10%)	8 (16%)
Calcium-containing phosphate binders (%)	30 (36%)	11 (26%)
Vitamin D analogues (%)	64 (77%)	32 (74%)
Cinacalcet (%)	10 (12%)	13 (30%)
Laboratory parameters		
Calcium (mmol/L)	2.34 ±0.14	2.35 ±0.13
Phosphate (mmol/L)	1.36 ±0.54	1.32 ±0.48
Parathyroid hormone (pmol/L)	17 (10–34)	18 (9–49)
C-reactive protein (mg/L)	3 (2–6)	3 (2–9)
Total alkaline phosphatase (IU/L)	83 (69–114)	73 (59–96)

Table 1. Continued.

	No vertebral fracture (<i>n</i> = 96)	Prevalent vertebral fracture (<i>n</i> = 50)
Bone mineral density and vertebral fracture		
Vertebral bone mineral density (mg/cm ³)	139 ±41	120 ±44
Number of vertebral fractures (%)		
- One	-	27 (54%)
- Two	-	14 (28%)
- Three	-	7 (14%)
- Four	-	2 (4%)
Highest vertebral fracture grade (%)		
- Grade 1	-	32 (64%)
- Grade 2	-	16 (32%)
- Grade 3	-	2 (4%)

Results are presented as mean ±standard deviation, median (interquartile range) or percentage.

*Data on medication use (except for corticosteroid use) were available in 126 patients

After a median follow-up of 1.8 years (IQR 1.3–2.7) or 137 person-years, 20 patients (29%) developed 24 new vertebral fractures. Compared to patients without incident vertebral fracture, patients with incident vertebral fracture were older (mean 60 versus 52 years) and had more often a previous vertebral fracture (55% versus 24%) (Table 2). Patient characteristics of patients that received a kidney transplant (*n*=23) and patients that remained on dialysis (*n*=47) were comparable (Appendix 2) although the use of corticosteroids and bisphosphonates during follow-up was higher among kidney transplant recipients (100% versus 21% and 17% versus none). The risk of incident vertebral fracture did not differ significantly for kidney transplant recipients (6/23 with incident vertebral fracture) compared to patients on dialysis (14/47 with incident vertebral fracture) after adjustment for age, sex, and follow-up time (adjusted RR for kidney transplant recipients compared to patients on dialysis 0.94, 95% CI 0.32 to 2.43).

Associations of vertebral trabecular BMD with vertebral fracture

Mean vertebral trabecular BMD was 139±41 mg/cm³ in patients without a prevalent vertebral fracture (*n*=96) and 120±44 mg/cm³ in patients with a prevalent vertebral fracture (*n*=50). Vertebral trabecular BMD was associated with a lower risk of vertebral fracture prevalence in unadjusted models 0.93 (95% CI 0.86 to 0.99) but not when adjusted for potential confounders 0.97 (95% CI 0.89 to 1.04) (Appendix 3).

Table 2. Characteristics of the subset of 70 patients with end-stage renal disease who had follow-up radiographs, stratified by incidence of vertebral fracture.

	No incident vertebral fracture (n=50)	Incident vertebral fracture (n=20)
Demographics and medical history		
Age (years)	52 ±13	60 ±13
Male (%)	31 (62%)	14 (70%)
Diabetes mellitus (%)	7 (14%)	2 (10%)
Current smoker (%)	5 (10%)	0
History of kidney disease		
Dialysis duration (months)	18 (10–39)	25 (18–50)
Renal replacement therapy during follow-up (%)		
– Haemodialysis	24 (48%)	11 (55%)
– Peritoneal dialysis	9 (18%)	3 (15%)
– Kidney transplant	17 (34%)	6 (30%)
Medication use during follow-up		
Corticosteroids (%)*	26 (52%)	7 (35%)
Bisphosphonates (%)	3 (6%)	1 (5%)
Calcium-containing phosphate binders (%)	24 (48%)	7 (35%)
Vitamin D analogues (%)	27 (54%)	12 (60%)
Cinacalcet (%)	4 (8%)	5 (25%)
Bone mineral density and vertebral fracture		
Vertebral bone mineral density (mg/cm ³)	132 ±39	119 ±36
Previous vertebral fracture (%)	12 (24%)	11 (55%)
Deterioration of existing fracture to higher grade (%)	-	1 (5%)
Number of new vertebral fractures (%)		
– One	-	16 (80%)
– Two	-	2 (10%)
– Three	-	1 (5%)
Highest incident vertebral fracture grade (%)		
– Grade 1	-	14 (70%)
– Grade 2	-	5 (25%)
– Grade 3	-	1 (5%)

Results are presented as mean ±standard deviation, median (interquartile range) or percentage.

*Acute rejections, treated with high doses of methylprednisolone, occurred in 3 patients who did not sustain a vertebral fracture, and in 2 patients who did sustain a vertebral fracture.

Associations of PTH with vertebral fracture and vertebral trabecular BMD

One hundred thirty-one patients had no history of parathyroidectomy and non-missing PTH values (Appendix 4). Vertebral fractures were the least prevalent in patients in the middle PTH tertile (16% versus 38% and 43%; $p < 0.05$) (Table 3). Compared to the middle tertile, the adjusted RR of vertebral fracture prevalence was 2.28 for the lowest tertile (95% CI 0.97 to 5.97) and 2.82 for the highest tertile (95% CI 1.22 to 7.27). Correspondingly, the continuous association of PTH with prevalent vertebral fracture risk appeared U-shaped, with the lowest risk around 29 pmol/L (Figure 1). Notably patients in the lowest tertile had significantly lower total alkaline phosphatase levels (median 69 versus 85 and 91 IU/L, $p = 0.02$).

Table 3. Associations of parathyroid hormone with vertebral bone mineral density and vertebral fractures in a subset of 131 patients with end-stage renal disease.

	Parathyroid hormone		
	Lowest tertile (n=45)	Middle tertile (n=44)	Highest tertile (n=42)
PTH (pmol/L)	7 (5–10)	19 (16–23)	50 (36–66)
Alkaline phosphatase (IU/L)	69 (57–89)	85 (73–105)	91 (69–126)
Vertebral fracture prevalence	17 (38%)	7 (16%)	18 (43%)
Relative risk			
– Crude model	2.37 (1.02 to 6.14)	1.00 (ref)	2.69 (1.17 to 6.93)
– Model 1	2.16 (0.92 to 5.61)	1.00 (ref)	2.80 (1.22 to 7.20)
– Model 2	2.28 (0.97 to 5.97)	1.00 (ref)	2.82 (1.22 to 7.27)
Vertebral BMD (mg/cm³)	116±38	130±35	148±38
Difference (mg/cm ³)			
– Crude model	-13.6 (-29.0 to 1.8)	0.00 (ref)	18.7 (3.0 to 140.5)
– Model 1	-9.4 (-22.5 to 3.7)	0.00 (ref)	14.2 (1.0 to 27.5)
– Model 2	-9.7 (-22.7 to 3.3)	0.00 (ref)	14.6 (1.4 to 27.8)

Values are mean ± standard deviation, median (interquartile range), percentage, relative risks estimated with Poisson regression (with 95% confidence intervals), or linear regression coefficients (with 95% confidence intervals).

Abbreviations: PTH: parathyroid hormone; BMD: bone mineral density.

Model 1: age (years) and sex.

Model 2: model 1 + dialysis duration (months) and diabetes (type I or type II/absent).

We repeated these analyses stratified by various patient characteristics (Appendix 5), which all showed similar trends. The U-shaped association of PTH with vertebral fracture risk appeared even stronger in vitamin D analogues users ($n=87$) (adjusted RR 3.68, 95% CI 1.12 to 16.52 for the lowest and 3.57, 95% CI 1.14 to 15.61 for the highest PTH tertile). Patient characteristics were similar between vitamin D analogue users and non-users (Appendix 6), except for higher phosphate (1.49 versus 1.19 mmol/L) and PTH values (23 versus 11 pmol/L) among vitamin D analogue users.

In the lowest PTH tertile, vertebral trabecular BMD tended to be lower with linear regression compared to the middle tertile (adjusted regression coefficient -9.7 mg/cm³, 95% CI -22.7 to 3.3), while in the highest tertile vertebral trabecular BMD was significantly higher (14.6 mg/cm³, 95% CI 1.4 to 27.8) (Table 3). For the continuous associations, lower PTH values tended to track with lower vertebral trabecular BMD values (Appendix 7).

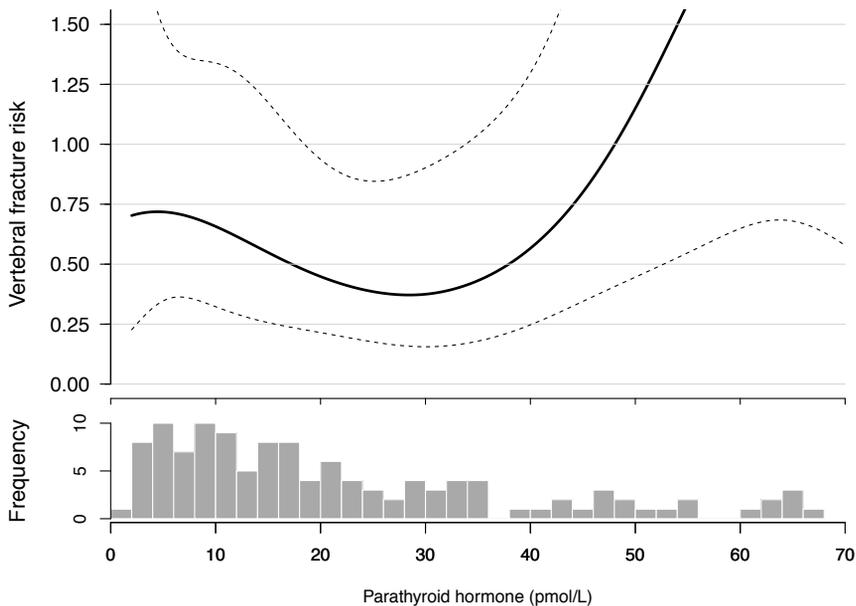


Figure 1. Continuous association of PTH with prevalent vertebral fracture risk

Discussion

Our study indicates that vertebral fractures have a high prevalence (34%) and incidence (29% after median 1.8 years follow-up) in a relatively young population (mean age 52 years) of patients with ESRD. Also, our data show no relationship of CT-measured vertebral trabecular BMD with vertebral fracture and suggest a U-shaped relationship of PTH with vertebral fracture.

The vertebral fracture prevalence in our study is remarkably high compared to the general population. In a population-based study of European men and women aged 50-54 years, the prevalence ranged between 5% and 17% as determined with morphometric approaches,²⁵ and between 2% and 11% in a population-based study of Dutch men and women aged 45-59 years as determined with algorithm-based qualitative methods and a morphometric approach.²⁶ In general, reproducibility is highest with algorithm-based qualitative methods,²⁷ followed by Genant's semiquantitative technique used by us, which in turn has higher reproducibility than morphometric approaches (e.g. the McCloskey and Eastell methods and quantitative morphometry).²⁸ Considering, vertebral fracture prevalence in our ESRD cohort is more than twice as high as in the general population, which could have been even higher if we had also evaluated the lower lumbar spine.

The prevalence of vertebral fractures is poorly documented in cohorts and dialysis registries⁷ and has been reported in only few studies of patients on dialysis.²⁹ Four studies reported prevalences between 21% and 33% for patients generally older (mean ages between 54 and 69 years),^{14,30-32} whereas one study reported 9% vertebral fractures without mentioning age of the study population or method of vertebral fracture assessment³³ and another study reported 11% vertebral fractures among slightly younger incident kidney transplant recipients (49.7 versus 52.2 years), although it was unclear whether only the lumbar spine was evaluated.³⁴ In general, our estimates might be higher due to geographic variation in vertebral fracture prevalence between Northern and Southern Europe²⁵ or different referral patterns for dialysis.³⁵ Also, one of these studies used stricter criteria for wedge fractures (the most common type of vertebral fracture)²⁶ only adjudicating grade 2 and 3 fractures,¹⁴ and another study did not specify vertebral fracture adjudication method.³⁴ Yet another study found 55% vertebral fractures in older patients on hemodialysis (mean 64 years old) but used quantitative morphometry.³⁶ We employed Genant's semiquantitative technique to adjudicate fractures, which allows to exclude other possible causes of vertebral deformity²¹ and has a higher reproducibility than morphometric approaches used in previous studies.²⁸ This supports the high vertebral fracture prevalence of 34% we currently report.

Our study is the first to report vertebral fracture incidence in patients with ESRD using radiographs to assess vertebral fractures. Two previous studies reported 4.8¹² and about 10³⁷ vertebral fractures per 1000 person-years in patients on dialysis, with vertebral fractures identified by International Classification of Diseases, Ninth revision (ICD-9) codes in claim files of the United States Renal Data system. However, this methodology is likely to underestimate vertebral fracture incidence because of clinical underdiagnosis.³ We used standardized methods by 2 independent trained physicians to adjudicate fractures, which is much more sensitive than ICD-9 codes. Our data indicate a high vertebral fracture incidence (146 per 1000 person-years) among patients with ESRD. Although causes of vertebral fracture may differ for patients on dialysis and kidney transplant recipients, our data showed similar vertebral fracture rates for both groups, far exceeding rates reported in placebo groups of large osteoporosis drug trials.³⁸ This high incidence warrants a better understanding of the impact of mineral metabolism disturbances on bone strength in order to prevent these fractures.

In this first study to measure vertebral trabecular BMD with cardiac CT in patients with ESRD, we did not find associations of vertebral trabecular BMD with vertebral fracture, similar to a previous study using quantitative CT.³² Cardiac CT vertebral trabecular BMD correlates well with quantitative CT lumbar spine BMD ($r=0.91-0.93$),¹⁹ which is considered a useful and appropriate method for BMD testing.^{39,40} The discrepancy between vertebral trabecular BMD and fracture might be explained by physiological anabolic effects of PTH, which are most pronounced on trabecular bone.⁴¹ Indeed, we found an association of higher PTH with higher vertebral trabecular BMD, whereas previous studies reported inconsistent associations.¹⁶⁻¹⁸ Because of this, vertebral trabecular BMD may not be useful to assess fracture risk in ESRD. Moreover, our findings indicate that BMD testing is redundant in these patients. The clinical purpose of BMD is to identify high-risk patients for fracture, but with the currently reported vertebral fracture risk, patients on dialysis can all be regarded as high-risk patients for fracture and rather may benefit from radiographic screening for vertebral fractures.

Our data suggest a U-shaped association of PTH with vertebral fracture risk. We used continuous associations to indicate the precise direction of the associations per PTH pmol/L. This allowed us to estimate the shape of fracture risk for the whole range of PTH compared to predefined PTH categories or quantiles, indicating the lowest vertebral fracture risk around 29 pmol/L. Our finding complements previous studies reporting optimal PTH values for fracture risk around 32 pmol/L,¹² above 21 pmol/L,¹³ above 7 pmol/L,¹⁴ between 16 and 32 pmol/L,¹⁵ and below 95 pmol/L.⁴² In order to draw conclusions about the target PTH range in clinical practice, randomized controlled trials are needed to define optimal PTH values for fracture.

Our results should be interpreted within certain limitations. First, the lateral chest radiographs did not allow for fracture assessment of the lower lumbar spine, as we could only evaluate the spine down to the first lumbar vertebra in most patients. Nevertheless, one could even expect a higher prevalence of vertebral fractures with additional lumbar spine radiography. Furthermore, the radiographs were performed as part of routine care which may have introduced indication bias. However, only two radiographs (1%) were performed with the indication of back pain. Other limitations are that PTH was measured with multiple assays, and that we did not have data on historical corticosteroid use or vitamin D status. Notwithstanding, most patients used vitamin D analogues, rendering vitamin D deficiency unlikely as cause of vertebral fractures. Finally, all patients in this study were eligible for transplantation and some were treated with home hemodialysis. This population may therefore be somewhat healthier than the average dialysis population. On the other hand, a high vertebral fracture risk in our population indicates an even higher risk in the general dialysis population.

This study has several strengths. We adjudicated fractures on radiographs based on 2 independent trained physicians, instead of recall of fracture history or radiographic reports. We thus also detected less severe fractures, corroborating the high vertebral fracture prevalence. Also, the patients on dialysis and kidney transplant recipients were well comparable, as all dialysis patients were eligible for transplantation, and all kidney transplant recipients were on dialysis before transplantation.

In conclusion, even relatively young and healthy patients with ESRD are at high risk of vertebral fractures. CT-measured vertebral trabecular BMD is not associated with vertebral fracture and may therefore not be useful to assess fracture risk in ESRD. Rather, patients may benefit from radiographic screening for vertebral fractures. The association of PTH with vertebral fracture risk appears to be U-shaped, with the lowest risk around 29 pmol/L. The target PTH range for fracture needs investigation by randomized controlled trials.

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Supplementary data

Appendix 1. Characteristics of the patients with end-stage renal disease included in the current analyses (n=146) and those excluded because of missing lateral chest radiographs (n=35)

	Included (n = 146)	Excluded (n = 35)	P-value
Demographics and medical history			
Age (years)	52.2 ±13.2	51.2 ±14.2	0.72
Male (%)	98 (67%)	23 (66%)	0.99
Body mass index (kg/m ²)	25.7 ±4.5	25.3 ±4.3	0.62
Diabetes mellitus (%)	18 (12%)	8 (23%)	0.18
Cardiovascular disease (%)	34 (23%)	6 (17%)	0.58
Current smoker (%)	15 (10%)	10 (29%)	0.01
History of kidney disease			
Dialysis vintage (months)	26 (13–55)	31 (15–74)	0.45
Previous transplantation (%)	36 (17%)	6 (17%)	0.47
Cause of end-stage renal disease (%)			0.11
– Cystic kidney disease	27 (18%)	2 (6%)	
– Interstitial nephritis	4 (3%)	3 (69%)	
– Glomerulonephritis	38 (26%)	10 (29%)	
– Vascular disease	32 (22%)	6 (17%)	
– Diabetic nephropathy	9 (6%)	5 (14%)	
– Other	18 (12%)	7 (20%)	
– Unknown	18 (12%)	2 (6%)	
Dialysis treatment (%)			0.86
– Haemodialysis	108 (74%)	27 (77%)	
– Peritoneal dialysis	38 (26%)	8 (23%)	

Appendix 2. Characteristics of the subset of 70 patients with end-stage renal disease who had follow-up radiographs, stratified by kidney transplantation or continued dialysis treatment

	Continued dialysis treatment (n=47)	Received kidney transplant (n=23)
Demographics and medical history		
Age (years)	53 ±13	55 ±14
Male (%)	31 (66%)	14 (61%)
Diabetes mellitus (%)	7 (15%)	2 (9%)
Current smoker (%)	4 (9%)	1 (4%)
History of kidney disease		
Dialysis duration (months)	20 (10–46)	30 (12–47)
Renal replacement therapy before inclusion (%)		
– Haemodialysis	35 (74%)	16 (70%)
– Peritoneal dialysis	12 (26%)	7 (30%)
Medication use during follow-up		
Corticosteroids (%)*	10 (21%)	23 (100%)
Bisphosphonates (%)	0	4 (17%)
Calcium-containing phosphate binders (%)**	18 (38%)	4 (36%)
Vitamin D analogues (%)	37 (79%)	9 (82%)
Cinacalcet (%)	7 (15%)	1 (9%)
Bone mineral density and vertebral fracture		
Vertebral bone mineral density (mg/cm ³)	129 ±37	126 ±43
Previous vertebral fracture (%)	17 (36%)	6 (26%)
Incident vertebral fracture (%)	14 (30%)	6 (26%)

Results are presented as mean ±standard deviation, median (interquartile range) or percentage.

*Acute rejections, treated with high doses of methylprednisolone, occurred in 5 kidney transplant recipients.

**Including calcium carbonate prescribed post-transplantation.

Appendix 3. Associations of vertebral bone mineral density with vertebral fracture prevalence in 146 patients on dialysis and with vertebral fracture incidence in 70 patients with end-stage renal disease.

Relative risk of vertebral fracture prevalence	N	Per 10 mg/cm ³ higher vertebral BMD
- Crude model	146	0.93 (0.86 to 0.99)
- Model 1	146	0.98 (0.90 to 1.06)
- Model 2	146	0.97 (0.89 to 1.04)
Relative risk of vertebral fracture incidence	N	Per 10 mg/cm ³ higher vertebral BMD
- Crude model	70	0.92 (0.81 to 1.04)
- Model 1	70	1.00 (0.85 to 1.15)
o Patients on dialysis only	47	0.94 (0.75 to 1.14)
o Kidney transplant recipients only	23	1.10 (0.87 to 1.48)

Model 1: age (years) and sex.

Model 2: model 1 + dialysis duration (months) and diabetes (type I or type II/absent).

For vertebral fracture incidence, all models were adjusted for follow-up time (years).

Values are relative risks estimated with Poisson regression (with 95% confidence intervals).

Abbreviations: BMD: bone mineral density.

Appendix 4. Patient characteristics stratified by parathyroid hormone tertiles (n=131)

	Lowest tertile (n = 45)	Middle tertile (n = 44)	Highest tertile (n = 42)	P-value
Demographics and medical history				
Age (years)	55 ±12	52 ±11	50 ±15	0.11
Male (%)	29 (64%)	30 (68%)	26 (62%)	0.83
Body mass index (kg/m ²)	25.1 ±4.4	26.1 ±4.3	25.8 ±4.8	0.52
Diabetes mellitus (%)	6 (13%)	5 (11%)	6 (14%)	0.92
Cardiovascular disease (%)	10 (22%)	10 (23%)	9 (21%)	0.99
Current smoker (%)	8 (18%)	1 (2%)	4 (10%)	0.05
History of kidney disease				
Dialysis duration (months)	21 (12–40)	21 (11–42)	29 (15–55)	0.30
Previous transplantation (%)	9 (20%)	5 (11%)	14 (33%)	0.04
Cause of end-stage renal disease (%)				0.57
– Cystic kidney disease	10 (22%)	8 (18%)	7 (17%)	
– Interstitial nephritis	0	0	1 (2%)	
– Glomerulonephritis	11 (24%)	15 (34%)	7 (17%)	
– Vascular disease	13 (29%)	7 (16%)	9 (21%)	
– Diabetic nephropathy	1 (2%)	3 (7%)	5 (12%)	
– Other	5 (11%)	6 (14%)	7 (17%)	
– Unknown	5 (11%)	5 (11%)	6 (14%)	
Dialysis treatment (%)				0.13
– Haemodialysis	37 (82%)	28 (64%)	29 (69%)	
– Peritoneal dialysis	8 (18%)	16 (36%)	13 (31%)	
Medication use at inclusion*				
Corticosteroids (%)	7 (16%)	4 (9%)	6 (14%)	0.59
Calcium-containing phosphate binders (%)	12 (33%)	12 (30%)	12 (32%)	0.95
Vitamin D analogues (%)	23 (64%)	31 (78%)	30 (87%)	0.07
Cinacalcet (%)	5 (14%)	3 (8%)	11 (29%)	0.03
Laboratory parameters				
Calcium (mmol/L)	2.38 ±0.11	2.32 ±0.13	2.35 ±0.16	0.18
Phosphate (mmol/L)	1.14 ±0.42	1.40 ±0.55	1.50 ±0.53	<0.01
Parathyroid hormone (pmol/L)	7 (5–10)	19 (16–23)	50 (36–66)	<0.01
C-reactive protein (mg/L)	3 (2–7)	4 (2–8)	2 (1–4)	0.36
Total alkaline phosphatase (IU/L)	69 (57–89)	85 (73–105)	91 (69–126)	0.02
Bone mineral density and vertebral fracture				
Vertebral bone mineral density (mg/cm ³)	116 ±38	130 ±35	148 ±38	<0.01
Prevalent vertebral fracture (%)	17 (38%)	7 (16%)	18 (43%)	0.02

Results are presented as mean ±standard deviation, median (interquartile range) or percentage.

P-values were calculated with one-way analyses of variance for compared normally distributed variables, with Kruskal-Wallis tests for non-normally distributed variables, and with Chi-squared tests for categorical data.

*Data on medication use (except for corticosteroid use) were available in 114 patients.

Conversion factors for units: calcium mg/dL to mmol/L, x0.2495; phosphate mg/dL to mmol/L, x0.3229.

