Phenotyping older patients needing intensive treatment

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1 GENERAL INTRODUCTION

Demographic changes

The world's population is ageing: almost every country in the world is experiencing growth in the number and proportion of older persons in their population. In Europe and Northern America, it is expected that the number of persons aged 60 years and older will rise from 261 million in 2017 to 370 million in 2050, representing 23% and 32% respectively of the total population living in those countries (Eurostat Statistics 2017). This increase can be explained by several demographic developments. First, life expectancy is increasing due to better hygienic, more prosperity and medical advances. Second, the post-war baby boom generation is becoming older. Third, fertility rates are declining [1]. The combination of these three demographic developments results in a both relative and absolute increase of the older population.

Ageing, multimorbidity and geriatric conditions

Ageing results from the accumulation of damage to the body due to internal and external stressors. This accumulated damage affects the functioning of cells and tissues. Consequentially, the capacity to maintain the homeostasis in the body is compromised which can lead to a higher chance of disease and death [2]. There are several consequences of the ageing process that makes the older patient different from the younger patient. First, compared with younger ages, physiology in the older body is different. These differences consist, amongst others, of a decreased renal function, liver function and an altered body composition, which can affect metabolism, distribution and clearance of pharmacotherapeutics [3]. Second, with increasing age the prevalence of disease increases, resulting in a high proportion of older adults suffering from multiple (chronic) diseases. The prevalence of these multiple chronic diseases, or multimorbidity, in community-dwelling older adults ranges from 35-65% in patients aged 60-69 years to 80-99% in patients aged 80 years and older [4]. Third, a higher age and multimorbidity are associated with the presence of geriatric conditions which are described as 'a collection of symptoms and signs common in older adults not necessarily related to a specific disease', for example, a decreased ability to perform activities of daily living (or functional impairment), cognitive impairment, delirium and falls [5, 6]. The combination of an increase of the number of older adults and an increase of the prevalence of multiple diseases in these older patients, it is expected that there will be more health care demand by older adults [7].

Geriatric assessment

Another difference between younger and older patients, is the complex relationship between the four domains of somatic status, mental functioning, physical functioning and social functioning [8].

Below a short description of what kind of assessment these different domains include.

- Somatic status: physical diseases and disabilities, number of prescribed drugs and nutritional status.
- Mental functioning: described by cognitive performance and psychiatric disorders like apathy and depression.
- Physical functioning: measured by the level of physical capacity (e.g. gait speed, hand-grip strength) and the ability to perform 'normal' instrumental activities of daily living.
- Social functioning: described by a combination of demographical, religious, racial diversities, including wellbeing, socio-economic and household characteristics – and the family, network and societal levels.

Taken together, the domains of mental, physical and social functioning characterise the total level of functioning of the older patient and next to the somatic status may mark the extent of increased vulnerability or 'frailty'. Frailty is a term widely used to denote a multidimensional syndrome of loss of reserves (energy, physical ability, cognition, health) that gives rise to an increased risk of health outcomes in response to a stressor [9]. There are many operational definitions for frailty such as the Fried Phenotype based on physical weakness and wasting [10] or the Frailty Index based on a count of accumulated deficits [11]. A way of phenotyping older patients is the use of a geriatric assessment (GA). In a GA different domains of somatic status, mental functioning, physical functioning and social functioning are explored, in order to detect conditions that contribute to 'frailty'.

Challenges in treating older patients

Because of the multimorbidity and the complex interaction between the four domains, clinical decision making in older patient can be challenging for clinicians. Treatment decisions are usually made based on monodisciplinary clinical guidelines [12], but one disease already can have a major impact on the quality life and functioning of the older patients and potentially influence and causing disability. Since older individuals often suffer from multiple chronic diseases, treatments according to monodisciplinary guidelines, focused on the management of a single disease result in impractical and unworkable treatment schemes [13]. Furthermore, clinical guidelines are generally based on clinical studies, from which older people are often excluded, due to exclusion criteria based on age, comorbidities, cognitive status and medical history [14]. In addition, when older adults are included in the clinical studies [15], they appear not to be representative for the general population of older adults [16]. The older adults that are participating in clinical studies are relatively in a good physical and mental condition compared to older patients consulting general practitioners and medical specialists [17].

It is known that a higher age and multimorbidity are associated with many adverse health outcomes such as disability, institutionalization, poorer quality of life and higher rates of side effects after treatment [18]. Components of the comprehensive geriatric assessment, for example physical capacity and functional dependency, appeared to be predictive for outcomes such as survival in community dwelling older adults [19]. But also home and hospital comprehensive geriatric assessment were shown to be consistently effective in predicting several health outcomes, including mortality, disability and cognitive functions [20]. However, only few studies have assessed the association of a geriatric screening on outcomes in vulnerable older patients with severe diseases, such as head and neck cancer, esophageal cancer or end-stage renal disease [20]. It are especially these vulnerable older patients with severe diseases in whom treatments can have major consequences on outcomes such as disability and quality of life.

Outcome measurements

Functional independency and quality of life appear to be important outcomes for older adults after treatment. Research conducted in community dwelling older adults and in older adults with comorbidities reported that older adults in general give more importance to quality of life than length of life [21-23]. However, most clinical studies in oncology assess treatment-related outcomes such as disease-free survival and mortality [24]. Recently, there is a growing interest in outcome measurements relevant for the (older) patient, also called patient-reported outcomes measures (PROMs) and that these, next to the treatment-related outcomes, could be taken in to account as an outcome of interest in (older) patients [24]. PROMs are defined as: 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else' [25]. More knowledge of these relevant outcomes for (older) patients could be an important contribution in order to personalize treatment decisions.

This thesis has 3 aims:

I) to quantify the lack of evidence in the literature regarding the reporting of geriatric assessment in older adults participating in clinical trials
II) to study the association between geriatric characteristics and adverse health outcomes in older patients with severe diseases
III) to assess the determinants of a patient reported outcome measurement in an older patient population.

Outline of this thesis

Chapter 2 evaluates what kind of older patients participated in randomized clinical trials, and if it is clear for clinicians to which older patients the results can be applied. In **chapter 3** we study the literature on the association between functional and cognitive impairment, social environment, frailty and as outcome adverse health outcomes in older patients with head and neck cancer. **Chapter 4** further elaborates on this topic but in another patient population by studying the literature on the association between functional and cognitive impairment, social environment, frailty and as outcome adverse health outcomes in older patients with esophageal cancer. In **chapter 5**, we prospectively study the association between geriatric characteristics and one-year mortality in older head and neck cancer patients. In another prospective study, **chapter 6** studies the determinants of cognitive function in older patients with end-stage renal disease. In **chapter 7** we study a patient reported outcome measurement; self-rated health (SRH). We identify the determinants of self-rated health (SRH) of older patients at presentation at the Emergency Department (ED) and three months after the ED visit. In **chapter 8** the main conclusions of this thesis are summarized and discussed, and future perspectives are proposed.

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2 EXTERNAL VALIDITY OF RANDOMIZED CONTROLLED TRIALS IN OLDER ADULTS, A SYSTEMATIC REVIEW

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ABSTRACT

Background To critically assess the external validity of randomized controlled trials (RCTs) it is important to know what older adults have been enrolled in the trials. The aim of this systematic review is to study what proportion of trials specifically designed for older patients report on somatic status, physical and mental functioning, social environment and frailty in the patient characteristics.

Methods PubMed was searched for articles published in 2012 and only RCTs were included. Articles were further excluded if not conducted with humans or only secondary analyses were reported. A random sample of 10% was drawn. The current review analyzed this random sample and further selected trials when the reported mean age was ≥ 60 years. We extracted geriatric assessments from the population descriptives or the in- and exclusion criteria.

Results In total 1396 trials were analyzed and 300 trials included. The median of the reported mean age was 66 (IQR 63-70) and the median percentage of men in the trials was 60 (IQR 45-72). In 34% of the RCTs specifically designed for older patients somatic status, physical and mental functioning, social environment or frailty were reported in the population descriptives or the in- and exclusion criteria. Physical and mental functioning was reported most frequently (22% and 14%). When selecting RCTs on a mean age of 70 or 80 years the report of geriatric assessments in the patient characteristics was 46% and 85% respectively but represent only 5% and 1% of the trials.

Conclusion Somatic status, physical and mental functioning, social environment and frailty are underreported even in RCTs specifically designed for older patients published in 2012. Therefore, it is unclear for clinicians to which older patients the results can be applied. We recommend systematic to transparently report these relevant characteristics of older participants included in RCTs.

INTRODUCTION

Older individuals are often underrepresented in randomized clinical trials (RCTs)[1-3]. They are frequently excluded as a result of direct and indirect exclusion criteria based on the presence of comorbidities and polypharmacy [4]. For instance, Van de Water et al. previously demonstrated that due to exclusion criteria based on age, comorbidities and medical history only a maximum of 12% of older breast cancer patients would have been suitable to enter breast cancer trials [5]. The consequence is that participants enrolled in clinical trials often do not represent the older patients in general medical practice and thus threaten the external validity of RCTs in the older patient population [6, 7].

Compared to younger patients, older patients are very heterogenic with respect to frailty, mobility, functional capacity, and cognitive function. These different domains can be systematically assessed by using geriatric assessments [8]. To critically interpret the outcome in RCTs and to allow clinicians to judge to which older patients the outcomes can be applied, it is important to know which older adults have been enrolled in the trials. In scientific literature, patient characteristics are usually described in the population descriptives or in the in- and exclusion criteria section. It is currently unknown how patient characteristics with respect to physical, mental and social functioning or frailty are reported in RCTs specifically designed for older adults.

Therefore, the aim of this systematic review is to study what proportion of RCTs specifically designed for older adults report on somatic status, physical and mental functioning, social environment and frailty in the patient characteristics.

METHODS

Study selection

For the present study we used the sample from the previously published systematic review by Broekhuizen et al. showing that only 7% of the RCTs published in 2012 were specifically designed for older adults [3]. The complete search strategy was published previously. In short, a systematic search was conducted to identify RCTs that were published in 2012 (n=26,740), and after removing duplicates a random sample was drawn (n=2375). Articles were further excluded when it was not written in English, had no RCT design, when the study included non-human subjects or reported secondary analyses. After applying the exclusion criteria and retrieved full-text, 1369 identified articles remained. For the current review we started with the sample of 1369, we defined "specifically designed for older patients" as a mean age of trial participants of 60 years

or older and we included all randomised controlled trials of which the mean age was 60 years or older.

Data extraction

Items extracted from each study included: publication data (author, year), patient characteristics (sample size, median age, percentage of males, disease categories and geriatric assessments). Disease category was classified according to the International Classification of Diseases (ICD-10) of the World Health Organization (WHO). Two researchers (FvD, IP) extracted the geriatric assessments and in case of disagreement, consensus was reached after discussion with a third co-author (SPM).

Geriatric assessments

For all studies we extracted if geriatric assessments were reported in the patient characteristics, which are usually reported in the population descriptives or in the in- and exclusion criteria section. The geriatric assessments were classified into five geriatric domains: somatic status, physical functioning, mental functioning, social environment and frailty. Somatic status was defined as the presence of assessments of somatic co-morbid diseases and polypharmacy. Co-morbid diseases had to be assessed by quantitative instruments that measure cumulative disease burden or quantitatively by adding up the number of chronic and acute medical illnesses. Polypharmacy had to be assessed by validated tools. Physical functioning was defined as assessments of functional performance, mobility, and objectively measured physical capacity such as hand grip strength, gait speed or balance tests. Mental functioning was defined as assessment of any domain within cognition, dementia diagnosis, and mood or depression. Assessments were classified to the social environment domain when they depicted information about the social support system (living alone or with partner, marital status, family care giver), domestic services (home help and care) and the way of living (self-reliant or community dwelling, assisted living or nursing home). Assessments were classified within the frailty domain when they were used as frailty index or instrument (for instance, Fried Frailty Phenotype, Rockwood Frailty Index, Groningen Frailty Indicator), which assessed the frailty status.

Statistical analysis

Measures of central tendency of continuous variables from the trials were recorded as mean with standard deviation (SD) or median with interquartile range (IQR). For dichotomous variables the number of subjects with the characteristic divided by the total number of subjects was recorded. We plotted the proportion of trials in which either geriatric assessment was reported in the population descriptives or in the in- and exclusion criteria. As a sensitivity analyses we used different cut-offs for the definition of

"specifically designed for older patients" using a minimum mean age of 70 years or 80 years instead of 60 years in the main analysis. All analyses were performed with IBM SPSS Statistics version 23.0.

RESULTS

The analysis in the present review started with 1369 articles. Of these 1369 articles, some articles described more than one RCT (adding a total of 24 RCTs), articles were further excluded because there was no RCT design after second review (n= 11) or no full-text was available (n= 1). After all the articles with a mean age <60 years or the articles were no mean age was available were removed. We ended up with 300 articles specifically designed for older people included for this analysis. (Fig 1) A full database of all 300 included publications, including authors, titles and journal of publication can be assessed (S1 Appendix; available online).

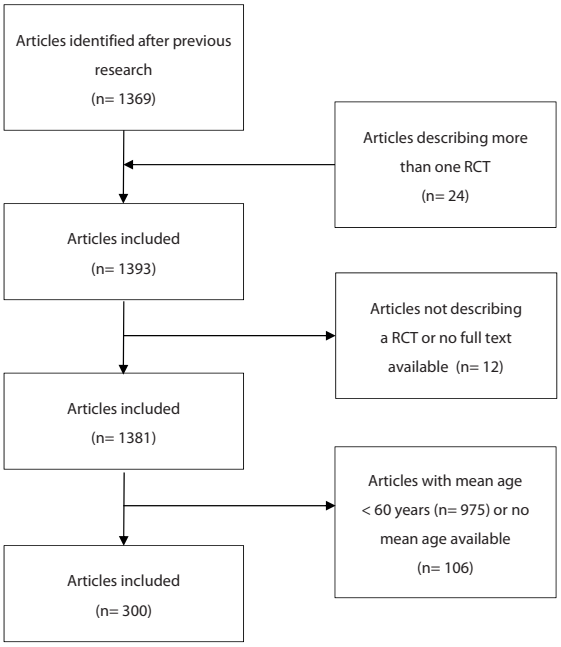

Fig 1. Flow chart for inclusion of studies. PRISMA flow chart of the result from the performed search strategy and selection process.

Table 1 shows a description of the main trial characteristics of these 300 trials. The median number of participants per trial was 114 (IQR 47-288), the median of the reported mean age of the participants in the trials was 66 (IQR 63-70) and the median percentage

of men included in the trials is 60 (IQR 45-72). Most of the trials were classified into WHO disease categories circulatory (25%), neoplasms (19%), musculoskeletal (9%), nervous (8%) and digestive (6%).

Table 1. Main trial characteristics of the 300 included RCTs

Main trial characteristics	n= 300
Number of participants, N (median, IQR[a])	114 (47-288)
Age of participants, years (median, IQR)	66 (63-70)
Percentage men included in trial (median, IQR) [b]	60 (45-72)
Disease categories, N (%)	
Circulatory	74 (25)
Neoplasms	56 (19)
Musculoskeletal	28 (9)
Nervous	23 (8)
Digestive	19 (6)
Other	100 (33)

[a]Interquartile range, difference between 25th and 75th percentile is reported
[b]Data are based on 288 (96%) trials

Fig 2 shows the proportion of RCTs that reported on geriatric assessments in the patient characteristics. In 102 trials (34%) somatic status, physical and mental functioning, social environment or frailty were reported in the patient characteristics. In 73 trials (24%) these geriatric domains were reported in the in-, or exclusion criteria , and in 83 trials (28%) geriatric domains were reported in the population descriptives. In total of the 300 trials somatic status was reported 23 times (8%), physical functioning 67 times (22%), mental functioning 41 times (14%), social environment 20 times (7%) and frailty was only reported 2 times (1%). (Fig 3)

When selecting trials with a reported mean age of 70 years and older (n=78), 46% of the trials report geriatric assessments in the patient characteristics. When selecting trials with a reported mean age of 80 years and older (n=13), 85% of all trials report on geriatric assessments in the patients characteristics (Fig 2).

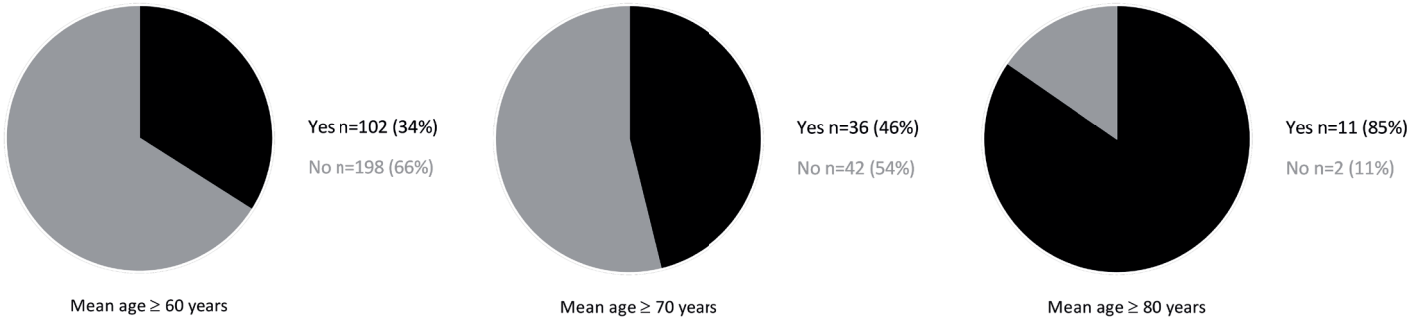

Fig 2: Proportion of RCT's in older patients that report on geriatric assessments in the patient characteristics. Showing the proportion of trials reporting geriatric assessments in the population descriptives or in- and exclusion criteria.

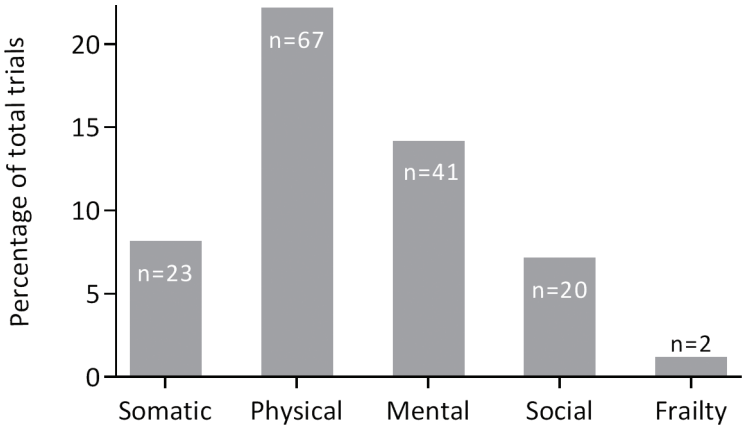

Fig 3: Proportion of RCT's in older patients that report on different geriatric assessments*. Showing the distribution of different geriatric measurements and expressed as percentage of the total trials (n=300). *Some articles reporting more than one domain: 14 articles reporting two geriatric domains, eight articles reporting three geriatric domains and only one article reports four geriatric domains.

DISCUSSION

The main finding of this article is that only in 34% of all trials specifically designed for older patients report of geriatric assessment in the patient characteristics.