Appendix 5. Associations of parathyroid hormone with vertebral fractures stratified by various patient characteristics in 131 patients with end-stage renal disease.

Age <50 years			
	PTH		
	Lowest tertile (n=12)	Middle tertile (n=16)	Highest tertile (n=22)
PTH (pmol/L)	5 (4–7)	17 (15–21)	64 (53–75)
Vertebral BMD	140 ±41	149 ±28	170 ±31
Vertebral fracture prevalence	25%	13%	32%
Relative risk of vertebral fracture prevalence			
– Unadjusted	2.00 (0.33 to 15.18)	1.00 (ref)	2.55 (0.62 to 17.08)
– Model 1	2.11 (0.35 to 16.16)	1.00 (ref)	2.77 (0.67 to 18.60)
– Model 2	3.80 (0.53 to 36.85)	1.00 (ref)	3.38 (0.76 to 24.76)
Male sex			
	PTH		
	Lowest tertile (n=29)	Middle tertile (n=30)	Highest tertile (n=26)
PTH (pmol/L)	6 (4–10)	19 (16–22)	45 (35–66)
Vertebral BMD	110 ±34	127 ±34	136 ±37
Vertebral fracture prevalence	45%	20%	50%
Relative risk of vertebral fracture prevalence			
– Unadjusted	2.24 (0.89 to 6.38)	1.00 (ref)	2.50 (0.99 to 7.12)
– Model 1	1.98 (0.77 to 5.69)	1.00 (ref)	2.38 (0.94 to 6.80)
– Model 2	2.08 (0.80 to 6.08)	1.00 (ref)	2.51 (0.98 to 7.21)
No history of diabetes			
	PTH		
	Lowest tertile (n=39)	Middle tertile (n=39)	Highest tertile (n=36)
PTH (pmol/L)	7 (5–9)	20 (16–23)	50 (41–66)
Vertebral BMD	115 ±36	130 ±37	149 ±40
Vertebral fracture prevalence	39%	18%	42%
Relative risk of vertebral fracture prevalence			
– Unadjusted	2.14 (0.90 to 5.61)	1.00 (ref)	2.32 (0.98 to 6.08)
– Model 1	1.97 (0.83 to 5.20)	1.00 (ref)	2.46 (1.04 to 6.45)
– Model 2	2.10 (0.87 to 5.58)	1.00 (ref)	2.45 (1.03 to 6.44)

Age \geq50 years			
PTH			
Lowest tertile (n=33)	Middle tertile (n=28)	Highest tertile (n=20)	
8 (5–10)	20 (16–25)	37 (34–47)	
107 \pm 34	118 \pm 34	124 \pm 30	
42%	18%	55%	
2.38 (0.91 to 7.35)	1.00 (ref)	3.08 (1.12 to 9.78)	
2.08 (0.79 to 6.50)	1.00 (ref)	2.43 (0.87 to 7.84)	
2.07 (0.78 to 6.44)	1.00 (ref)	2.44 (0.87 to 7.86)	
Female sex			
PTH			
Lowest tertile (n=16)	Middle tertile (n=14)	Highest tertile (n=16)	
7 (5–10)	19 (16–23)	62 (51–73)	
126 \pm 44	136 \pm 37	169 \pm 32	
25%	7%	31%	
3.50 (0.52 to 68.47)	1.00 (ref)	4.38 (0.71 to 83.82)	
3.41 (0.50 to 66.74)	1.00 (ref)	5.79 (0.91 to 111.72)	
3.92 (0.57 to 77.49)	1.00 (ref)	5.14 (0.77 to 100.72)	
History of diabetes			
PTH			
Lowest tertile (n=6)	Middle tertile (n=5)	Highest tertile (n=6)	
7 (5–10)	15 (15–17)	49 (33–79)	
119 \pm 57	125 \pm 34	143 \pm 26	
33%	0%	50%	
-	1.00 (ref)	-	
-	1.00 (ref)	-	
-	1.00 (ref)	-	

Appendix 5. Continued

No history of cardiovascular disease			
	PTH		
	Lowest tertile (n=35)	Middle tertile (n=34)	Highest tertile (n=33)
PTH (pmol/L)	6 (4–9)	18 (15–22)	56 (42–72)
Vertebral BMD	121 ±40	136 ±36	158 ±35
Vertebral fracture prevalence	37%	18%	39%
Relative risk of vertebral fracture prevalence			
– Unadjusted	2.10 (0.83 to 5.99)	1.00 (ref)	2.23 (0.88 to 6.35)
– Model 1	1.76 (0.68 to 5.09)	1.00 (ref)	2.33 (0.92 to 6.64)
– Model 2	1.88 (0.72 to 5.53)	1.00 (ref)	2.28 (0.89 to 6.55)
No current smoker			
	PTH		
	Lowest tertile (n=37)	Middle tertile (n=43)	Highest tertile (n=38)
PTH (pmol/L)	6 (4–9)	19 (16–23)	50 (40–71)
Vertebral BMD	119 ±40	130 ±35	150 ±37
Vertebral fracture prevalence	38%	14%	42%
Relative risk of vertebral fracture prevalence			
– Unadjusted	2.71 (1.09 to 7.66)	1.00 (ref)	3.02 (1.24 to 8.41)
– Model 1	2.27 (0.90 to 6.48)	1.00 (ref)	3.18 (1.31 to 8.85)
– Model 2	2.34 (0.92 to 6.71)	1.00 (ref)	3.25 (1.33 to 9.09)
No history of transplantation			
	PTH		
	Lowest tertile (n=36)	Middle tertile (n=39)	Highest tertile (n=28)
PTH (pmol/L)	6 (4–9)	18 (16–22)	45 (34–62)
Vertebral BMD	119 ±41	128 ±35	142 ±38
Vertebral fracture prevalence	28%	15%	50%
Relative risk of vertebral fracture prevalence			
– Unadjusted	1.81 (0.67 to 5.31)	1.00 (ref)	3.25 (1.30 to 9.18)
– Model 1	1.42 (0.52 to 4.22)	1.00 (ref)	2.67 (1.06 to 7.62)
– Model 2	1.44 (0.53 to 4.27)	1.00 (ref)	2.67 (1.06 to 7.62)

History of cardiovascular disease		
	PTH	
Lowest tertile (n=10)	Middle tertile (n=10)	Highest tertile (n=9)
9 (6–10)	23 (18–26)	43 (35–49)
98 ±25	107 ±19	112 ±25
40%	10%	56%
-	1.00 (ref)	-
-	1.00 (ref)	-
-	1.00 (ref)	-
Current smoker		
	PTH	
Lowest tertile (n=8)	Middle tertile (n=1)	Highest tertile (n=4)
8 (5–10)	16	46 (35–56)
104 ±30	128	128 ±47
38%	100%	50%
-	1.00 (ref)	-
-	1.00 (ref)	-
-	1.00 (ref)	-
History transplantation		
	PTH	
Lowest tertile (n=6)	Middle tertile (n=5)	Highest tertile (n=6)
7 (5–10)	15 (15–17)	49 (33–79)
119 ±57	125 ±34	143 ±26
33%	0%	50%
-	1.00 (ref)	-
-	1.00 (ref)	-
-	1.00 (ref)	-

Appendix 5. Continued

	Haemodialysis		
	PTH		
	Lowest tertile (n=37)	Middle tertile (n=28)	Highest tertile (n=29)
PTH (pmol/L)	7 (5–10)	18 (16–22)	52 (39–66)
Vertebral BMD	118 ±39	126 ±33	151 ±34
Vertebral fracture prevalence	35%	18%	48%
Relative risk of vertebral fracture prevalence			
- Unadjusted	1.97 (0.74 to 6.13)	1.00 (ref)	2.70 (1.03 to 8.37)
- Model 1	1.80 (0.68 to 5.61)	1.00 (ref)	2.98 (1.14 to 9.22)
- Model 2	2.01 (0.74 to 6.39)	1.00 (ref)	3.10 (1.18 to 9.64)
	No prednisone use		
	PTH		
	Lowest tertile (n=36)	Middle tertile (n=40)	Highest tertile (n=36)
PTH (pmol/L)	6 (4–10)	19 (16–23)	49 (35–66)
Vertebral BMD	121 ±40	130 ±36	147 ±39
Vertebral fracture prevalence	28%	18%	47%
Relative risk of vertebral fracture prevalence			
- Unadjusted	1.59 (0.61 to 4.37)	1.00 (ref)	2.70 (1.16 to 6.98)
- Model 1	1.41 (0.54 to 3.91)	1.00 (ref)	2.67 (1.15 to 6.92)
- Model 2	1.49 (0.56 to 4.14)	1.00 (ref)	2.55 (1.10 to 6.63)
	No calcium-containing phosphate binder use		
	PTH		
	Lowest tertile (n=24)	Middle tertile (n=28)	Highest tertile (n=26)
PTH (pmol/L)	8 (5–10)	19 (15–24)	55 (43–71)
Vertebral BMD	117 ±43	135 ±36	141 ±35
Vertebral fracture prevalence	42%	14%	50%
Relative risk of vertebral fracture prevalence			
- Unadjusted	2.92 (0.98 to 10.63)	1.00 (ref)	3.50 (1.24 to 12.43)
- Model 1	3.09 (1.01 to 11.45)	1.00 (ref)	3.46 (1.22 to 12.30)
- Model 2	2.98 (0.97 to 11.09)	1.00 (ref)	3.52 (1.24 to 12.54)

Peritoneal dialysis		
PTH		
Lowest tertile (n=8)	Middle tertile (n=16)	Highest tertile (n=13)
5 (4–9)	22 (16–26)	47 (35–66)
108 ±36	136 ±39	142 ±46
50%	13%	31%
-	1.00 (ref)	-
-	1.00 (ref)	-
-	1.00 (ref)	-
Prednisone use		
PTH		
Lowest tertile (n=7)	Middle tertile (n=4)	Highest tertile (n=6)
9 (7–10)	18 (14–22)	64 (51–95)
93 ±27	127 ±30	154 ±36
100%	0%	17%
-	1.00 (ref)	-
-	1.00 (ref)	-
-	1.00 (ref)	-
Calcium-containing phosphate binder use		
PTH		
Lowest tertile (n=12)	Middle tertile (n=12)	Highest tertile (n=12)
6 (5–8)	19 (16–22)	50 (41–68)
121 ±33	111 ±27	164 ±43
33%	17%	25%
2.00 (0.39 to 14.43)	1.00 (ref)	1.50 (0.25 to 11.39)
2.41 (0.44 to 18.50)	1.00 (ref)	1.52 (0.24 to 12.04)
-	1.00 (ref)	-

Appendix 5. Continued

No vitamin D analogue use			
	PTH		
	Lowest tertile (n=13)	Middle tertile (n=9)	Highest tertile (n=5)
PTH (pmol/L)	6 (5–9)	18 (16–20)	66 (63–94)
Vertebral BMD	129 ±52	104 ±31	153 ±12
Vertebral fracture prevalence	31%	33%	60%
Relative risk of vertebral fracture prevalence			
- Unadjusted	-	1.00 (ref)	-
- Model 1	-	1.00 (ref)	-
- Model 2	-	1.00 (ref)	-
No cinacalcet use			
	PTH		
	Lowest tertile (n=31)	Middle tertile (n=37)	Highest tertile (n=27)
PTH (pmol/L)	7 (5–10)	19 (16–23)	49 (35–74)
Vertebral BMD	122 ±41	128 ±37	149 ±44
Vertebral fracture prevalence	32%	16%	37%
Relative risk of vertebral fracture prevalence			
- Unadjusted	1.99 (0.74 to 5.85)	1.00 (ref)	2.28 (0.85 to 6.71)
- Model 1	1.96 (0.72 to 5.77)	1.00 (ref)	2.29 (0.85 to 6.75)
- Model 2	2.25 (0.82 to 6.83)	1.00 (ref)	2.65 (0.97 to 8.00)

Values are mean ±standard deviation, median (interquartile range), percentage, risk ratios estimated with Poisson regression (with 95% confidence intervals). Regression was not performed when any tertile within one stratus consisted of <10 subjects.

Vitamin D analogue use			
PTH			
Lowest tertile (n=23)	Middle tertile (n=31)	Highest tertile (n=33)	
7 (5–10)	21 (15–25)	48 (39–66)	
113 ±30	134 ±34	148 ±41	
44%	10%	39%	
4.49 (1.37 to 20.04)	1.00 (ref)	4.07 (1.31 to 17.76)	
4.21 (1.28 to 18.86)	1.00 (ref)	3.90 (1.25 to 17.05)	
3.68 (1.12 to 16.52)	1.00 (ref)	3.57 (1.14 to 15.61)	
Cinacalcet use			
PTH			
Lowest tertile (n=5)	Middle tertile (n=3)	Highest tertile (n=11)	
9 (6–10)	24 (20–27)	56 (47–105)	
95 ±15	120 ±10	148 ±23	
80%	0%	55%	
-	1.00 (ref)	-	
-	1.00 (ref)	-	
-	1.00 (ref)	-	

Abbreviations: PTH: parathyroid hormone; BMD: bone mineral density.

Model 1: age (years) and sex.

Model 2: model 1 + dialysis duration (months) and diabetes (type I or type II/absent).

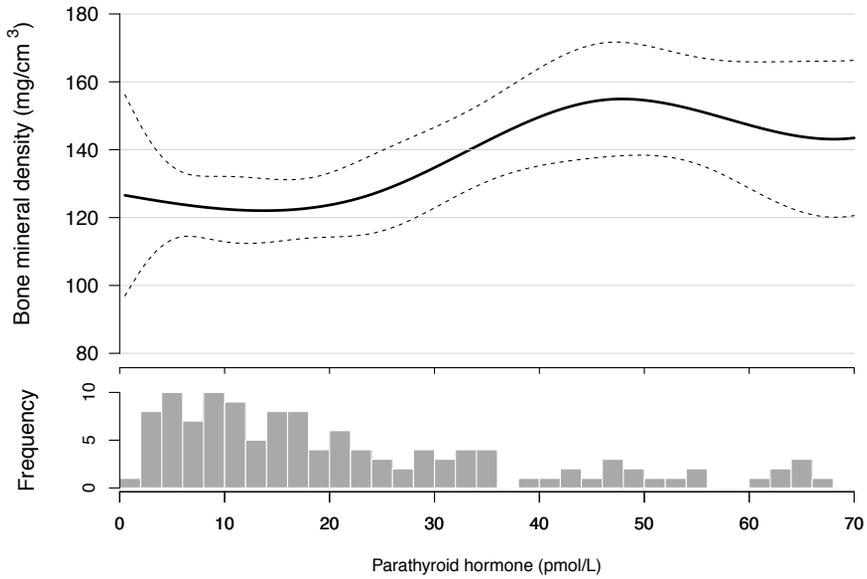
Appendix 6. Patient characteristics stratified by vitamin D analogue users and non-users (n=114)*

	Vitamin D analogue users (n = 87)	Non-users (n = 27)
Demographics and medical history		
Age (years)	52 ±12	54 ±11
Male (%)	55 (63%)	18 (67%)
Body mass index (kg/m ²)	25.6 ±4.5	26.3 ±5.1
Diabetes mellitus (%)	10 (11%)	5 (19%)
Cardiovascular disease (%)	19 (22%)	8 (30%)
Current smoker (%)	8 (9%)	5 (19%)
History of kidney disease		
Dialysis duration (months)	25 (13–48)	30 (11–44)
Previous transplantation (%)	21 (24%)	5 (19%)
Cause of end-stage renal disease (%)		
– Cystic kidney disease	10 (11%)	8 (30%)
– Interstitial nephritis	1	0
– Glomerulonephritis	24 (28%)	6 (22%)
– Vascular disease	20 (23%)	6 (22%)
– Diabetic nephropathy	6 (7%)	2 (7%)
– Other	13 (15%)	3 (11%)
– Unknown	13 (15%)	2 (7%)
Dialysis treatment (%)		
– Haemodialysis	59 (68%)	23 (85%)
– Peritoneal dialysis	28 (32%)	4 (15%)
Laboratory parameters		
Calcium (mmol/L)	2.36 ±0.14	2.31 ±0.15
Phosphate (mmol/L)	1.49 ±0.52	1.19 ±0.32
Parathyroid hormone (pmol/L)	23 (11–44)	12 (6–20)
C-reactive protein (mg/L)	3 (2–6)	4 (2–8)
Bone mineral density and vertebral fracture		
Vertebral bone mineral density (mg/cm ³)	134 ±38	125 ±43
Prevalent vertebral fracture (%)	26 (30%)	10 (37%)

Results are presented as mean ±standard deviation, median (interquartile range) or percentage.

*Data on medication use were available in 114 patients.

Conversion factors for units: calcium mg/dL to mmol/L, x0.2495; phosphate mg/dL to mmol/L, x0.3229.



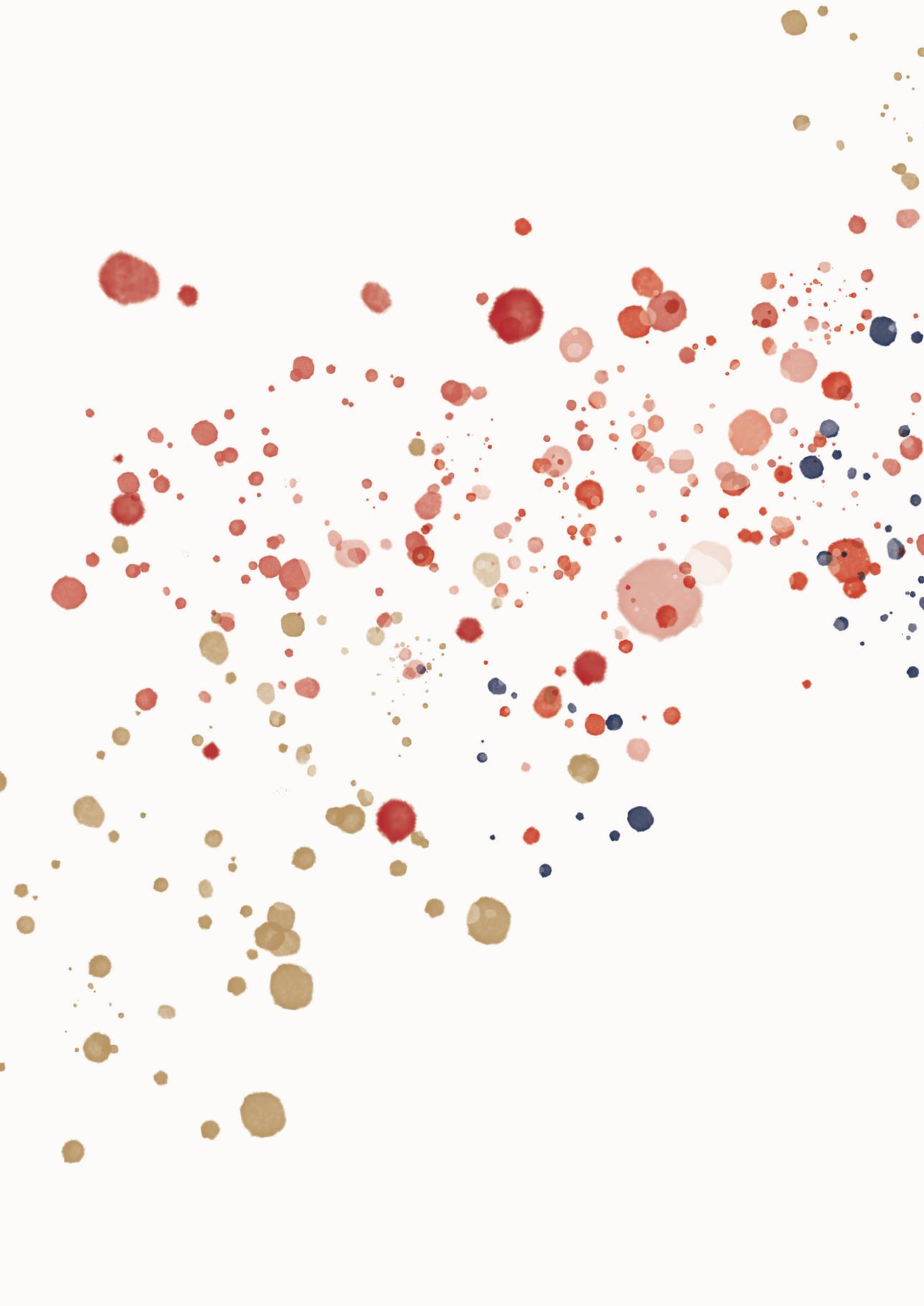
Appendix 7. Continuous associations of parathyroid hormone with vertebral trabecular bone mineral density in 131 patients with end-stage renal disease adjusted for age- and sex. A histogram of parathyroid hormone is shown at the bottom.



Part 3



Functional outcome,
quality of life and
caregiver burden





Chapter 9

Association of initiation of maintenance dialysis with functional status and caregiver burden

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Abstract

Background and objectives: Little is known about the functional course after initiating dialysis in the elderly patient with end-stage kidney disease (ESKD). The aim of this study was to assess the association of the initiation of dialysis in an elderly population with functional status and caregiver burden.

Design, setting, participants & measurements: This study included participants ≥ 65 years with ESKD who were enrolled in the Geriatric assessment in Older patients starting Dialysis (GOLD) study. All underwent a geriatric assessment and a frailty screening (Fried Frailty Index and Groningen Frailty Indicator) at the time of dialysis initiation. Functional status (ADL (activities of daily life) and IADL (instrumental activities of daily life)) and caregiver burden were assessed at baseline and after 6 months. Decline was defined as a loss of ≥ 1 domains in functional status, stable as no difference between baseline and follow-up and improvement as a gain of ≥ 1 domains in functional status. Logistic regression was performed to assess the association between the combined outcome functional decline/death and potential risk factors.

Results: Of the 196 included participants functional data were available for 187 participants. Mean age was 75 ± 7 years; 33% were women. At the start of dialysis, 79% were care dependent in functional status. After 6 months, 40% experienced a decline in functional status, 34% remained stable, 18% improved and 8% died. The prevalence of high caregiver burden increased from 23% to 38% ($p=0.004$). In the multivariable analysis age (OR 1.05, 95% CI 1.00-1.10 per year older at baseline) and a high Groningen Frailty Indicator compared to a score of < 4 (OR 1.97, 95% CI 1.05-3.68) were associated with functional decline/death.

Conclusions: In patients ≥ 65 years, functional decline within the first 6 months after initiating dialysis is highly prevalent. The risk is higher in older and frail patients. Loss in functional status was mainly driven by decline in IADL. Moreover, the initiation of dialysis seems to be accompanied with an increase in caregiver burden.

Introduction

The group of elderly on maintenance dialysis is increasing.¹ This is due to aging of the population, an increase in the prevalence of chronic kidney disease, and more liberal acceptance of elderly into dialysis programs.² Elderly patients are a very heterogeneous group with a high prevalence of comorbidity and geriatric problems.³ One of these problems is functional dependence. This can be defined as the loss of the ability to carry out activities essential to independent living, including tasks needed for self-care (such as bathing, dressing and continence) and more complex tasks that support independent living in a community (such as shopping, housecleaning, and telephone use).⁴ The ability to perform these tasks depends on cognitive, motor (e.g. mobility), and perceptual capacities. In elderly patients on dialysis, functional dependence is highly prevalent.^{5,6} It is strongly associated with mortality,^{5,7} therapy withdrawal and time to first hospitalization.⁵ Furthermore, functional dependence can negatively influence quality of life,^{8,9} increase caregiver burden and increase the use of health services. Another essential point is that when it comes to prognosis, elderly patients value maintaining independence most.¹⁰

Therefore, it is important to understand what impact the initiation of dialysis has on the course of functional status. Moreover, it is important to try to predict in which patients functional status will improve after initiating dialysis (assumed through improvement of uremic complaints) and in which it will decline (due to e.g. burden of dialysis therapy). This can inform patients about prognosis and aid (shared) decision making regarding dialysis. Furthermore, knowledge about functional change may guide interventions to prevent functional decline or initiate improvement in high risk patients, such as rehabilitation programs or physical training.

Unfortunately, little is known about the functional trajectory after initiating dialysis in the elderly patient with end-stage kidney disease (ESKD). Two previous studies reported high rates of functional decline,^{11,12} but these studies were performed in a very specific population (nursing home patients), or were performed in a small single center cohort, and do not inform us about the general older dialysis population.

Therefore, the aim of the study was to assess the association of the initiation of maintenance dialysis with functional status and caregiver burden in a community dwelling elderly ESKD population. Furthermore, we explored which variables are associated with functional change after initiating dialysis.

Methods

Study participants

To describe the trajectory in functional status in elderly patients initiating dialysis, data were used from the Geriatric assessment in OLder patients starting Dialysis (GOLD) study. This is a prospective, multicenter cohort study assessing the relationship of geriatric assessment with outcome in patients with ESKD. Participants were enrolled from 17 centers across the Netherlands in the period from August 2014 to September 2017. Patients initiating dialysis (peritoneal dialysis (PD) and hemodialysis (HD)) who were ≥ 65 years were included. Participants were recruited from the pre-dialysis outpatients clinics by their treating nephrologists. If inclusion criteria were met, participants were contacted by one of the researchers or research nurses to make an appointment for inclusion. Of the contacted participants, 3 were excluded because of communication problems or because they died before inclusion (n=2). Furthermore, participants refused to participate because they felt not fit enough (n=19), the family disagreed with participation (n=2) or they already participated in another study (n=1). The aim was to include patients eligible for dialysis between 3 weeks before and 2 weeks after dialysis initiation. Participants were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language, or if they suffered from a terminal nonrenal-related condition. After 6 months participants and caregivers were contacted by telephone for follow up.

The study was conducted in accordance with the declaration of Helsinki and approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all participants before enrollment.

Data collection

Baseline data were collected by one of the two investigators or one of the two trained research nurses. Participants were either visited at home or in the dialysis center, before starting the dialysis session. Baseline data included: demographic data (age, sex, living, social situation, smoking and alcohol use), information obtained from clinical charts (dialysis modality, cause of kidney failure), and a geriatric assessment. The geriatric assessment consisted of validated questionnaires or structured assessment of seven domains (Chapter 2, Appendix 2): activities of daily living (ADL, Katz),¹³ instrumental activities of daily living (IADL, Lawton and Brody),¹⁴ comorbidity burden (Cumulative Illness Rating Scale -Geriatric, CIRS-G),¹⁵ depressive symptoms (Geriatric Depression Scale, GDS-15),^{16,17} mobility (Timed up and go test, TUG),¹⁸ nutrition (Mini nutritional assessment, MNA)¹⁹ and cognition. The latter was assessed with the Mini Mental State Examination (MMSE),²⁰ semantic fluency test,²¹ clock drawing test²² and enhanced cued recall test (ECR)²³. The outcome of the geriatric assessment was composed by the sum of

impairment in the seven geriatric domains. Participants were considered frail according to the geriatric assessment if they scored ≥ 2 impairments.^{24,25} In addition, two frailty screening instruments were applied: the Fried frailty index²⁶ and Groningen Frailty Indicator.²⁷ The Groningen Frailty Indicator is a 15-item frailty screening instrument that measures loss of function in four domains: physical (mobility, general health, malnutrition, polypharmacy, hearing, vision), social (emotional isolation), cognitive (cognitive dysfunction) and psychological (depressed mood and feelings of anxiety). The range of the Groningen Frailty Indicator score is 0 to 15, with higher scores indicating more severe impairment. Participants were considered frail according to the Groningen Frailty Indicator if they scored ≥ 4 points.

All participants alive at 6 months after inclusion were interviewed by phone by a research nurse or investigator. During this interview, questionnaires about functional status (ADL, IADL) were completed.

Functional status

We scored overall functional status by combining ADL and the IADL; a cumulative score of 0 out of a possible 13 points indicates not care dependent, 1-5 mild/moderate dependence and >5 severe care dependence.⁵ For baseline and follow-up, the number of dependencies in functional status was counted. The difference in number of dependencies between these moments was defined as functional outcome. Functional outcome was categorized in improvement (score $\geq +1$), stable (score of 0), decline (score ≤ -1) and death.

Caregiver

For all participants, a relevant caregiver was approached (if available), and when participating, informed consent was obtained. Questionnaires for caregivers were either completed during the visit to the participant or sent by mail, preferably returned within two weeks of enrollment of the participant. After 6 months, if the participant was still alive, caregivers were asked to fill out the questionnaires for a second time.

Caregivers received three questionnaires: the neuropsychological inventory (NPI),²⁸ the interview of deterioration in daily life dementia (IDDD)²⁹ and the SPPIC (Self-perceived Pressure from Informal Care, a Dutch questionnaire assessing caregiver burden)³⁰. Cut-off points for the different test are shown in Chapter 2, Appendix 2.

Statistical analysis

Categorical variables were reported as proportions, continuous variables were reported as means with standard deviations (SD) or medians with interquartile range (IQR) for non-parametric data. For subgroup analysis participants were divided into different

groups according to age (65-69, 70-74 and ≥ 75 years) and functional dependency (independent, mild/moderate dependent and severely dependent). Differences between groups were assessed by the Chi-square test or Fisher exact test for categorical data, the one-way ANOVA for parametric continuous data and the Kruskal Wallis for non-parametric continuous data. To assess the difference between the different age categories and functional dependencies the Chi-square test for trend was used. Furthermore, to assess differences between baseline and follow-up data, the paired t-test was used for paired parametric data, the Wilcoxon signed rank test for non-parametric paired data and the McNemar test for paired binary data. To assess the association between functional outcome and the results of the different caregiver questionnaires the Chi-square test was used.

To investigate the association between functional outcome and different potential predictors logistic regression was performed. For this analysis functional outcome was dichotomized in a composite outcome "functional decline/death" and "stable/improvement". A composite outcome was used because death in the chronic and frail elderly is usually preceded by slow functional decline with steadily progressive disability before dying from complications.³¹ Components of the geriatric assessment were assessed in a univariable analysis. Variables were considered as potential risk factors when $p < 0.20$ in the univariable analysis and were included in a multivariable logistic regression analysis (including age and sex). Additionally, the association between different frailty tools (geriatric assessment, Groningen Frailty Indicator, Fried frailty Index) and the composite outcome was assessed with logistic regression.

A two-sided probability of $p < 0.05$ was considered statistically significant. Outcomes were calculated with a 95% confidence interval (95% CI). Data were analyzed using SPSS software (IBM SPSS statistics version 21).

Results

During the study period, 196 incident dialysis participants were included. Of these participants, 5 (3%) were lost to follow up and 4 (2%) participants were excluded from analysis because there was too much time between inclusion and start of dialysis (>3 months), leaving 187 participants for analysis. The majority of the participants had their baseline assessments shortly after the start of dialysis (median 8 days, IQR 1.5-12.5). Baseline characteristics are shown in Table 1. The mean age of the population was 75±7 years and 33% of the participants were women. The main cause of ESKD was vascular disease (50%), followed by diabetes (16%). Of all participants, 77% started in-center hemodialysis and 23% peritoneal dialysis. No differences were seen for the different age categories (Table 1).

At baseline, 21% of the participants were independent in functional status, 52% was mildly/moderately dependent and 27% was severely dependent. Prevalence of severe dependence was the highest in the age category of ≥75 years (69% vs. 12% in the age category 65-69 years). Severely dependent participants experienced more symptoms of depression (54% vs. 12%), were more impaired in mobility (56% vs. 0%) and more frail according to frailty tools (geriatric assessment 96% vs. 24%, Fried frailty index 84% vs. 13%, Groningen Frailty Indicator 92% vs. 39%) compared to the independent participants (Appendix 1).

Functional change after initiating dialysis

After 6 months follow up, 8% had died and 2% received a kidney transplant. Of the participants still alive (including participants that received a kidney transplant), 40% experienced decline in functional status, 34% were stable and 18% of the participants improved. The decline in functional status was mostly due to loss in IADL independence (37% decline vs. 17% improvement). For ADL most participants remained stable (66%). Figure 1 shows changes in ADL, IADL and overall functional status. Specific impairments in functional status for baseline and follow-up are shown in Appendix 2.

Table 1. Baseline characteristics of 187 incident dialysis patients in the Geriatric assessment in Older patients starting dialysis study

Participant Characteristics	Total (n=187)	Age category in years		
		65-69 (n=41)	70-74 (n=49)	≥75 (n=97)
Age mean (±SD)	75 (7)			
Women	61 (33%)	16 (39%)	15 (31%)	30 (31%)
Single/widow	78 (42%)	19 (46%)	21 (43%)	38 (39%)
Living at nursing home	10 (5%)	1 (2%)	1 (2%)	8 (8%)
Smoker* (n, %)	137 (73%)	30 (79%)	37 (80%)	70 (74%)
Current alcohol use	73 (41%)	13 (35%)	19 (41%)	41 (43%)
Underlying kidney disease				
– Diabetes	29 (16%)	5 (12%)	10 (20%)	14 (14%)
– Vascular	93 (50%)	17 (42%)	26 (53%)	50 (52%)
– Other/unknown	65 (34%)	19 (46%)	13 (27%)	33 (34%)
Hemodialysis (n,%)	144 (77%)	28 (68%)	39 (80%)	77 (79%)
Geriatric assessment				
1. Impaired ADL at baseline (n,%)	56 (30%)	11 (27%)	13 (27%)	32 (33%)
2. Impaired IADL at baseline (n,%)	146 (78%)	30 (73%)	36 (74%)	80 (83%)
3. Impaired cognition (n,%)	123 (67%)	26 (65%)	27 (57%)	70 (73%)
4. Severe comorbidity burden (n,%)	80 (43%)	18 (44%)	23 (47%)	39 (40%)
5. Severely impaired mobility (n,%)	35 (20%)	7 (18%)	8 (17%)	20 (22%)
6. Symptoms of depression (n,%)	56 (30%)	12 (29%)	11 (22%)	33 (34%)
7. Malnutrition (n,%)	10 (5%)	3 (7%)	3 (6%)	4 (4%)
Frail according to GA (≥2 impairments)	148 (77%)	32 (78%)	34 (69%)	78 (80%)
Frail according to Fried Frailty Index (≥3)	82 (46%)	17 (46%)	20 (44%)	45 (47%)
Frail according to Groningen Frailty Indicator (≥4)	115 (62%)	24 (59%)	29 (59%)	62 (64%)

ADL, Activities of daily living; IADL, Instrumental activities of daily living; GA, Geriatric assessment, GFI, Groningen frailty indicator.

* Smoker; if the participant has smoked but stopped, or is still smoking cigarettes.

The following variables had missing data: cognition (2.1%), Fried frailty index (4.8%), mobility (5.3%) and smoking (4.3%)

Data on functional change and mortality stratified by age and baseline functional status are shown in Table 2 and Figure 2. Elderly participants more frequently experienced poor outcome compared to younger participants ($p=0.002$): None of the independent participants or participants in the age category 65-69 years died. In the younger age categories, more participants improved/stabilized (65-69 68%, 70-74 57% and ≥75 43%). In participants ≥75 years, more than half experienced functional decline (45%) or death (11%). Furthermore, elderly participants died more frequently compared to the younger age

categories (65-69 0%, 70-74 8%, ≥75 11%). No significant differences were seen for baseline functional status and functional outcome. However, severely dependent participants tended to die more frequently compared to the participants in the more independent group (12% in the severely dependent group vs. 9% in the mild/moderate dependent group vs. 0% in the independent group).

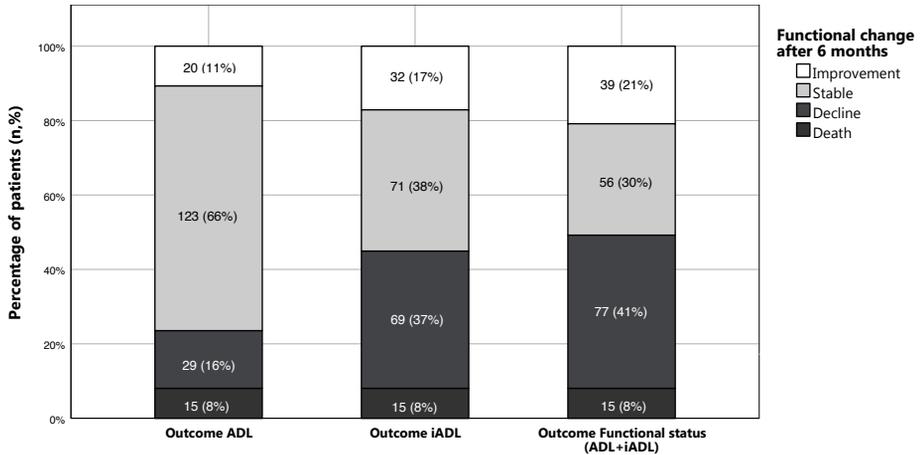


Figure 1. Change in functional status over six months from dialysis initiation as defined by changes in activities of daily living (ADL), changes in instrumental activities of daily living (IADL), or changes in activities of daily living and instrumental activities of daily living (functional status)

Table 2. Change in functional status over six months from dialysis initiation according to baseline age or functional dependence

Participant characteristics	Functional outcome after 6 months			P-value
	Improvement/stable	Decline	Death	
All participants (n, %)	98 (52%)	74 (40%)	15 (8%)	
<u>Age category in years at baseline</u>				0.002
- 65-69 (n,%)	28 (68%)	13 (32%)	0 (0%)	
- 70-74 (n,%)	28 (57%)	17 (35%)	4 (8%)	
- ≥75 (n,%)	42 (43%)	44 (45%)	11 (11%)	
<u>Functional dependence at baseline</u>				0.26
- Independent (n,%)	23 (58%)	17 (43%)	0 (0%)	
- Mild/moderate (n,%)	48 (50%)	39 (41%)	9 (9%)	
- Severe (n,%)	27 (53%)	18 (35%)	6 (12%)	

Table 3. Associations between demographics, geriatric assessment and functional decline/death

Participant characteristics	Number of participants with functional decline/death	
	Exposure present	Exposure not present
	N (%)	N (%)
Age (continuous)	NA	NA
Sex (reference female)	29/61 (48%)	60/126 (48%)
Single/widow	32/78 (41%)	57/109 (52%)
Geriatric assessment		
1. Dependent in ADL at baseline	29/56 (52%)	60/131 (46%)
2. Dependent in IADL at baseline	71/146 (49%)	18/41 (44%)
3. Impaired cognition	56/123 (46%)	31/60 (52%)
4. Severe comorbidity burden	41/80 (51%)	48/107 (45%)
5. Impaired mobility	20/35 (57%)	63/142 (44%)
6. Symptoms of depression	32/56 (57%)	57/131 (44%)
7. Malnutrition	5/10 (50%)	84/177 (48%)

NA, not applicable; OR, Odds ratio, 95% CI, 95% confidence interval; ADL, Activities of daily living, IADL, instrumental activities of daily living

Factors associated with functional decline after initiating dialysis

Table 3 shows the univariable logistic regression model for the association between demographics, components of the geriatric assessment and the composite outcome functional decline/death within 6 months after initiating dialysis. Age, single/widow status, symptoms of depression and an impaired mobility all had a $p < 0.20$ and were used in a multivariable model. In the multivariable analysis, only age (OR 1.05 per year older at baseline, 95% CI 1.00-1.10) remained independently associated with poor outcome. When the same analysis was performed with a higher cut-off score for decline (decline ≥ 2 or more points lost) different potential risk factors were found in univariable analysis, but also only age was independently associated with poor outcome (OR 1.07 per year older at baseline, 95% 1.02-1.13) (data not shown).

When overall frailty, instead of individual domains, was adjusted for age and sex in the multivariable model, frailty according to the Groningen Frailty Indicator was associated with the composite outcome decline/death compared to the non-frail population (OR 1.97, 95% CI 1.05-3.68). Frailty according to the Fried frailty index or frailty according to the geriatric assessment were not significantly associated with functional decline and death when compared to non-frail patients (Fried frailty index ≥ 3 OR 1.46 (95% CI 0.80-2.68), Geriatric assessment ≥ 2 impairments OR 1.65 (95% CI 0.81-3.35). Results are shown in Appendix 3.

Logistic regression						
Univariable analysis			Multivariable analysis*			
OR	95% CI	P-value	OR	95% CI	P-value	
1.06	1.01-1.11	0.02	1.05	1.00-1.10	0.04	
1.00	0.54-1.85	0.99	0.85	0.42-1.70	0.64	
1.58	0.88-2.84	0.13	1.85	0.96-3.55	0.07	
1.27	0.68-2.38	0.45				
1.21	0.60-2.43	0.59				
0.78	0.42-1.45	0.44				
1.29	0.72-2.31	0.39				
1.67	0.79-3.53	0.18	1.53	0.67-3.47	0.31	
1.73	0.92-3.26	0.09	1.37	0.69-2.70	0.37	
1.11	0.31-3.96	0.88				

* Adjusted for age, sex, single/widow, impaired mobility and symptoms of depression

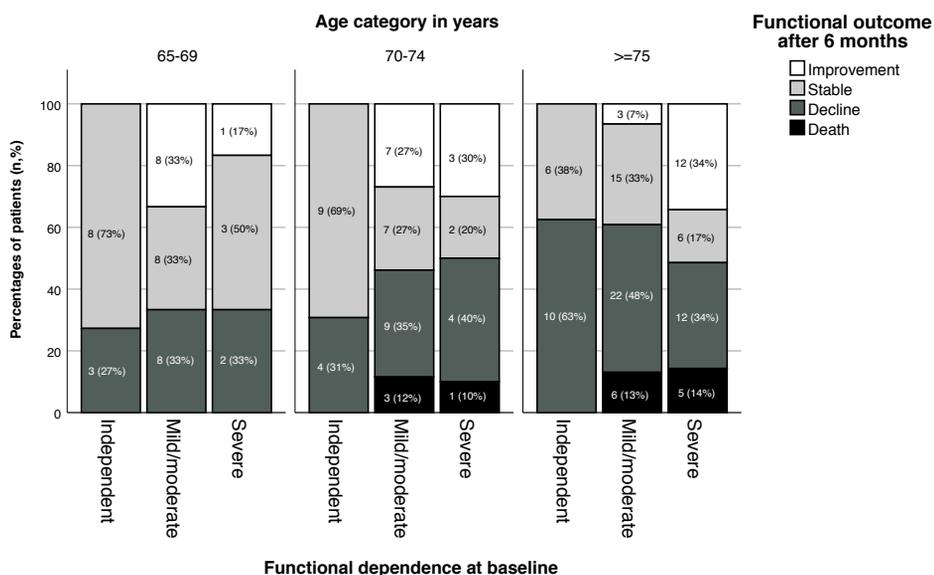


Figure 2. Change in functional status over six months from dialysis initiation according to baseline age and functional dependence

Caregiver

Of the 114 caregivers at baseline, 13 were excluded because the corresponding participants were excluded (n=4) or had died (n=9) and another 9 caregivers were lost to follow-up. Thus, follow-up data were available for 92 caregivers. Results for the different questionnaires are shown in Table 4.

More than half of the caregivers reported that the participant showed deterioration in one or more daily activities during the first six months after dialysis initiation. The activities most frequently affected were writing (27%), doing groceries (22%), dressing (20%), closing zippers/buttons and tying shoelaces (20%). Overall, caregivers did not report more neuropsychiatric symptoms of the participants at follow-up (56% at baseline vs. 59% at follow-up, $p=0.84$). However, they did see an increase in symptoms of apathy (9% vs. 21%, $p=0.007$) and irritability (17% vs. 33%, $p=0.008$). Additionally, caregiver burden was more prevalent during follow-up (23% moderate to high burden at baseline vs. 38% at follow-up, $p=0.004$), and also increased (median baseline 2.0 (IQR 1.0-3.0) compared to median follow up 3.0 (IQR 1.0-5.0), $p<0.001$).

Table 4. Caregiver questionnaires (n=92)

Caregiver questionnaires	Prevalence at follow-up (n, %)
Patient deterioration in Daily Activities (IDDD ≥ 1)	47 (51%)
Patient neuropsychiatric symptoms (NPI ≥ 1)	54 (59%)
Caregiver reported pressure from informal care (SPICC ≥ 4)	35 (38%)

IDDD, interview for deterioration in daily activities; NPI, Neuropsychiatric inventory; SPPIC, Self-perceived Pressure from Informal Care.

The following variables had missing data; NPI (1.1%) and SPICC (4.3%).

Discussion

In this prospective multicenter, cohort study of 187 elderly incident dialysis patients, the prevalence of functional dependence was high; 4 out of 5 participants were dependent in functional status (30% ADL, 78% IADL) at initiation of dialysis. Furthermore, almost half of the participants experienced decline in functional status (40%) or died (8%) within the first 6 months after initiating dialysis. This decline was mostly due to loss of IADL abilities (37% decline in IADL vs. 16% in ADL). Older age and a high score on the Groningen frailty indicator were associated with the composite outcome functional decline/death. In addition, the percentage of caregivers reporting a high burden of care increased from 23% to 38% ($p < 0.004$) after dialysis initiation.

To our best knowledge, this is one of the first studies that prospectively assessed functional course after initiating dialysis in community-dwelling elderly with ESKD. A previous study performed in nursing home patients at initiation of dialysis ($n=3,702$) showed a very high rate of mortality and functional decline in ADL compared to our study population: within 3 months 61% had died or had a decrease in ADL.¹¹ Furthermore, this study showed an acceleration in decline of ADL in the 3 months before the initiation of dialysis, a stabilization between 1 and 4 months, followed by a further downward trajectory.¹¹ However, this population of frail nursing home patients is not comparable to most elderly patients initiating dialysis. Another study ($n=97$) assessed the changes in living status after initiating dialysis in patients aged 80 years and older, and found that within 6 months after the start of dialysis more than 30% of patients required newly community or private-caregiver support or moved to a nursing home.¹² A stabilization in functional status was seen over the next 2 years. However, this study did not report baseline data on frailty or geriatric impairments or the reason why people needed support (ADL or IADL). Therefore, it is not possible to make a comparison with our study results. Furthermore, another study that used the Karnofsky Performance Status and Short-Form 36 to evaluate functional status did not find a change in physical health after initiation of dialysis.³² However, this study is difficult to compare due to the relatively younger age of the patients that initiated dialysis (mean age was 60.6 years) and due to different evaluation moments. In our study, we assessed functional status only at two time points; at the start and six months after start of dialysis. Since functional dependence can vary even in stable dialysis patients,³³ more frequent assessments, including the pre-dialysis phase and with longer follow-up, are needed to elucidate the full functional trajectory and assess the impact of hospitalization or life-events.

In the current study, we used a cut-off point of 1 as the definition of decline in functional status. Although this cutoff point is frequently used in prior studies,^{5,34,35} there is no consensus which cutoff point is clinically relevant. One of the main goals of dialysis (especially in the elderly population) is improving quality of life. Since functional status is such an important part of quality of life, loss of 1 point may be clinically relevant. Furthermore, one new functional impairment could lead to another. For example, if a patient is not able to do grocery shopping anymore, this can lead to less mobilization which can eventually lead to further loss of physical fitness, which can subsequently lead to difficulties in housekeeping, transportation and malnutrition. This theory is also referred to as the geriatric snowball effect.³⁶

In our study more caregivers reported a high caregiver burden after initiating dialysis. Furthermore, caregiver burden increased already within 6 months after the initiation of dialysis. Although caregiver burden is common in the dialysis population³³⁷⁻³⁹ only few studied the impact of initiation of dialysis on caregivers.³⁸ Unfortunately, most studies were performed in caregivers of relatively young patients (<60 years), using various outcomes (e.g. quality of life) and questionnaires, and were therefore not comparable to our study. Only one study used the SPPIC questionnaire in caregivers of elderly patients on maintenance hemodialysis.³ Although patients are comparable with our study population (same country, age and cut-off point), this study showed a far higher burden (85%) in caregivers. One possible explanation could be that caregiver burden will even further increase 6 months after starting dialysis. As caregiver burden is associated with a decreased quality of life,³⁹ more symptoms of depression,³⁹ and could also lead to negative outcomes for patients,^{40,41} it is important to reduce and prevent caregiver burden. Therefore, physicians should periodically ask caregivers about caregiver burden to address factors that may cause distress (e.g. physical burden, psychosocial burden, behavioral problems). Additional support, such as extended homecare, social work, but also education⁴² can be used to decrease and prevent caregiver burden.