Our results are in line with the limited evidence that geriatric characteristics are under-reported in RCTs. Benraad et al. described that geriatric characteristics are rarely taken into account in RCTs on anti-depressant drugs in late-life depression [9]. There are a number of possible explanations of the limited report of somatic, physical and mental functioning, social environment and frailty in RCTs published in 2012. First, the under-reporting of somatic, physical and mental functioning, social environment and frailty might suggest that they were not taken into account at all. Second, it is possible that assessments of somatic, physical and mental functioning, social environment and frailty were included in the study protocol but were not reported in the published paper. This is also known from literature, describing that in 12% of the trials published in high-impact general medical journals the exclusion criteria were not well reported [6]. Third, the included participants in RCTs might have been implicitly selected based on protocol level, patient level or physician level. An example of protocol level is that the study protocol prescribes to visit the research facility three times a week. Older patients who have an impaired mobility or do not have a caregiver available, will be less likely to participate and are implicit selected on the functional or social domain. A form of implicit selection on patient level is a form of healthy user bias in which only the healthy older adults

are willing to participate. Implicit selection on physician level is a phenomenon also described in literature, in which eighteen percent of the treating physicians stated that they had not offered their older patients a clinical trial because of comorbid conditions that might have affected their response to treatment, even though they had met the eligibility criteria for the trial [10]. In conclusion, as a result of the very limited report of somatic, physical and mental functioning, social environment and frailty, the external validity of the trial results is very limited. This might hamper the extrapolation of the trial results to individual older patients who suffer from functional impairment or frailty.

Literature describes that assessment of external validity is complex [11] but at least the characteristics of the included study population should be described in a transparent fashion [12] and therefore at least include patient and disease characteristics [13]. The included study population can be assessed by the description of the in- and exclusion criteria and patient and disease characteristics are usually found in the population descriptives. Especially in case of older adults, because of their huge heterogeneity as described previously, it is important to have a complete insight of the patient characteristics. We realise that insufficient time or funding can be one of the reasons not taking the geriatric assessment into account. However, this step has to be taken to gain better insight whether the results are applicable to older adults seen in regular practice [14, 15]. The choice of the domain assessed and instruments used depends on the patient population, the intervention and the outcome, unfortunately literature has no consensus on this point yet. From the present review we can conclude that it is currently difficult for the clinician to judge for which older adult the results of RCTs can be applied. This adds to the lack of evidence that already exists because of the very limited number of trials that specifically targets older patients.

We included only RCT's with a median age of 60 years or older. It is not expected that trials including younger adults perform geriatric assessments. Although the age of 60 years and older is chosen rather arbitrarily, it is striking that even in this sub-selection only one third of the trials reports on geriatric assessments to describe its population. Even when selecting the RCTs with a median age of 70 and older, not even half of the trials reporting on geriatric assessments. Only when selecting RCTs with a median age of 80 and older, the report on geriatric assessments 85%, however this is just representing less than one percent of all the included trials.

There are a few limitations to this systematic review. Our search was limited to a 10% random sample of the identified publications from 2012. However, since it contains a random sample, we can assume this is a representative sample, although we did not formally test this. Second, we excluded 106 articles in were no mean age was reported.

The main strength of this review is that it is was currently not known how somatic status, physical and mental functioning, social environment and frailty are used and reported in RCTs. This review gains more insight in the external validity of RCTs for older adults.

Conclusion

Somatic status, physical and mental functioning, social environment and frailty are underreported even in RCTs specifically designed for older patients published in 2012. Therefore, it is unclear for clinicians to which older patients the results can be applied. We recommend systematic to transparently report these relevant characteristics of older participants included in RCTs.

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3 FUNCTIONAL AND COGNITIVE IMPAIRMENT, SOCIAL ENVIRONMENT, FRAILTY AND ADVERSE HEALTH OUTCOMES IN OLDER PATIENTS WITH HEAD AND NECK CANCER, A SYSTEMATIC REVIEW

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ABSTRACT

Objectives Older head and neck cancer patients are at increased risk for adverse health outcomes, but little is known about which geriatric assessment associates with poor outcome. The aim is to study the association of functional or cognitive impairment, social environment and frailty with adverse health outcomes in patients with head and neck cancer.

Methods Four libraries were searched for studies reporting on an association of functional or cognitive impairment, social environment and frailty with adverse outcomes in head and neck cancer patients.

Results Of 4158 identified citations, 31 articles were included. The mean age was ≥60 years in twelve studies (39%). Geriatric conditions were prevalent: between 40-50% of the included participants were functional impaired, around 50% had depressive symptoms, and around 40% did not have a partner. Functional impairment was assessed in 18 studies, two studies reported on a cognitive test, eight studies examined mood and social status was depicted by 14 studies. None of the included studies addressed frailty or objectively measured physical capacity such as hand grip strength, gait speed or balance tests. In 64% of the reported associations, a decline in functional or cognitive impairment, mood or social environment was associated with adverse outcomes.

Conclusion Functional and cognitive impairment, depressive symptoms and social isolation are highly prevalent in head and neck cancer patients and associate with high risk of adverse health outcomes. In the future, these measurements may guide decision-making and customize treatments, but more research is needed to further improve and firmly establish clinical usability.

INTRODUCTION

With population ageing there will be an increasing number of older patients with cancer. This trend can also be observed in the patient population presenting with head and neck cancer. In the USA, it is estimated that between 2010 and 2030 the incidence of oral cavity and pharyngeal cancer in people aged 65 years and over will approximately increase from 19.000 patients in 2010 to 31.000 patients in 2030. This would be an increase with more than 60% [1]. Older patients are very heterogenic with respect to functional capacity, cognitive functioning, mobility and frailty, therefore it remains challenging to identify older patients who are at highest risk for adverse health outcomes such as delirium, side-effects, prolonged length of hospital stay, reduced quality of life or mortality. Besides, head and neck cancer patients have a severe prognosis with an estimation of 50% after 5 years with large variations across tumor sites [2, 3]. However, the prognostic value of functional capacity, cognitive functioning, mobility and frailty to assist clinical decision making in older head and neck cancer patients has not been systematically evaluated.

Head and neck cancer patients have a high prevalence of previous excessive alcohol drinking and smoking [4-6] putting this group at high risk for deterioration in functional [7] and cognitive decline [6, 8]. Previously identified risk predictors in older patients with head and neck cancer are the burden of comorbidities [9] and nutritional status [10, 11]. A recent review concluded that there was strong evidence for a positive association of pre-treatment physical functioning with survival and change in global quality of life [12]. But, with regard to other HRQoL domains (emotional, cognitive and social functioning) there was insufficient evidence. In other fields of geriatric medicine the value of measures of functional capacity, cognitive functioning, the role of social environment and frailty [13-15], has been firmly established, but these have not been reviewed for older patients with head and neck cancer.

Therefore, the aim of this present systematic review is to study the association of functional or cognitive impairment, social environment and frailty with adverse health outcomes in patients with head and neck cancer.

METHODS

Search strategy

We aimed to identify original longitudinal studies in head and neck cancer patients in which the association between a measurement of functional and cognitive impairment, social environment or frailty prior to treatment initiation and adverse health outcome after follow-up was examined. A head and neck tumour was defined as cancers in the sinonasal, nasopharyngeal, oral, oropharyngeal, hypopharyngeal, supraglottic, glottis, subglottic regions or laryngeal cancer. Since the etiologic, risk factors and treatment for skin tumors and thyroid cancer are different from mucosal tumors, skin tumors and thyroid cancers were not included in the search. As baseline measurement we assessed the presence of functional impairment (including assessment of functional performance, mobility, and objectively measured physical capacity such as hand grip strength, gait speed or balance tests), cognitive impairment (including assessment of cognition, dementia diagnosis, and mood or depression), social environment (living situation, social support and marital status) and frailty (the use of a frailty index or instrument such as Fried Frailty Phenotype or the Groningen Frailty Indicator). We assessed adverse health outcomes as mortality, functional or cognitive decline, adverse events during or after treatment (such as side-effects or delirium), prolonged length of hospital stay (LOS) and health related quality of life (HRQoL) of global quality of life (QoL) after follow-up.

On April 28th 2016, we searched four electronic bibliographic databases (PubMed, Embase, Web of Science and the Cochrane Library) using synonyms of head and neck cancer, combined with synonyms of the different domains of geriatric assessment. No limits in age were applied. For full Medline search, see Supplemental Material A (available online).

Article selection

The eligibility of all studies identified by the search was independently evaluated by two of the authors (F.v.D and A.S). Of any article that seemed potentially relevant based on title and abstract, full text was retrieved and screened. Studies were included if the full text contained original data reporting on an association between any geriatric measure at baseline and outcome after follow-up in head and neck cancer patients in a longitudinal study design. In case of disagreement between the two authors (F.v.D., A.S.), consensus was reached after discussion with two other co-authors (S.P.M., L.vd.V.). The reference list of the included publications was used for cross-referencing to ensure we identified all relevant articles.

Data extraction and quality assessment

Items extracted from each study included: publication data (author, year), study design and setting, patient characteristics (sample size, mean age, treatment modality), tumor type and tumor site measurement of functional or cognitive impairment, social environment or frailty, follow up duration, outcome measure and results of the association functional and cognitive impairment, social environment and frailty with adverse health outcome. Treatment modality can include therapy with a curative intent such as surgery, radiation therapy, chemoradiation (or as a combination) or with no curative intent such as chemotherapy, and also no treatment with palliative intent was taken into account as a treatment modality. To assess the methodological quality and risk of bias of the included studies, we adapted the Newcastle-Ottawa scale [16] to the purpose of this review (Supplemental Material B, available online). In case of disagreement between the two authors (F.v.D., A.S) with regards to data extraction or quality assessment, consensus was reached after discussion with the other two co-authors (S.P.M., L.vd.V.).

Data presentation

Study characteristics are tabulated per individual study. Accumulated descriptives of the selected studies are presented by calculating the proportion of studies reporting on measurement of functional or cognitive impairment, social environment or frailty, endpoints or treatment modalities. Sample size aggregate of the included studies is expressed as median- and interquartile range (IQR), calculated with SPSS software version 20. Main findings with respect to the association of measurement of functional or cognitive impairment, social environment or frailty with outcome are tabulated. In case the hazard ratios (HR), odds ratios (OR) and relative risk (RR) are at least adjusted for age in the multivariate analysis this is mentioned as aHR, aOR and aRR. If studies are adjusted for other factors than age, this is reported in the abbreviations.

RESULTS

Search results and study selection

The database searches identified 4158 unique citations (Figure 1). After the initial screening of title and abstract, 106 articles were considered potentially eligible. After full-text review, another 76 were excluded; the remaining 30 articles were included. Cross referencing yielded one additional relevant article, which resulted in a total of 31 studies that were included in the present review.

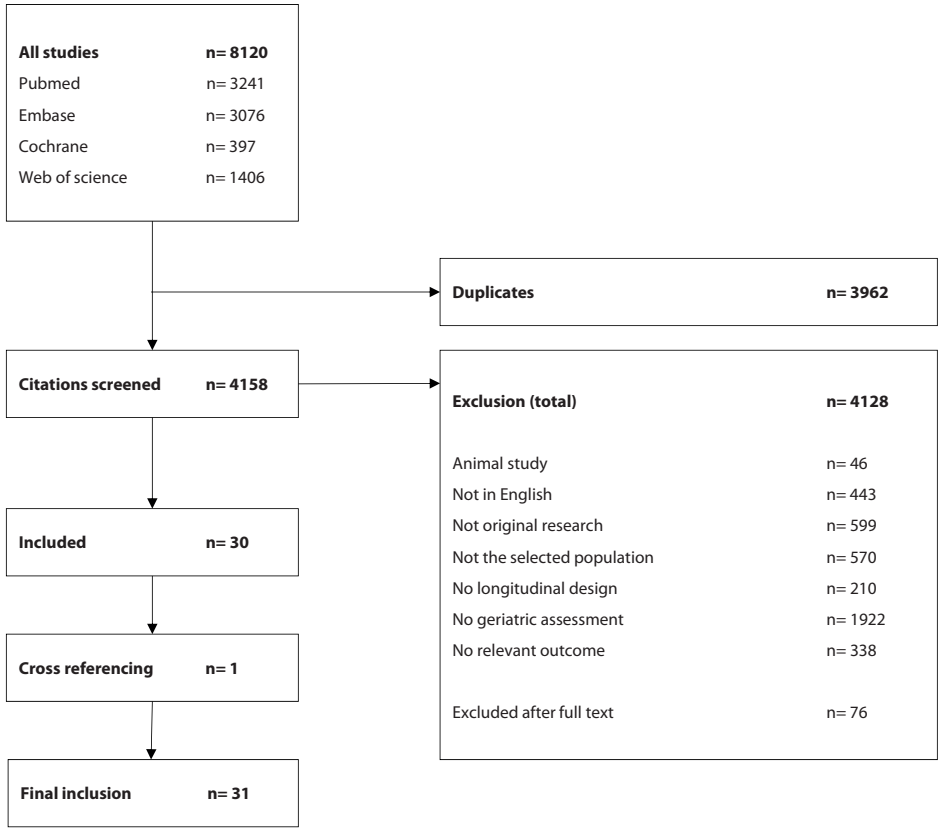

Fig 1 Flowchart

Study characteristics

Table 1 shows an overview of the study characteristics of the 31 included studies. The median sample size of all 31 studies included was 306 (IQR 124-600) and the mean age was over 60 years in twelve studies (39%). Twenty-one studies (68%) were conducted in Europe, the United States or Canada. Most studies consisted of head and neck cancer patients with various cancer types and locations combined, six studies included patients with a specific kind of tumor, five studies had specific inclusion criteria such as stage III/IV or (locally) advanced cancer and six studies included only one treatment modality. Only three studies focused exclusively on older patients and included age ≥70 years in their study population [17-19]. Several studies used specific exclusion criteria: four excluded patients with cognitive impairment, five excluded specific cut off for age, such as excluding aged over 70, 75 or 80 years, some functional impairment (n=3) or patients with no curative intent (n=8).

Table 1. Characteristics of included studies

Publication		**Patients**		**Study population**		
Author	*Publication year*	*Number of patients*	*Age, yr (mean)*	*Tumor characteristics*	*Exclusion criteria*	*Treatment modality**
Aarstad[39]	2005	79	59.9	SCC (maxilla, oral cavity, pharynx and larynx)	Not able to answer questions, aged >80, KPS <75, female	NA
Barber[38]	2015	71	59.7	Mucosal squamous cell carcinoma, salivary gland tumors and skin cancer	Pre-existing psychiatric history, not able to read or complete questionnaires, not able to give consent, not willing to complete follow-up	S, C
Borggreven†[46]	2007	80	58	Advanced SCC of the oral cavity or oropharynx	>75 year, cognitive impairment, not speaking Dutch	S with or without RTx
Epstein[48]	2005	573	62.4	Oropharyngeal cancer	No exclusion criteria available	NA
Fang[25]	2004	102	52.6¶	Stage III or IV head and neck cancer of the oral cavity, oropharynx, hypopharynx or larynx	Recurrent malignancies, synchronous malignancies, not able to complete QOL questionnaire	RTx with or without C
Gerude[17]	2014	67	78ᶜ	SCC of upper aerodigestive tract	≤ 74 year, unable to walk, unable to answer questions due to hearing, cognitive or speech deficits, impossibility anthropometric measurements	S
de Graeff[26]	2001	208	60	SCC of the oral cavity, oropharynx, hypopharynx or larynx	≥ 80 year, recurrent malignancies, synchronous malignancies, cognitive impairment, not speaking Dutch, no curative intent	S, RTx or combination
Hall[20]	2009	856	46.3¶	SCC of the hypopharynx	No exclusion criteria available	S, RTx, C or combination
Hammerlid[35]	2001	232	61	Primary head and neck cancer (larynx, oral cavity, pharyngeal and other)	Not able to answer question due to cognitive impairment, mental disturbance or severe disease	S, RTx, CRTx or combination
Howren[36]	2010	306	60	Upper aerodigestive tract carcinoma (oral cavity, pharynx, larynx or other)	No exclusion criteria available	S, RTx or combination
Howren[47]	2013	364	59.6	Upper aerodigestive tract carcinoma (oral cavity, pharynx, larynx or other)	No exclusion criteria available	S, RTx or combination
Hsieh[21]	2011	151	NA	SCC of the head and neck (oral, oralpharynx, hypopharynx and larynx)	Nasopharyngeal cancer, medical conditions associated with leucocytosis and thrombocytosis, anaemia, metastatic cancer, non-head and neck SCC	NA
Karvonen[40]	2008	495	58.4	Head and neck cancer of the upper aerodigestive tract	Pregnancy, < 18 years, not speaking English, recurrent tumor	S, RTx, C or combination
Kim[41]	2015	241	61§	SCC of the oral cavity, oropharynx, larynx or hypopharynx	No curative intent, distant metastasis, recurrent tumor, aged <18 or >80 years.	S, RTx, C or combination

Table 1. Characteristics of included studies (*continued*)

Publication		**Patients**		**Study population**		
Author	*Publication year*	*Number of patients*	*Age, yr (mean)*	*Tumor characteristics*	*Exclusion criteria*	*Treatment modality**
Konski‡[27]	2003	1073	NA	Locally advanced SCC (oral cavity, oropharynx, hypopharynx and supraglottic) of head and neck	No exclusion criteria available	RTx
Lotfi[28]	2008	258	57.7	Head and neck malignant neoplasm (mouth/lip/submandibular gland, oropharynx, larynx, hypopharynx)	No curative intent	S
Mell[22]	2010	479	56.2	Stage III-IV carcinoma (oropharynx, larynx, hypopharynx, oral cavity, nasopharynx and other) of the head and neck	No exclusion criteria available	CRTx, C or S
Oskam†[42]	2010	80	58	Advanced SCC of the oral cavity or oropharynx	≥75 year, serious cognitive impairment, not speaking Dutch	S with or without RTx
Osthus[45]	2013	106	61	SCC (laryngeal, oral cavity or oropharyngeal) of the head and neck	≥ 78 year, cognitive impairment, no curative intent	S, C, or RTx
Pedruzzi[31]	2008	361	57	Primary SCC of the oropharynx	Distant metastasis	RTx with or without C
Ronis[37]	2008	316	58.6	SSC (oral cavity, pharynx, larynx, oropharynx and nasopharynx)	Pregnancy, < 18 years, not speaking English or mentally unstable	S, C, or RTx
Sadat[29]	2012	169	NA	SCC (oral cavity, oropharynx, hypopharynx, and larynx) of the head and neck	Operable SCC	RTx or CRTx
Sanabria[18]	2007	310	76	Head and neck cancer (larynx, oral cavity, oropharynx and hypopharynx)	< 70 year, no curative intent, distant metastasis, recurrent disease, surgery for thyroid cancer, skin cancer or melanoma, orbit tumors	S, RTx or combination
Shah[32]	2012	774	63	SCC of the head and neck	No exclusion criteria available	S
Siddiqui‡[30]	2008	1093	NA	Several different cancers in two cohort-studies	No exclusion criteria available	RTx, C, S
Sze[19]	2012	990	74§	Nasopharyngeal carcinoma	Palliative treatment, disseminated disease	RTx with or without C
Tarsitano[43]	2012	124	60	SSC of the oral cavity	Recurrent disease, palliative treatment	S with or without RTx
Urba[23]	2012	704	57.7	SCC (hypopharynx, larynx, oral cavity or oropharynx) head and neck cancer	Performance score ≥3, abnormal liver/kidney function, <18 year, recurrent or metastatic cancer	C
Wang[24]	2015	600	62.3	Primary SCC of the oral cavity, oropharynx, larynx or hypopharynx	No SCC, unknown primary, treatment with palliative intent	S, RTx, C or combination

Table 1. Characteristics of included studies (*continued*)

Publication		**Patients**		**Study population**		
Author	*Publication year*	*Number of patients*	*Age, yr (mean)*	*Tumor characteristics*	*Exclusion criteria*	*Treatment modality**
Weed[34]	1995	138	64	All kinds of head and neck cancer needing major surgery	No exclusion criteria available	S
Wong[44]	2006	1010	51.7	Oral cancer (lip, mouth floor, tongue, gingiva, buccal mucosa, palate, retromolar trigone, palatine tonsil, tongue base, and posterior pharyngeal wall)	No pathological rapport, treated at other institute, no complete therapeutic protocol, inadequate chart records	S with or without RTx, C, CRTx

* abbreviations: C=chemotherapy, CRTx= chemoradiation, RTx = radiotherapy, S= surgery, SCC= squamous cell carcinoma, NA= not available

†: Both studies are used in the same cohort

‡: Studies conducted partly on same trial, Siddiqui et al used partly the same patients (n= 689) as Konski et al

§: Median

¶: by approach, calculated from data

Table 2 shows an overview of the associations of measures of functional or cognitive impairment, social environment and frailty with adverse health outcomes after follow up. The thirty-one studies reported on a total of 45 associations. Functional impairment was assessed in 18 studies, there were two studies reporting on a cognitive test, eight studies examined depressive symptoms and social status was studied in 14 studies. None of the studies addressed frailty or objectively measured physical capacity (such as hand grip strength, gait speed or balance tests). Survival (overall, total or disease specific survival) was the main outcome of interest in 21 studies (68%), the remaining studies assessed quality of life (global or health related, 19%), side effects (7%), the development of post-treatment delirium (7%) or prolonged length of stay in the hospital (7%). No studies were found reporting on cognitive or functional decline after treatment for head and neck cancer. Of the 45 reported associations, twenty-nine times (64%) a decline in functional or cognitive performance, mood or social environment was associated with an increased risk of one of the adverse outcomes (Figure 2).

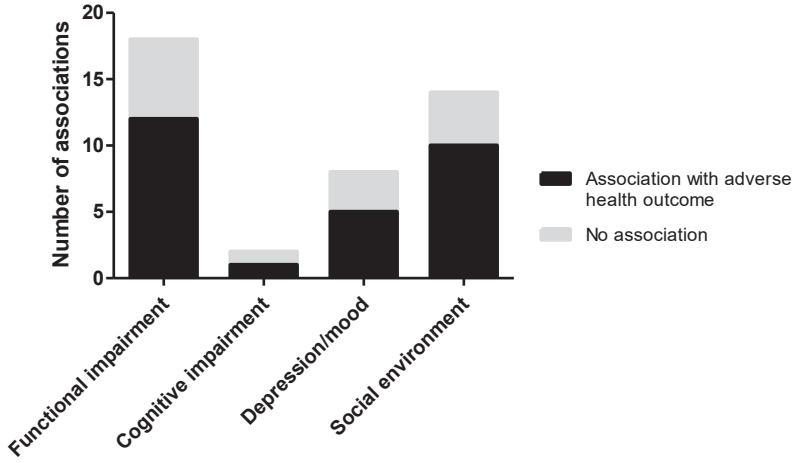

Figure 2: Graphic representation of association of functional or cognitive impairment and social environment with adverse health outcomes in patients with head and neck cancer.
No studies reported the association between frailty and adverse health outcomes.

Functional impairment

Functional performance was assessed in 18 studies, mostly using the Eastern Cooperative Oncology Group Scale (ECOG-scale, 6 studies)[19-24], or the Karnofsky Performance Score (KPS, 8 studies)[17, 18, 25-30]. Functional impairment was prevalent in most studies. For instance, the largest study of Siddiqui et al, included 1093 patients and 517 (47%) had a KPS between 60 and 80, indicating patients were not able to work or need some help with daily care. Functional impairment was associated with increased risk of adverse outcomes in 12 out of 18 studies (67%). Functional performance was found to

Table 2. Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes

Study		Geriatric measure and measured method	Outcome	Association
Author	**No. of patients**			
Aarstad[39]	79	Depression measured by (BDI)	Total and disease specific survival, quality of life	Depression at baseline associated with worse overall survival (aHR 1.13 per increase in depression level p=0.03) and disease specific survival (aHR 1.19; p<0.001) No correlation between depression at diagnosis en QOL at follow-up (in subset of n=27).
Barber[38]	71	Depression measured by Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)	FACT-NH-score, LOS, overall survival	Moderate-Severe depressive symptoms (QIDS-SR score 11-27) is a significant predictor of worse postoperative FACT-HN scores (aRR 5.66, p=0.03), and a prolonged length of stay (p=0.02) in comparison to normal-mild depressive symptoms. The overall survival was significantly worse in the moderate-severe group.
Borggreven†[46]	80	Social environment depicted by marital status	Global quality of life	Not having a partner was significant associated with lower global QOL after six months (no estimate reported; p=0.017), but not after 12 months (no estimate or p-value reported).
Epstein[48]	573	Social environment depicted by living situation	Overall and disease free survival	Living in a long-term care facility associate with a significantly reduced overall (aRR 2.33 p=<0.001) and disease specific survival (aRR2.16, p <0.001) when compared to independently-living.
Fang[25]	102	Social environment depicted by marital status Functional capacity measured by KPS	Survival	Marital status is no predictor for overall survival (p=0.095). KPS (<80 vs ≥80) was an independent prognostic factor for survival (HR#2.03 (95% CI 1.27-3.24)).
Gerude[17]	67	Functional capacity measured by ADL (Katz), IADL (Lawton-Brody) and KPS	Postoperative complications, (LOS)	IADL dependence (score≥18) was significantly associated with postoperative complications (RR 2.19 (95% CI 1.21-3.94), p=0.005) and a prolonged length of stay (RR 1.97 (95% CI 1.07-3.61) p=0.02) There was no association of ADL or the KPS with postoperative complications or a prolonged length of stay.
de Graeff[26]	208	Social environment depicted by marital status. Functional capacity measured by KPS. Depression measured by CES-D.	Survival, time to event (=progression or death)	Marital status (unmarried) was significantly related to survival (RR 1.82 (95% CI 1.03-3.23)), compared to married status. CES-D and KPS were both no prognostic factor for survival or time to event.
Hall[20]	856	Functional capacity measured by the ECOG-scale	Overall and disease specific survival	ECOG-score was an independent predictor for overall (aHR 1.24 (95% CI 1.12-1.38)) and disease specific survival (aHR 1.26 (95% CI 1.10-1.43)).
Hammerlid[35]	232	Depression measured by HADS	Global quality of life	Depression at diagnosis was an independent predictor for global QOL after 3 years (adjusted for age, p=<0.05, no estimate reported).
Howren[36] (2010)	306	Depression measured by BDI	Health related quality of life	Depressive symptoms at time of diagnosis, negatively affect HRQOL over time.
Howren[47] (2013)	364	Social environment measured by the (SPS)	Global and head and neck specific HRQOL	Greater perceived support present at diagnosis significantly predicted more favourable global and head and neck cancer specific HRQOL (on subdomains speech, eating, aesthetics, social disruption) at 3 and 12 months, adjusted for age.

Table 2. Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes (*continued*)

Study		Geriatric measure and measured method	Outcome	Association
Author	**No. of patients**			
Hsieh[21]	151	Functional capacity measured by the ECOG-scale	Overall survival	ECOG performance status (0-1 vs ≥2) had a significant adverse impact on survival (aRR 5.203 (95% CI 2.257-11.993)).
Karvonen[40]	495	Depression measured by the GDS-SF Social environment depicted by marital status	Survival	Depressive symptoms were no prognostic factor for survival (HR 1.30 (95% CI 0.98-1.73)). Marital status (married) was significantly associated with survival (aHR 0.62 (95% CI 0.47-0.83))
Kim[41]	241	Depression measured by de BDI-II, a revised form of the BDI	Overall survival	Pretreatment depression was not significantlt predictive for 3-year overall survival (aHR 1.52 (95% CI 0.82-2.81)).
Konski†‡[27]	1073	Functional capacity measured by KPS	Overall survival	KPS (90-100 vs 60-80) was an independent prognostic factor for overall survival (HR^{y} 1.90 p=<0.0001).
Lotfi[28]	258	Functional capacity measured by KPS	Surgical-site infection	There was no association with the risk of surgical-site infection and the KPS (p=0.489)
Mell[22]	479	Functional capacity measured by ECOG-scale	Competing mortality	Univariate analysis ECOG performance status (1 to 2) was significantly associated with mortality (HR 1.57 (95% CI 1.05-2.36)). Multivariate analysis showed no association
Oskam†[42]	80	Social environment depicted by marital status	Overall and disease specific survival	Marital status (partner vs no partner) was predictive for disease specific survival (aRR 3.10 (95% CI 1.36-7.06)) and overall survival (no estimate reported)
Osthus[45]	106	Social environment depicted by marital status	Overall survival	Marital status (married vs other) was no prognostic factor for survival (aHR 0.68 (95% CI 0.34-1.35))
Pedruzzi[31]	361	Functional capacity measured by Zubrod-scale	Death	Zubrod-scale scores of 2 and 3 were independent prognostic factors risk of death(aHR 1.49 (95% CI 1.1-2.0) and aHR 1.94 (95% CI 1.2-3.3))
Ronis[37]	316	Depression measured by GDS-SF Social environment depicted by marital status	Health related quality of life with SF-36 and HNQoL	Depressive symptoms at baseline is a significant predictor of change HRQOL one year after diagnosis, across various domains of SF-36 and HNQoL (p=<0.05), adjusted for age Marital status is not a predictive factor.
Sadat[29]	169	Functional capacity measured by KPS and ECOG-scale	Overall survival	KPS (≤70), and ECOG (≥2) were an independent prognostic factor for overall survival (aHR 1.51 (95% CI 0.97-2.35))
Sanabria[18]	310	Functional capacity measured by KPS	Overall and cancer specific survival	KPS (≤80) was an independent prognostic factor for overall and cancer specific survival (aHR 2.0 (95% CI 1.40-2.87) and aHR 2.28 (95% CI 1.43-3.64))

Table 2. Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes (*continued*)

Study		Geriatric measure and measured method	Outcome	Association
Author	**No. of patients**			
Shah[32]	774	Functional capacity measured by Specific Activity Scale (SAS) Social environment depicted by living situation Cognitive impairment as any history or physical findings of a stroke, TIA or dementia	Delirium yes/no	There was no significant correlation with SAS (HR 2.43 (95% CI 0.78-7.63)) or living situation (HR 1.18 (95% CI 0.69-2.01) and the development of postoperative delirium. Cognitive impairment was significantly correlated with a postoperative delirium (aHR 3.83 (95% CI 1.70-8.63)
Siddiqui‡[30]	1093	Functional capacity measured by KPS Social environment depicted by marital status	Overall survival	KPS (60-80 vs 90-100, with aHR 1.507 (95% CI 1.268-1.791)) and marital status (with or without partner with aHR 1.235 (95% CI 1.218-1.747)) were independent prognostic factor for overall survival
Sze[19]	990	Functional capacity measured by ECOG-scale	Overall and cancer specific survival	ECOG performance status (2-3 vs 0-1) was not a prognostic factor for overall (aHR 1.01 (95% CI 0.55-1.84) or cancer specific survival (aHR 0.85 (95% CI 0.28-2.54))
Tarsitano[43]	124	Social environment depicted by marital status	Overall survival	Having a partner was predictive for survival (no estimate or p-value reported)
Urba[23]	704	Functional capacity measured by ECOG-scale	Overall survival and progression free survival	ECOG performance status (0-1 vs 2) had a significant effect on overall survival (aHR 0.56 (95% CI 0.42-0.75)) and progression free survival (aHR 0.71 (0.53-0.93))
Wang[24]	600	Functional capacity measured by ECOG-scale	Overall and cancer specific survival	ECOG performance status was associated with borderline statistical significance (aHR 2.89 (95% CI 1.00-8.35)) with overall survival but not with cancer specific survival (aHR 0.86 (95% CI 0.11-6.48))
Weed[34]	138	Cognitive status measured by MMS-questionnaire Functional capacity measured by SAS Social environment depicted by living situation	Delirium yes/no	Patient living alone developed significantly more frequent a postoperative delirium (no estimate reported, p=0.005). Cognitive status and functional capacity had no effect
Wong[44]	1010	Social environment depicted by marital status	Overall survival	Marital status (married vs unmarried) had a significant difference in overall survival (aRR 1.528, p=0.008)

aHR, aRR, aOR= this are the adjusted values at least for age.
†: Both studies are the same cohort
‡: Studies conducted partly on same trial, Siddiqui et al used partly the same patients (n= 689) as Konski et al
#: Multivariate model contained: AJCC stage (IV vs III), N-status (N2-3 vs N0-1), KPS (<80 vs. ≥80)
ɣ: Multivariate model contained: race, educational level, TN-classification, KPS, site. Stratified by treatment

be associated with (overall) survival in 9 out of 12 studies (75%) [18, 20, 21, 23, 25, 27, 29-31]. Siddiqui et al and found that KPS (90-100 vs 60-80) was an independent prognostic factor for overall survival (aHR 1.51 (95% CI 1.27-1.79)).

Cognitive impairment

There were only two articles that reported on the association between cognitive status and adverse health outcome. Shah et al reported a prevalence of cognitive impairment of 5%, defining pre-existing cognitive impairment as any history or physical findings of stroke, transient ischemic attack or dementia [32]. The outcome measured was the development of a postoperative delirium, and 11 out of 39 patients with cognitive impairment developed a postoperative delirium (28%). Pre-existing cognitive impairment was significant correlated with a postoperative delirium (aHR 3.83 (95% CI 1.70-8.63)). Weed et al measured cognitive function using the Folstein Mini-Mental State questionnaire (MMS) [33]. In this study 24 out of 138 patients (17%) developed a postoperative delirium, and these 24 patients had a mean MMS-score of 26.3 [34]. In this small sample size, there was no association reported of cognitive status measured by the the Folstein Mini-Mental State questionnaire with the development of postoperative delirium.

Eight studies examined depression by using five different types of inventories using different scales. The study of Ronis et al, assessed depression by using the GDS-SF and 156 of 316 patients (49%) had significant depressive symptoms at baseline, and about the same prevalence was found in other studies. Five out of eight studies (62.5%) found a significant association of depression with an increased risk of one of the adverse health outcomes. In four studies assessing depressive symptoms was found that depressive symptoms at baseline were associated with lower global/health related quality of life after follow-up [35-38]. Depressive symptoms at baseline were a significant predictor of a negative change in HRQoL one year after diagnosis (adjusted for age p=<0.05, no estimation reported). The association of mood/depression and survival as outcome is inconsistent. One study [39] found that depression, measured by Beck Depression Inventory (BDI), at baseline predicts overall survival (aHR 1.13; p=0.03) and disease specific survival (aHR 1.19; p<0.001). On the other hand Karvonen et al measured depression by the Geriatric Depression Scale Short Form (GDS-SF) and found that this was no significant prognostic factor for overall survival (HR 1.30 (95% CI 0.98-1.73))[40] and also Kim et al found that pre-treatment depression was not significant predictive for three-year overall survival (aHR 1.52 (95% CI 0.82-281))[41].

Social environment

Fourteen studies examined social environment and this was mostly assessed by marital status (34%) and living situation (10%), one study used Social Provision Scale (SPS).

Around 35% of the participants did not have a (married) partner. Ten out of fourteen studies (71%) found an association of social environment with one of the outcomes. Six studies found that marital status (not married or not having a partner) was associated with a worse overall survival [26, 30, 40, 42-44] and two studies did not find an association [25, 45]. The quality of life after 3, 6 or 12 months was lower in patients who did not have a partner compared to patients who did have a partner [46, 47]. There was only one study assessing the living situation with overall survival, this study found that patients living dependently had a higher risk for a reduced overall survival (aRR 2.33, p=<0.001) and disease specific survival (aRR2.16, p=<0.001) [48].

Quality assessment

The overall study quality assessed by the modified Newcastle-Ottowa scale was moderate (Table 3). Overall there were some concerns regarding the validity of the selection, the determination of outcome or reporting of the duration of follow up. The greatest concern with a majority of the studies was the representativeness of the study population, as 14 studies (48%) examined the association between a geriatric measure at baseline with outcome in a selected population in which only one kind of tumor, one kind of treatment modality or treatment intent was used. Furthermore, in several studies a risk of selection bias persisted because of various reasons: excluding older patients, cognitive impaired patients or with a restriction on the functional performance [17, 26, 27, 30, 35, 37, 39, 41, 42, 45, 46].

Table 3. Quality Assessment

Publication		Selection		Outcome		
First author	Publication year	Representativeness of the exposed cohort	Ascertainment of exposure (geriatric measure)	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Aarstad	2005	-	+	+	+	?
Barber	2015	+	+	+	+/-	+
Borggreven	2007	+/-	+	+	+	-
Epstein	2005	-	+	+	+	?
Fang	2004	+/-	+	+	?	?
Gerude	2011	-	+	+	+	+
Graeff, de	2001	+/-	+	+	+	?
Hall	2009	+/-	+	+	+	+
Hammerlid	2001	+	+	+	+	-
Howren	2010	+	+	+	+	+
Howren	2013	+	+	+	+	+
Hsieh	2011	-	+	+	+	?
Karvonen	2008	+	+	+	+	?

Table 3. Quality Assessment (*continued*)

Publication		Selection		Outcome		
First author	Publication year	Representa-tiveness of the exposed cohort	Ascertainment of exposure (geriatric measure)	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Kim	2015	+	+	+	+/-	+
Konski	2003	+/-	+	+	?	?
Lotfi	2008	+	+	+	+	+
Mell	2010	+/-	+	+	+	?
Oskam	2010	+/-	+	+	+	?
Osthus	2013	+	+	+	+	+
Pedruzzi	2008	+/-	+	+	+	?
Ronis	2008	+	+	+	+	+
Sadat	2012	-	+	+	+	?
Sanabria	2007	+	+	+	+	?
Shah	2012	+/-	+	+	?	?
Siddiqui	2008	+/-	+	+	+	?
Sze	2012	+/-	+	+	+	?
Tarsitano	2012	-	+	+	+	?
Urba	2012	+/-	+	+	+/-	+
Wang	2014	+	+	+	+	?
Weed	1995	+/-	+	+	?	?
Wong	2006	+/-	+	+	+	?

DISCUSSION

In the present systematic review, we identified 31 articles reporting on the association of functional or cognitive impairment, social environment or frailty with adverse outcomes in patients with head- and neck cancer. There were three main findings: first, the decline in functional performance, depressive symptoms and decline in social environment were prevalent. Second, the majority of the studies reported a statistically significant association of impairment in functional and cognitive performance, mood or social environment with a higher risk of adverse outcome. Third, cognitive function was only assessed in two studies and frailty and objectively measured physical capacity, were not assessed at all in patients with head and neck cancer.

Impairment in functional performance, depression and social environment were highly prevalent, which emphasizes that the head and neck cancer patients are a very vulnerable patient group. Possibly, the observed associations in the present review are underestimated due to the relatively young population in the studies compared to the average population in the clinic, with only twelve studies (39%) reaching a mean age of

60 years and older. According to the Surveillance, Epidemiology, and End Results database, approximately 47% of all patients diagnosed with head and neck cancer (HNC) in the U.S. between 1973 and 2013 were 65 years and older [49]. It is not surprising that we find limited number of older patients in these studies. A review in 2012 showed that only 7% of all randomized clinical trials are specially designed for older adults [50]. It is also known over various fields in medicine that older patients are underrepresented in clinical studies as a result of excluding individuals over a certain age or with a high burden of morbidities [50, 51]. As a consequence, subjects enrolled in clinical trials, even those in the oldest cohort, often do not represent older patients in the general population [52, 53]. Based on the results of the studies included in our review, we cannot determine which individual patient would experience adverse health outcomes and therefore the external validity of the individual studies is limited. The limited external validity is caused by the heterogeneous population, investigating a wide range of head and neck cancer types and treatment modalities and regimes, inclusion criteria, number of included patients, used geriatric assessment, age groups and outcome measurements.