The major strength of this study is a large multicenter inception cohort with extensive geriatric assessment and with only few lost to follow-up. A limitation is that most patients were included just after start of dialysis. This could have led to both over- and underestimation of the functional decline at the start of study. Patients could have felt better due to an improvement of uremic complaints by dialysis and could therefore be more independent of care. It could also have led to an underestimation, because the initiation period of dialysis can be challenging and could cause complaints (e.g. fatigue, cramps). Furthermore, as our six-month mortality was lower than expected,⁴³⁻⁴⁵ it is likely that a relatively healthy elderly population was included into this study. A possible reason could be that patients with a more impaired health status were less likely to participate

in our study. Unfortunately, we do not have any details of patients that refused to participate after being invited by their treating nephrologists. Therefore, we cannot test this hypothesis. This may imply that the findings we report may not be fully generalizable to all elderly patients initiating dialysis and consequently that functional decline may be even higher for this population. Another limitation is that due to the low rate of events, our multivariable models were relatively underpowered and therefore potential associations could be missed. Furthermore, no separate analysis could be performed for functional improvement, because patients that were fully independent at baseline could not improve during follow up because they already had the best score (ceiling effect). Therefore, no additional analysis for protective factors of functional decline could be performed. Since none of the patients had the worst score in functional status at baseline, this was not the case for decline.

The results that we report may have implications for the care of elderly patients with ESKD. In our study, the rate of functional decline 6 months after initiation of dialysis (especially in the patients aged ≥ 75 years) is high. However, this decline was mainly through loss of IADL activities and seems therefore much less severe in our study population compared to previously mentioned studies that found severe loss of independency.^{11,12} Despite this, caregiver burden does increase, so the initiation of dialysis seems to have a negative effect on the situation at the start of dialysis. Moreover, the impact of functional loss is highly dependent on personal values and patient preferences. Thus, it is important to use the pre-dialysis phase to explore individual's health goals (e.g. living at home, engage in social activities) and current quality of life.⁴⁶ This could improve shared-decision-making regarding dialysis and conservative management. In addition, interventions may be initiated to prevent functional decline by engaging physical activity.⁴⁷

In conclusion, in patients ≥ 65 years, functional decline within the first 6 months after initiating dialysis is highly prevalent. Frail and older patients are especially at risk for functional decline. Moreover, the initiation of dialysis seems to be accompanied with an increase in caregiver burden. Further research should focus on improving the identification of patients at risk for functional decline and interventions that could maintain functional status. Better identification of the patient at risk for functional decline could lead to better decision-making, and therefore less suffering and less healthcare costs. Moreover, it could lead to preventive strategies with regard to functional decline.

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Supplementary data

Appendix 1. Baseline characteristics for the different functional dependencies

	Total (n=187)	Functional dependence at baseline		
		Independent (n=40)	Mild/ moderate (n=96)	Severe (n=51)
Age mean (\pm SD)	75 (7)	73 (5)	75 (6)	78 (7)
Women	61 (33%)	8 (20%)	33 (34%)	20 (39%)
Single/widow	78 (42%)	21 (53%)	35 (37%)	22 (43%)
Living at nursing home	10 (5%)	0 (0%)	1 (1%)	9 (18%)
Intoxications				
- Smoker* (n, %)	137 (73%)	31 (82%)	68 (74%)	38 (78%)
- Current alcohol use	73 (41%)	19 (50%)	35 (39%)	19 (39%)
Underlying kidney disease				
- Diabetes	29 (16%)	3 (8%)	13 (14%)	13 (26%)
- Vascular	93 (50%)	22 (55%)	47 (49%)	24 (47%)
- Other/unknown	65 (34%)	15 (38%)	36 (38%)	14 (27%)
Hemodialysis (n,%)	144 (77%)	26 (65%)	74 (77%)	44 (86%)
Geriatric assessment				
- Impaired ADL at baseline (n,%)	56 (30%)	0 (0%)	16 (17%)	40 (78%)
- Impaired IADL at baseline (n,%)	146 (78%)	0 (0%)	95 (99%)	51 (100%)
- Impaired cognition (n,%)	123 (67%)	22 (55%)	64 (68%)	37 (76%)
- Severe comorbidity burden (n,%)	80 (43%)	11 (28%)	43 (45%)	26 (51%)
- Severely impaired mobility (n,%)	35 (20%)	0 (0%)	7 (8%)	28 (57%)
- Symptoms of depression (n,%)	56 (30%)	5 (13%)	23 (24%)	28 (55%)
- Malnutrition (n,%)	10 (5%)	0 (0%)	5 (5%)	5 (10%)
Frail according to GA (\geq 2 impairments)	148 (77%)	10 (25%)	85 (89%)	49 (96%)
Frail according to Fried Frailty Index (\geq 3)	82 (46%)	5 (14%)	36 (39%)	41 (84%)
Frail according to GFI (\geq 4)	115 (62%)	16 (40%)	52 (54%)	47 (92%)

ADL, Activities of daily living; IADL, Instrumental activities of daily living; GA, Geriatric assessment, GFI, Groningen frailty index.

* Smoker, if the participant has smoked but stopped, or is still smoking cigarettes.

The following variables had missing data: cognition (2.1%), Fried frailty index (4.8%), mobility (5.3% and smoking (4.3%)

Appendix 2. Overview of impairments in (I)ADL at baseline and after 6 months of follow-up

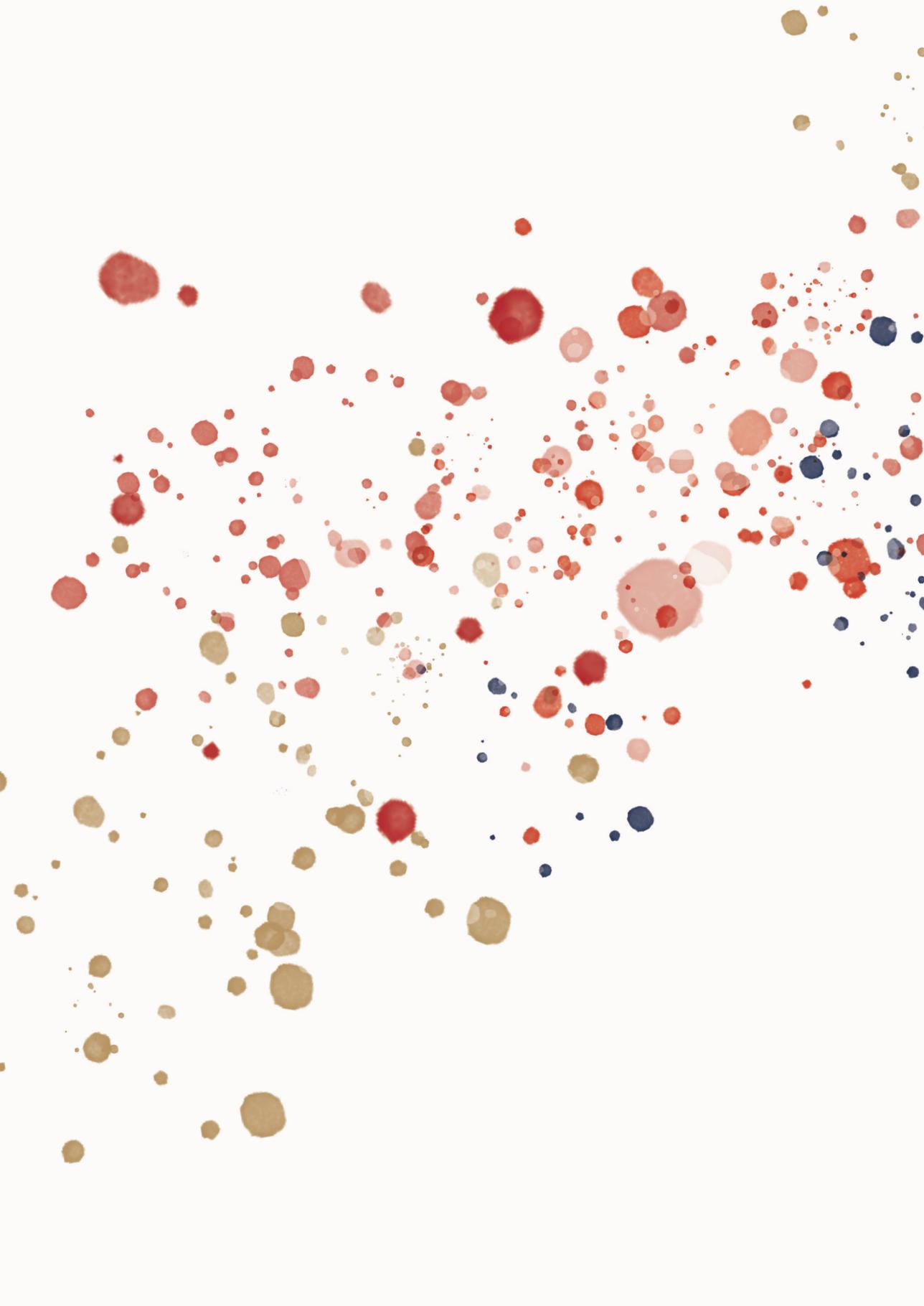
	Baseline (n=187)	Follow-up (n=173)	P-value
Activities of daily living (patients with impairment, %)			
Bathing	37 (20%)	33 (19%)	1.0
Dressing	29 (16%)	24 (14%)	1.0
Toileting	8 (4%)	7 (4%)	1.0
Transferring indoors	8 (4%)	8 (5%)	1.0
Incontinence	32 (17%)	29 (17%)	1.0
Feeding	1 (1%)	1 (1%)	1.0
Instrumental activities of daily living (patients with impairment, %)			
Ability to use telephone	18 (10%)	22 (13%)	0.21
Shopping	96 (51%)	92 (53%)	0.43
Food preparation	76 (41%)	81 (47%)	0.08
Housekeeping	83 (44%)	79 (46%)	0.72
Laundry	104 (56%)	106 (61%)	0.06
Mode of transportation	71 (38%)	70 (41%)	0.42
Responsibility for own medications	86 (46%)	98 (57%)	<0.01

Appendix 3. Association between frailty tools and functional decline/death

	Univariate analysis			Multivariate analysis*		
	OR	95% CI	P-value	OR	95% CI	P-value
Geriatric assessment (≥ 2)	1.74	0.86-3.49	0.12	1.65	0.81-3.35	0.17
Fried Frailty Index (≥ 3)	1.56	0.86-2.83	0.14	1.46	0.80-2.68	0.22
Groningen Frailty Indicator (≥ 4)	1.95	1.07-3.56	0.03	1.97	1.05-3.68	0.03

OR, Odds ratio, 95% CI, 95% confidence interval; ADL, Activities of daily living, IADL, instrumental activities of daily living

*Adjusted for age and gender





Chapter 10

Quality of life after the initiation of dialysis or maximal conservative management in elderly patients

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Abstract

Background: Maximal conservative management (MCM) may be an appropriate option for dialysis in some elderly patients with end-stage kidney disease (ESKD). Evidence about the impact of dialysis or MCM on quality of life (QoL) in older patients is sparse. In the GOLD (Geriatric assessment in OLder patients starting Dialysis) Study the trajectory of QoL was assessed in patients starting dialysis or MCM.

Methods: Patients ≥ 65 years old were included just prior to dialysis initiation or after decision for MCM. Baseline data included demographics, frailty as measured with a geriatric assessment, comorbidity (CIRS-G) and QoL, measured with the EQ-5D-3L (EQ-5D Index and overall self-rated health). Six months follow-up data included QoL, hospitalizations and mortality. Change of QoL was assessed with paired t-tests. Cox-regression was used to assess survival of MCM and dialysis patients.

Results: The cohort comprised 192 dialysis and 89 MCM patients. The MCM patients were older (mean age 82 ± 6 vs. 75 ± 7 years, $p < 0.01$) and mean kidney function was better (eGFR 11.5 ± 4.0 vs. 8.0 ± 2.9 ml/min/1.73m², $p < 0.01$). Baseline QoL did not differ significantly between the groups. After six months, EQ-5D Index did not improve significantly in the dialysis group with mean \pm standard error (SE) 0.026 ± 0.014 ($p = 0.10$; not clinically relevant), but a small but clinically relevant decline was seen in the conservative group: 0.047 ± 0.022 ($p < 0.01$; between group difference $p < 0.01$). Hospitalization occurred in 50% of dialysis patients vs. 24% of conservative patients ($p < 0.01$). In patients over 80 years old, no survival benefit could be found for patients starting dialysis vs. MCM.

Conclusion: A small decline of QoL was found for conservative patients, while QoL did not change in dialysis patients. However, hospitalization rate was higher in patients starting dialysis. In patients over 80 years, no survival benefit was found.

Introduction

The end-stage kidney disease (ESKD) population is ageing, which has resulted in a growing number of elderly patients starting dialysis.¹ In this population, comorbidity burden is high and functional and cognitive impairment are frequently encountered.^{2,3} Almost half of the octogenarians and nonagenarians die within the first year of dialysis initiation.^{4,5} In older patients with multiple comorbidities, starting dialysis does not seem to prolong life as compared to conservative care,⁶ but does increase the risk of hospitalisation.⁷ For elderly patients, the focus of care has shifted from prolonging life to maximizing quality of life. Consequently, maximal conservative care has become an accepted alternative for patients with ESKD, especially in those who are frail. However, it is difficult to predict how dialysis or forgoing dialysis would impact on a patient's symptom burden and quality of life. Evidence on this trajectory in patients choosing maximal conservative care is sparse. This leads to insecurity in the process of shared decision-making.⁸

In the GOLD (Geriatric assessment in OLder patients starting Dialysis) Study, elderly patients (≥ 65 years old) were followed in the first six months after the start of renal replacement therapy or the decision for maximal conservative therapy only. Quality of life was assessed at baseline and at six-months follow-up, and mortality and hospitalization data were also collected. The goal of this analysis is to assess quality of life in patients starting dialysis and patients choosing maximal conservative care.

Methods

Study design and patient selection

The GOLD (Geriatric assessment in OLder patients starting Dialysis) study is a multicenter, prospective cohort study assessing the relation between a geriatric assessment and poor outcome in ESKD patients. Participants were enrolled from 17 different hospitals across the Netherlands (Chapter 2, Appendix 1) in the period from August 2014 to September 2017. The population consisted of two consecutive groups: patients starting dialysis and patients choosing maximal conservative care. For the dialysis group, eligible patients were included between 3 weeks before and 2 weeks after the first dialysis session. If dialysis would start >3 week after the geriatric assessment, patients were excluded from the follow-up. For the second group, patients were included < 3 months after the decision to forgo dialysis had been made after shared-decision making according local practice of the pre-dialysis clinic, *and* if GFR was <15 ml/min (either estimated with CKD-EPI or measured with 24-hours urine creatinine clearance). The decision to forego was made after shared-decision making according local practice of the pre-dialysis clinic. If patients had made the decision for conservative therapy, but creatinine clearance was above the cut-off value, they were followed and approached again for enrollment once GFR had fallen below 15 ml/min. Patients were excluded if informed consent was not provided, if they had insufficient understanding of the Dutch language or if they suffered from a terminal non-renal related condition. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the medical ethics review boards of all participating hospitals and written informed consent was obtained from all patients prior to enrollment.

Data collection

Baseline demographic data collected from the medical charts and during the baseline assessment included age, sex, educational level and living situation. Other clinical characteristics included cause of kidney failure, blood pressure, body mass index (BMI) and smoking habit. For dialysis patients, type of dialysis and dialysis access were recorded.

For the baseline assessment, including a health related quality of life (HRQOL) questionnaire and a geriatric assessment (GA), participants were either visited at home (on a non-dialysis day for hemodialysis patients) or in the dialysis center, before starting the dialysis session. The assessments were performed by the investigators (IL or NG) or by one of the trained research nurses.

Health related quality of life

HRQOL was measured using the EuroQol-5D-3L, which consists of two parts.⁹ First, a self-reported 5-item questionnaire addressing the amount of problems experienced in mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Impairment was scored per item, as no, moderate or severe impairment. An impaired health status was defined as ≥ 1 moderate or severe problem. The domains were subsequently converted into a single summary index, "EQ-5D Index", by applying a formula that attaches values to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). Subsequently, we used the Dutch Tariff for correction of the societal valuation of QoL in The Netherlands.¹⁰ Second, all patients were asked to indicate overall self-rated health on the EQ-5D-3L visual analogue scale (VAS, scale 0 to 10 where 0 is the worst imaginable health state and 10 the best imaginable health state).

Geriatric assessment

Frailty was assessed with a geriatric assessment, generally considered the best systematic approach for identification of frailty.¹¹⁻¹³ It focuses on the following domains: (instrumental) activities of daily living, mobility, cognition, mood, nutritional status and comorbidity burden. Comorbidity burden was assessed with the Cumulative Illness Rating Scale-Geriatrics (CIRS-G) and $\geq 2 \times$ score 3 or $\geq 1 \times$ score 4 was considered a severe comorbidity burden.¹⁴ Patients were considered frail if they had impairments in ≥ 2 geriatric domains.¹⁵ More detailed information can be found in Chapter 2, Appendix 2.

Follow-up

After six months, data on and complications were collected from each center. Mortality data were collected at 6 and 12 months. The patients who were alive after six months were contacted by telephone and the EuroQol-5D-3L questionnaire was applied again.

Statistical analysis

Data were summarized using means with standard deviation (SD), medians with interquartile ranges, or proportions when appropriate. Differences between the dialysis patients and conservative patients regarding baseline characteristics and outcomes were assessed using chi-squared tests for dichotomous variables, t-tests for normally distributed continuous variables and non-parametric tests for non-normally distributed continuous variables. For the difference in health related QoL domains at baseline and at follow-up, a logistic regression was subsequently applied, adjusting for age (years) and eGFR (ml/min/1.73m²).

The difference in EQ-5D Index and overall self-rated health status between baseline and follow-up was assessed with a paired t-test, the between group differences was assessed with a t-test. The change of the EQ-5D Index and global health between dialysis and conservative patients was assessed with a t-test. A difference of ≥ 0.03 point of the EQ-5D Index is considered the minimal clinically important difference (MCID).¹⁶ For global health (EQ-5D VAS) a difference of 0.7 or 0.8 is considered the MCID.^{17,18} Follow-up outcomes of the EQ-5D Index were defined as: improved (≥ 0.03 point improvement, or having received a kidney transplant), equal (change < 0.03 point), deterioration (≥ 0.03 point decline) or death. Analysis of baseline EQ-5D Index and VAS and change over time was repeated with sensitivity analyses, which excluded the dialysis patients on the waiting list and patients who received a kidney transplant during follow-up.

As we hypothesized that most dialysis patients may have a lower eGFR compared to conservative patients (who were included with a GFR < 15 ml/min), a subgroup analysis was performed for patients with an eGFR < 10 ml/min/ 1.73m^2 and patients with an eGFR ≥ 10 ml/min/ 1.73m^2 . In addition, a subgroup analysis was performed for patients aged < 80 years and ≥ 80 years old, as QoL becomes even more relevant in this group as dialysis does not seem to prolong life in this population.¹⁹

Mortality rates between dialysis and conservative patients were assessed with a log-rank test. As 6-month mortality rate was low, an extended multivariate analysis was performed for 12-month mortality rate. A Cox-regression model was used, adjusting for age (years), comorbidity burden and eGFR category.

A two-tailed $p < 0.05$ was considered statistically significant. Data analysis was performed with SPSS version 22 software.

Results

Baseline characteristics

A total of 281 patients were included in the GOLD Study, of whom 192 started dialysis (23% PD) and 89 choose maximal conservative therapy. Another 42 patients were screened, but excluded because of reasons mentioned in the Flowchart (Appendix 1). The baseline characteristics of the dialysis patients and conservative patients are summarized in Table 1. Conservative patients were older (mean±SD 82±6 vs. 75±7, $p<0.01$) and more likely to live alone (56% vs. 42%, $p=0.03$). In addition, kidney function of conservative patients was more preserved; in 61% of patients choosing conservative care eGFR was >10 ml/min/1.73m², compared to 22% of dialysis patients ($p<0.01$). Haemoglobin and albumin levels were significantly higher in conservative patients (Table 1).

Frailty was prevalent in 88% of the conservative patients vs. 78% of the dialysis patients ($p=0.06$). Of all dialysis patients, 26 (13%) were on the waitlist for kidney transplantation.

Quality of life at baseline

The EQ-5D summary index of conservative patients (mean score ±standard deviation (SD) 0.77±0.21) did not differ significantly from the score of dialysis patients (0.82±0.18 SD, $p=0.05$); nor did it differ from the score of dialysis patients not on the waiting list (0.81±0.18 SD, $p=0.10$).

In addition, overall self-rated health (EQ-5D VAS) was comparable at the moment of choosing conservative care and initiating dialysis: 6.3±1.3 for conservative patients vs. 6.3±1.4 in dialysis patients ($p=0.91$). The latter score was the same for those not on the waiting list.

Figure 1 shows the 5 EQ-5D domains at baseline. For the domain pain/discomfort, 69% of conservative patients reported an impaired health status compared to 51% of dialysis patients ($p<0.01$; Table 2). Anxiety/depression was reported in 31% of dialysis patients vs. 24% of conservative patients ($p=0.22$). Mobility was impaired in 58% of dialysis patients vs. 71% of conservative patients ($p=0.04$). After adjusting for age and eGFR, pain/discomfort remained significantly higher in the conservative group compared to dialysis (OR 2.25, 95%CI 1.18-4.30) and anxiety/depression was lower in the conservative group (OR 0.45, 95%CI 0.22-0.92). There were no significant differences in mobility, usual activities and self-care.

Table 1. Baseline characteristics

	Dialysis (n=192)	Conservative (n=89)	P-value
Demographics			
Age, years, mean \pm SD	75 \pm 7	82 \pm 6	< 0.01
Gender (% male)	128 (67%)	50 (56%)	0.07
Clinical parameters			
Cause of kidney failure (%)			0.40
- Renal vascular	96 (50%)	45 (51%)	
- Diabetes	31 (16%)	17 (19%)	
- Nephritis	12 (6%)	5 (6%)	
- Other	54 (28%)	25 (28%)	
Dialysis modality (% PD)	44 (23%)	-	
Access: Central venous line (% of HD)	73 (38%)	-	
BMI (kg/m ²), mean (\pm SD)	27 \pm 5	26 \pm 5	0.43
Systolic blood pressure (mmHg) ^a	150 \pm 22	151 \pm 26	0.73
Diastolic blood pressure (mmHg) ^a	75 \pm 14	75 \pm 13	0.74
Smoking (former, now), n (%)	148 (77%)	62 (70%)	0.19
Severe comorbidity ^b	79 (41%)	39 (44%)	0.69
Frailty ^c	148 (77%)	78 (88%)	0.06
Laboratory values^d			
Hemoglobin (mmol/L)	6.4 \pm 0.9	7.1 \pm 0.9	<0.01
Albumin (g/L)	34 \pm 6	37 \pm 6	<0.01
eGFR CKD-EPI in ml/min/1.73m ²	8.0 \pm 2.9	11.5 \pm 4.0	<0.01
< 10 ml/min/1.73m ² (%)	152 (79%)	35 (39%)	<0.01
\geq 10 ml/min/1.73m ² (%)	40 (21%)	54 (61%)	
Social setting			
Living alone	81 (42%)	50 (56%)	0.03
Living in a nursing home facility	10 (5%)	7 (8%)	0.36
University	40 (21%)	16 (18%)	0.50
Polypharmacy			
Mean no of drugs \pm SD	12 \pm 5	10 \pm 3	<0.01

SD, standard deviation; PD, peritoneal dialysis; HD, Hemodialysis; BMI, body mass index; eGFR, estimated glomerular filtration rate

^a Measured before dialysis session in dialysis patients

^b Measured with CIRS-G, severe comorbidity is \geq 2x score 3 or \geq 1x score 4,

^c Measured with the geriatric assessment (see Appendix 3)

^d Measured before the first dialysis session in dialysis patients

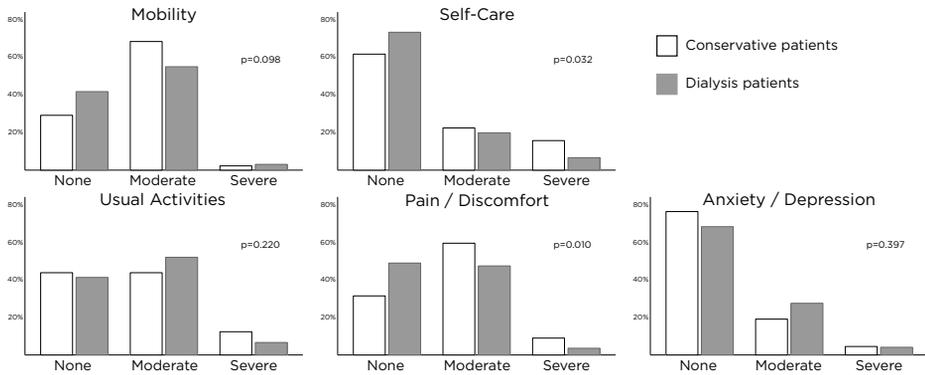


Figure 1. EQ-5D domains at baseline

Table 2. Percentage of patients with impaired health status¹

	Dialysis, n (%)	Conservative care, n (%)	P-value
Baseline			
Mobility	111 (58)	63 (71)	0.04
Self-care	51 (27)	34 (38)	0.05
Usual activities	112 (58)	50 (56)	0.73
Pain/Discomfort	98 (51)	61 (69)	<0.01
Anxiety/Depression	59 (31)	21 (24)	0.22
Follow-up			
Mobility	95 (55)	57 (78)	<0.01
Self-care	42 (24)	30 (41)	<0.01
Usual activities	92 (53)	46 (63)	0.16
Pain/Discomfort	76 (44)	48 (66)	<0.01
Anxiety/Depression	33 (19)	17 (24)	0.42

¹Percentage of patients with moderate or severe impairment in the EQ-5D domains. Result of the univariate analysis

Follow-up

Mortality

No patients crossed over from the conservative group to the dialysis group. Transplantation rate was 2% (n=3). Six-months mortality rate differed between the groups, but not significantly: mortality rate in conservative patients was 15% compared to 8% in dialysis patients (p=0.12).