Despite the heterogeneity of the studies and the low numbers of studies studying older patients it is the majority of included studies reported a significant association of functional impairment and social environment and some on cognitive impairment with adverse outcomes. These associations also have been shown in other oncology patients [54-56] and in community dwelling older people [14, 57]. In general oncology, geriatric assessments are frequently used to guide treatment decision-making. General oncologists often assess functional capacity by assigning KPS and ECOG-score, and both assessments are independent prognostic factors for outcomes [58, 59]. In (oncological) surgery cognitive impairment is a well-known risk factor for postoperative complications such as delirium and mortality [60-62]. In two recent meta-analyses depression diagnosis and higher levels of depressive symptoms in patients with different kind of cancers predicted elevated mortality [63, 64]. Social isolation has been linked to an increased risk of mortality in geriatric and oncology literature [65, 66]. This could be explained by the intensive treatment program for (head and neck) cancer, the chances of success of the intensive treatment is highest when there is a good social support. Although we cannot rule out publication bias with negative associations not being published, our findings are in line with the literature describing associations of impairments with adverse outcome. Most of the studies identified in the present systematic review, found an association with social status, depicted by marital status, and a worse overall survival.

Multiple promising geriatric assessments, such as various frailty indices and objectively measured physical capacity were not assessed in patients with head and neck cancer. Objective geriatric measurements, such as gait speed, handgrip strength or Timed

Up to GO Test (TUGT) can be useful geriatric screenings tools for the physician to risk stratify patients. Several studies examining the relation between physical capacity and outcomes as mortality or disability, found an association both in general and in oncological patient populations [67-70]. Frailty is associated with adverse health outcomes in surgical patients [61] as well in community dwelling older adults [14]. In addition, in a recent review in older cancer patients, frailty is associated with an increased risk of chemotherapy intolerance, postoperative complications and mortality [71]. In conclusion, both objective geriatric measurements and frailty are predictive of poor outcomes in general oncology, (oncologic) surgical patients, as well as community dwelling older adults. However, in older head and neck cancer patients evidence of physical capacity and frailty and its associations with adverse health outcomes is lacking.

A limitation of our study was that, due to heterogeneity among the included studies, especially with respect to the geriatric measure that was used, the reported measure of association (HR, OR, and relative risk), outcome measures, and covariate adjustments, made it impossible to compare outcomes of studies in a meta-analysis or to make a proper sub group analysis. Secondly, interpretation of the results may be hampered by possible publication bias, as negative associations in multivariate analyses may not have been reported in the studies. Strengths of this review include the systematic search we performed in several databases, assessing all potential relevant associations of functional and cognitive impairment, social environment and frailty with adverse health outcomes in head and neck cancer patients. Furthermore, quality assessment of the studies was undertaken to identify potential factors hampering external validity.

Our findings implicate that apart from specialists in head and neck oncology (such as head and neck surgeons and oncologists) the older head and neck cancer patient could benefit from an even more multidisciplinary approach. This could be implemented for instance by including a geriatrician in the multidisciplinary team in both the pre- and post-operative phase.

Conclusion

Functional and cognitive impairment, depressive symptoms and social isolation are highly prevalent in head and neck cancer patients and associate with high risk of adverse health outcomes. In the future, these measurements may guide decision-making and customize treatments, but more research is needed to further improve and firmly establish clinical usability.

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4 FUNCTIONAL AND COGNITIVE IMPAIRMENT, SOCIAL FUNCTIONING, FRAILTY AND ADVERSE HEALTH OUTCOMES IN OLDER PATIENTS WITH ESOPHAGEAL CANCER, A SYSTEMATIC REVIEW

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ABSTRACT

Background Older patients with esophageal cancer are at high risk of adverse health outcomes, but the association of geriatric assessment with adverse health outcomes in these patients has not been systematically evaluated. The aim of this systematic review was to study the association of functional and cognitive impairment, social environment and frailty with adverse health outcomes in patients diagnosed with esophageal cancer.

Methods We searched Pubmed, Embase, Web of Science and Cochrane Library for original studies reporting on associations of functional or cognitive impairment, social environment and frailty with adverse outcomes (mortality, functional or cognitive decline, adverse events during treatment, prolonged length of hospitalization (LOS) and health related quality of life (HRQoL)) after follow-up in patients with esophageal cancer.

Results Of 1.391 identified citations, nineteen articles were included that reported on 53 associations. The median sample size of the included studies was 110 interquartile range (IQR 91-359). Geriatric conditions were prevalent: between 14 and 67% of the included participants were functionally impaired, around 42% had depressive symptoms and between 5 and 23% did not have a partner. In nineteen of 53 (36%) associations functional or cognitive impairment or frailty were significant associated with adverse health outcomes, but the studies were small. In four out of six (67%) associations with the largest sample size (n≥359), functional impairment or social environment were significant associated with adverse health outcomes.

Conclusion Functional and cognitive impairment, depression and social isolation are prevalent in patients with esophageal cancer, and associate with adverse health outcomes. Geriatric measurements may guide decision-making and customize treatments, but more large studies are needed to explore the clinical usability.

INTRODUCTION

Esophageal cancer incidence strongly increases with age. In 2016 in the Netherlands there were 2545 newly diagnosed patients with esophageal cancer and in > 65% of these diagnoses the patient was 65 years of older [1]. Also the UK and the USA report similar numbers [2]. Esophageal cancer is associated with a poor prognosis, having an overall five-year survival ranging between 15 and 20% depending on the stage and treatment intention [3]. It is a challenge to select the older patients who are at high risk for adverse health outcomes, such as mortality, prolonged length of stay and reduced quality of life. This is mostly due to their varying levels of functional and cognitive capacity, mobility and frailty. However, it is unclear how geriatric impairments, such as functional and cognitive impairment or frailty, associate with adverse outcomes in patients diagnosed with esophageal cancer.

The optimal treatment for locally advanced esophageal cancer consists of preoperative concomitant chemoradiotherapy followed by surgical resection [4, 5] and the optimal treatment for early stage esophageal cancer is surgical or endoscopic resection [6]. In patients aged 70 years and older, esophagectomy has been associated with higher mortality and morbidity rates compared to patients younger than 70 years [7-10]. Often there is reluctance to have older patients undergo the general treatment modalities [11], because of their comorbidities, polypharmacy or poor physical functioning [12]. In other fields of medicine, recent research has shown that performing a geriatric assessment including the domains of functional or cognitive functioning, social functioning and frailty may guide decision making for older patients undergoing general surgery [13].

The aim of this systematic review was to study the association of functional and cognitive impairment, social environment and frailty prior to any treatment with adverse health outcomes (mortality, functional or cognitive decline, adverse events during treatment, prolonged length of hospitalization (LOS) and health related quality of life (HRQoL) after follow-up) in patients diagnosed with esophageal cancer.

METHODS

Search Strategy

We aimed to identify original longitudinal studies in patients with esophageal cancer with all disease stages, in which the association between a measurement of functional and cognitive impairment, social environment or frailty prior to any treatment initiation and adverse health outcome (mortality, functional or cognitive decline, adverse events during treatment, LOS and health related quality of life (HRQoL) after follow-up) after follow-up was examined.

One of the purposes of a geriatric assessment is to systematically explore different domains (functional status, cognitive status, social environment and frailty) as a reflection of patients' health [14, 15]. Therefore, using the geriatric assessment at baseline we determined functional capacity (including assessment of functional performance, mobility, and objectively measured physical capacity such as hand grip strength, gait speed or balance tests), cognitive capacity (including assessment of cognition, dementia diagnosis, and mood or depression), social environment (living situation, social support and marital status) and frailty (as measured using a frailty index or instrument such as Fried Frailty Phenotype or the Groningen Frailty Indicator). The geriatric assessment had to be done before treatment initiation. In this review articles describing patients treated with any of the available treatments are eligible (surgery, chemotherapy, (chemo)radiotherapy, palliative supportive care). We expect that a geriatric assessment mostly will be performed in older patients, though they might be relevant to younger patients as well. To decrease the risk of missing relevant articles we did not apply age limits in the search strategy. An esophageal tumor was defined as squamous cell carcinoma (SCC) or adenocarcinoma carcinoma (AC) of the esophageal wall or gastro-esophageal junction, all disease severity stages were included. Adverse health outcomes were defined as mortality, functional or cognitive decline, adverse events during treatment (e.g. delirium or side-effects), prolonged length of hospitalization (LOS) and health related quality of life (HRQoL) or global quality of life (QoL) after follow-up.

On December 19th 2016, we searched four electronic bibliographic databases (PubMed, Embase, Web of Science and the Cochrane Library) using synonyms of esophageal cancer, combined with synonyms of the different domains of geriatric assessment. For the full Medline search, see Appendix A (available online).

Article selection

The eligibility of all studies identified by the search was independently evaluated by two authors Floor van Deudekom (FvD) and Henk Klop (HK). Of any article that seemed

potentially relevant based on title and abstract, full text was retrieved and screened. Studies were included if the full text contained original data reporting on the association between any of the geriatric measures at baseline and outcome after follow-up in patients with esophageal cancer in a longitudinal study design. In case of disagreement between the two authors (HK, FvD), consensus was reached after discussion with two other co-authors (MS and SM). In 1372 of the 1391 articles HK and FvD had consensus, making a 98% agreement overall. The reference list of the included publications was used for cross-referencing to ensure we identified all relevant articles.

Data extraction

Data extracted from each study included: publication data (author, year), study design and setting, patient characteristics (sample size, mean age, treatment modality), tumor type (SCC or AC) measurement of functional or cognitive impairment, social environment or frailty, follow up duration, outcome measures and results of the association functional and cognitive impairment, social environment and frailty with adverse health outcome. Treatment modality can include therapy with a curative intent such as endoscopic resection, surgery, surgery in combination with neoadjuvant chemoradiation, chemoradiation alone or treatment with no curative intent such as palliative chemotherapy or palliative radiotherapy or esophageal stent placement. Also, best supportive care was considered as a treatment modality. To assess the methodological quality and risk of bias of the included studies, we adapted the Newcastle-Ottawa scale [16] for the purpose of this review (Appendix B). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist, which is a checklist for evidence-based minimum set of items for reporting in systematic reviews [17], is available (online) see Appendix C.

Data presentation

Study characteristics are tabulated per individual study. Accumulated descriptive statistics of the selected studies are presented by calculating the proportion of studies reporting on measurements of functional or cognitive impairment, social environment or frailty, endpoints or treatment modalities. Combined sample size of the included studies is expressed as median and interquartile range (IQR). To get a complete overview we describe the total of significant associations with outcomes. All calculations are made with Statistical Package for the Social Sciences (SPSS) software version 23. In this review with an "association" is meant the relation between the geriatric determinant at baseline and the outcome after follow up. Main findings of the studies with respect to the association of measurement of functional or cognitive impairment, social environment or frailty with outcome are tabulated. If possible, a fully adjusted model controlling for possible confounders, including multiple known risk factors for poor outcome, such as comorbidity burden, was tabulated.

Supplementary analysis

Because of a low average sample size in the found articles, which can result in low power to detect statistical significance, we performed a supplementary analysis. In this analysis we analyzed the five studies with the largest sample size and describe the association of measurement of functional or cognitive impairment, social environment or frailty with the outcome of interest.

RESULTS

Search results and study selection

The database searches identified 1391 unique citations (Figure 1). After screening of title and abstract, 66 articles were considered potentially eligible. After full-text review, 47 were excluded; the remaining nineteen articles were included. Cross-referencing did not result in additional articles, so a total of nineteen articles were included in this review.

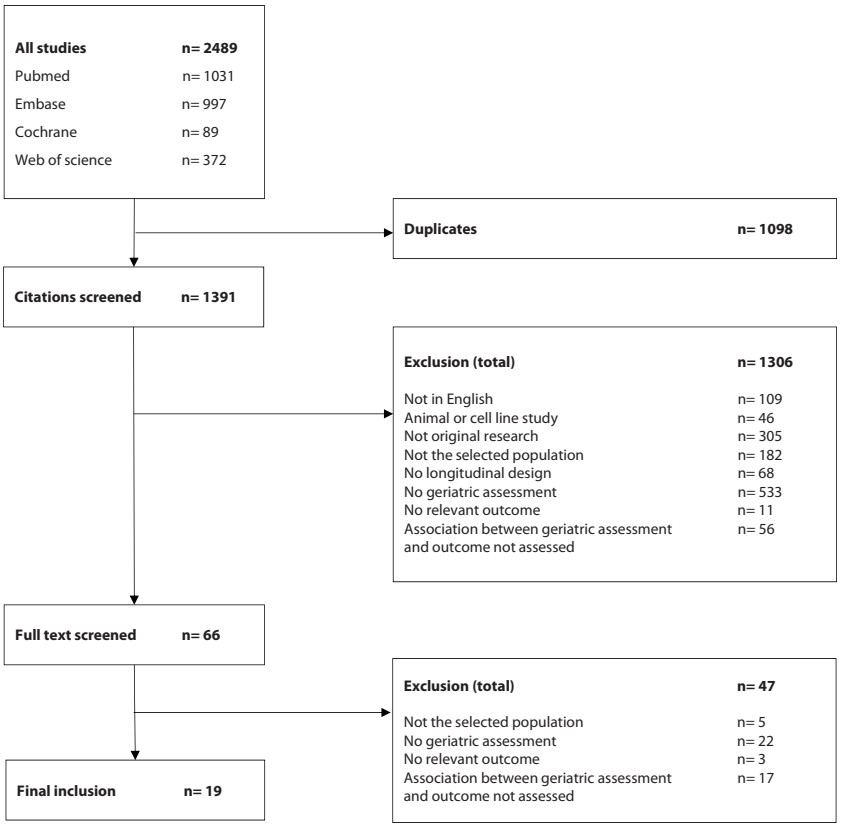


Fig 1. Flowchart

Study characteristics

Table 1 shows an overview of the study characteristics of the nineteen included studies. Eighteen out of nineteen studies (95%) were published after the year 2000. The median sample size of the included studies was one hundred ten (interquartile range (IQR) 91-359). Ten out of nineteen studies (53%) were conducted in the United States or Europe. Out of the nineteen studies, thirteen studies (68%) included adenocarcinoma and squamous cell carcinoma; six studies (32%) included patients with only one of those two types. Four studies had specific selection criteria such as (locally) advanced cancer, ability to complete self-report questionnaires and seven studies included only one treatment modality. Only two studies (11%) focused on older patients and included exclusively patients aged 70 years and older in their study population.

Association of measures for functional status, cognitive or social functioning with adverse health outcomes

Table 2 shows an overview of the associations of measures of functional or cognitive impairment, social environment and frailty with adverse health outcomes after follow up. The nineteen studies reported on a total of 53 associations between various determinants with adverse outcomes: 25 out of 53 associations (47%) assessed functional impairment, ten out of 53 associations (19%) were reporting on cognitive function, two out of 53 associations (4%) examined depressive symptoms, social status was studied in eleven out of 53% associations (21%) and physical capacity was studied in five out of 53 associations (9%) (Figure 2). Objectively measured physical capacity, such as hand grip strength or the six-minute walking test was examined in five associations (9%). None of the studies used an instrument to measure frailty as a determinant of adverse health outcomes.

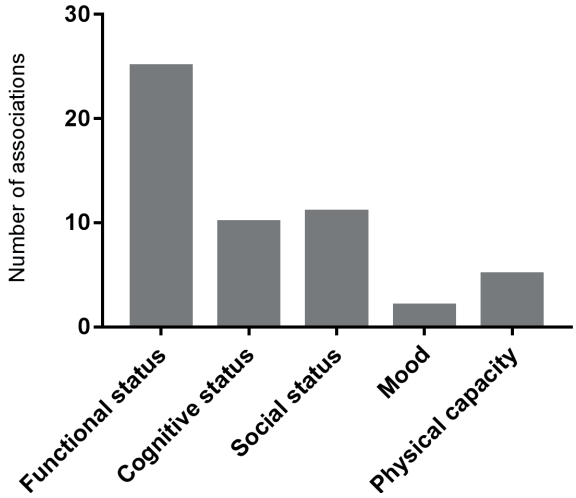


Fig. 2 Graphic representation of the number of associations described per geriatric domain

Table 1. Characteristics of included articles

Publication characteristics			Study population			Clinical characteristics	
Author	**Year**	**Country**	**Number of patients**	**Age, yr (mean)**	**Patient selection**	**Tumor characteristics**	**Treatment modality**
Bergquist *et al.*[24]	2007	Sweden	94	67	Patients with newly diagnosed cancer. Exclusion: declined participation, unable to complete the questionnaires, expected survival < 1 month	AC and SCC	Any
Bergquist *et al.* [18]	2008	Sweden	96	74	Patients with incurable cancer Exclusion: withdrawn consent, previous esophagectomy or concomitant malignancy, expected survival < 1 month	AC, SCC and 2% other	P (stent, brachytherapy, anti-reflux valve)
Blazeby *et al.*[19]	2001	UK	89	70§	Exclusion: no obtained QOL data	AC and SCC	S, C, RTx, P or intubation
Brusselaers *et al.*[30]	2014	Sweden	606	NA	Exclusion: no marital status available	AC and SCC	S
Chang *et al.*[33]	2014	Taiwan	99†	55.5	Exclusion: patient unable to self-report, inoperable tumor	AC and SCC	S with or without CRTx
Chang *et al.*[20]	2016	Taiwan	67†	56§	Exclusion: mortality < 6 months, circumferential margin tumor R1 or R2	AC and SCC	S
Dandara *et al.*[32]	2015	South Africa	1868	60§	All patients with carcinoma of the esophagus	AC and SCC	Any
Egmond et *al.*[23]	2016	Netherlands	94	63.8	All esophageal patients with cancer scheduled for esophagectomy. Exclusion: severe cognitive impairment, functional or nutritional impairments.	All tumor types	CRTx and S
Fakhrian *et al.*[61]	2012	Germany	163	62	Patients with stages T1-T4,N0-1, cM0 Exclusion: cM1, adjuvant or salvage radiation treatment, exclusive intraluminal brachytherapy (IBT)	SCC	CRTx
Fang *et al.*[21]	2004	Taiwan	110	NA	Newly diagnosed patients Exclusion: no Stage T1–T4N0-N1M0-M1a preoperative or postoperative RT, a radiation dose < 50 Gy, treatment with brachytherapy, had tumor recurrence or synchronous malignancies, or were unable to complete the questionnaire.	SCC	RTx

Table 1. Characteristics of included articles (*continued*)

Publication characteristics			Study population			Clinical characteristics	
Author	**Year**	**Country**	**Number of patients**	**Age, yr (mean)**	**Patient selection**	**Tumor characteristics**	**Treatment modality**
Ghadimi *et al.*[31]	2012	Iran	359	55.23	No selection criteria available	All tumor types	Any
Healy *et al.*[22]	2008	Ireland	185	61.6	Patients offered surgery or multimodal treatment with clinical stage T1-3 N0-1 M0	AC and SCC	CRTx with or without additional S
Kawashima *et al.*[25]	1998	Japan	362	72§	Patients treated with Definitive Radiotherapy (DRT) Exclusion: No description of survival	SCC, AC and 1.7% other	RTx without S
Kim *et al.*[62]	2008	Korea	180	64§	3 RCTs: patients locally advanced, but resectable cancer	SCC	CRTx with or without additional S
Mak *et al.*[63]	2010	USA	34	79.5§	Aged ≥ 75, full-dose chemoradiation (> 45 Gy) with at least ≥ 1 cycle of concurrent chemo	AC, SCC and poorly differentiated (5.9%)	CRTx with or without additional S
Murphy *et al.*[26]	2013	USA	191	60§	Patients with locally advanced cancer Exclusion: synchronous primary cancers, cancer of cervical or proximal esophagus, emergency, redo and salvage esophagectomies.	AC	CRTx and S
Raymond *et al.*[27]	2016	USA	4321	63.3	Patient with esophageal cancer needing surgery. Exclusion: benign disease, missing clinical stage and tumor histology	AC and SCC	S
Tatematsu *et al.*[29]	2013	Japan	51	65.0	Patients with esophageal cancer Exclusion: gait disturbances requiring assistive devices	SCC	S
Yamamoto *et al.*[28]	2016	Japan	91	78.4	Patients aged ≥ 75 with esophageal cancer Exclusion: two-stage surgery, no SCC	SCC	S

* abbreviations C=chemotherapy, CRTx= chemoradiation, RTx = radiotherapy, S= surgery, P= palliative, SCC= squamous cell carcinoma, AC= Adenocarcinoma, NA= not available
↑ Studies are used in the same cohort
§ Median

Table 2. Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes

Authors	No. of patients	Geriatric measure and measured method	Outcome	Association
Bergquist *et al.*[24]	94	Functional status by KPS Depression by HADS	Anxiety and Depression, Overall Survival	No significant change in the HADS total score over time was found in patients with a different KPS. No correlations were found between any of the HADS scores at inclusion and survival.[ϒ]
Bergquist *et al.* [18]	96	Functional status by KPS Functional, cognitive and social status by EORTC QLQ-C30.	Overall Survival	Functional (HR 0.91, p=0.02 and cognitive scales (HR 0.92, 0.03) were significantly associated with survival, Cognitive functioning was not (HR0.93, p=0.161). Social scale showed trend with survival (HR 0.93, p=0.05). KPS was significantly associated with survival (HR 0.98, 0.002).[‡]
Blazeby *et al.*[19]	89	Functional, cognitive and social status by EORTC QLQ-C30.	Overall Survival	Higher functional (HR 0.88, p=0.002) and social scores (HR 0.91, p=0.028) were associated with lower likelihood of death. After adjusting for associations between the score, only functional scale was significantly associated with survival (HR 0.88, p = 0.002).
Brusselaers *et al.*[30]	606	Social status by marital status	Overall 5-year survival	Marital status was not significant associated with overall survival in any of the regression models (HRs ranging from 0.79 – 1.02).
Chang *et al.*[33]	99[†]	Functional status by ECOG (0 vs. 1-4)	QOL via EORTC QLQ-C30	Functional status at baseline showed no significant association with any of the QOL scales 1 and 6 months after surgery (difference in score -4.4 compared to baseline, p>0.05).
Chang *et al.*[20]	67[†]	Functional, cognitive and social status by EORTC QLQ-C30	Survival after 6 months post-surgery	Functional, cognitive and social status at baseline were not significantly associated with survival after 6 months postoperatively (HR's 0.989-0.999, p>0.05).[‡]
Dandara *et al.*[32]	1868	Functional status by ECOG	Overall Survival	Patients with ECOG ≤ 2 had statistically improved survival over those with ECOG 3-4.
Egmond et *al.*[23]	94	Functional status by LAPAQ. Physical status by IMS and HGS, EORTC QLQ-C30	Postoperative complications (< 30 days or during hospital stay)	Functional and physical status[ϒ] were not associated with postoperative complications (ORs 0.99-1.00, p>0.05). EORTC QLQ-C30 domains were not associated with postoperative complications (OR 1.02, p=0.22).[‡]
Fakhrian *et al.*[61]	163	Functional status by ECOG	Overall Survival	Higher functional status at baseline was significantly associated with better OS in multivariate analysis (HR 0.50, p=0.005).[ϒ]

Table 2. Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes (*continued*)

Authors	No. of patients	Geriatric measure and measured method	Outcome	Association
Fang *et al.*[21]	110	Functional, cognitive and social status by EORTC QLQ-C30. Functional status by KPS	Survival	In univariate analysis, physical functioning (HR 0.9789, p=0.0007), social functioning (HR 0.9883, p=0.02) and KPS <80 (p=0.02) were associated with survival and cognitive functioning was not associated (HR 0.9986, p=0.83). Functional status by EORTC QLQ-C30 was the only significant association in multivariate analysis (RR 0.98, p=0.0002).
Ghadimi *et al.*[31]	359	Social function by marital status	Overall Survival	Marital status was not a prognostic factor for survival in any of the models (HR/RR range 1.06-1.23, p>0.05).
Healy *et al.*[22]	185	Functional, cognitive and social status by EORTC QLQ-C30.	Postoperative morbidity, in-hospital mortality, early recurrence and 1-year survival	None of the EORTC QLQ-C30 scales (physical, cognitive and social) associated significantly with the different outcomes in univariate (p>0.05) or multivariate analysis (ORs 1.0 p-values > 0.05)
Kawashima *et al.*[25]	362	Functional status by KPS	Overall Survival	Patients with a KPS ≥ 80 (HR 1.56, p=0.0009) had a significantly better overall survival.[†] The overall survival rate of octogenarians was significantly affected by KPS (p=0.009), while the KPS did not affect the survival of younger patients (p=0.958).
Kim *et al.*[62]	180	Functional status by ECOG	Overall Survival	In univariate analysis, a good functional status (score 0 or 1) was associated with higher survival, both in the entire study population (HR 2.37, p=0.001) and in patients that had esophagectomy (HR 2.64, p=0.001).
Mak *et al.*[63]	34	Functional status by ECOG	Toxicity and OS	Functional status was not statistically associated with either survival or risk of grade 3 toxicity.[ϒ]
Murphy *et al.*[26]	191	Functional status by Zubrod performance score	Prolonged length of stay (LOS)	Decreased functional status (0 vs ≥1) was associated (β=0.1514, p=0.021) with increased LOS (10 v 11 days, p=.024).
Raymond *et al.*[27]	4321	Functional status by Zubrod score	Perioperative mortality and morbidity (< 30 days)	Functional impairment, indicated by a Zubrod score > 1 vs 0, was significantly associated with morbidity (OR 1.89, p<0.001) and mortality (OR 3.31, p<0.001).

Table 2. Association of functional and cognitive impairment, social environment and frailty with adverse health outcomes (*continued*)

Authors	No. of patients	Geriatric measure and measured method	Outcome	Association
Tatematsu *et al.*[29]	51	Physical status by knee-extensor muscle strength, 6-minute walking distance and IPAQ (METs*h/wk)	Postoperative complications	Only low level physical status measured by IPAQ was significantly associated with postoperative complications in multivariate analysis (OR 28.3, p=0.02 (95%CI 3.5-227.7)).
Yamamoto *et al.*[28]	91	Functional status by Barthel index and IADL Cognitive status measured by MMSE, Depression by GDS15.	Postoperative delirium	Functional status was not associated with postoperative delirium (p>0.05). Cognitive status (OR 1.4, p<0.0001) and depression (OR 1.3, p=0.004) were associated with postoperative delirium.

* abbreviations: ECOG= The Eastern Cooperative Oncology Group; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; GDS15= Geriatric Depression Scale 15; HADS= Hospital Anxiety and Depression Scale; HGS= handgrip strength; HR=Hazard ratio; IADL= Instrumental Activities of Daily Living; IMS= inspiratory muscle strength; IPAQ= International Physical Activity Questionnaire, KPS= Karnofsky Performance Status; LAPAQ= LASA physical activity questionnaire; MMSE= the Mini-Mental State Examination; OR=Odds Ratio, , RR=Relative Risk.

† Studies performed in the same cohort

‡ Univariate analysis

ɣ Details of multivariate model not available in the original article

Survival (overall, total or disease specific survival) was the main outcome of interest in 26 out of 53 associations (49%). From the remaining associations seventeen assessed side effects (32%), QoL or HRQoL was assessed by one association (2%), four assessed the development of post-treatment delirium (7.5%), one assessed depressive symptoms (2%), three assessed early recurrence (5.5%) and one assessed LOS (2%). No studies reported on cognitive or functional decline after treatment for esophageal cancer.

In nineteen out of 53 associations (36%) in all included studies and in four out of six (67%) of the studies with the largest sample size, functional, cognitive or social functional impairment was statistically significantly associated with a higher risk of adverse health outcomes.

Functional impairment and physical impairment

Nine of the associations reporting on overall functional performance used the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30 [18-23], four used the Karnofsky Performance Score (KPS) [18, 21, 24, 25], six used the Eastern Cooperative Oncology Group (ECOG) score, three used the Zubrod performance score [26, 27] and two used Barthel index and Instrumental Activities of Daily Living (IADL) [28]. Functional impairment was prevalent in most of the studies with rates between 14-67%. For example, one of the largest studies of Kawashima *et al.* included 362 patients and 158 (43.6%) had a KPS$\leq$70, which indicates that patients are unable to carry on active work or require assistance. Functional impairment was found to be associated with increased risk for any adverse outcome in twelve of the 25 associations (47%). Kawashima *et al.* reported that a higher KPS ($\geq$80 versus $\leq$70) was associated with a higher overall survival in patients treated with definitive radiotherapy (RR 1.56 p = 0.0009). If the data were stratified for age, the overall survival rate of 31 octogenarians (stage I/II) was significantly higher with increasing KPS (p = 0.009), while it did not associate with increasing survival in the 63 younger patients (p = 0.958) [25].

Two associations used inspiratory muscle strength and handgrip strength [23], while the other three used knee-extensor muscle strength, six-minute walking distance and International Physical Activity Questionnaire (IPAQ) [29]. Physical impairment was associated with higher risk adverse outcomes in one out of the five reported associations (20%). The study by Tatematsu *et al.,* included 51 participants and assessed the association between physical impairment and postoperative complications showing that physical impairment was statistically significantly associated with postoperative complications in multivariate analysis (odds ratio (OR) 28.3 95% confidence interval (CI) 3.5-227.7) [29].

Cognitive impairment and depressive symptoms

Cognitive status was measured with the European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) cognitive scale, which contains one self-report question on cognitive performance, in nine out of the ten associations [18-23]. Cognitive status was found to be associated with increased risk for any adverse outcome in two out of ten associations (20%). The prevalence of cognitive impairment was not reported. Only one study by Yamamoto *et al.* used an objective assessment to measure cognition, the Mini-Mental State Examination (MMSE). In this study 24 of the 91 individuals developed postoperative delirium and these patients had a lower mean MMSE score of 23 compared to 27 in patients without delirium, indicating a lower cognitive status. In this study, a one point decrease in MMSE score associated with a 40% increased risk of delirium (odds ratio (OR) 1.4 (95% CI 1.2-1.6)) [28].

Depressive symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) [24] and the Geriatric Depression Scale fifteen (GDS15) [28]. One study reported a prevalence of 42% patients having depressive symptoms. Depressive symptoms were associated with an increased risk for adverse outcomes in one out of two associations (50%). The study that assessed the association between depression and postoperative delirium used the GDS15. This study showed that for the 24 patients who developed a delirium, the mean score was 4.92 compared to a mean score of 2.45 for patients without delirium. A one point increase in GDS15 score, indicating a higher chance of depression, was associated with a 30% increased risk for delirium (odds ratio (OR) 1.3 (95% CI 1.1-1.6)) [28]. The other study used the HADS questionnaire in 94 participants to assess if depressive symptoms and anxiety at baseline were associated with survival, reporting no significant correlations between any of the HADS scores at baseline and survival [24].

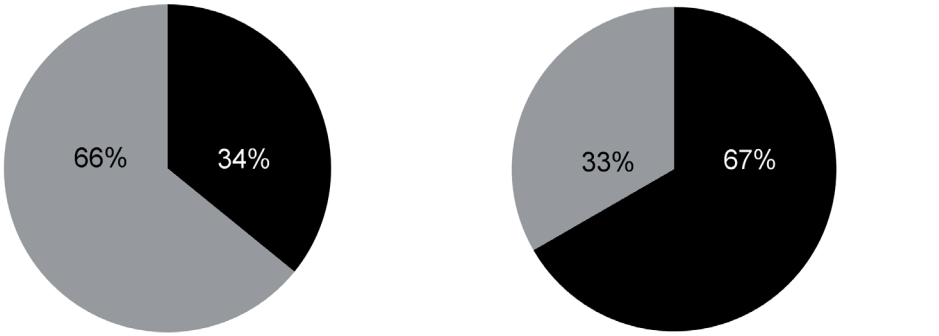
Social functioning

Social impairment was mostly measured with the EORTC QLQ-C30 social scale, in nine of the eleven associations [18-23]. Between 5% and 23% of the included participants were single and 30% lived alone. Social impairment was found to be associated with increased risk for any adverse outcome in three of the eleven associations (27%). A study by Brusselaers *et al.* assessed the association between social functioning, depicted by marital status and overall five-year mortality in 606 participants. Of these patients, 334 were married and 272 had a different marital status (e.g. unmarried or remarried). Marital status was not significantly associated with five-year mortality [30].

Supplementary Analysis

To test the robustness of our finding that 36% of the associations reported a significant association of functional, cognitive or social functional impairment with a higher risk of adverse health outcomes, we performed a supplementary analysis.

The average sample size in the articles is relatively low resulting in low power to detect statistical significance, which may explain the low number of reported significant associations. To test this hypothesis, we analyzed the five studies with the largest sample size [25, 27, 30-32]. This resulted in six associations, with a minimal sample size of 359 patients. Three assessed functional status and two investigated social status, while in all associations survival was the main outcome. In four out of six (67%) associations a significant association of functional, cognitive or social functional impairment with a higher risk of adverse health outcomes was reported (Figure 3).



A. All associations **B.** Associations of studies with largest samples size

Fig. 3 Visual representation of significant associations in different selections.
Legend: Black: significant. Grey: not significant.

Quality assessment

The overall study quality assessed by the modified Newcastle-Ottowa scale was moderate (Table 3). Overall the biggest concern was the representativeness of the study populations. In six out of the nineteen studies (31.6%), the association between a geriatric measure and outcome was examined in a preselected population with specific tumor characteristics (e.g. only locally advanced) or only one treatment modality was used. Furthermore, several studies had specific selection criteria, such as excluding patients who were cognitively impaired [21, 24, 33] or with an impaired physical status at baseline [29], which may increase the risk on selection bias. Finally, only in ten out of nineteen (53%) studies the interpretation of the results were reliable because the confounders and the way there was controlled for these confounders were reported.

Table 3. Quality assessment of the included studies

Publication		Selection		Results	Outcome		
First author	Publication year	Representativeness of the exposed cohort	Ascertainment of exposure (geriatric measure)	The reliability of interpretation of the results by reporting the confounders	Assessment of outcome	Sufficient duration of follow-up	Adequacy of follow-up
Bergquist[24]	2007	+	+	?	+	+	+
Bergquist[18]	2008	+/-	+	-	+	+	?
Blazeby[19]	2001	+	+	+	+	+	+
Brusselaers[30]	2014	+	+	+	+	+	?
Chang[33]	2014	+	+	?	+	+	?
Chang[20]	2016	+/-	+	-	+	+	?
Dandara[32]	2015	+	+	+	+	+	+
Egmond[23]	2016	+	+	-	+	+	?
Fang[21]	2004	+/-	+	+	+	+	?
Fakhrian[61]	2012	+/-	+	?	+	+	?
Ghadimi[31]	2012	+	+	+	+	+	?
Healy[22]	2008	+/-	+	+	+	?	?
Kawashima[25]	1998	+/-	+/-	?	+	+	?
Kim[62]	2008	+/-	+	-	+	+	?
Mak[63]	2010	+/-	+	?	+	+	?
Murphy[26]	2013	+/-	+	+	+	+	?
Raymond[27]	2016	+/-	+/-	+	+	+/-	?
Tatematsu[29]	2013	+/-	+	+	+	+	?
Yamamoto[28]	2016	+/-	+	+	+	+/-	?

DISCUSSION

In the present systematic review, there were four main findings. First, geriatric impairments such as functional impairment, social isolation and depressive symptoms were prevalent. Second, we identified nineteen articles reporting on 53 associations of functional or cognitive impairment or social environment with adverse outcomes in patients with esophageal cancer. Third, one-third of all studies, and 67% of the studies with the largest sample size, reported a significant association of functional, cognitive or social impairment with increased risk for adverse health outcomes. Fourth, objectively measured functional and cognitive function were only assessed in one study, while frailty was not assessed at all in patients with esophageal cancer.

In the nineteen articles we identified, functional, physical and cognitive impairment, depressive symptoms and impairment in social environment were prevalent, this confirms that patients with esophageal cancer are vulnerable. Major risk factors, especially for squamous cell carcinoma, include alcohol consumption and tobacco use. Both factors were also associated for deterioration in functional and cognitive decline as well [34, 35]. Possibly, the reported prevalence in the different studies could be explained by the relatively young included study population, this review reports only two studies who exclusively included patients aged 70 years and older in their study population.

Based on the incidence of esophageal cancer in the general population [36] and based on experience with other reviews in head and neck patients with cancer [37] and patients with end-stage renal disease [38], we had expected to find more articles. The mean age in the included population in this systematic review was above 60 years in only eight of the nineteen studies (42%), while the median age of patients with esophageal cancer is 68 years and 56% of the patients are aged 70 over at time of diagnosis [12]. It is a known phenomenon that clinical trials include limited numbers of older patients. This underrepresentation can be explained by the exclusion of older adults because of age, comorbidities and polypharmacy [39] and this is also known from drug trials [40], cardiology trials [41, 42] and oncology trials [43]. The consequence of this underrepresentation is that it is unknown if the results can be applied to the individual patient in the outpatient department and therefore the external validity is limited. The large heterogeneity in inclusion criteria, treatment modalities, geriatric assessment and outcome measures, hampers drawing definitive conclusions for individual patients.

In this review, more than one-third of the reported associations found a significant association of functional, cognitive or social impairment with increased risk for adverse health outcomes. In general oncology, oncologists often assess functional capacity by

assigning KPS and ECOG-score, to guide treatment decision-making. Both assessments are independent prognostic factors for survival [44-46]. Also, IADL has been identified as a significant prognostic factor for survival in lung cancer [44] and in patients with cancer undergoing surgery [47, 48]. In this review, one study assessed objectively assessed cognitive status and found an association with postoperative delirium [28]. This is in line with previous research that reported impaired cognitive status to be associated with adverse outcomes in patients undergoing thoracic surgery [49] and older patients [50]. In this review, social assessment by marital status, assessed in one study, was not associated with survival. In a recent systematic review in patients with head and neck cancer, social status depicted by marital status was associated with adverse health outcomes such as overall survival [37]. In general, the number of associations between functional, cognitive or social impairment with increased risk for adverse health outcomes was higher in other patients with cancer [37, 51]. One possible explanation may be the lack of statistical power of the included studies, as the median sample size was low (< 100 patients). This hypothesis is supported by our finding that 67% of the associations in the articles with the highest sample size, associations of functional impairment or social environment with adverse health outcomes, did reach statistical significance. On the other hand, the number of significant associations may inversely be affected by publication bias, as negative associations in multivariate analyses may not have been reported in some of the studies. Overall, we conclude that in older patients with esophageal cancer impairments on functional, cognitive or social environment in 67% of the reported associations there was an increased risk of adverse outcomes.

Objectively measured functional and cognitive status were assessed in only one study [28]. The predictive value of a geriatric assessment, which extensively examines functional, physical, cognitive and social performance, has been established in other patients with cancer [44, 52, 53], but was not reported for patients with esophageal cancer. An often used concept 'frailty' has not been studied in patients with esophageal cancer. This is surprisingly since frailty is extensively described in other oncological fields [54-56]. Frailty also has been associated with increased risk of mortality, treatment complications and treatment completion in older patients with cancer [57, 58]. However, in older patients with esophageal cancer evidence of physical capacity and frailty and its associations with adverse health outcomes is lacking.

A limitation of the present review is that we did not perform a meta-analysis. Due to the heterogeneity of the included studies with respect to the low number of included patients, geriatric measures that were used, outcome measures and the reported association measure (HR, OR and RR) and often the absence of an estimate of the effect, a summary statistic would be hard to interpret. A cumulative statistic of associations

would only provide information to the reader about whether an overall association exists in a statistical way. Clinical usefulness of such a summary statistic would be minimal as it is unclear what determinant associates with what outcome and whether or not there is confounding or bias. Strengths of this review include the systematic search we performed, assessing all potential relevant associations of functional and cognitive impairment, social environment and frailty with adverse health outcomes in patients with esophageal cancer. Furthermore, quality assessment of the studies was performed to identify potential factors that may impede external validity.