In the extended 12-months analysis, mortality rate in conservative patients was 34% compared to 16% in dialysis patients ($p=0.01$). Transplantation rate was 4% ($n=8$). After adjusting for age, comorbidity level and GFR category, hazard ratio (HR) for twelve-month mortality for conservative care vs. dialysis was 2.12 (95%CI 1.12-4.03) (Figure 2). Among patients over 80 years old, conservative care vs. dialysis was not related to mortality (adjusted HR 1.30, 95%CI 0.58-2.91) (Figure 2).

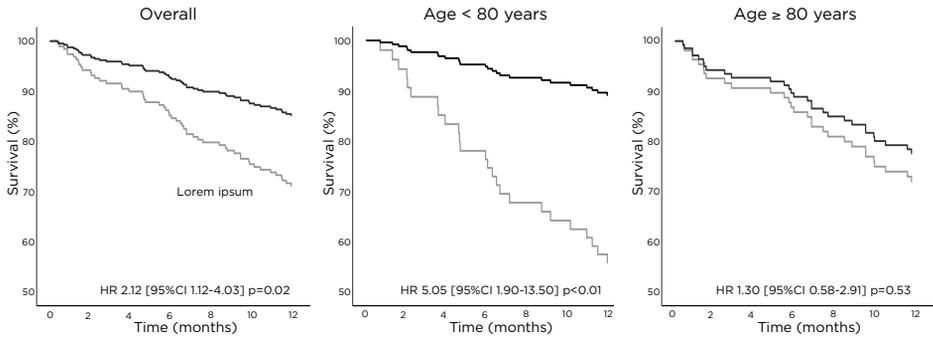


Figure 2. Cox regression conservative 1 year mortality conservative care vs. dialysis

Adjusted for age, comorbidity and eGFR. Legend: grey= conservative patients, black=dialysis patients

Trajectory of quality of life

Follow-up QoL data were available for 98% of dialysis patients and for 92% of conservative patients (Appendix 3). After six months, anxiety/depression decreased in the dialysis group from 31% to 21% ($p<0.01$), while in the conservative group this remained stable (24%, Table 2); the other domains did not change significantly. Overall, more impairment was found in the conservative group at follow-up. Mobility impairment (78% conservative vs. 55% dialysis, $p < 0.01$), self-care impairment (41% vs. 24%, $p<0.01$) and pain/discomfort (66% vs. 44%, $p<0.01$) were more prevalent in the conservative group. However, when adjusted for age and eGFR no significant differences in EQ-5D domains were found between the two groups (data not shown).

The EQ-5D Index did not change significantly and relevantly in the dialysis group with $0.026\pm 0.014(\pm SE)$ ($p=0.10$), but a small but clinically relevant decline was seen in the conservative group with $(0.047\pm 0.022(\pm SE))$ ($p<0.01$; difference between the groups $p<0.01$). The sensitivity analysis which excluded patients on the waiting list, showed no significant change either $(0.026\pm 0.027(\pm SE))$ ($p=0.09$), between group difference $p<0.01$.

In the dialysis patients, two-thirds showed a stable or improved EQ-5D score while this occurred in half of the conservative patients ($p < 0.001$, Table 3). The same results were found for older patients (≥ 80 years) and for patients with a low GFR. However, for patients with a high GFR the differences between the dialysis group and the conservative group were less pronounced and no significant difference could be found (Table 3).

Table 3. Trajectory of Quality of life first 6 months (EQ-5D Index)

All	Total (n)	Outcome				P-value
		Dead	Decline	No change	Improvement/ Transplantation	
Conservative, n (%)	83	18(16)	26(31)	32(39)	12(15)	
Dialysis, n (%)	185	16(9)	41(22)	53(29)	75(42) (2%) [#]	<0.001
Sub analyses						
<i>Creatinine clearance</i>						
eGFR <10 ml/min/1.73m ²						
Conservative, n (%)	32	5(16)	11(34)	13(41)	3(9)	0.01
Dialysis, n (%)	145	13(9)	28(19)	42(29)	62(43) (1%) [#]	
eGFR ≥ 10 ml/min/1.73m ²						
Conservative, n (%)	51	8(16)	15(29)	19(37)	9(18)	0.27
Dialysis, n (%)	39	3(8)	12(31)	11(28)	13(33) (2%) [#]	
<i>Age</i>						
< 80 years						
Conservative, n (%)	21	4(19)	6(29)	8(38)	3(14)	0.08
Dialysis, n (%)	132	10(8)	31(24)	37(28)	54(41) (2%) [#]	
≥ 80 years						
Conservative, n (%)	62	9(15)	20(32)	24(39)	9(15)	0.02
Dialysis, n (%)	53	6(11)	10(19)	16(30)	21(40)	

[#]Including transplantation (total n=3)

Overall self-rated health score of dialysis patients improved with 0.3 ± 1.4 points ($p < 0.01$), while QoL score of conservative patients decreased with 0.4 ± 1.1 points ($p < 0.01$; difference between the groups $p < 0.01$), but this was not clinically relevant. The same results were found when patients on the waiting list were excluded (0.3 ± 1.1 points ($p = 0.02$, between group difference $p < 0.01$).

Other complications

Hospitalizations (≥ 1 in six months) occurred in 50% of dialysis patients and in 24% of conservative patients ($p < 0.01$). Among hospitalized patients, median number of admissions was 1 (range 1-5) for dialysis patients and 1 (range 1-4) for conservative patients ($p = 0.27$). Median number of admission days was 7 (interquartile range, IQR, 3-15) for dialysis patients and 4 (IQR 2-12) for conservative patients ($p = 0.22$). Three dialysis patients and one conservative patient moved to a nursing home facility and one conservative patient was admitted to a hospice. Six dialysis patients withdrew from dialysis due to poor overall quality of life or severe complications.

Discussion

In this analysis, quality of life was compared between prospective cohorts of older patients starting dialysis and older patients choosing conservative care. Several conclusions can be drawn from this study. First, patients starting dialysis experience less pain/discomfort compared to patients choosing conservative care, but overall QoL is comparable. Second, over time, QoL remained stable in the dialysis group, while a small decline of QoL was seen in the conservative group. Third, significantly more dialysis patients were hospitalized at least once compared to conservative patients, despite the conservative patients being older. And finally, 12-month survival in patients over 80 years old is not significantly longer in patients starting dialysis compared to patients choosing conservative care.

So far, only few studies prospectively compared the trajectory of QoL of conservative care patients with dialysis patients or patients preparing for dialysis.²⁰⁻²² An Australian study assessed QoL by means of the Short-Form 36 Survey (SF-36) and compared the QoL trajectory of 140 pre-dialysis patients with 30 conservative patients (mean GFR 16 ml/min).²⁰ Baseline QoL was worse in conservative patients compared to patients planned for dialysis, but change over a 12-months follow-up period was comparable between the groups. Two other studies using the SF-36 found QoL to be stable over a two-year period in conservative patients and patients who were planned for or started dialysis.^{21,22} All studies were small, including 30-68 patients who were conservatively managed, and none of the studies focused specifically on elderly dialysis patients. Our study expands the prior observations, with a larger cohort of conservative patients and a very high follow-up rate, showing that EQ-5D QoL slightly decreases after the decision for conservative care has been made, but remains stable in elderly incident dialysis patients over a six months period. In addition, while overall self-rated quality of life was comparable between the groups at baseline, the mean score of 6.3 on a scale from 0 (poor)-10 (good) is much worse compared to community dwelling elderly (7.9±2.3).⁹

Another way of looking at quality of life is looking at admission rate and complications. In our study, half of the dialysis patients were hospitalized compared to one out of four of the conservative patients. In a UK cohort with a better survival rate for patients choosing dialysis (n=173) compared to conservative care (n=29), the number of hospital-free days was comparable between the groups, when both hospitalization and dialysis days were taken into account.²³ This suggests that overall the number of days at home is more comparable between the two treatment modalities than would be expected based on survival only. In addition, in the dialysis patients in our cohort, 6 out of 15 deaths (40%) in the first six months after dialysis initiation occurred after withdrawal of dialysis, indicating poor tolerance of the therapy or dissatisfaction with QoL. In a large cohort of more than 12,000 dialysis patients and 800 conservative patients, that focused on the final months before

death, conservative patients had significantly less hospitalizations (OR 0.40, 95%CI 0.34-0.46), less invasive procedures (OR 0.15, 95%CI 0.10-0.22), more palliative care consultation (OR 4.19, 95%CI 3.58-4.90), more hospice deaths (OR 3.32, 95%CI 2.83-3.89) and less hospital deaths (OR 0.78, 95%CI 0.74-0.82).²⁴ More qualitatively good days at home and a better anticipation to death in the last phase, suggest that some aspects of QoL may be better in conservative patients compared to dialysis patients. Although it is difficult to capture this in (health related) QoL assessments, it is valuable information to discuss with patients.

There are several limitations in the comparison of QoL between dialysis patients and conservative patients. First there may be a significant lead-time bias, i.e. conservative patients were likely to be included earlier in their illness trajectory, as reflected by higher GFR level. This factor may have led to a relatively higher EQ-5D score for the conservative patients, compared with the score they would have had at a GFR level of < 10 ml/min. We corrected for this by dividing the cohort into two groups (eGFR under and above 10 ml/min/1.73m²) and performed the major analyses in two groups.

A second limitation is that we have included conservative patients just after the decision for conservative management had been made, provided that GFR fell below 15 ml/min. However, in clinical practice, the decision may have been pending for a while (even years) in some patients and patients may still switch to dialysis therapy further in their illness trajectory. This should be borne in mind when interpreting these results, as this may have contributed to overestimation of QoL of conservative patients as well.

In addition, follow-up period is fairly short and we only had two QoL measurements. Impact of hospitalization, which in the elderly often involves deterioration of functional abilities, and thus QoL, without full recovery,²⁵ could have been missed by our assessment. However, although the transition to dialysis can have a large impact on elderly patients, our results show that in two-thirds of patients QoL improves or remains stable afterwards. Finally, QoL measurements have been developed based on perceived quality of health in the general population. Although the EQ-5D has been widely used among CKD patients²⁶, other values may apply in the conservative care population. When discussing conservative care it is important to find out which values and aspects of physical, cognitive and psychosocial domains matter most to the patient.

The EQ-5D does not only capture objective aspects of quality of life, but also includes a subjective or self-rated part, the visual analogue score. In our cohort, the between group difference of overall self-rated quality of life at follow-up was 0.7 points. This number is considered the minimum clinically important difference (MCID) in cancer,¹⁸ although others found 0.8 points was a better cut-off value in COPD.¹⁷ No MCID for ESKD

exists. As the within group differences were small and the between group difference was borderline relevant, we considered the change not clinically relevant overall. But one could argue that conservative patients have also some lower self-rated QoL over time, when interpreting the results more strictly.

Conclusion

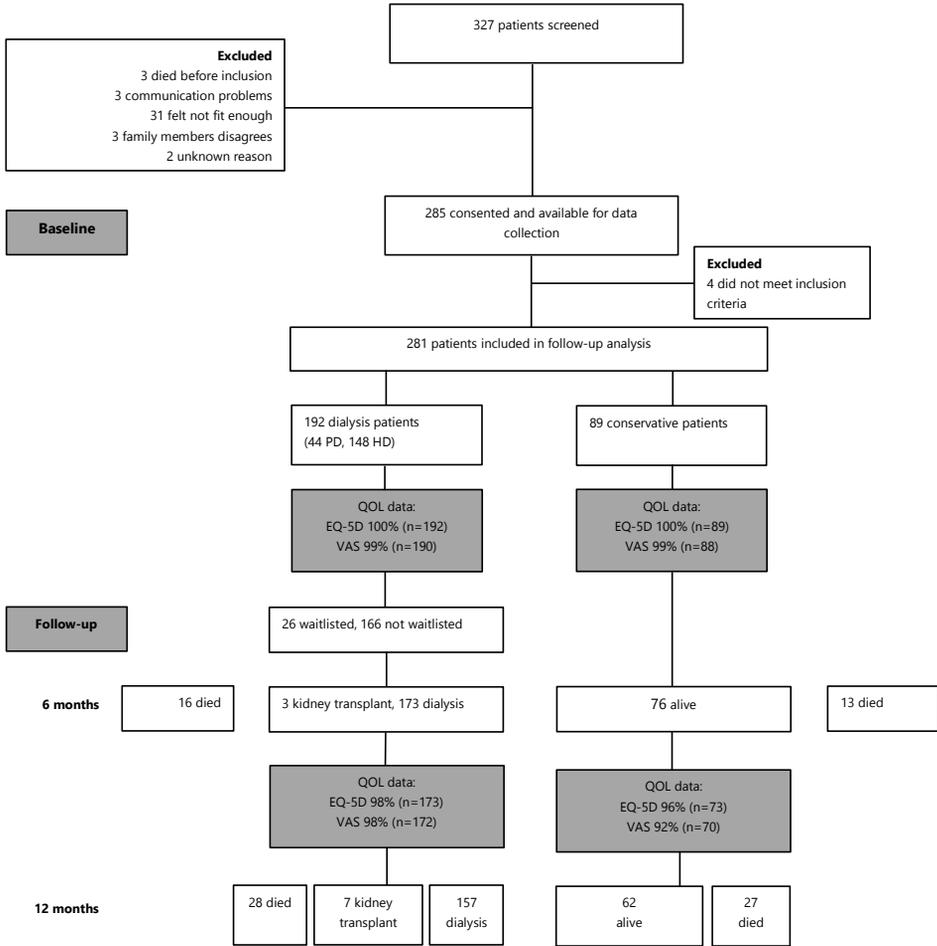
Based on the findings from this study, the trajectory of QoL seems slightly better in elderly patients (≥ 65 years old) starting dialysis compared to patients choosing conservative care in the first six months of follow-up. Two-thirds of dialysis patients remain in a stable or better QoL, while this occurs in half of the conservative patients. Overall, mean EQ-5D Index did not improve in the dialysis group, and a small decline was seen in the conservative group. On the other hand, twice as many dialysis patients were hospitalized within this period. In addition, in patients over 80 years old, no survival benefit could be found for dialysis patients starting dialysis vs. patients choosing conservative care. Overall, in octogenarians and nonagenarians, conservative care may be a good alternative for dialysis.

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Supplementary data



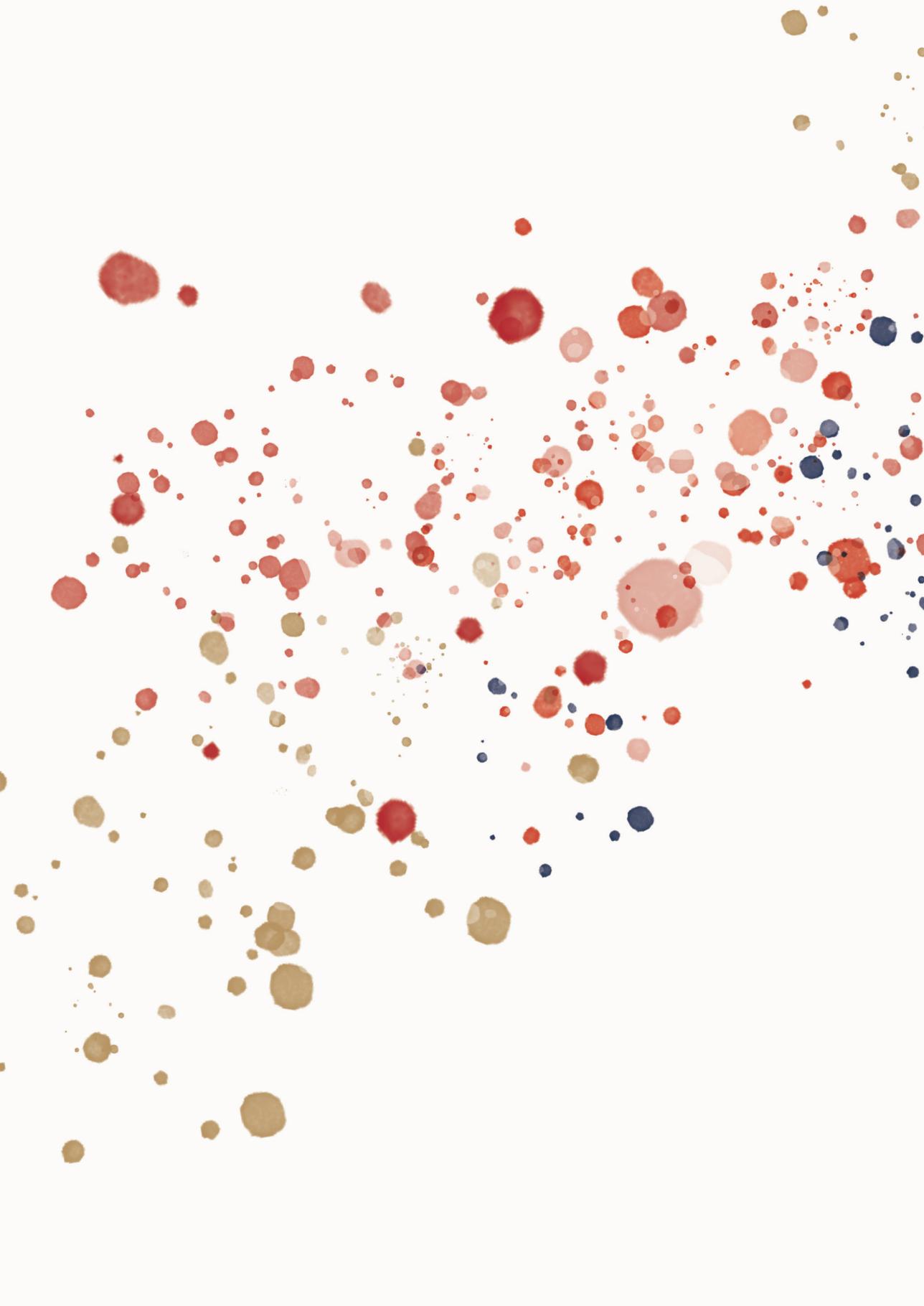
Appendix 1. Patient flow diagram

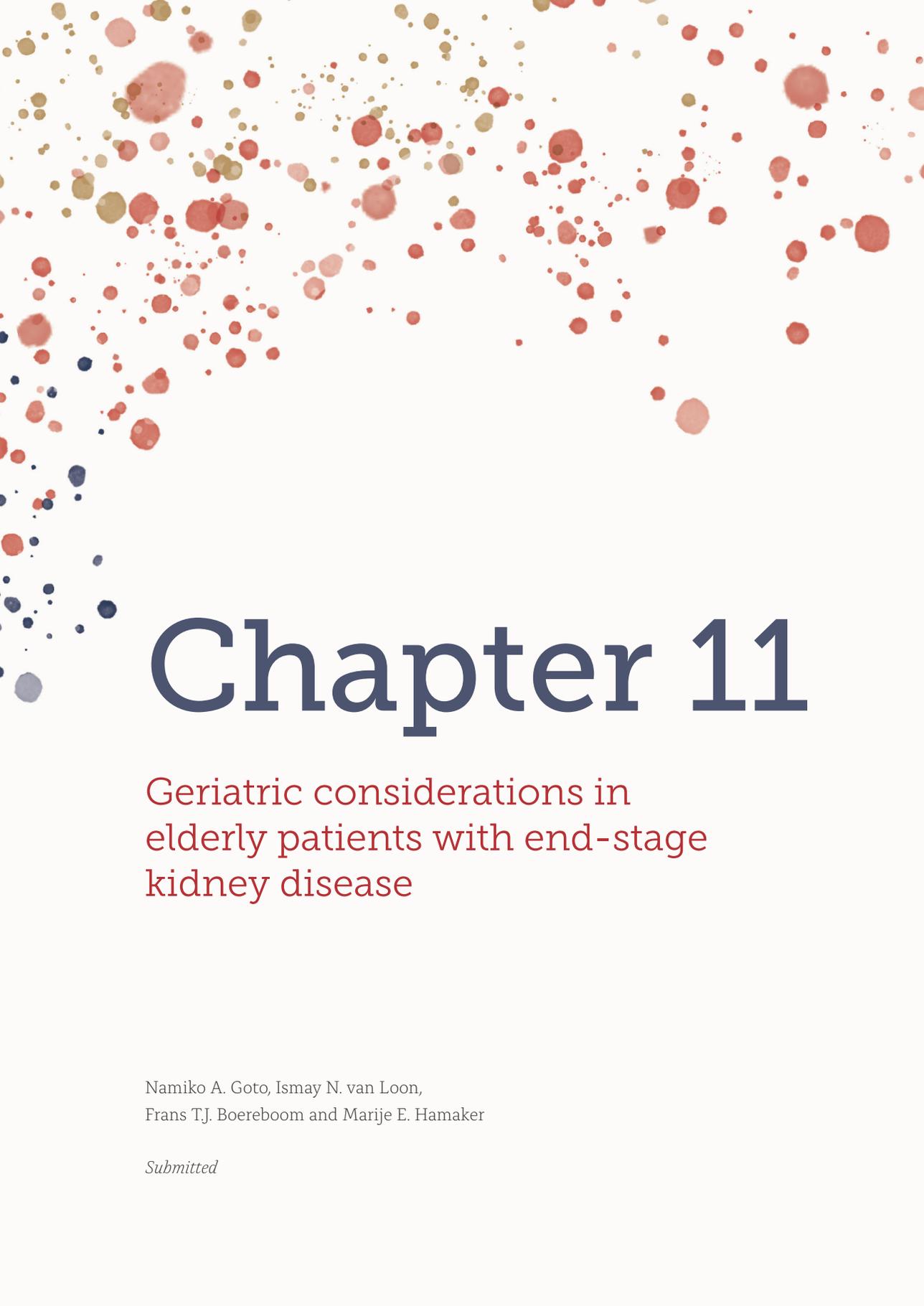


Part 4



Clinical implications of geriatric impairments in chronic kidney disease





Chapter 11

Geriatric considerations in
elderly patients with end-stage
kidney disease

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Submitted

Abstract

Decision-making in the elderly end-stage kidney disease (ESKD) population regarding dialysis initiation is highly complex. While some elderly patients improve by dialysis and maintain a good quality of life, others experience less benefit and multiple complications due to a high morbidity burden and (early) mortality. Geriatric impairments are highly prevalent among this population and these impairments may complicate the care of the elderly patient with ESKD. Knowledge on these impairments can potentially help to improve care and decision-making regarding initiation and advance care planning. Therefore, the aim of this review is to give healthcare providers an insight on the existing literature on geriatric impairments in elderly patients with ESKD. Furthermore, specific areas of concern will be discussed, in combination with some practical advice.