Given the high prevalence of geriatric impairments described in this review it is likely that systematic geriatric screening and a multidisciplinary approach could be of added value in the treatment of older patients with esophageal cancer. Patients who are at high risk for adverse outcomes can be identified and preventive measures, for example to prevent for a delirium or functional decline, could be taken. This benefit is already described in different patient populations [59, 60]. Furthermore, we advise that future observational studies should report their outcomes in such a way that a meta-analysis is possible.

Conclusion

Functional and cognitive impairment, depression and social isolation are prevalent in patients with esophageal cancer, and associate with adverse health outcomes. Geriatric measurements may guide decision-making and customize treatments, but more large studies are needed to explore the clinical usability.

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5 GERIATRIC ASSESSMENT AND ONE-YEAR MORTALITY IN OLDER PATIENTS WITH CANCER IN THE HEAD AND NECK REGION, A COHORT STUDY

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ABSTRACT

Background The aim is to describe the association of functional capacity and cognitive functioning with one-year mortality in older patients with cancer in the head and neck region.

Methods We performed a cohort study in which all patients aged 70 years and older, received a geriatric screening prior to treatment. Main outcome was one-year mortality.

Results 102 patients were included. Median age was 78.7 years (IQR) 72.3-84.5), 25% were cognitive impaired, 40% were malnourished, and 28.4% used a walking device. Overall, one-year mortality was 42.3%. Male gender (HR) 4.30; 95% CI 1.35-13.67), malnutrition (HR 2.55; 95% CI 1.19-5.16) and using a walking device (HR 2.80; 95% CI 1.13-6.93) were associated with higher mortality risk, independent of stage and comorbidities.

Conclusion In older patient with head and neck cancer the mortality rates are high. Nutritional status and mobility are determinants of one-year mortality, independent of tumor stage, age and comorbidity.

INTRODUCTION

Patients diagnosed with head and neck cancer (HNC) are, in case of curative intention, generally facing major treatment options, like extensive operation and/ or (chemo)radiation therapy. Older patients in general are at higher risk for adverse health outcomes (such as delirium, complications and longer length of stay) after treatment, but the risk for HNC patients is even higher because of a high prevalence of previous excessive alcohol drinking and smoking [1-3] making this group more susceptible for cognitive [3, 4] and functional [5] decline. It could be important to make a careful selection of the patients who are suitable for the intensive treatment. In the USA it is expected that between 2010 and 2030 the incidence of oral cavity and pharyngeal cancer in patients aged 65 years and older will increase with 61% [6]. Besides, the five-year survival is poor with an estimated survival of 50% with a large variation between the different tumor localizations [7, 8]. However, limited evidence is available on the association of a geriatric assessment with adverse health outcomes and the role of assisting clinical decision-making in older patients with HNC.

Across a variety of (surgical) oncologic populations and cancer types, components of the geriatric assessment, such as cognition, functional status and social status, are predictive for adverse health outcomes such as postoperative complications, institutionalization after discharge and mortality [9, 10]. Several guidelines recommend for a form of geriatric assessments as part of routine preoperative care [11, 12]. A recent systematic review in older HNC patients showed that geriatric conditions were prevalent and in 64% of the included studies there was a statistically significant association of geriatric impairments with a higher risk of adverse outcome [13]. However, cognitive function and objectively measured physical capacity were not assessed.

The aim of this study is to describe the association in older patients with cancer in the head and neck region of geriatric measurements, including functional capacity and cognitive functioning, with one-year mortality.

METHODS

Study design and setting

We performed a retrospective cohort study (from October 2014 until January 2017) in older patients presenting with cancer in the head and neck region in the Leiden University Medical Centre (LUMC). From October 2014, a routine clinical care pathway was implemented in which all older head and neck cancer patients were referred to the department of Gerontology and Geriatrics for a geriatric screening prior to treatment. The result of this geriatric screening was discussed in the multidisciplinary team. Patients were referred when aged 70 years and older, or younger but with multiple comorbidities, diagnosed with stage III-IV HNC, or diagnosed with a lower stage HNC but needing invasive treatment, for geriatric screening prior to their invasive treatment. In this study head and neck cancer was considered as cancer in the head and neck region needing invasive treatment by the head and neck surgeon. This includes cancer in the sinonasal or oral regions, nasopharynx, oropharynx, hypopharynx, supraglottic, the larynx, the salivary glands or the proximal oesophagus. But also patients with large or regionally metastasized dermal cancer, lymphoma, an unknown primary or a recurrent tumor were referred for geriatric assessment. Thyroid cancer patients are not included in this study, because in the Netherlands thyroid cancer is not treated by a head and neck surgeon. For the retrospective collection and analysis of the data from these patients, the Medical Ethical Committee of the LUMC issued a "certificate of no objection".

Determinants

Collected demographics were age, gender, marital status and level of education. High education level was defined as university or higher vocational training and low education is defined as elementary school, community college and secondary education. The Adult Comorbidity Evaluation-27 score (ACE-27) was calculated [14]. The ACE-27 has specifically been developed for cancer patients in general. This index contains 27 different comorbidities from various organ systems. Grade 0 corresponds to no comorbidity, grade 1 to mild comorbidity, grade 2 to moderate comorbidity and grade 3 to severe comorbidity [15, 16]. Disease severity indicators consisted of tumor site, tumor stage and whether the tumor was a new primary tumor. Tumor stage was directly extracted from the medical record [17]. Geriatric measurements were the Katz Index of Independence in Activities of Daily Living (Katz ADL) [18], the Lawton Instrumental Activities of Daily Living (IADL)[19], the 6 Item Cognitive Impairment Test (6CIT) [20], the Mini Nutritional Assessment (MNA) [21] and the Identification of Seniors At Risk – Hospitalized Patients questionnaire (ISAR-HP) [22]. The Katz ADL score ranges from 0-6 and the Lawton IADL score ranges from 0-24, a higher score corresponds with more functional dependency. The 6CIT is a short cognition test [20] and has a maximum score of 28 points, in this

routine clinical care pathway, a score ≥8 is considered as abnormal, suggesting cognitive impairment. Nutritional status was assessed with the MNA questionnaire, a screening tool consisting of 6 questions to estimate the risk of malnutrition [21], a cut-off point of ≤ 11 was used to define (the risk for) malnutrition. The ISAR-HP ranges from 0-5 and is a screening tool to assess the risk for development of functional decline. A cut-off point of ≥2 points was used to define this risk [22]. Furthermore, the use of a walking device was extracted from the medical record.

Outcome

The main outcome of this study was mortality at twelve months of follow-up after start of treatment. Mortality data were extracted from the municipal records.

Statistical methods

Baseline characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as numbers with percentages (%). Different groups were compared using the t-test for continuous normally distributed data, chi-square test for categorical data and the Mann-Whitney U test for skewed data. To investigate the association between baseline characteristics and mortality a Cox regression model was used. In the multivariable model (table 2) treatment intention was not used as a determinant, to avoid overcorrection, because treatment intention is based on all the other determinants. In the multivariable analysis reported in table 3 we stratified the analysis for curative intention. Hazard ratios with 95% confidence intervals (CI) were calculated and a p-value of <0.05 was considered significant. All analyses were performed using SPSS (IBM version 23; IBM Corp., Armonk, New York, USA).

RESULTS

A total of 102 older patients with head and neck cancer were included in the present study. Table 1 shows the baseline characteristics of this population. The median age was 78.7 years (interquartile range (IQR) 72.3-84.5) and 71 patients (69.6%) were male. Mild or moderate comorbidity was observed in 71 patients (69.6%) and 25 patients (24.5%) had severe comorbidity. A minority of the patients were diagnosed with skin cancer in the head and neck region (24.5%). Most patients (n=72) had a newly diagnosed head and neck tumor (70.6%) and 62 patients (65.6%) had stage III-IV cancer. More than 25% of the patients had cognitive impairment, almost 40% had (risk for) malnutrition, more than 40% had an abnormal ISAR-HP and 28.4% of the included patients used a walking device.

Table 1. Baseline characteristics of the total study population

Characteristics	Participants, n = 102	
Patient characteristics		
Age (years), median (IQR)	78.7	(72.3-84.5)
Male gender, n (%)	71	(69.6)
Married, n (%)	55	(53.9)
Educational level, n (%)		
Low	67	(75.3)
High	22	(24.7)
ACE-27 score, n (%)		
No comorbidity	6	(5.9)
Mild comorbidity	37	(36.3)
Moderate comorbidity	34	(33.3)
Severe comorbidity	25	(24.5)
Number of drugs, median (IQR)	6	(2.3-8)
BMI, median (IQR)	24.6	(21.6-26.9)
Smoking history, n (%)	82	(83.7)
Alcohol units/week, median (IQR)	5.0	(0-14)
Disease specific		
Tumor site, n (%)		
Oral cavity	24	(23.5)
Pharynx	24	(23.5)
Larynx	9	(8.8)
Salivary gland	8	(7.8)
Skin of head and neck region	24	(24.5)
Other[1]	13	(12.7)
New primary tumor	72	(70.6)
Stage grouping, n (%)		
Stage I-II	33	(34.4)
Stage III-IV	62	(65.6)
Treatment goal, n (%)		
Curative	67	(65.7)
Palliative	35	(34.3)
Geriatric domains		
Cognitive impairment, n (%)	25	(25.3)
Functional dependent, n (%)	14	(13.7)
Dependent in IADL function, n (%)	10	(9.9)
Risk of malnutrition or malnourished, n (%)	40	(39.2)
Risk for functional decline after hospitalisation, n (%)	24	(41.4)
Use of a walking device, n (%)	29	(28.4)

Abbreviations: n=number, IQR= interquartile range, ACE-27=Adult Comorbidity Evaluation Score, MNA= Mini Nutritional Assessment, IADL = Independent Activities in Daily Living.
Data incomplete for: educational level (n=89), number of drugs (n=100), BMI (n=101), smoking history (n=98), alcohol consumption (n=97), stage of disease (n=96), 6-CIT score (n= 99), IADL score (n=101). [1] In the other group were included: unknown primary tumor, sinonasal tumor, proximal oesophagus tumors, lymphoma of head and neck and vestibular schwannoma

Figure 1 shows the cumulative survival curve of all included patients. Within one year 42.3% of the patients were deceased. Table 2 shows the risk of one-year mortality for baseline determinants for all included patients. In the univariable analysis several determinants were associated with an increased mortality; a low BMI with a hazard ratio (HR 0.89; 95% CI 0.83-0.95) compared to a higher BMI, stage III-IV (HR 4.12; 95% CI 1.61-10.60) compared to stage I-II and treatment with palliative intention (HR 5.16; 95% CI 2.74-9.72) compared to curative intention. Also (risk for) malnutrition was associated with an increased mortality (HR 3.40; 95% CI 1.83-6.33) compared to no (risk for) malnutrition and also dependency in IADL functioning (HR 1.07; 95% CI 1.02-1.12) compared with no dependency. Independent factors for a higher risk for one-year mortality were male gender (HR 4.30; 95% CI 1.35-13.67), an abnormal MNA-score (HR 2.55; 95% CI 1.19-5.16) and the use of a walking device (HR 2.80; 95% CI 1.13-6.93).

Table 2. The association between baseline characteristics and mortality after one year of follow-up of all included patients.

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.99	0.95-1.03	0.500	1.00	0.96-1.05	0.908
Male gender	1.58	0.78-3.20	0.207	4.30	1.35-13.67	**0.014**
Marital status						
Married	Ref	-	-			
Single	1.00	0.58-1.82	0.992	-	-	-
ACE-27 score						
Score 0-1	Ref	-	-	Ref	-	-
Score 2-3	1.77	0.91-3.44	0.091	1.42	0.65-3.08	0.383
Number of drugs	1.00	0.92-1.07	0.790	0.97	0.89-1.07	0.586
BMI	0.89	0.83-0.95	**0.001**	-	-	-
Stage of disease						
Stage 0-II	Ref	-	-	Ref	-	-
Stage III-IV	4.12	1.61-10.60	**0.003**	2.03	0.79-5.27	0.144
Goal of treatment						
Curative	Ref	-	-			
Palliative	5.16	2.74-9.72	**<0.001**	-	-	-
Cognitive impairment	1.73	0.91-3.29	0.094	1.76	0.61-5.07	0.294
(risk for) malnutrition	3.40	1.83-6.33	**<0.001**	2.55	1.23-5.26	**0.011**
Functional dependent	1.07	0.93-1.18	0.436	-	-	-
Dependent in IADL function	1.07	1.02-1.12	**0.010**	1.07	0.97-1.17	0.197
Use of a walking device	1.77	0.95-3.29	0.070	2.80	1.13-6.93	**0.026**

Abbreviations: HR=hazard ratio, 95% CI = 95% confidence interval, ACE-27 = Adult Comorbidity Evaluation Score, 6-CIT = 6-Item Cognitive Impairment Test, MNA= Mini Nutritional Assessment, ADL = Activities in Daily Living, IADL = Independent Activities in Daily Living. Multivariate analysis was done with complete data for 85 patients.

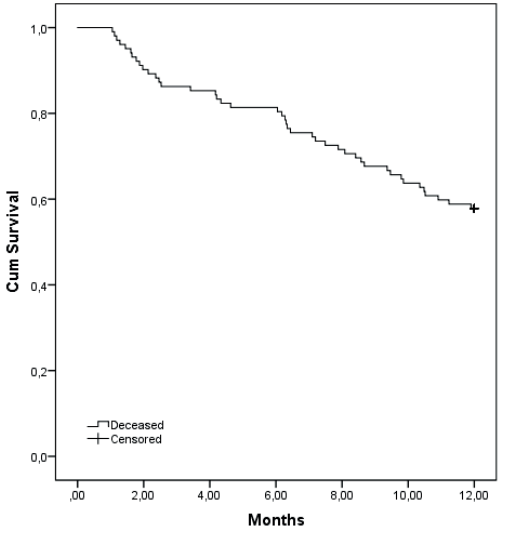

Figure 1 (left) Cumulative survival curve of the total study population

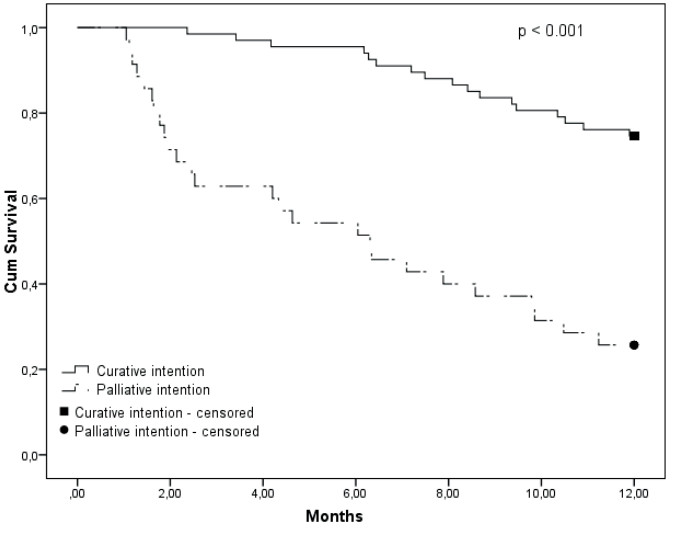

Figure 2 (right) Cumulative survival curve stratified into treatment intention

Figure 2 shows the sensitivity analysis in which we stratified the cumulative survival to treatment intention. After 12 months of follow-up 74.3% (n=26) of the patients treated with palliative intention were deceased in contrast to 25.4% (n=17) of the patients treated with curative intention. The median survival for the patients treated with palliative intention was 6.3 months. Table 3 shows the risk of one-year mortality for baseline determinants for the patients treated with curative intention. Independent factors for a higher risk for one year mortality were male gender (HR 27.64; 95% CI 1.56-490.1), (risk for) malnutrition (HR 6.81; 95% CI 1.84-25.22) compared to no (risk for) malnutrition and the use of a walking device (HR 6.93; 95% CI 1.58-30.46) compared with no use of a walking device.

Table 3. Independent determinants for one-year survival in curative treated patients

Variable	**Multivariable analysis**		
	HR	95% CI	p-value
Age	1.04	0.95-1.14	0.353
Male gender	27.64	1.56-490.1	**0.024**
ACE-27 score			
Score 0-1	Ref	-	-
Score 2-3	2.41	0.65-8.95	0.190
Number of drugs	1.00	0.86-1.16	0.990
Stage of disease			
Stage 0-II	Ref	-	-
Stage III-IV	0.77	0.19-3.02	0.703
Cognitive impairment	2.74	0.51-14.85	0.243
(risk for) malnutrition	6.81	1.84-25.22	**0.004**
Dependent in IADL functioning	1.05	0.88-1.24	0.590
Use of a walking device	6.93	1.58-30.46	**0.010**

Abbreviations: HR=hazard ratio, 95% CI = 95% confidence interval, ACE-27 = Adult Comorbidity Evaluation Score, 6-CIT = 6-Item Cognitive Impairment Test, MNA= Mini Nutritional Assessment, ADL = Activities in Daily Living, IADL = Independent Activities in Daily Living. Multivariate analysis was done with complete data for 60 patients.

DISCUSSION

The main findings of this study are that the mortality rate is high, even in the patients treated with curative intent and that (the risk for) malnutrition and mobility were determinants associated with one-year mortality, independent of tumor stage, age and comorbidity in older patients with cancer in the head and neck region.

In our study, several geriatric impairments were associated with one-year mortality, but after correcting for gender, age and disease specific determinants, only the use of a walking device was independently associated with one-year mortality. Our recently published systematic review reports that in 64% of the reported associations, a decline in functional or cognitive impairment, mood or social environment was associated with adverse outcomes [13]. Very little is known about the use and the predictive value of a geriatric assessment in HNC, because most of the studies included low patient numbers and therefore have a lack of power. In other fields of medicine a geriatric assessment is well established to guide decision-making or to identify unknown geriatric impairments (such as cognitive impairment and functional dependency), which can be taken into account before or during treatment [23, 24]. To our knowledge it is not previously reported that the use of a walking device is associated with one-year mortality.

In this cohort the one-year mortality rates are high: 42.3% overall in the included patients, but also 25% of the patients treated with curative intent are deceased within one-year. In general, the five-year survival in HNC patients is around 50% depending on tumor stage, tumor type and treatment intention [7, 8]. Treatment with curative intention can contain chemoradiation or an operation (depending the type of HNC) and followed by (chemo)radiation therapy when indicated. In patients aged 70 years and older, adding chemotherapy to radiotherapy does not contributed to higher survival rates [25, 26]. Life expectancy is obviously lower when getting older, and therefore could be taken in to account. The knowledge of the survival rates, the extensiveness of the treatment and the predictors reported in this study and in order to personalize the treatment plan for this vulnerable population, more research should be done.

We found a relative high prevalence of geriatric impairments. For example, a quarter of the included patients were cognitive impaired. Compared to the limited literature available, the proportion patient who are cognitively impaired reported in our study could potentially even be higher. Williams et al. describes 83 adults with HNC prior to treatment and reports that more than 50% were cognitively impaired [27]. The study of Bond et al. describes 70 HNC patients and reports around 47% of cognitively impaired patients [28]. So, probably the cognition test used in our study was not comprehensive enough to recognize subtle cognitive impairment. The clinical implications of cognitive impairment prior treatment are not well described in literature, but most likely negatively affects HNC patients like in other fields of oncologic medicine [29]. In these fields it is known that being cognitive impaired prior to treatment gives a higher risk for adverse health outcomes such as toxicity, not able to finish treatment, side effects and mortality [28, 30]. Besides, it is probably more difficult for patients with cognitive dysfunction to weigh the risk and benefits for cancer treatment, which impedes good shared decision

making, to comply with the treatment plan and to adequately ask for medical attention if necessary. Therefore it could be informative for the patient as well as the treating specialist to have insight in the cognitive status and to take this information into account.

There are some limitations to our study. First, the included study population was relatively small. Second, the outcome of this study was mortality, while remaining functional and cognitive independent and quality of life would be also interesting outcomes to assess. Finally, the tumor types in the present study were heterogeneous. Strengths of this study include the relatively unselected patient cohort which has as result that the included patients in this study were a reflection of the older HNC patient seen in clinical practice. All included participants underwent a comprehensive geriatric assessment. And this study complements the, until now limited, available literature.

Conclusions

In older patient with head and neck cancer the mortality rates are high. Nutritional status and mobility are determinants of one-year mortality, independent of tumor stage, age and comorbidity.

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6 PATTERNS AND DETERMINANTS OF COGNITIVE FUNCTIONING IN OLDER PATIENTS REACHING END STAGE RENAL DISEASE, THE COPE-STUDY

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Submitted

ABSTRACT

Background The prevalence of impaired cognitive functioning in older patients with end stage renal disease (ESRD) is high. We aim to describe patterns of memory, executive function or psychomotor speed and to identify nephrologic, geriatric and neuroradiologic determinants associated with cognitive impairment in older patients reaching ESRD who have not yet started with renal replacement therapy (RRT).

Methods the Cognitive Decline in Older Patients with ESRD (the COPE-study) is a prospective cohort study including 157 participants aged 65 years and older reaching ESRD (eGFR ≤20 ml/min/1.73 m^2) prior to starting with RRT. Apart from routinely collected clinical parameters related to ESRD, such as vascular disease burden and parameters of metabolic disturbance, patients received a full geriatric assessment, including extensive neuropsychological testing. In a subgroup of the patients (n=93) a brain MRI was performed.

Results The median age was 75.3 years. Compared to the normative data of neuropsychological testing participants memory performance was in the 24th percentile, executive function in the 18th percentile and psychomotor speed in the 20th percentile. Independent determinants of impairment in memory, executive and psychomotor speed were high age, low educational level and low functional status (all p-values <0.003). A history of vascular disease (p= 0.007) and more white matter hyperintensities on brain MRI (p= 0.013) were associated with a lower psychomotor speed.

Conclusion Older patients reaching ESRD have a high prevalence of impaired memory, executive function and psychomotor speed. High age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease were determinants. The patterns of cognitive impairment and brain changes on MRI are suggestive of vascular cognitive impairment.

BACKGROUND

Older patients reaching end stage renal disease (ESRD) are, compared to younger patients, at increased risk for adverse health outcomes in general [1] and for impaired cognitive functioning [2], with a high prevalence ranging from 30% to around 87% in dialysis patients [3, 4]. Cognitive impairment has a major impact on outcomes in (older) patients receiving renal replacement therapy (RTT)[5]. Understanding patterns and determinants of cognitive functioning in the phase before RTT may guide informed treatment decisions and ultimately minimize the risk for further cognitive decline.

Several pathophysiological mechanisms are suggested for the high prevalence of impaired cognitive function in patients reaching ESRD such as vascular, neurodegenerative and metabolic processes [6-8]. The brain and kidney are both low resistance end organs, exposed to high blood flow and vulnerable to vascular damage [9]. If vascular damage plays a role in developing the kidney disease, this may also affect the cerebral vasculature, leading to structural brain abnormalities and cognitive impairment, mostly in the executive domains and psychomotor speed [10]. Accumulation of uremic toxins may cause cerebral endothelial dysfunction, and lead to neurodegenerative damage in brain regions that play a dominant role in cognitive domains of attention and speed [11]. Only a few studies report on the systematic assessment of patterns of cognitive functioning and their determinants in older patients reaching ESRD with only little attention on the actual brain damage observed on brain MRI [12].

In the Cognitive decline in Older Patients with ESRD (COPE) study [13] we aimed to describe patterns of memory, executive function or psychomotor speed and to identify nephrologic, geriatric and neuroradiologic determinants associated with cognitive impairment in older patients reaching ESRD who have not yet started with renal replacement therapy (RRT).

METHODS

Study design

The full design of the COPE study, methods and rationale have been published previously [13]. In brief, the COPE study is a prospective, multicentre cohort study in four hospitals in the Netherlands in patients aged 65 years and older reaching ESRD (estimated glomerular filtration rate (eGFR) ≤ 20 ml/min/1.73 m^2), and attending the pre-dialysis outpatient between April 2014 and December 2017. As part of routine pre-dialysis nephro-geriatric work-up, a comprehensive geriatric assessment (CGA), physical examination, laboratory investigation, neuropsychological testing and a brain MRI scan (in case there was no contra-indication) were performed. The study protocol was approved by the medical ethics committee (METC) of all participating centres.

Routine renal care

Of patients attending the pre-dialysis outpatient clinic, the following clinical parameters were routinely collected: kidney function, metabolic state (urea, phosphate, calcium) and parameters on vascular status (blood pressure, ankle/arm index). eGFR was estimated glomerular filtration rate using the Modified of Diet in Renal Disease (MDRD)[14] or Chronic Kidney Disease Epidemiology Collaboration (CKD-epi)[15] depending on the method used in the different hospitals. Patients were allocated to in vascular and non-vascular cause of kidney disease according to the ERA-EDTA primary renal diagnosis code, assessed by the treating nephrologist. Vascular disease burden was determined as the cause of the kidney disease (vascular versus non-vascular), ankle-brachial index, the presence of diabetes and the history of vascular disease (previous of myocardial infarction and/or cerebral vascular incident (CVA) and/or peripheral vascular disease). We considered urea, phosphate and calcium as parameters of metabolic disturbance.

Geriatric work-up

As part of the nephro-geriatric work-up, all patients underwent a comprehensive geriatric assessment (CGA). For a more detailed description of the tests used in the COPE study, see the previously published study protocol [13]. Briefly, the CGA work-up consisted the following tests; to asses nutrition, the Normal Subjective Global Assessment (SGA) score [16] and the SNAQ score [17] were administered. To asses frailty the Fried Frailty Index (FFI) was used and a score of ≥3 was considered as frail [18]. Functional dependence was assessed by the Groningen Activity Restriction Scale (GARS), with higher scores are indicative of increased dependence (range 18-72)[19], and the The Lawton Instrumental Activity of Daily Living (IADL) score, with a score ≥11 being considered as functionally dependent [20]. Furthermore, to assess physical capacity the handgrip strength and 6-meter gait speed were measured.

Neuropsychological testing

Trained geriatric or dialysis nurses administered a standardized neuropsychological test battery. It was designed to assess different domains of cognitive functioning such as global cognition, visuoconstruction, memory, executive function and psychomotor speed. The test battery has been successfully used in several study cohorts over the past 20 years [21-23] and is based on clinical experience, scientific literature and relevance for clinical interference [21]. To test global cognition the Mini Mental State Examination (MMSE) was used, ranging from 0-30 points with higher scores indicating better cognitive performance [24]. Clock drawing was used to assess visuoconstructive abilities and executive function, with scores ranging from 0-14 points and higher scores indicating better performance [25, 26]. Memory, was tested with tested with the 15-Word Verbal Learning Test (WVLT) both immediately (total score after five trials) and delayed recall was used, higher scores indicating better function [27]. To test memory reproduction the Visual Attention Test (VAT) was used, with higher scores indicating better function [28]. Executive function assessed with visual attention and task switching were tested with the Trail Making Test A and B (TMT-A and TMT-B), with lower scores indicating better function [29]. To distinguish between processing speed or cognitive (in)flexibility as an explanation of the test result the score on the TMT-B was corrected for the score on the TMT-A. Also the Stroop Colour Word Test (SCWT) was used, with lower scores indicating better function [30-31]. To distinguish between processing speed and cognitive inhibition as an explanation of the test result the score on the Stroop III (interference card) was corrected for the score on the Stroop II (colour naming card). To test psychomotor speed the Letter Digit Substitution Test (LDST), Stroop II and TMT-A was used. For the LDST the number of correct substitutions made in 60 seconds was used, with higher scores indicating better function [32].

Normative data of neuropsychological testing

To compare the cognitive test results of the current study with a general population, Dutch normative data for neuropsychological tests corrected for age, gender and educational level were used [33]. These normative data are commonly used in the Netherlands for clinical ratings in daily practice and were available for the 15-WVLT, TMT-A, TMT-B and the SCWT. The norms were based on between 300-1000 healthy participants aged 14-90 years.

MRI of the brain

As part of routine nephrogeriatric work-up a brain MRI was performed in all patients without a contra-indication for MRI. Brain MRI scans were acquired on a Philips Ingenia 3T scanners at the LUMC (Philips Medical Systems, Best, The Netherlands) according to a standardized scanning protocol. The scanning protocol included T1-weighted images

(repetition time (TR) = 8.2ms; echo time (TE) = 4.5ms; flip angle 8°, voxel size 1x1x1mm^3), fluid-attenuated inversion recovery (FLAIR) images (TR = 4800 ms; TE = 313 ms; inversion time (TI) = 1650 ms; voxel size 1.11x1.11x1.11mm^3) and susceptibility-weighted imaging (TR=45ms; TE 31ms; flip angle 13°; voxel size 0.8x0.8x1.6mm^3). The brain MRI scans were scored for markers of small vessel disease (white matter hyperintensities) and lacunes of presumed vascular origin and microbleeds) according to the STRIVE criteria [34]. White matter hyperintensities were assessed by the Scheltens scale [35].

Statistical methods

Baseline characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as number (n) with percentages (%). Mean functioning on the different cognitive domains (memory, executive function and psychomotor speed) are presented as percentiles (mean with IQR), according to the *normative data neuropsychological testing* (see above). To assess determinants of cognitive functioning in different domains, different cognitive tests are stratified in tertiles and mean scores of the different determinants are calculated over the tertiles of cognitive functioning, presented as mean (standard error (SE)). Crude and adjusted p-values were calculated with univariable and multivariable linear regression models, respectively, with the continuous score of cognitive performance as dependent variable. In multivariable model we adjusted for age, gender, educational level, in order to make a balanced comparison between the tertiles. The MRI abnormalities were also assessed as determinant of cognitive function. The p-values are presented crude and adjusted (again for age, gender and educational level). All analyses were carried out using SPSS (IBM version 23; IBM Corp., Armonk, New York, USA).

RESULTS

Table 1 shows the baseline characteristics of the study population. The study population consisted of 157 participants with a median age of 75 years and 103 (66%) participants were male. At study enrolment, the mean eGFR was 16.2 ml/min (standard deviation (SD) 4.4) and over the past three years the mean decline in eGFR was 9.1 ml/min (SD 8.0). In 99 (63%) patients a vascular cause, mainly hypertension or diabetes mellitus, was the origin of their primary kidney disease. Almost half of the participants (n=74; 47%) had a history of vascular disease. According to the Fried Frailty Index (FFI) 37 (25%) patients were frail. Functional dependence, according to an Instrumental Activities of Daily Living (IADL) score of ≥11, was present in 8 (5%) of the patients.

Table 1. Baseline characteristics of the included study population

Patient characteristics	
Total	157
Age, median (IQR)	75.3 (70.8-80.8)
Male gender, n (%)	103 (65.6)
Caucasian origin, n (%)	138 (89.0)
Married/living together, n (%)	94 (61.4)
Higher Educational level, n (%)	48 (30.6)
Current smoking	23 (15.0)
Alcohol consumption	77 (50.3)
Disease specific	
eGFR at study enrolment, mean (SD)	16.2 (4.4)
Δ eGFR (ml/min), mean (SD)*	9.1 (8.0)
Primairy kidney disease	
Non-vascular cause, n (%)	56 (35.7)
Vascular cause, n (%)	99 (63.1)
Diabetes mellitus, n (%)	63 (40.1)
(history of) malignancy, n (%)	47 (29.9)
History of vascular disease, (n%)	74 (47.4)
Ankle-brachial index (right), mean (SD)	0.96 (0.23)
Medication use	
Polypharmacy (the use of ≥5 medications), n (%)	139 (89.7)
Glucose lowering medication, n (%)	54 (34.4)
Antihypertensive medication, n (%)	145 (92.4)
Diuretics, n (%)	94 (60.3)
Cholesterol lowering drugs, n (%)	112 (71.3)
Vitamin D supplement, n (%)	131 (83.4)
Nutrition status	
Normal Subjective Global Assessment (SGA) score	42 (49.4)
SNAQ score	
Malnourished	8 (10.7)
Risk for malnutrition	9 (12.0)
BMI, median (IQR)	27.4 (24.6-30.9)
Special diet, n (%)	127 (83.0)
Geriatric assessment	
Frail according to FFI, n (%)	37 (24.5)
Functional dependence by GARS-score, mean (IQR)	26 (20.0-35.0)
Dependent in IADL function, n (%)	8 (5.0)
Handgrip strength (kg), mean (SD)	
Females	17.2 (6.3)
Males	29.4 (8.1)
Walking speed, mean (SD) (m/s)	1.13 (0.98)

*Δ eGFR= difference between eGFR three years before and at study enrolment. Abbreviations: IQR= interquartile range, eGFR= Estimated glomerular filtration rate, SNAQ= Short Nutritional Assessment Questionnaire, BMI= body mass index, FFI= Fried Frailty Index, GARS-score= Groningen Activity Restriction Score, IADL= Instrumental Activities of Daily Living. Data complete for; race (n=155), level of education (n=153), marital status (n=153), smoking and alcohol consumption (n=153), eGFR (n=151), primary kidney disease unknown=2, polypharmacy (n=155), diet (n=153), SGA-score (n=85), SNAQ=score (n=75), Fried Frailty Index (n=141), Handgrip strength (n=152), walking speed (n=145).

Supplemental table 1 reports the performance on the global cognitive function and different cognitive domains. The population had a median Mini-Mental State Examination (MMSE) of 28 out of 30 points (IQR 27-29). Mean functioning on the memory test (15-Word Verbal Learning Test (15-WVLT)) was in the 24th percentile (IQR 10-54) with a mean score of 31.2 words remembered (SD 9.9). The mean functioning on the executive function (Trail Making Test B (TMT-B)) was in the 18th percentile (IQR 3-54) with a mean score 177.4 seconds (SD 79.5). The mean functioning on psychomotor speed (Letter Digit Substitution Test (LDST) was in the 20th percentile (IQR 10-50) with a mean score of 21.7 correct substitutions (SD 6.9).

Table 2 and 3 and in supplemental table 2 we report the determinants of three different cognitive domains, namely memory, executive function and psychomotor speed, respectively. In all three cognitive domains, as expected, older age and lower level of education were significantly associated with cognitive impairment (all p-values ≤0.007). For example, the patients who performed in the worst tertile in memory function, compared to the best tertile, were on average 5 years older (p<0.001) and had a higher chance of having received a lower educational level (for memory function: 20% versus 33%, p=0.001).

Table 2 shows the determinants of the memory domain. After adjusting for age, gender and educational level a higher level of functional dependence (IADL-score) was significantly associated with a more impaired memory function (p=0.003). Patients who performed in the worst tertile of memory function were more functionally dependent compared to the patients who performed in the best tertile (mean IADL-score of 4.6 (SE 0.6) versus a mean IADL-score 2.0 (SE 0.4); p<0.003). Having a history of vascular disease associated with a more impaired memory function, although the association lost statistical significance after adjustment for age, gender and educational level. Parameters of metabolic disturbance were not associated with an impaired memory function.

Table 3 presents the determinants of the cognitive domain of executive function. After adjusting for age, gender and educational level, a higher level of functional dependence (p<0.001), the presence of frailty (p=0.001) and a lower handgrip strength (p=0.020) were significantly associated with a more impaired executive functioning. For example, in the tertile with the worst executive function, the presence of frailty was higher compared to the best tertile (mean Fried Frailty Index of 2.1 (SE 0.2) versus a mean Fried Frailty Index 1.0 (SE 0.2); p=0.001). Having a history of vascular disease associated with an impaired executive function, although the association lost statistical significance after adjustment for age, gender and educational level. Parameters of metabolic disturbance were not associated with an impaired executive function.

Table 2. Determinants of memory function

	Memory function			p-value	
	Best tertile N=51	**Middle tertile N=54**	**Worst tertile N=50**	**crude**	**adjusted**
Age, mean (SE)	73.8 (0.9)	75.8 (0.9)	78.7 (0.9)	<0.001	<0.001*
Gender, n (%)				0.032	0.003*
Female	19 (37.3%)	21 (38.9%)	13 (26%)		
Male	32 (63.7%)	33 (61.1%)	37 (74%)		
Higher educational level, n (%)	17 (33.3%)	20 (37.0%)	10 (20.0%)	0.003	0.001*
eGFR, mean (SE)	16.4 (0.7)	16.1 (0.6)	16.2 (0.6)	0.922	0.664
ΔeGFR, mean (SE)	10.1 (1.7)	8.3 (1.0)	9.1 (1.0)	0.598	0.779
Urea, mean (SE)	20.4 (0.8)	20.9 (0.9)	21.7 (0.8)	0.904	0.582
Phosphate, mean (SE)	1.3 (0.04)	1.3 (0.03)	1.3 (0.04)	0.258	0.527
Calcium, mean (SE)	2.3 (0.02)	2.4 (0.02)	2.3 (0.02)	0.401	0.547
Vascular vs non-vascular cause, n (%)				0.946	0.884
Vascular	28 (56.0%)	39 (72.2%)	31 (63.2%)		
Non-vascular	22 (44.0%)	15 (27.7%)	18 (36.7%		
Ankle-Brachial index (right), mean (SE)	0.98 (0.03)	0.90 (0.04)	0.99 (0.04)	0.526	0.572
Presence of diabetes, n (%)	18 (35.3%)	24 (44.4%)	21 (42.0%)	0.195	0.286
History of vascular disease, n (%)	19 (37.3%)	26 (48.1%)	28 (56%)	0.004	0.163
Polypharmacy (≥5), n (%)	43 (84.2%)	51 (94.4)	44 (88%)	0.622	0.512
Fried Frailty Index, mean (SE)	1.3 (0.2)	1.6 (0.2)	1.9 (0.2)	0.055	0.082
IADL, mean (SE)	2.0 (0.4)	3.2 (0.5)	4.6 (0.6)	<0.001	0.003
Walking speed, mean (SE)	1.2 (0.05)	1.0 (0.04)	1.2 (0.25)	0.795	0.545
Handgrip strength, mean (SE)	25.5 (1.4)	24.4 (1.3)	26.1 (1.4)	0.527	0.529

Memory tested by the 15-WVLT. Tertiles of the 15-WVLT: best tertile mean 42.6 (SD 6.3) n=51; middle tertile mean 29.7 (SD 2.8) n=54; worst tertile mean 21 (SD 3.9) n=50
Δ EGFR available for n=41, n=48, n=39. Ankle-Brachial index available for n=35, n=37, n=39. Walking speed available for n=46, n=50, n=47. Model I: linear regression including correction for age, gender and educational level. *In model I age is only adjusted for gender and educational level;
gender is only adjusted for age and educational level; educational level is only adjusted for age and gender.