Introduction

Currently, more than half of the prevalent and incident dialysis patients in the Netherlands is 65 years or older.¹ Taking patients who forego dialysis into consideration, the percentage of older patients among those with end-stage kidney disease (ESKD) is likely to be much higher (although exact numbers are currently lacking)². Furthermore, as the Dutch population also is aging,³ this number is likely to increase even further over the coming decades. The elderly population is a very heterogeneous group, in terms of comorbidities, polypharmacy and geriatric impairments,⁴ such as cognitive impairment, accidental falls, functional impairment, symptoms of depression and frailty.⁴

As a result of this heterogeneity, decision-making considering the initiation of dialysis and dialysis modality is highly complex. While a part of the elderly patients function very well and improve through dialysis therapy, other elderly patients experience high morbidity⁵⁻⁸ and increased mortality, especially early after dialysis initiation.⁹⁻¹¹ As the geriatric impairments influence prognosis,¹² knowledge on the presence of such impairments can potentially help decision-making on dialysis treatment and advance care decisions in the elderly ESKD population.

In this paper, we use four cases to illustrate the heterogeneity in elderly patients with ESKD and address different geriatric considerations that may be relevant in decision-making regarding treatment for ESKD.

Cases

Patient A is a 76-year-old female with ESKD caused by amyloidosis. For the amyloidosis she has been treated with multiple courses of chemotherapy, which resulted in hematological regression, but also complaints of polyneuropathy. Consequently, Patient A experiences difficulty with undoing buttons and getting pills out of the box. In addition to the amyloidosis, she has a medical history of osteoporosis and multiple abdominal herniations (umbilical, epigastric) for which she was treated with surgery. She is a widow, with 2 children and 4 grandchildren. Because of progression of the ESKD, Patient A has to choose whether she wants to start dialysis. Patient A chooses peritoneal dialysis, because she wants to maintain her active lifestyle and wants to remain independent.

Patient B is an 85-year-old male with ESKD caused by hypertension and diabetes. He has a severely reduced exercise capacity due to ischemic heart disease, for which he has been treated with multiple percutaneous interventions. Furthermore, he has experienced multiple fall incidents of unknown etiology. Patient B is married and has an adult son. In addition to home care three times a day, his wife and son support him with transport and help with daily activities. Due to his limited exercise

capacity and a recent fall, he only walks inside the house with a walking cane. Although he is very dependent on his surroundings, he enjoys life to the fullest, and is determined to live as long as possible. Despite some hesitation from his treating nephrologist, he decides to start in-center hemodialysis

Patient C is an 82-year-old male with ESKD caused by hypertension. Furthermore, he has a medical history of deep vein thrombosis and pulmonary embolism treated with anticoagulants. Patient C is fully independent and lives with his wife. In the past, a good friend of patient C with ESKD chose maximal conservative management. He has experienced this as a good way to maintain quality of life and in the end experienced a peaceful death at home. Although patient C is fit and has an active lifestyle, he decides that dialysis will have too much impact on his quality of life. Therefore, he chooses maximal conservative management.

Patient D is a 75-year old female with ESKD caused by diabetes. In addition, her medical history includes peripheral artery disease, recurrent urinary tract infections (UTI) and multiple deliriums caused by infections. She is married and has no children or additional home care. However, since her last UTI six months ago, Patient D appears slow, depressed and is more dependent on her husband in daily activities. After consulting a geriatrician she is diagnosed with vascular type dementia, which was a surprise for both the husband and the nephrologist, who had treated her for several years. After deliberating with Patient D and her husband, the nephrologist decides to advise against starting dialysis. The patient and her husband agree with conservative management.

Treatment options for elderly patients with ESKD

Treatment options for elderly ESKD patients do not differ from younger patients and include in-center hemodialysis, (assisted) home hemodialysis, (assisted) peritoneal dialysis (both automatic peritoneal dialysis (APD) and continuous ambulatory peritoneal dialysis (CAPD)), kidney transplantation and maximal conservative management. Although kidney transplantation is an option in selected elderly patients (e.g. the Eurotransplant Senior Program (ESP), in which a kidney of a deceased patient older than 65 years is donated to a patient older than 65 years), due to shortage of transplants and health requirements by far most elderly patients will start dialysis¹ and remain on this therapy for the rest of their life.

Hemodialysis can take place at a center or at home; in which case additional help of trained home care or help of family members can be arranged for patients who are not capable to perform dialysis independently in the home setting (assisted home hemodialysis). The same can be arranged for peritoneal dialysis, which is performed in the home setting. Potential advantages of home dialysis are the flexibility in treatment schedule, less time spent in the hospital and no need for transits to and from the center.¹³ Furthermore,

home hemodialysis facilitates more frequent and shorter treatment schedules, which yield in some patients a shorter post-dialysis recovery time, less depressive symptoms and an improved sleep quality.¹⁴ Subsequently, there is evidence that home dialysis leads to a higher quality of life.¹⁵ However, in addition to the logistical and financial barriers,¹³ patients and their caregivers sometimes find the burden of responsibility for self-care too much.¹⁶ Furthermore, some patients, such as elderly with a limited social network value the advantage of socialization of in-center dialysis.

In addition, patients can choose maximal conservative management (MCM). This treatment focuses on symptom management to maintain quality of life as much as possible. Over the past years, there is increasing evidence that MCM, in patients older than 80 years and patients older than 75 years with a high comorbidity burden, has a survival similar to dialysis therapy.¹⁷⁻¹⁹ Furthermore, patients on MCM treatment are less likely to be hospitalized²⁰ and more likely to die at home or in a hospice.⁸

In our case descriptions, fear of the potential loss of quality of life was the reason Patient C choose MCM, despite his good clinical condition. Although he had the reserves and the resilience to undergo dialysis, his good condition also meant he potentially had a lot to lose (such a lot of time spend on the dialysis therapy, potential complications and hospitalizations).²⁰ Therefore, MCM should always be actively discussed as an option in the (elderly) patient with ESKD, irrespective of their health status.

Geriatric impairments

Cognitive impairment

Cognitive impairment is an important issue in patients with ESKD. As illustrated in Patient D, it is an impairment that is frequently overlooked by both healthcare providers and family members.²¹ For example, in a study in hemodialysis patients, 37% had a severely impaired cognition when tested, but only 3% of all patients had a documented history of cognitive impairment.²² The prevalence of cognitive impairment in this study is in line with previous research, with most studies reporting more than half of the elderly ESKD patients having mild to severe cognitive impairment.^{4,22}

Cognitive domains that are frequently affected are attention and executive function.²³ Both are crucial in making an informed decision, because patients have to understand the information required for the decision and have to realize how the information given will impact their own life and circumstances. Furthermore, patients should be able to use the information and subsequently logically reason which treatment option they prefer.²⁴ Although, it makes sense that decision-making capabilities can be troubled in patients with severe cognitive impairment,²⁵ the effect has rarely been studied in ESKD.^{26,27}

Possible solutions to the diminished attention span is to dose information over multiple appointments. Furthermore, health care providers should regularly check if the information is understood (for example asking the patient to paraphrase the given information). Moreover, as problems in executive functioning can lead to difficulties in anticipating new situations, health care providers should ascertain if patients can comprehend the potential implications of their decision for their daily life.²⁴

Besides potential problems with decision-making, cognitive impairment is associated with a higher risk of mortality²⁸⁻³¹ and dialysis withdrawal³⁰⁻³². For example, the average time to death for patients with dementia was 1 year compared to 2.7 year in patients without dementia.³¹ Although it is not completely clear how different aspects of dialysis (e.g. clearance of uremic toxins, shifts in cerebral blood flow) affect cognitive impairment, the start of dialysis in the elderly population is more often associated with a loss of function than improvement.^{33,34}

Hence, screening for cognitive impairment in the elderly population with ESKD is recommended, for example by the use of the Montreal Cognitive Assessment (MOCA).³⁵ In case of cognitive impairment that interferes with self-care and therapy adherence, referral to a memory clinic is advisable. This information can subsequently be used for prognostication and to assess decision-making capacities.

Depression

In patients treated by dialysis, depression is present in approximately 23%³⁶ and depressive symptoms in one-third of the patients.^{4,36} As depressive symptoms are associated with a lower medical adherence, a higher morbidity,³⁷ withdrawal from treatment³⁸ and mortality,³⁷⁻³⁹ this is an important issue to be aware of.

Depressive symptoms can be indicated by the 36-Item Short Form Health Survey (SF-36) or RAND-36.⁴⁰ The diagnosis of depression is made by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, which include mood and somatic symptoms during at least two weeks, not explained by a somatic disease.⁴¹ The latter criterion poses difficulties in ESKD, as uremic complaints such as insomnia, fatigue and a decreased appetite frequently overlap with the somatic symptoms of depression. Sometimes the course of the symptoms can help in discriminating between depression and progression of ESKD. For example, if new complaints in combination with depressive symptoms and/or anhedonia, are not accompanied by changes in physical examination and/or laboratory results, the diagnosis of depression should be considered.

Of note, late onset depression is associated with dementia.⁴² This is illustrated by Patient D, for whom the differential diagnosis of her lethargy, depressive symptoms and increased care dependence was broad and may consist of uremia, depression, adjustment disorder, medication induced mood disorder and cognitive impairment. Furthermore, a depression is treated differently than depressive symptoms caused by other disorders, making a correct diagnosis essential. Therefore, in case of doubt, the consultation of an expert (e.g. psychiatrist, geriatrician) may be beneficial.

Although based on sparse data of medium quality, there is some evidence that different non-pharmacological (e.g. exercise training, cognitive behavior treatment)⁴³ and pharmacological treatment strategies^{43,44} can be beneficial in treating depression in patients with ESKD. Nevertheless, besides attention for a reduced renal excretion of medication, caution is advised in the elderly population for the potential anticholinergic effects of anti-depressants (mainly tricyclic antidepressants), which can lead to a broad spectrum of symptoms including sedation, postural hypotension, confusion and even delirium.⁴⁵ Furthermore, a higher risk of falling is reported with the use of anti-depressants.⁴⁶⁻⁴⁸ Therefore, the potential benefits and burdens should be carefully weighed for the individual patient.

To our best knowledge, no research is performed on the influence of depression on decision-making in elderly patient with ESKD. However, previous studies in the general population have shown that patients with depression are less likely to accept a life-sustaining treatment,⁴⁹ while remission of depression is associated with an increase in acceptance of treatments.⁴⁹ Therefore, it is recommended to timely screen for depression and refer patients suspected for depression for additional diagnostics and management preferably before making a definitive decision regarding dialysis.

Accidental falls

Patient B experienced multiple falls of unknown etiology. Falls are definitely not uncommon in the elderly population with ESKD, with approximately between 30 and 55% of the patients on dialysis therapy falling every year.⁵⁰⁻⁵² Interestingly, especially the post-dialysis initiation period is high-risk for falls incidents.⁵¹ Injurious falls in the dialysis population are also common⁵² and are associated with loss of independence⁴⁷ and increased mortality⁵³. Besides injury, falls can also lead to fear of falling, which can subsequently lead to loss of mobility and social isolation.⁵⁴

Most risk factors for accidental falls in elderly patients with ESKD are similar to the general population and include age, previous fall, diabetes, frailty, mobility impairment, use of anti-depressants and decrease of systolic blood pressure.⁵⁴ Thus, additional analysis of a patient such as Patient B in falls clinic before the start of dialysis is recommended to identify potentially modifiable risk factors. In the general population there is extensive evidence that a multifactorial fall risk assessment and management program can lower the number of falls⁵⁵ and subsequently fall-related injury.⁵⁶ In addition, considering most patients do not tell their healthcare providers they have experienced a fall,⁵⁷ it is recommended to periodically ask patients with ESKD about falls.

Functional impairment

Approximately 80% of the elderly patients with ESKD are dependent on others in one or more (instrumental) daily activities.⁴ These include activities that are necessary for self-care (such as bathing, dressing and continence) and more complex tasks that are essential for independent living (such as shopping, housecleaning, and telephone use). To perform these tasks, cognition, physical ability and perceptual capacities are necessary. For example, patient A has severe polyneuropathy in both hands, limiting her in performing activities that require fine motor skills. This could potentially affect her ability to connect to the PD-machine. This is important to consider, especially since the main reason Patient A had chosen peritoneal dialysis was remaining independent.

The fact is that irrespective of treatment modality the start of dialysis in elderly patients is frequently accompanied by a loss of independence, both in short⁷ and long term⁵⁸. For example, we showed that older patients starting dialysis, 40% experienced a decline in functional status within six months.⁷ This rate was even higher in frail adults.⁷ Similar results were seen in very frail nursing home patients, of whom only 13% maintained their functional status one year after start of dialysis.⁵ In contrast, the (limited) data on functional course of maximal conservative management shows that the loss of independence does not occur until the month before death.⁵⁹ In addition, functional dependence is strongly associated with mortality,^{60,61} therapy withdrawal,⁶⁰ time to first hospitalization⁶⁰ and can negatively influence quality of life.^{62,63} Regarding Patient A, this information could have assisted her, her caregivers and treating physicians in making a well informed decision.

A potential treatment strategy to maintain functional status is to improve physical functioning. Different studies showed that regular exercise training is able to improve physical functioning⁶⁴ by enhancing aerobic capacity, muscular functioning, cardiovascular function and walking capacity.^{65,66} Interestingly, patients that exercised during dialysis demonstrated more frequent improvement compared to patients that exercised outside

the dialysis unit.⁶⁴ This is probably the result of a better compliance with exercise during dialysis.⁶⁴ Hence, it may be beneficial to encourage physical activity in elderly patients with ESKD, for example by offering intradialytic exercise.

Caregiver burden

Caregivers of patients with end-stage kidney disease are at risk for high burden, because of high prevalence of symptoms (e.g. fatigue, anorexia, sleep disturbance, pruritus)⁶⁷ and the frequent coexistence of other impairments, such as cognitive impairment, depressive symptoms and functional impairment.⁴ High caregiver burden is associated with a decreased quality of life and more depressive symptoms for the caregiver.⁶⁸ Also for the patient it is important to maintain good social support, as poorer social support is associated with a higher mortality risk,^{69,70} lower adherence to medical care⁷⁰ and poorer physical quality of life.⁷⁰ On the other hand, being a caregiver also comprise positive experiences, such as feelings of personal growth and gratification.⁷¹ Furthermore, help of a caregiver can give both the patient and the caregiver potentially more freedom. For example, in the setting of home dialysis, a caregiver who facilitates the dialysis procedure can create more flexibility in treatment schedule. Thus, when aiming to optimize care for older patients, supporting the caregiver, and regularly inquiring after the burden of care they experience, is as important as the support given to patients themselves.

Frailty

Frailty is frequently defined as a “biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, resulting in increased vulnerability to adverse outcomes”⁷² Multiple operationalizations of frailty exist, and the diagnostic method strongly affects the prevalence of frailty. However, irrespective of this, at least half of ESKD patients appear to be frail.⁷³ Previous research in ESKD shows that frailty is associated with functional deterioration,⁷ hospitalizations^{74,75} and mortality⁷⁶. Therefore, especially in frail elderly, conservative management seem to be a good alternative of dialysis therapy as these patients are less likely to benefit from dialysis.

One of the ways in which frailty is operationalized is through the number of geriatric domains found to be impaired in a geriatric assessment. This multidimensional assessment includes physical, functional and psychosocial domains and includes all the impairments previously discussed. For elderly ESKD patients, a regularly performed geriatric assessment (e.g. yearly, or when major events occur) may be beneficial to ensure a timely diagnosis of issues that are potentially modifiable or can influence treatment decisions and care provision. However, it is yet unclear how a geriatric assessment will affect decision-making regarding the start of dialysis and dialysis modality. This is the focus of two

studies currently ongoing in the Netherlands: the “Pathway for Older Patients Reaching End Stage Renal Disease (POLDER)”⁷⁷ and “DIALysis or not Outcomes in older kidney patients with Geriatric Assessment (DIALOGICA)”⁷⁸.

Health outcome priorities in elderly patients with ESKD

It is important to realize that most elderly patients may identify more with problems or outcomes that are not disease-specific.⁷⁹ For example, a recent study in the United States showed that most elderly patients with advanced chronic kidney disease value maintaining independence as their top health priority.⁸⁰ In addition, a study in elderly non-CKD patients with a limited life expectancy, showed that if the outcome is increased survival, but with severe functional impairment or cognitive impairment, most patients would not choose for treatment.⁸¹ However, as illustrated with Patient B and Patient C, how quality of life is experienced is very personal and strongly affects their treatment decision. Therefore, identifying and prioritizing patients healthcare goals (e.g. living independently at home, take care of a loved one as long as possible) should be an important part of the management of ESKD in all patients.

Knowing healthcare goals can also help to discuss end-of-life choices. A recent study showed that in only 35% of the patients with advanced chronic kidney disease, the healthcare provider was aware of their patients top health priority.⁸⁰ This suggests that these questions are currently insufficiently discussed in clinical practice. Furthermore, another study showed that elderly ESKD patients had lower rates of advance care planning near the end of life than similar patients dying of cancer, resulting in higher treatment intensity at the end of life and more patients dying in the hospital.⁸² This is also illustrated by Patient C, who highly valued dying at home, something that is relatively easy to accomplish if this is established early on.

Conclusions

As the ESKD population is aging, geriatric impairments become more and more prevalent, and decision-making regarding dialysis becomes more complex. Knowledge on geriatric impairments can help to improve decision-making regarding dialysis therapy and modality by improving information on prognosis and decision-making capacities. Furthermore, treatment strategies could be implemented to optimize health and quality of life. A geriatric assessment covers all important geriatric impairments and could therefore be used to identify these problems. Subsequently, depending on personal health goals, an individualized treatment plan could be made, preferably together with family and/or potential caregivers.

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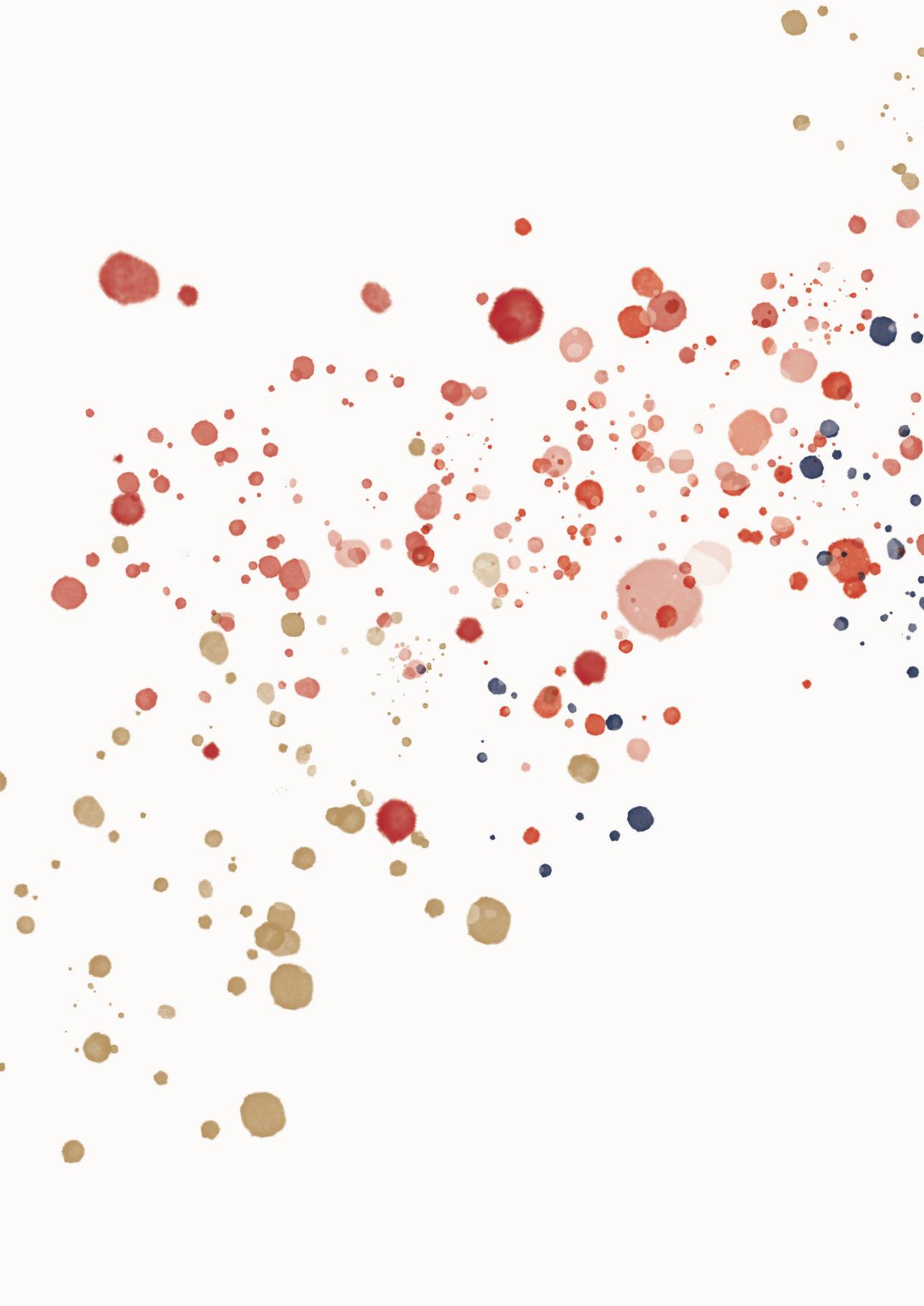
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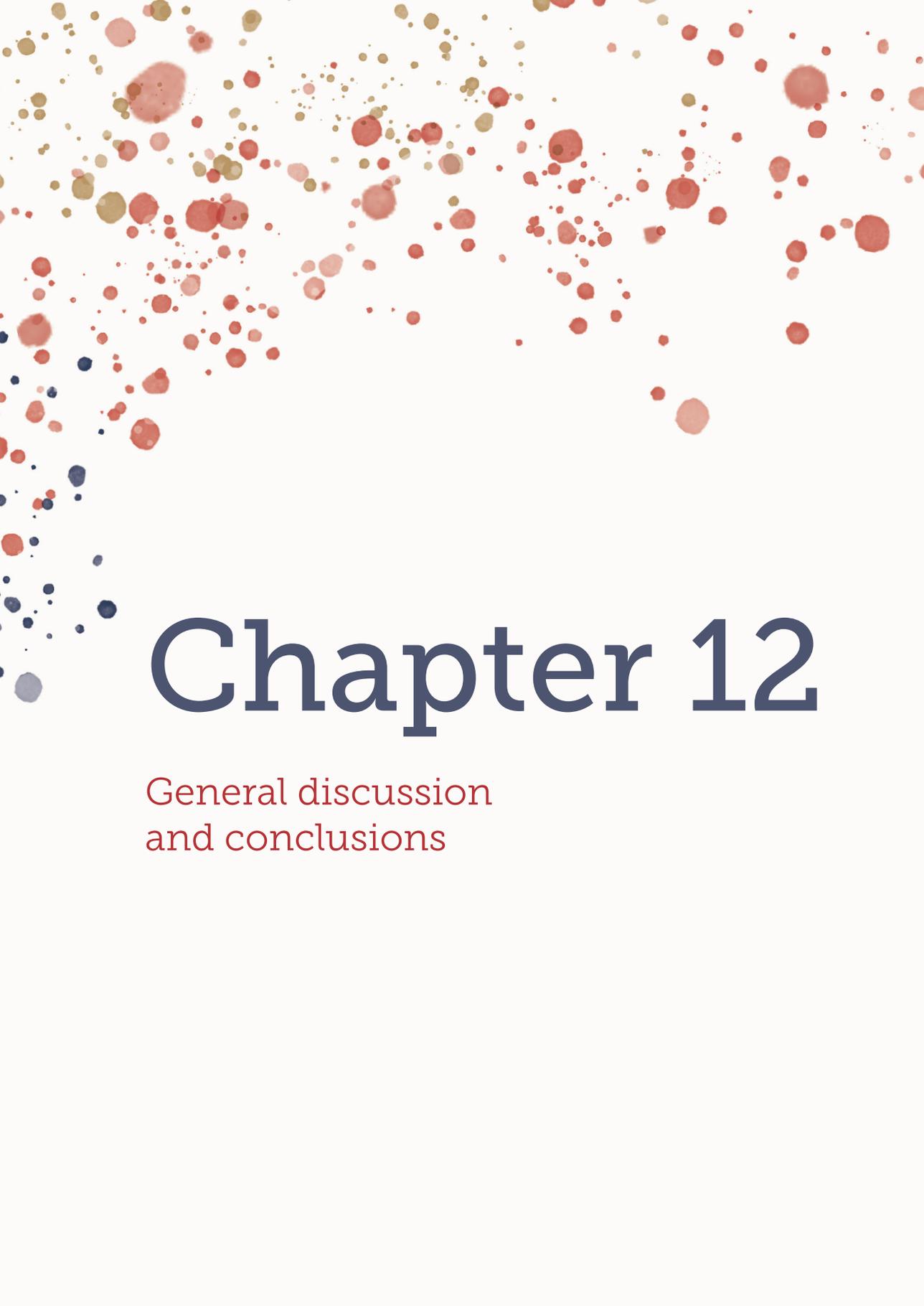
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Chapter 12

General discussion
and conclusions

General discussion

In this thesis, we investigated the prevalence of geriatric impairments in patients with chronic kidney disease as well as the prevalence of early poor outcome in elderly patients starting dialysis. Furthermore, we have assessed the association between geriatric impairments and poor outcome. In this final chapter, the results of these studies will be placed in a broader perspective and clinical implications and recommendations for future research will be given.

Frailty in chronic kidney disease

We demonstrated that frailty is highly prevalent in elderly patients initiating dialysis (**Chapter 3 & Chapter 4**). Although the prevalence differed depending on how frailty was assessed, the prevalence was consistently much higher compared to the general community-dwelling elderly population. For example, in our study population 46% was frail according to the Fried Frailty Index vs. 12% in the general elderly population.¹ Various specific geriatric impairments, such as functional impairment, cognitive impairment and depressive symptoms were also highly prevalent (**Chapter 3**). It is important to note that these impairments would not be observed using only a screening frailty instrument, such as the Fried Frailty Index or the Groningen Frailty Indicator. Notwithstanding, these impairments can potentially influence decision-making considering dialysis and treatment during dialysis therapy (**Chapter 12**).

Various studies showed a graded risk of prevalent and incident frailty as kidney function worsens.²⁻⁵ A theory that could potentially explain this increasing prevalence of frailty is the model of accelerated aging,⁶ which suggests that there are similarities between uremic state and aging. This theory argues a multifactorial process with several pathogenic factors (e.g. telomere loss, accumulation of advanced glycation end products and increased oxidative stress) that leads to accelerated aging,⁶ leading to an accumulation of deficits⁷ and eventually a final common pathway with geriatric syndromes. Interestingly, accelerated aging is a process that is also seen in other types of chronic disease, such as chronic obstructive pulmonary disease and HIV.^{8,9} However, this theory does not completely explain why some patients with end-stage kidney disease do not become frail (and therefore seem to be more resilient to adversities), or why some patients without any other comorbidity become very frail. More knowledge on this difference and on resilience of patients could help better select patients that potentially could benefit from dialysis. For example, more detailed information on the course of frailty before and after the start of dialysis in elderly patients could provide valuable information.

In this thesis, we showed that frailty according to the geriatric assessment, Fried Frailty Index and Groningen Frailty Indicator is associated with functional decline, hospitalizations and mortality (**Chapter 5 & Chapter 10**). However, the geriatric assessment does have multiple advantages over a frailty screening instrument. First, the geriatric assessment provides information on all relevant domains of aging. For example, cognition is not assessed objectively in the Fried Frailty Index nor the Groningen Frailty Indicator. Second, a geriatric assessment could be a framework to analyze impairments, capacities and needs for care of a patient and subsequently create a multidimensional tailored treatment plan in a multidisciplinary team (Comprehensive geriatric assessment). For example, if a patient has cognitive impairment, a case-manager could be involved, medication intake and medical adherence could be assessed and/or day care could be implemented. Furthermore, knowledge about geriatric impairments could alter treatment decisions. For example, in frail patients it might be beneficial to maintain less strict diet restrictions, to maintain appropriate protein intake and to prevent additional muscle wasting.¹⁰ In addition, in patient who are prone to falls, tight blood pressure control may be less beneficial, considering this can contribute to falls.^{11,12} Third, a geriatric assessment could support a conversation on advanced care planning and decision-making. For example, in a patient with cognitive impairment, a conversation should take place about current quality of life and higher chance of poor prognosis. Furthermore, a geriatric assessment could help to clarify patients' priorities in life. That there is a need for more attention for patients' priorities is emphasized by a recent study that showed that in only 35% of the patients with advanced chronic kidney disease the nephrologist knew what their main health priority was.¹³

Unfortunately, the potential benefits of the use of a (comprehensive) geriatric assessment have thus far not been studied in patients with chronic kidney disease. A pilot study in the pre-dialysis setting did show that the results of the geriatric assessment influenced the care processes in approximately 40% of the included patients (e.g. additional diagnostic tests, medication changes, further clinical evaluation).¹⁴ Furthermore, in 20% of the patients the geriatric assessment contributed to dialysis decision-making discussions that favored conservative management.¹⁴ In addition, there are some studies that showed an effect of optimization for various individual geriatric domains. These interventions primarily concern improving physical function and preventing falls, by the use of exercise training,¹⁵ geriatric rehabilitation,¹⁶ staff education¹⁷ and environmental modifications.¹⁷ Furthermore, in various study populations (e.g. geriatric oncology, inpatients consultation units), the use of a comprehensive geriatric assessment led to an improved survival, function, treatment tolerance and treatment completion in elderly patients.^{18–20} Additionally, patients were more likely to remain living in their own homes.²¹ More research is needed to assess the effects of a (comprehensive) geriatric assessment in

the ESKD population. Interestingly, both “Pathway for Older Patients Reaching End Stage Renal Disease (POLDER)”²² and “DIALysis or not Outcomes in older kidney patients with Geriatric Assessment (DIALOGICA)”²³ will assess the effect of a geriatric assessment in patients with ESKD on clinical outcomes and may provide more knowledge on this topic.

A frequently used argument against the use of a comprehensive geriatric assessment is that it is time consuming and labor intensive. Therefore, a frailty screening instrument, that can preselect frail patients that could potentially benefit from a geriatric assessment, but also can reliably exclude non-frail patients for further evaluation, could be helpful. In our study (**Chapter 4**) we demonstrated that frailty screening instruments lack the discriminating capacities to preselect patients for a geriatric assessment. Therefore, it is recommended to perform a geriatric assessment in all elderly patients with end-stage kidney disease. Although it takes time, considering it could potentially prevent unnecessary harm caused by dialysis and could improve quality of life, in the end, it probably saves time and costs and ultimately prevent unnecessary harm caused by dialysis.

Falls & Fractures in chronic kidney disease

In this thesis we showed that there is a graded risk of fractures when kidney disease gets worse (**Chapter 6**). This is most likely the result of a combination of a high risk of falls (**Chapter 6 & Chapter 7**),^{11,24} osteoporosis and renal osteodystrophy.²⁵ The latter is a component of chronic kidney disease-mineral bone disease (CKD-MBD),²⁶ and causes an additional impairment of bone morphology, above that of age/hormone-related osteoporosis.²⁷

Considering the high fracture risk in chronic kidney disease, it would be valuable to reliably estimate fracture risk. However, there is no regularly tool to estimate fracture risk in patients with chronic kidney disease. In the general population, the World Health Organization (WHO) recommends the use of the “Fracture risk assessment (FRAX) tool” to estimate 10-year fracture risk for a major osteoporotic fracture or hip fracture.²⁸ This risk assessment assesses 10 clinical risk factors, including risk factors for secondary osteoporosis, such as type I diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition, malabsorption and chronic liver disease.²⁹ Although chronic kidney disease is mentioned as a cause of secondary osteoporosis,^{28,30} this risk factor is not included in the FRAX model.²⁸ Interestingly, previous studies that assessed the predictive value of FRAX in patients with chronic kidney disease showed a relation between the FRAX-score and mild stages of chronic kidney disease,³¹ an inconsistent association with more advanced stages of chronic kidney disease,³² and no association

in patients treated by hemodialysis.³³ This may suggest that in the more advanced stages of chronic kidney disease, in addition to the traditional risk factors (e.g. age, sex, diabetes) ³⁴, other risk factors that are not included in the FRAX-score may become more important. Hence, caution is required when estimating fracture risk with FRAX in patients with chronic kidney disease, especially in the advanced stages of chronic kidney disease. Nevertheless, it would be interesting to assess the additional value of an estimate of kidney function in the FRAX score. In addition, further research is needed to develop a reliable fracture risk assessment for the advanced stages of chronic kidney disease.

The treatment of CKD-MBD is mainly focused on lowering high serum phosphate, maintaining serum calcium and treatment of abnormal PTH levels,²⁶ with limited evidence of osteoporosis medications, such as bisphosphonates, teriparatide, raloxifene and denosumab.³⁵ Remarkably, there are no recommendations on fall prevention in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.³⁶ This is interesting, when considering that 90% of the low-energetic fractures in patients older than 50 years are caused by a fall²⁸ and that falls are associated with increased number and longer duration of hospitalizations,³⁷ more nursing home admissions^{37,38} and greater mortality.^{37,39} In the general population there is extensive evidence that a multifactorial fall risk assessment and management program can lower the number of falls.⁴⁰ As risk factors of accidental falling in the chronic kidney disease population overlap with the general population (e.g. age, diabetes mellitus, history of falls and frailty),^{12,24,41} an analysis in the fall clinic should be considered in CKD patients with a history of falls, or patients that experienced a recent fracture. As falls are often underreported by patients unless prompted,⁴² nephrologists should be aware of falls and should periodically inquire after fall incidents.

A special type of fracture is the vertebral fracture. In contrast to most other fractures, approximately two-thirds of vertebral fractures remain undiagnosed.⁴³ One of the main reasons is their atypical presentation.⁴⁴ For example, in contrast to many other fractures, most vertebral fractures are not caused by an accidental fall, but (depending on degree of decreased bone strength) can be caused simply by the strain of normal daily activities, such as bending forward or stepping out of the bath tub. They may lead to back pain, functional limitations,⁴⁵ and poorer quality of life.⁴⁶ In this thesis we have demonstrated that vertebral fractures in patients with ESKD are common (**Chapter 8 & 9**), with a prevalence of 34% in a relatively young and fit population that was treated by chronic dialysis and a prevalence of 43% in an elderly population at the start of dialysis. In addition, 22% of the incident dialysis patients had hyperkyphosis.

Vertebral fractures and hyperkyphosis are important, because they can provide information about prognosis. For instance, chronic dialysis patients with a prevalent vertebral fracture have a high risk for a new vertebral fracture (**Chapter 9**), which could potentially lead to an increase of functional limitation or back pain. In addition, hyperkyphosis, especially in combination with vertebral fractures, in incident dialysis patients is related to an increased early mortality after start of dialysis (**Chapter 8**). Similar increased mortality rates were also observed in previous studies assessing chronic dialysis patients.^{47,48} A possible reason for the higher rate of mortality may be that hyperkyphosis (possibly in combination with vertebral fractures) could be an indicator of physical dysfunction (**Chapter 8**). More awareness of hyperkyphosis and vertebral fractures could therefore help to identify patients at risk for poor outcome.

One essential point in improving awareness is that vertebral fractures are often overlooked in radiographs.⁴⁹ Considering that in almost every patient with end-stage kidney disease a chest radiograph is performed, more awareness for vertebral fractures and hyperkyphosis could help identify patients at risk for poor outcome. Identifying these patients can potentially prevent or reduce poor outcome. For example, in the general population, there is evidence that non-pharmacological treatment, such as physiotherapy, can reduce pain,⁵⁰ improve physical function⁵⁰ and can even reduce the incidence of new vertebral fractures up to 8 years after cessation of intervention.⁵¹ However, additional research is needed to assess the benefit of pharmacological and non-pharmacological treatment strategies in patients with advanced kidney disease.

Functional status, quality of life and caregiver burden

In order to make a decision considering start of dialysis therapy, patients and their caregivers have to be fully informed about the benefits and burdens of dialysis and the consequences of not starting dialysis.⁵² Unfortunately, various studies showed that patients felt that they did not receive the information needed to make an informed decision.^{53,54} As mentioned previously, it is unclear if dialysis provides a survival benefit over conservative management in elderly (comorbid) patients (**Chapter 11**).^{55,56} Data on functional dependence in relation to starting or withholding dialysis is even more limited, despite multiple studies demonstrating that maintaining independence is the main health priority in most elderly patients.^{3,57}

Functional dependence can be seen as one of the consequences of frailty⁵⁸ and is highly prevalent in patients with ESKD (**Chapter 3**).⁵⁹ Furthermore, functional dependence is an important risk factor for poor outcome, such as mortality and hospitalizations.^{60,61} Prior studies have shown that elderly incident dialysis patients are at increased risk of experiencing functional decline after start of dialysis (**Chapter 10**).^{62,63} However, the

decline varied from mainly loss in ADL independency in the very frail nursing home patients⁶³ to much lower rates of ADL loss and mainly loss of IADL independency in the community-dwelling elderly population (**Chapter 10**). The ability to perform functional tasks depends on cognitive, motor and perceptual capacities. Considering that in many patients who start dialysis both physical and cognitive decline is seen,^{64,65} this may contribute to the loss of dependence.

Also in the prevalent dialysis population the rate of physical decline is high: in patients of 75 years and older only 1 out of 25 patients maintained a good physical function over a period of 2 years.⁶⁶ It is plausible that this subsequently may have led to a higher dependence in daily activities. This was seen in a relatively young cohort of prevalent dialysis patients, with no ADL disabilities at baseline, of whom 20% experienced a decline in their functional status during 1-year of follow-up.⁶⁷ Furthermore, patients treated by dialysis therapy are more likely to be hospitalized, compared to patients treated by conservative management (**Chapter 11**).⁶⁸ Besides the potential effects on quality of life, hospital admissions are also associated with (at least) short-term decline in functional status (ADL and IADL) and physical performance in older dialysis patients.⁶⁹ Thus, not only in the pre-dialysis phase, but also after choosing for a treatment, it is important to keep evaluating functional status and its impact on quality of life.

However, if maintaining functional independence is the main interest, it is also important to know what happens with functional status in the patients that chose for maximum conservative management. Unfortunately, the literature on the trajectory of functional status in patients choosing conservative management is scarce. One prospective study, including patients with stage 5 chronic kidney disease that chose for conservative management, showed that functional status remained stable during the last year of life, but subsequently declined fast in the last month of life.⁷⁰ Another single-center study, performed in 41 patients, showed no significant decline in functional status in the 6 months prior to death. However, they did see a decrease in mobility and quality of life that already started approximately 6 months before death.⁷¹ More research, comparing the functional trajectories between dialysis and maximal conservative management is needed to inform patients better on prognosis.

As patients become more dependent, it is likely that caregiver burden will be higher, particularly as most do not have a choice about being a caregiver or not. In **Chapter 10** we demonstrated an increase of prevalence and severity of caregiver burden. Similarly high burden of care is reported by caregivers of adults on maintenance dialysis therapy,^{72,73} even more so than in caregivers of acutely admitted cancer patients.⁷⁴ Prior studies showed that caregiver burden is associated with negative outcomes for the caregiver, such as

a decreased quality of life and more symptoms of depression.⁷⁵ In addition, poor social support for the patient is associated with an increased mortality risk,^{76,77} lower adherence to medical care,⁷⁷ and poorer physical quality of life.⁷⁷ Therefore, it is important to regularly ask the caregiver about the burden of care and, whenever possible, involve the caregiver in decision-making considering dialysis. More research is needed on potential interventions, but also on differences in caregiver burden and quality of life between home and center dialysis.

Interestingly, our study found that despite a high frequency of functional decline and hospitalizations among elderly patients starting dialysis, self-reported quality of life remained stable and self-rated health score even improved slightly in the first six months after start of dialysis (**Chapter 11**). However, it is important to note that most quality of life questionnaires measure the level of experienced impairment and not the level of impact or importance of disability to daily life of the patients. Although, the results that we report in this thesis suggest a high rate of poor outcome in the frail elderly, it is important to note that the experience of burden is highly dependent on personal values and current quality of life (**Chapter 12**). Therefore, exploring individual's health goals (e.g. living at home, engage in social activities, to care for a loved one as long as possible) to optimize personal care and support decision-making considering dialysis is one of the most important interventions when aiming to provide individually tailored care to ESKD patients.

Clinical implications and conclusions

Geriatric impairments are highly prevalent in elderly patients with chronic kidney disease. As the number of patients with chronic kidney disease will further increase in the coming years, this will become an even greater challenge. Considering patients with ESKD have many similarities with the geriatric population, geriatric expertise may be a valuable addition to nephrology care. So what can geriatrics add to the care for elderly with chronic kidney disease? First, considering geriatric impairments are frequently missed when not searched for (e.g. cognitive impairment, vertebral fractures), more awareness is needed for the presence of geriatric impairments. A geriatric assessment may be a solution to assess the health of elderly patients with ESKD by focusing on somatic, psychological, functional and social domains. This could be regularly used (e.g. yearly or when major events occur) from the predialysis phase to ensure a timely diagnosis of issues that are potentially modifiable or can influence treatment decisions or care provision. In clinics where geriatric care cannot yet be provided for all elderly with ESKD, a trained (nephrology) nurse can perform a standardized geriatric assessment. Nevertheless, interpretation of the tests by a geriatrician is recommended. An important pitfall of a standardized geriatric assessment is that the cut-off scores are not personalized. For example, a highly educated patient with

a low normal score on a cognition test is remarkable and needs to be further addressed. On the other hand, a patient with low premorbid intellectual functioning can have an abnormal score, without any underlying pathology. The same applies to other geriatric impairments, such as falls and functional impairment. Therefore, it is recommended that a geriatrician joins the multidisciplinary nephrology team when the geriatric assessments of elderly patients are discussed. Second, a personalized optimization plan should be made, in which the geriatric impairments are addressed. For example, for a patient who experienced multiple falls, a multifactorial fall risk assessment should be performed to identify and treat potentially modifiable risk factors (e.g. less strict blood pressure control, stop medication that can increase fall risk, improve postural instability) to prevent any additional falls and fall related injury and decline. Third, the findings and the prognostic implications should be summarized and communicated to the patient to improve shared decision-making, to subsequently, based on individual's health goals, a decision regarding dialysis initiation can be made. Additional research is needed to assess whether geriatric interventions, based on findings of the geriatric assessment, can improve quality of life and/or survival for the elderly ESKD patient.

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Addendum



- A. Summary
- B. Summary in Dutch
- C. List of authors with affiliations
- D. Acknowledgments
- E. Dankwoord
- F. List of publications
- G. Curriculum vitae

Summary

The chronic kidney disease population is aging. Currently, more than half of the patients with end-stage kidney disease (ESKD) in the Netherlands is 65 years or older. As patients age, geriatric impairments, such as frailty, falls, functional dependence and cognitive impairment, become more prevalent. Nevertheless, there is high variance between patients, ranging from no geriatric impairment to accumulation of multiple deficits. Subsequently, the prevalence of these impairments may potentially influence prognosis and may therefore facilitate the decision-making process regarding the start of dialysis. In this thesis, we assessed the prevalence and course of geriatric impairments and their relation with outcome in patients with chronic kidney disease. The foundation for this thesis are the results of the "Geriatric assessment in OLder patients starting Dialysis (GOLD)" study. This is a prospective multicenter cohort study assessing the relation between a geriatric assessment and outcome in elderly patients with ESKD.

The studies in this thesis are presented in four themes: Frailty (Part 1), Falls & Fractures (Part 2), Functional outcome, quality of life and caregiver burden (Part 3) and Clinical implications of geriatric impairments in chronic kidney disease (Part 4).

Part 1: Frailty

In **Chapter 2** the prevalence of geriatric impairments was assessed through a cross-sectional analysis of the baseline measurements of the Geriatric in OLder patients starting Dialysis (GOLD study). In total, 196 dialysis patients (77% hemodialysis and 23% peritoneal dialysis) and 89 patients who chose maximal conservative management (MCM) were included. All patients underwent a geriatric assessment: patients starting dialysis between two weeks before initiating till three weeks after initiating of dialysis and the MCM-patients when estimated glomerular filtration rate was lower than 15ml/min/1.73m² and they made the decision to forego dialysis. The mean age of the population was 78 years (SD 7) and 36% were women.

Of the 196 patients that were starting dialysis, only 12 patients (6%) had no geriatric impairments in any of the major domains (cognition, mood, mobility, functional performance, comorbidity burden and nutritional status). Most frequently impaired domains were functional performance (instrumental activities of daily living (IADL) 79% and activities of daily living (ADL) 29%), cognition (67%) and comorbidity burden (41% of the patients had besides end-stage kidney disease (ESKD) another severe chronic disease). Seventy-seven percent of the patients had two or more geriatric impairments.

Although the two groups were not fully comparable considering the different timing of inclusion (MCM patients at the beginning of stage 5 ESKD and dialysis patients in a more advanced stage of ESKD), interestingly, no differences were seen between the MCM group and the dialysis group in prevalence of impairment in cognition, symptoms of depression, malnutrition and severe comorbidity burden. However, patients in the conservative group were more frequently care-dependent (ADL 45%, IADL 85%) and had more frequently a reduced mobility compared to the dialysis group. In the MCM group, 88% had two or more geriatric impairments.

In **Chapter 3** the diagnostic value of different frequently used frailty screening tools (Identification of Seniors at Risk-Hospitalized (ISAR-HP), Veiligheidsmanagement systeem kwetsbare ouderen (VMS), Fried Frailty Index, Groningen Frailty Indicator (GFI), Geriatric8 (G8) and the surprise question) was compared with the geriatric assessment. All patients that were starting dialysis (n=123) who were included in the GOLD-study at that time were included in the analysis. A screening tool could potentially provide an opportunity to preselect patients that should undergo an extensive geriatric assessment.

The prevalence of frailty according to the different frailty screening tools varied between 48 and 88%. Sensitivity was highest for the G8 (92%). However, only 12% of all patients were scored as fit, which resulted in low specificity (26%). The Identification of ISAR-HP scored best with a high specificity (79%) and a fairly good sensitivity (72%). However, the differences between the different tools were small, and none of the tests score >60% for their negative predictive value.

Thus, while screening tools are able to detect geriatric impairment in patients eligible for dialysis, none of the applied screening tools had the discriminating abilities to adequately rule out frailty compared with a geriatric assessment. Therefore, screening tools cannot preselect patients that should undergo a geriatric assessment.

In **Chapter 4** the prognostic value of different frailty models was assessed. In this prospective analysis of the GOLD-study, we assessed if frailty according to different frailty assessments was associated with mortality and hospitalizations. For this analysis all incident dialysis patients (n=192) were included, of whom 48% had ≥ 3 geriatric impairments and were considered frail. According to the Fried Frailty Index, 46% of patients were considered frail.

After six months of follow-up 8% of the patients had died and almost half of the patients (49%) had been hospitalized one or more times. Impairment in ADL, IADL, depressive symptoms and frailty according to the clinical judgement of the nephrologist (surprise question) were all associated with hospitalization. The one-year mortality rate was 15%. After correcting

for potential confounders, the presence of three or more impairments was associated with a higher mortality risk. Furthermore, patients that were frail according to the Fried Frailty Index and patients that were considered frail according to the surprise question had a higher mortality risk.

Part 2: Falls & Fractures

This part of the thesis starts in **Chapter 5** with a systematic review that assesses the association between chronic kidney disease, falls and fractures. Generally, the risk of fractures increased when kidney function worsened, with the highest risks in the patients with stage 5 CKD or dialysis. This effect was most pronounced for hip fractures and any type of fractures. Results on the association between CKD and accidental falling were contradictory. Compared to the general population, falls and fractures are highly prevalent in patients with CKD.

In **Chapter 6** the association between accidental falls and chronic kidney disease was assessed in a large geriatric cohort. A cross-sectional analysis was performed with all participants of 65 years and above with available glomerular filtration rate ($n=1,000$) that visited the day clinic of the department of geriatric medicine at the University of Medical Center Utrecht (UMCU). Participants were stratified into different stages of kidney disease (<45 , 45-59 and ≥ 60 ml/min per 1.73m^2). Of all participants, mean age was 79.4 years and 38% had an estimated glomerular filtration rate of <60 ml/min per 1.73m^2 .

Patients with chronic kidney disease fell more often compared to patients without chronic kidney disease (prevalence of accidental falls in the previous year eGFR <45 71%, eGFR 45-59 63% and eGFR ≥ 60 59%). However, when adjusted for potential confounders, no association remained between falls and chronic kidney disease. Thus, this higher prevalence seems to be related with the risk profile of patients with CKD and not with a decreased eGFR itself.

In **Chapter 7** the prevalence of vertebral fractures and hyperkyphosis on a lateral chest radiograph was assessed in the incident dialysis patients of the GOLD study. In addition, we prospectively assessed if vertebral fractures and hyperkyphosis were associated with accidental falls, functional decline and mortality.

In our study population, vertebral fractures were highly prevalent (43%). Furthermore, 22% of the participants had hyperkyphosis. In contrast to the results of prior research in the general population, we did not find an association between vertebral fractures and poor outcome. Remarkably, hyperkyphosis was associated with a higher one-year mortality (20%) compared to patients without hyperkyphosis. Interestingly, all patients with hyperkyphosis that died also had vertebral fractures. Patients with hyperkyphosis were more impaired in ADL at baseline, were more frequently living in a nursing home and tended to be more frail

according to the Fried Frailty Index. Hence, hyperkyphosis could be an indicator of physical dysfunctions, such as a decrease in muscle mass and muscle strength, which could lead to frailty and subsequent poor outcome. Therefore, additional frailty screening and optimization of physical performance before start of dialysis could be especially beneficial in these patients.

In **Chapter 8** we described the prevalence and incidence of vertebral fractures on a lateral chest radiograph in a cohort of patients eligible for transplantation on chronic dialysis (n=146) from the multicenter NOCTx study. This is a prospective study that is designed to compare progression of coronary artery calcification on computed tomography (CT) between patients treated with different renal replacement therapies. We investigated the relation between prevalent and incident vertebral fractures, vertebral trabecular bone mineral density (BMD) and parathyroid hormone (PTH). Bone mineral density (BMD) was determined by measuring volumetric trabecular BMD on a CT-scan of three consecutive thoracic vertebrae in the T7-T10 range.

The mean age of the participants was 52 years, 67% were male. Median dialysis duration was 26 months. In 34% of the participants vertebral fractures were present at inclusion. After a median follow-up of 1.8 years, 29% of the participants developed a new vertebral fracture. More than half of the patients that developed an incident vertebral fracture already had a prevalent fracture (compared to 24% prevalent fractures in the group without an incident fracture). Vertebral trabecular BMD was not associated with prevalence or incidence of vertebral fractures. The association of PTH appeared to be U-shaped: higher and lower PTH was associated with higher risk of vertebral fractures.

Part 3: Functional outcome, quality of life and caregiver burden

In **Chapter 9** we described the functional course after start of dialysis. Furthermore, we focused on the impact of dialysis initiation on caregiver burden. For this analysis we used the prospective data of the GOLD study of 187 participants and data of 92 corresponding caregivers. At the start of dialysis, 79% of the patients were care dependent in functional status (30% ADL, 78% IADL).

After 6 months of follow-up, 8% had died and 2% received a kidney transplant. Of the patients still alive, 40% experienced decline in functional status, 34% were stable and 18% of the patients improved. The decline in functional status was mostly due to loss in IADL dependence. Factors that were associated with the composite outcome of functional decline/mortality were age (OR 1.05 (95% CI 1.00-1.10 per increasing year) and frailty according to the Groningen Frailty Indicator (OR 1.88, 95% CI 1.05-3.68). In the 92 caregivers with follow-up data, caregiver burden was more prevalent during follow-up (23% moderate to high burden at baseline vs. 38% at follow-up, $p=0.004$).

In **Chapter 10** we prospectively assessed the course of quality of life in GOLD study participants starting dialysis (n=192) or choosing maximal conservative care (n=89), using the EQ-5D questionnaire completed at baseline and after 6 months of follow-up. At baseline, no differences were between incident dialysis patients and maximal conservative patients on EQ-5D summary index and overall self-rated health (6.3 ± 1.3 MCM vs. 6.3 ± 1.4 dialysis patients).

After six months of follow-up 15% of the MCM patients and 8% of the dialysis patients died. Patients on dialysis therapy did not show any difference in quality of life at follow-up, compared to baseline situation. However, for the MCM patients a small decline in quality of life was observed. On the other hand, patients on dialysis therapy had significantly more hospitalizations (50% in dialysis patients vs. 24% in MCM patients). Furthermore, in a sub analysis of 115 patients 80 years and above, there was no survival benefit for patients that started dialysis compared to maximal conservative management.

Part 4: Clinical implications of geriatric impairments in chronic kidney disease

In **Chapter 11** we used four cases to illustrate the heterogeneity in elderly patients with ESKD. Furthermore, we addressed different geriatric impairments that may be relevant in decision-making regarding treatment for ESKD, such as cognitive impairment, depression, accidental falls, functional impairment and caregiver burden.

In **Chapter 12** the results of this thesis are placed in a broader perspective and clinical implications and recommendations for future research are given.

In conclusion, geriatric impairments are highly prevalent in elderly patients with ESKD. Interestingly, also in a younger relatively fit ESKD population and in elderly patients with milder stages of chronic kidney disease, problems such as accidental falls and vertebral fractures are more prevalent than in the general population. We showed that the presence and accumulation of various geriatric impairments was related to functional decline, mortality and hospitalizations. As frailty screening tools are inadequate to discriminate frail from non-frail patients and geriatric impairments may potentially be missed, it is recommended to use a geriatric assessment to assess the health status of the elderly patient. A regularly (e.g. yearly, or when major events occur) performed (standardized) geriatric assessment may be beneficial to ensure a timely diagnosis of issues that are potentially modifiable or can influence treatment decisions and care provision. Considering it may facilitate decision-making regarding dialysis and could potentially help with optimization, it is recommended to perform this assessment from the predialysis phase in close cooperation with a geriatrician.

Nederlandse samenvatting

De Nederlandse bevolking vergrijst. Dit zie je ook terug in de patiëntengroep met nierfalen, waarbij op dit moment meer dan de helft van de patiënten 65 jaar of ouder is. Deze oudere groep patiënten is vaak anders dan de jongere patiënten; waar het bij de jongere patiënten vaak gaat om één ziekte en voornamelijk ziekte gerelateerde klachten op de voorgrond staan, gaat het bij de oudere patiënt vaak om meerdere ziektes met daarbij ook vaak klachten die niet per se gerelateerd zijn aan één specifieke ziekte, zoals bijvoorbeeld vallen, functionele achteruitgang en geheugenproblematiek. De variatie tussen ouderen is echter groot: waar de ene 80-jarige nog actief en zelfstandig is en geen geriatrische problemen heeft, kan de andere 80-jarige sterk afhankelijk zijn van zorg en meerdere geriatrische problemen hebben. Het bestaan van deze geriatrische problematiek kan potentieel invloed hebben op de prognose van deze patiënten en kan daardoor ook invloed hebben op het beslisvormingsproces ten aanzien van de start van dialyse.

Het doel van dit proefschrift was om de prevalentie en het beloop van geriatrische problemen en hun relatie met uitkomsten te onderzoeken bij patiënten met nierfalen. De basis van dit proefschrift wordt gevormd door de resultaten van de “Geriatric Assessment in OLder patients starting Dialysis (GOLD)” studie. Het is een prospectief, multicenter onderzoek, dat de relatie onderzoekt tussen een geriatrisch assessment en uitkomsten als overleving, functionele achteruitgang en ziekenhuisopnames bij oudere patiënten met nierfalen.

De studies in dit proefschrift zijn onderverdeeld in vier thema's: Kwetsbaarheid (Deel 1), Vallen en fractures (Deel 2), Functionele uitkomsten, kwaliteit van leven en mantelzorgbelasting (Deel 3) en Klinische implicaties van geriatrische problemen in patiënten met nierinsufficiëntie (Deel 4).

Deel 1: Kwetsbaarheid

In **Hoofdstuk 2** onderzochten we de prevalentie van geriatrische problemen in patiënten van 65 jaar of ouder met nierfalen die meededen aan de GOLD studie: er deden 196 patiënten mee die begonnen met dialyse (77% hemodialyse en 23% peritoneaal dialyse) en 89 patiënten die kozen voor een conservatieve behandeling. Alle patiënten ondergingen een geriatrisch assessment: patiënten die begonnen met dialyse kregen dit onderzoek binnen 2 weken voor start tot uiterlijk 3 weken na de start van dialyse en de patiënten die kozen voor conservatieve behandeling wanneer hun klaring onder 15 ml/min/1,73m² kwam. De gemiddelde leeftijd van de populatie was 78 jaar en 36% was vrouw.

Van de 196 patiënten die startten met dialyse hadden slechts 12 patiënten (6%) geen enkel geriatrisch probleem in de domeinen cognitie, stemming, mobiliteit, functioneren, ernstige co-morbiditeit en voedingsstatus. De meest frequent aangedane domeinen waren functioneren (29% had problemen in de algemene dagelijkse levensverrichtingen (ADL) en 79% had problemen in de instrumentele activiteiten in het dagelijks leven (IADL)), cognitie (67%) en ernstige co-morbiditeit (41%). Zevenenzeventig procent van de incidentie dialyse patiënten had problemen in twee of meer geriatrische domeinen.

Al hoewel de dialyse en conservatieve groep niet geheel op een vergelijkbaar moment zijn geïncludeerd (de conservatieve groep in een vroege fase van stadium 5 nierfalen en de dialysepopulatie juist in een meer gevorderde fase van stadium 5 nierfalen) werden er geen verschillen gezien in het voorkomen van problemen in de cognitie, stemming, ondervoeding en ernstige comorbiditeit tussen beide groepen. De patiënten die kozen voor een conservatieve behandeling waren echter wel meer zorgafhankelijk (45% afhankelijk in ADL en 85% in IADL) en minder mobiel dan de dialyse groep. Van de conservatieve patiënten had 88% twee of meer geriatrische problemen.

In **Hoofdstuk 3** onderzochten we de diagnostische waarde van verschillende veel gebruikte frailty screening tools (Identification of Seniors at Risk-Hospitalized (ISAR-HP), Veiligheidsmanagement systeem kwetsbare ouderen (VMS), Fried Frailty Index, Groningen Frailty Indicator (GFI), Geriatric8 (G8) en de surprise question) ten opzichte van het geriatrisch assessment (gouden standaard). Een veel genoemd nadeel van het geriatrisch assessment is namelijk dat het relatief veel tijd kost om het te verrichten. Een goede screeningtool zou tijd kunnen besparen door enkel patiënten te selecteren die potentieel baat zouden kunnen hebben van een geriatrisch assessment. Voor de diagnose kwetsbaarheid volgens het geriatrisch assessment werd een afkappunt van twee of meer geriatrische problemen aangehouden.

Alle patiënten die destijds waren geïncludeerd in de GOLD studie en begonnen met dialyse werden meegenomen in de analyse (n=123). Op basis van de verschillende screeningtools was 48-88% van de geïncludeerde patiënten kwetsbaar ten opzichte van 75% van de patiënten met het geriatrisch assessment. De sensitiviteit was het hoogste voor de G8 (92%). Alleen werd met deze screeningsmethode slechts 12% van de patiënten gescoord als niet kwetsbaar, wat resulteerde in een lage specificiteit (26%). De ISAR-HP scoorde het beste met een sensitiviteit van 79% en een specificiteit van 72%. De verschillen tussen de screening tools waren echter klein en geen van de testen had een negatief voorspellende waarde van >60%.

Concluderend zijn de verschillende screeningtools in staat om diverse geriatrische problemen in deze populatie te detecteren. Geen van de geteste screening tools had echter voldoende onderscheidend vermogen ten opzichte van een geriatrisch assessment om kwetsbaarheid betrouwbaar genoeg uit te sluiten. Daarom kunnen screening tools niet worden gebruikt om een selectie te maken voor een uitgebreid geriatrisch assessment en is het advies om een geriatrisch assessment te gebruiken voor het in kaart brengen van de gezondheid van een oudere patiënt met nierfalen.

In **Hoofdstuk 4** onderzochten we de prognostische waarde van verschillende methoden om kwetsbaarheid te meten. In deze prospectieve analyse van de GOLD studie onderzochten we of kwetsbaarheid, gemeten door verschillende meetinstrumenten, was geassocieerd met sterfte en ziekenhuisopnames. Voor kwetsbaarheid volgens het geriatrisch assessment werd een afkappunt van drie of meer geriatrische problemen aangehouden.

Voor deze analyse werden alle patiënten die begonnen met dialyse meegenomen in de analyse (n=192), hiervan had 48% drie of meer geriatrische problemen en werd beschouwd als kwetsbaar. Volgens de Fried Frailty Index was 46% van de patiënten kwetsbaar.

Zes maanden na start van het onderzoek was 8% van de patiënten overleden en bijna de helft van de patiënten (49%) had één of meerdere ziekenhuisopnames doorgemaakt. Beperkingen in ADL, IADL, stemming en kwetsbaarheid volgens de klinische blik van de nefroloog (surprise question) waren allen geassocieerd met ziekenhuisopnames. De éénjaarssterfte was 15%. Na correctie voor mogelijke confounders was de aanwezigheid van drie of meer beperkte domeinen geassocieerd met een verhoogd overlijdensrisico. Verder hadden ook patiënten die kwetsbaar waren volgens de Fried Frailty Index en volgens de surprise question een hoger overlijdensrisico.

Deel 2: Vallen en fracturen

Dit deel van het proefschrift start in **Hoofdstuk 5** met een systematische review over de associatie tussen chronische nierinsufficiëntie, vallen en fracturen. Hierbij observeerden we een oplopend risico bij een slechtere nierfunctie, met de hoogste risico's bij patiënten met stadium 5 nierfalen die wel of niet werden behandeld met dialyse. Dit effect werd het sterkste gezien voor heupfracturen en alle typen fracturen. De resultaten voor de associatie tussen nierinsufficiëntie en vallen waren tegenstrijdig, waarbij bij de ene studie wel een associatie werd gevonden en andere niet. Ten opzichte van de algemene populatie komen vallen en fracturen veelvuldig voor in patiënten met chronische nierinsufficiëntie.

In **Hoofdstuk 6** onderzochten we de associatie tussen chronische nierinsufficiëntie en valincidenten in een groot geriatrisch cohort. Alle patiënten van 65 jaar of ouder die de polikliniek geriatrie bezochten in het UMCU en informatie beschikbaar hadden over de nierfunctie werden meegenomen in de analyse (n=1,000). Patiënten werden onderverdeeld in verschillende groepen van nierfunctie (<45, 45-59 en ≥60ml/min/1,73m²). De gemiddelde leeftijd van de deelnemers was 79,4 jaar en 38% had een klaring onder de <60ml/min/1,73m².

Patiënten met nierinsufficiëntie vielen vaker dan patiënten zonder nierinsufficiëntie. Dit risico viel echter weg na correctie voor potentiële confounders. Dit effect lijkt dus samen te hangen met het risico profiel van patiënten (vaker oudere afhankelijke patiënten met meer comorbiditeit) met een nierinsufficiëntie en niet met een verminderde klaring zelf.

In **Hoofdstuk 7** onderzochten we het voorkomen van wervelfracturen en een versterkte kromming van de wervelkolom (hyperkyfose) bij alle patiënten die begonnen met dialyse en die meededen aan de GOLD studie en bij wie ook een laterale thoraxfoto was gemaakt. Verder onderzochten we ook de relatie tussen wervelfracturen, hyperkyfose en vallen, functionele achteruitgang en sterfte.

In onze studie populatie had 43% van de patiënten mild tot ernstige wervelfracturen en 22% van de patiënten een hyperkyfose. In tegenstelling tot eerder verricht onderzoek vonden we geen associatie tussen wervelfracturen en slechte uitkomst. Hyperkyfose daarentegen, was geassocieerd met een hogere éénjaarssterfte vergeleken met patiënten zonder hyperkyfose. Een interessante bevinding was dat alle patiënten met hyperkyfose die overleden, ook wervelfracturen hadden. De groep met patiënten met hyperkyfose hadden bij start van het onderzoek meer beperkingen in ADL bij inclusie, woonden vaker in een verpleeghuis en waren ook vaker kwetsbaar volgens de Fried Frailty Index dan de groep met patiënten zonder hyperkyfose. Mogelijk is hyperkyfose dus een graadmeter voor fysieke beperkingen, zoals een verminderde spiermassa en spierkracht, wat vervolgens kan leiden tot een verhoogde kwetsbaarheid en meer kans op slechte uitkomsten. Derhalve zouden juist deze patiënten profijt kunnen hebben van een aanvullend kwetsbaarheidsonderzoek en optimalisatie van de fysieke functie.

In **Hoofdstuk 8** onderzochten we het voorkomen van prevalentie en nieuwe wervelfracturen bij patiënten die waren geïncludeerd in de NOCTx studie waarbij een laterale thoraxfoto was gemaakt in de reguliere zorg (n=146). De NOCTx is een studie die oorspronkelijk is opgezet om de progressie van kalk in de coronair arteriën tussen verschillende niervervangende therapieën te vergelijken op CT-scan. In deze studie werd een relatief gezonde populatie geïncludeerd, die allen in aanmerking kwamen voor

een niertransplantatie. We onderzochten de relatie tussen prevalentie wervelfracturen, trabeculaire botdichtheid van de wervels en parathormoon (PTH). Botdichtheid werd gemeten door het trabeculaire volume op CT te meten ter hoogte van thoracale 7 tot en met thoracale 10.

De gemiddelde leeftijd van de deelnemers was 52 jaar en 67% was man. Mediane dialyse duur was 26 maanden. Bij 34% van de deelnemers waren er wervelfracturen zichtbaar bij start van het onderzoek. Na een mediane follow-up van 1,8 jaar had 29% van de deelnemers een nieuwe wervelfractuur ontwikkeld. Meer dan de helft van de patiënten die een nieuwe wervelfractuur ontwikkelden tijdens het onderzoek had al een fractuur bij start van het onderzoek (vergeleken met 24% prevalentie fracturen in de groep zonder nieuwe wervelfractuur). Trabeculaire botdichtheid was niet geassocieerd met prevalentie of nieuwe wervelfracturen. De associatie tussen PTH met wervelfracturen was U-vormig: zowel een hoger als een lager PTH was geassocieerd met een hoger risico op wervelfracturen.

Part 3: Functional outcome, quality of life and caregiver burden

In **Hoofdstuk 9** beschrijven we het beloop in functioneren van patiënten na de start van dialyse. Verder onderzochten we de mantelzorgbelasting voor en na start van dialyse. Voor deze analyse gebruikten we de prospectieve data van de GOLD studie van 187 incidentie dialyse patiënten en 92 bijbehorende mantelzorgers. Bij de start van dialyse was 79% van de patiënten afhankelijk in functioneren (30% ADL, 78% IADL).

Zes maanden na start van dialyse was 8% van de patiënten overleden en had 2% een niertransplantatie ondergaan. Van de patiënten die nog leefden na zes maanden was 40% achteruitgegaan in functioneren, 34% stabiel gebleven en 18% was zelfstandiger geworden. Patiënten verloren voornamelijk hun zelfstandigheid in IADL; activiteiten waar patiënten vaak meer hulpbehoevend in waren geworden waren medicatiegebruik, wassen en koken. Factoren die waren geassocieerd met functionele achteruitgang en overlijden waren leeftijd (Odds Ratio (OR) 1,05 (95% CI 1,00-1,10 per jaar) en kwetsbaarheid volgens de Groningen Frailty Indicator (OR 1,88, 95% CI 1,05-3,68). Bij de 92 mantelzorgers waarbij we beschikten over follow-up data, was een hoge mantelzorgbelasting meer aanwezig na 6 maanden vergeleken met de periode rondom start van dialyse (23% van de mantelzorgers had een gemiddeld tot hoge mantelzorgbelasting rondom start van dialyse vergeleken met 38% van de mantelzorgers zes maanden na start van dialyse, $p=0,004$).

In **Hoofdstuk 10** onderzochten we het beloop van kwaliteit van leven van de GOLD deelnemers die begonnen met dialyse ($n=192$) of kozen voor conservatieve behandeling ($n=89$) door middel van de EQ-5D vragenlijst. Deze vragenlijst werd afgenomen bij

start van de studie en na zes maanden. Bij inclusie werden er geen verschillen gezien in kwaliteit van leven tussen de groep van dialyse patiënten en de conservatieve patiënten. Ook de eigen beoordeling van de gezondheid verschilde niet tussen de groepen ($6,3 \pm 1,3$ conservatieve groep vs. $6,3 \pm 1,4$ in de dialyse groep).

Na zes maanden was 15% van de conservatieve groep en 8% van de dialyse groep overleden. Patiënten die waren gestart met dialyse lieten geen verandering zien in kwaliteit van leven ten opzichte van de uitgangssituatie. Voor de conservatieve groep werd er een kleine daling gezien in kwaliteit van leven. Aan de andere kant had de dialyse groep significant meer ziekenhuisopnames (50% in de dialyse groep vs. 24% in de conservatieve groep). In een aanvullende subanalyse van 115 patiënten van 80 jaar en ouder werd er verder geen overlevingswinst gezien voor patiënten die startten met dialyse ten opzichte van patiënten die kozen voor conservatieve therapie.

Part 4: Klinische implicaties van geriatrische problemen in patiënten met chronische nierinsufficiëntie

In **Hoofdstuk 11** illustreren we de heterogeniteit van de oudere patiënt met nierfalen aan de hand van casuïstiek. Verder worden verschillende geriatrische problemen die potentieel belangrijk zijn voor de beslisvorming omtrent dialyse verder uitgediept.

In **Hoofdstuk 12** plaatsen we de resultaten van dit proefschrift in een breder perspectief en worden er aanbevelingen gedaan voor de klinische praktijk en verder toekomstig onderzoek.

De conclusie van dit proefschrift is dat geriatrische problemen veelvuldig voorkomen bij oudere patiënten met nierfalen. Interessant genoeg zagen we ook in een jongere, relatief fitte populatie en in mildere stadia van nierinsufficiëntie dat problemen als vallen en fracturen vaker voorkomen dan in de algemene populatie. In dit proefschrift hebben we verder aangetoond dat de aanwezigheid en de opeenstapeling van geriatrische problematiek is geassocieerd met functionele achteruitgang, sterfte en ziekenhuisopnames bij nierfalen. Aangezien frailty screening tools onvoldoende onderscheidend vermogen hebben om kwetsbare patiënten van niet-kwetsbare patiënten te onderscheiden, en frailty screening tools ook niet alle geriatrische problemen in kaart brengen, is het advies om een geriatrisch assessment te gebruiken voor het bepalen van de gezondheidstoestand van de oudere patiënt. Een periodiek (gestandaardiseerd) geriatrisch assessment (bv. jaarlijks of na grote belangrijke gebeurtenissen) vanaf de predialyse fase kan behulpzaam zijn om tijdig problemen te signaleren en te optimaliseren. Aangezien zicht op geriatrische problematiek tevens kan helpen bij de beslisvorming rondom start van dialyse is het advies om het geriatrisch assessment reeds te verrichten in de predialyse fase, in nauwe samenwerking met de geriatrie.

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Curriculum vitae



Namiko Anna Goto was born September 30th 1988 in Noordwijk, the Netherlands. She attended secondary school at 'het Atrium' in Amersfoort, from which she graduated in 2006. Initially, she decided she wanted to become a pharmacist, which she has studied from 2006 to 2007. However, she discovered that a more clinical approach fitted her better, after which she started medicine in 2007.

After obtaining her medical degree in 2013, Namiko spent half year travelling through South-East Asia, Australia, New Zealand and America. After travelling, she subsequently started her residency training in Geriatric Medicine in 2008. As part of her residency training, she worked 2 years at the Internal Medicine department of the Meander Medisch Centrum (supervisor R.J. Bosma) and 1 year at the Geriatric Medicine department of the University Medical Center Utrecht (Supervisor H.J.J. Verhaar). During her residency, Namiko came in contact with Ismay van Loon and Marije Hamaker who were working at the "Geriatric assessment in OLder patients starting Dialysis (GOLD)" study and were looking for a second PhD-student. Therefore, in September 2017, she interrupted her residency training to start as a PhD-student on the GOLD project. Namiko will continue her residency in September 2019.

Namiko is married to Cyriel Verkroost and has one son (Yuki).