Table 3. Determinants of executive function

	Executive function			p-value	
	Best tertile N=51	**Middle tertile N=52**	**Worst tertile N=52**	**crude**	**model I**
Age, mean (SE)	72.9 (0.8)	76.3 (0.9)	78.9 (0.9)	<0.001	<0.001*
Gender, n (%)				0.418	0.858*
Female	18 (35.3%)	14 (26.9%)	22 (42.3%)		
Male	33 (64.7%)	38 (73.1%)	30 (57.7%)		
Higher educational level, n (%)	20 (39.2%)	16 (30.8%)	11 (21.2%)	0.003	0.007*
eGFR, mean (SE)	15.6 (0.6)	16.5 (0.6)	16.5 (0.7)	0.246	0.177
ΔeGFR, mean (SE)	10.3 (1.5)	8.0 (1.1)	8.9 (1.1)	0.567	0.962
Urea, mean (SE)	21.1 (0.8)	21.9 (0.9)	19.7 (0.8)	0.100	0.053
Phosphate, mean (SE)	1.4 (0.04)	1.3 (0.03)	1.2 (0.04)	0.064	0.160
Calcium, mean (SE)	2.4 (0.02)	2.3 (0.02)	2.4 (0.02)	0.425	0.299
Vascular vs non-vascular cause, n (%)				0.574	0.566
Vascular	32 (64.0%)	35 (67.3%)	30 (58.8%)		
Non-vascular	18 (36.0%)	17 (32.7%)	21 (41.2%)		
Ankle-Brachial index (right), mean (SE)	0.99 (0.03)	0.89 (0.04)	1.02 (0.04)	0.500	0.303
Presence of diabetes, n (%)	21 (41.2%)	17 (32.7%)	25 (48.0%)	0.199	0.157
History of vascular disease, n (%)	16 (31.4%)	28 (53.8%)	28 (53.8%)	0.012	0.089
Polypharmacy (≥5), n (%)	44 (88.0%)	47 (90.4%)	46 (90.2%)	0.899	0.696
Fried Frailty Index, mean (SE)	1.0 (0.2)	1.7 (0.2)	2.1 (0.2)	<0.001	0.001
IADL, mean (SE)	1.6 (0.3)	2.7 (0.4)	5.0 (0.6)	<0.001	<0.001
Walking speed, mean (SE)	1.2 (0.05)	1.3 (0.2))	0.9 (0.04)	0.089	0.101
Handgrip strength, mean (SE)	27.5 (1.5)	25.9 (1.3)	22.6 (1.2)	0.003	0.020

Executive function assessed by the TMT-B. Tertiles of the TMT-B: best tertile mean 99.5 (SD 21.8) n=51; middle tertile mean 162.8 (SD 21.3) n=52; worst tertile mean 262.2 (SD 37.1) n=52. Δ EGFR available for n=42, n=43, n=43. Ankle-Brachial index available for n=38, n=42, n=31. Walking speed available for n=51, n=47, n=46.Model I: linear regression including adjustment for age, gender and educational level.

*In model I age is only adjusted for gender and educational level; gender is only adjusted for age and educational level; educational level is only adjusted for age and gender.

Supplemental table 2 shows the determinants on the cognitive domain of psychomotor speed. After adjusting for age, gender and educational level, a higher presence of frailty (p=0.001), a higher level of functional dependence (p<0.001) and a lower handgrip strength (p=0.026) were significantly associated with impaired performance on psychomotor speed. For example, the patients who performed in the worst tertile of psychomotor speed had a lower handgrip strength compared to the patients who performed in the best tertile (mean handgrip strength of 24.9 (SE 1.3) versus a mean handgrip strength 26.8 (SE 1.4); p=0.026). After adjusting for age, gender and educational level, having a history of vascular disease was associated with an impaired performance on psychomotor speed (p=0.007). Again, parameters of metabolic disturbance were not associated with an impaired performance psychomotor speed.

The cerebrovascular MRI features in a subpopulation (n=93) are presented in Supplemental table 3. The mean Scheltens score of the white matter hyperintensities was 15.8 (SD 7.6). Lobar microbleeds were present in 37 (40%) of the included participants and 19 (20%) participants had non-lobar microbleeds. Lacunes of presumed vascular origin were present in 44 (48%) participants. Table 4 shows which brain MRI abnormalities are determinants of the different neuropsychological domains memory, executive function and psychomotor speed. When adjusting for age, gender and educational level, only a higher burden of white matter hyperintensities was significantly associated with worse psychomotor speed. Patients who performed in the worst tertile of psychomotor speed on average had more white matter hyperintensities compared to patients who performed in the best tertile (mean white matter hyperintensities of 18.6 (SE 1.6) versus a mean white matter hyperintensities 14.6 (SE 1.2); p=0.013). A trend was observed for the association between a higher burden of white matter hyperintensities and lower executive function scores (p=0.054).

Table 4. Association between brain MRI features with domains of cognitive function

MRI features	Best tertile	Middle tertile	Worst tertile	p-value (crude)	p-value (adjusted)¥
			Memory		
Presence of microbleeds, n (%)					
Lobar	12 (38.7%)	16 (50%)	9 (31.0%)	0.548	0.287
Non-lobar	9 (29%)	4(12.5%)	6 (20.7%)	0.209	0.048
Presence of lacunes *, n (%)	12 (38.7%)	16 (50%)	15 (51.7%)	0.279	0.635
Total white matter hyperintensities, mean (SE)	14.0 (1.2)	14.9 (1.2)	18.6 (1.7)	0.058	0.096
			Executive function		
Presence of microbleeds, n (%)					
Lobar	13 (43.3%)	11 (35.5%)	11 (36.7%)	0.821	0.683
Non-lobar	3 (10%)	8 (25.8%)	8 (26.7%)	0.229	0.744
Presence of lacunes*, n (%)	14 (46.7%)	14 (46.2%)	14 (46.7%)	0.945	0.635
Total white matter hyperintensities, mean (SE)	13.2 (1.0)	16.0 (1.4)	17.4 (1.6)	0.046	0.054
			Psychomotor speed		
Presence of microbleeds, n (%)					
Lobar	12 (40%)	12 (38.7%)	13 (46.6%)	0.633	0.871
Non-lobar	5 (16.7%)	7 (22.6%)	7 (21.9%)	0.445	0.993
Presence of lacunes*, n (%)	16 (53.3%)	12 (38.7%)	16 (50%)	0.455	0.139
Total white matter hyperintensities, mean (SE)	14.5 (1.2)	14.2 (0.99)	18.6 (1.6)	0.009	0.013

Memory function tested with the 15-WVLT: best tertile mean 43.0 (SD 5.7) n=31; middle tertile mean 31.0 (SD 2.9) n=32; worst tertile mean 21.2 (SD 4.4) n=29. Executive function assessed by the TMT-B: best tertile mean 89.9 (SD 16.3) n=30; middle tertile mean 142.8 (SD 17.7) n=32; worst tertile mean 248.8 (SD 47.2) n=30. Psychomotor speed tested by LDST: best tertile mean 30.1 (SD3 3.1) n=30; middle tertile mean 23.0 (SD 1.9) n-31; worst tertile mean 15.2 (SD 4.0) n=32. ¥linear regression analysis and adjusted for age, gender and educational level. *Both gliotic and hemorrhagic parenchymal defects in the supratentorial white matter, the brain stem and basal ganglia.

DISCUSSION

The main findings of the present study are twofold. First, impaired cognitive function is highly prevalent in patients reaching ESRD not yet started with RTT and are present in the domains of memory, executive function and psychomotor speed. Second, determinants of a worse cognitive function in the domains memory, executive and psychomotor speed were high age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease, whereas parameters of metabolic disturbance were not.

In the present study, older patients reaching ESRD performed worse on all cognitive domains tested in comparison to the general population. This is consistent with a study in younger patients at a pre-dialysis clinic in which impairments in psychomotor efficiency and processing speed were more evident than impairments in the domains of learning efficiency or attention and working memory[36]. Only one other study [37] reported on older patients with chronic kidney disease (N=385), with median creatinine clearance of 19 ml/min. This study also found deficits in all cognitive domains, with the largest deficiencies found in recall, attention and executive function. We found that determinants of a worse cognitive function in the domains memory, executive and psychomotor speed were high age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease. In different other populations with CKD, age, history of falls, functional status and a history of vascular disease were previously described determinants associated with impaired cognition [6, 37]. Literature describes that geriatric impairments, such as dependency in activities of daily living (ADLs) and cognitive impairment, are also prevalent in younger patients with ESRD [38, 39]. The association between white matter hyperintensities and an impaired cognitive function, particularly in impairment in attention, executive function and information processing speed, has also been described in older community dwelling and hospitalised patients [40-42]. In our study, parameters of metabolic disturbance (urea, phosphate, calcium) were not associated with a worse cognitive function. There were conflicting results reported on the association of metabolic determinants and the association with a worse cognitive function [11, 43]. In summary, the patterns and determinants of cognitive impairment and the neuroradiological findings in our study population are in line with the previous limited literature.

There are several possible pathophysiological mechanisms that could explain the patterns and determinants of cognitive impairment and the neuroradiological findings in the older patients with ESRD described in our study. First, it could be that ESRD and cerebral vascular damage, are endpoints of the same pathophysiological pathway.

Both the brain and kidney share similar vascular anatomy, as low resistance end organs exposed to high volume blood flow into their small vessels, and both have an autoregulatory system. Because of this unique system, small vessels in kidney and brain, both afferent arterioles and deep perforating arterioles, are particularly prone to be injured by systemic hypertension and other vascular disease [44] as well as by damage due to endothelial dysfunction. Small vessel disease can affect both kidney and the brain, white matter hyperintensities is considered as a neuroradiological marker for small vessel disease, which could explain the correlation between an impaired renal function and MRI markers of cerebral small vessel disease found in earlier studies [45]. However, extensive research on brain, perfusion and cardiac structure in older ESRD patients is scarce. Second, the high burden of vascular and metabolic morbidity in patients with ESRD lead to a higher biological age, resulting in different phenotypes such as premature vascular aging, muscle wasting, bone disease, cognitive dysfunction and frailty [39]. Taken together, the patterns of cognition and neuroradiological imaging are suggestive of vascular cognitive impairment in older patients with ESRD. Further research is needed to unravel the exact underlying pathophysiological mechanism.

Our results could have some clinical implications. When patients reach ESRD several treatment options, such as RRT including dialysis or transplantation or conservative treatment, are considered. When making treatment decisions, it can be important to have insight into the cognitive function of the patient for several reasons. First, cognitive impairment is independently associated with increased mortality, also in patients on RRT [4, 46]. Second, patients with cognitive impairment in general have a higher risk for adverse health outcomes such as delirium. Third, shared decision-making is leading in the process of decision-making when RTT is considered, and it is known that an impaired cognitive functioning can affect decision-making capacity [47].

There are several limitations of the current study. First, the study is integrated in routine clinical care and probably has some patient selection bias. It could be that the patients in worse condition were less likely to participate, which could result in an underestimation of the observed prevalence of cognitive impairment. Second, the study has a relatively small group, which could cause a lack of power. Third, the present analysis reports the cross-sectional association between several determinants and cognition as a consequence that a causal association cannot be established. Our study also has several strengths. First, to our knowledge this is the first study in which cognitive function is described so extensively in combination with brain MRI's in an older population reaching ESRD. Second, the patients included in this study all have a eGFR < 20ml/min and are not on RRT yet, a study population that previously only received limited scientific attention. Third, this study focusses exclusively on older patients (included median age of 75.3

(IQR 70.8-80.8)), while it is known that older individuals very often do not participate in clinical trials due to exclusion criteria.[48, 49] With the limited exclusion criteria applied in the COPE-study, the included study population reflects the patients in daily clinical practice.

CONCLUSION

Older patients reaching ESRD have a high prevalence of impaired memory, executive function and psychomotor speed. High age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease were determinants. The patterns of cognitive impairment and brain changes on MRI are suggestive of vascular cognitive impairment.

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Supplemental table 1. Performance on the different cognitive domains

	Score	Percentile* mean (IQR)
Global cognition		
MMSE score (points), median (IQR)	28 (27-29)	
Visuoconstruction		
Clock drawing, mean (IQR)	12 (11-13)	
Memory		
15-Word Verbal Learning Test (words remembered)		
Immediate recall score, mean (SD)	31.2 (9.9)	24 (10-54)
Delayed recall score, mean (SD)	5.8 (3.2)	22.5 (9.5-58)
Visual Association Test (pictures remembered) , median (IQR)	12 (11-12)	29.0 (20-29)×
Executive function		
TMT-B (sec), mean (SD)¥	177.4 (79.5)	18 (3-54)
TMT-B (sec) corrected for TMT-A		27 (12-58)
Stroop III (sec), mean (SD)	172.6 (79.6)	18 (5-38)
Stroop III (sec) corrected for Stroop II (sec), mean (SD)	88.9 (70.2)	46 (24-69)
Psychomotor Speed		
LDST (correct in 60 sec), mean (SD)	21.7 (6.9)	20 (10-50)
TMT-A (sec), mean (SD)	69.3 (38.5)	24 (6-56)
Stroop II (sec), mean (SD)	83 (28.9)	16 (4-31)

*Corrected for age, gender and educational level.
Abbreviations: IQR= interquartile range, 15-WVLT= 15-Word Verbal Learning Test, TMT= Trail Making Test, Stroop III= Stroop Color Word Test III, LDST= Letter Digit Substitution Test. Data incomplete for: 15-WVLT (n=155), VAT (n=155),
TMT (n=153), STROOP (n=151), Clock drawing (n=157). ¥: 16 patients did not completed the total test. They have been assigned the maximum number of 300 seconds. ×: 110 patients had the maximum score ending in ≥29th percentile.
Score not corrected for age and gender.

Supplemental table 2. Determinants of psychomotor speed

	Psychomotor speed			p-value	
	Best tertile N=51	Middle tertile N=53	Worst tertile N=52	crude	model I
Age, mean (SE)	73.9 (0.9)	75.4 (0.9)	78.9 (0.9)	0.001	<0.001*
Gender, n (%)				0.284	0.038*
Female	19 (37.3%)	21 (39.6%)	14 (26.4%)		
Male	32 (62.7%)	32 (60.4%)	39 (73.6%)		
Higher educational level, n (%)	21 (41.2%)	16 (30.2%)	11 (20.8%)	<0.001	<0.001*
eGFR, mean (SE)	16.8 (0.7)	15.4 (0.5)	16.3 (0.6)	0.319	0.217
ΔeGFR, mean (SE)	9.3 (1.3)	10.3 (1.3)	7.8 (1.1)	0.920	0.635
Urea, mean (SE)	20.1 (0.9)	21.7 (0.9)	21.2 (0.8)	0.138	0.247
Phosphate, mean (SE)	1.3 (0.03)	1.3 (0.04)	1.3 (0.03)	0.934	0.620
Calcium, mean (SE)	2.4 (0.02)	2.3 (0.02)	2.4 (0.02)	0.711	0.835
Vascular vs non-vascular cause, n (%)				0.856	0.875
Vascular	28 (54.9%)	35 (66.0%)	36 (67.9%)		
Non-vascular	22 (43.1%)	18 (34%)	16 (30.2%)		
Ankle-Brachial index (right), mean (SE)	0.95 (0.03)	0.96 (0.03)	0.98 (0.05)	0.927	0.732
Presence of diabetes, n (%)	15 (29.4%)	26 (49.0%)	22 (41.5%)	0.426	0.589
History of vascular disease, n (%)	15 (29.4%)	24 (45.3%)	35 (67.3%)	<0.001	0.007
Polypharmacy (≥5), n (%)	45 (88.2%)	46 (86.8%)	48 (90.6%)	0.413	0.918
Fried Frailty Index, mean (SE)	1.1 (0.2)	1.7 (0.2)	2.0 (0.2)	<0.001	0.001
IADL, mean (SE)	1.3 (0.3)	3.1 (0.4)	5.3 (0.6)	<0.001	<0.001
Walking speed, mean (SE)	1.2 (0.04)	1.2 (0.2)	0.9 (0.04)	0.123	0.067
Handgrip strength, mean (SE)	26.8 (1.4)	24.3 (1.3)	24.9 (1.3)	0.102	0.026

Determinants of psychomotor speed tested nu the LDTS. Tertiles of the LDST: best tertile mean 29.5 (SD 3.2) n=51; middle tertile mean 21.7 (SD 1.8) n=53; worst tertile mean 14.2 (SD 3.7) n=52. Δ EGFR available for n=45, n=43, n=42. Ankle-Brachial index available for n=33, n=41, n=38.
Walking speed available for n=46, n=48, n=51. Model I: linear regression including adjustment for age, gender and educational level. *In model I age is only adjusted for gender and educational level; gender is only adjusted for age and educational level; educational level is only adjusted for age and gender.

Supplemental Table 3. Cerebrovascular MRI features in the study population

MRI feature (n=93)	Prevalence
Presence of microbleeds, n (%)	
Lobar	37 (39.8%)
Non-lobar	19 (20.4%)
Presence of lacunes*, n (%)	44 (47.3%)
Total white matter hyperintensities (Scheltens score), mean (SD)	15.8 (7.6)

*Both gliotic and hemorrhagic parenchymal defects in the supratentorial white matter, the brain stem and basal ganglia.

Data complete for: microbleeds (lobair (n=93), non-lobair and cerebellair (n=92)), lacunes (n=93)

7 DETERMINANTS OF SELF-RATED HEALTH IN OLDER ADULTS BEFORE AND THREE MONTHS AFTER AN EMERGENCY DEPARTMENT VISIT

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ABSTRACT

Objectives Self-Rated Health (SRH) is an important Patient Reported Outcome (PRO), but little is known about SRH after a visit to the Emergency Department. We investigated the determinants of decline in SRH during three months after an ED visit in older patients.

Design This was a multi-center prospective cohort study including acutely presenting older (≥70 years) patients in the ED (the Netherlands). Patients were asked to self-rate their health between 0-10. The main outcome was a decline in SRH defined as a transition of a SRH ≥6 to a SRH <6 three months after the patient's visit to the ED.

Results Three months after the ED visit 870 patients had a stable SRH (71.4%) and 209 patients declined in SRH (11.5%). Independent predictors with a decline in SRH were: male gender (OR 1.84) living alone (OR 1.58), living in residential care or nursing home (OR 2.76), number of different medications (OR 1.08), using a walking device (OR 1.73), and the Katz-ADL score (OR 1.23). Patients with functional decline three months after an ED visit, show a steeper decline in mean SRH (0.68 points) than patients with no functional decline (0.12 points, $p<0.001$).

Conclusion Decline in SRH after an ED visit in older patients is at least partly dependent on factors of functional capacity and functional decline. Preventive interventions to maintain functional status may be the solution to maintain SRH, but more research is needed to further improve and firmly establish clinical usability of these findings.

INTRODUCTION

Older patients present to the Emergency Department (ED) more frequently than younger patients [1, 2], and often experience adverse health outcomes after an ED visit [3]. Within 3 months after an ED visit, 30% of the older patients experienced functional decline and around 10% died [4]. Besides mortality, Patient Reported Outcome (PROs) are more and more an outcome of interest in medicine [5]. PROs are measurements of health, reported by the patient, and can include physical and mental symptoms, functioning, self-rated health (SRH) and quality of life (QOL) [6, 7]. Self-rated health is a subjective assessment in which individuals rate the current status of their health. But, there are only a few reports on SRH and its determinants in older patients visiting the ED.

SRH can be simply assessed with a single question and there is widespread agreement that this single question provides useful information on how patients perceive their overall health status [8, 9]. SRH is mostly evaluated in community-dwelling older adults [10] as well in patients with cancer [11] and is associated with mortality and functional decline [10]. To our knowledge, there is only one study focussing on SRH in the older adult presenting to the emergency department [12], which reports that SRH predicts functional decline and mortality. By identifying determinants which are consequently associated with SRH, clinicians could intervene on those and therewith maintain SRH. However, it is currently unknown how SRH develops after an ED visit and which determinants are associated with a decrease in SRH in the three months after the ED visit.

In the current study, we aim to identify the determinants of SRH at presentation at the ED, to describe the change of SRH after an ED visit and to identify the determinants of a decline in SRH three months after an ED visit. We performed an analysis in a prospective study of patients aged 70 years and older presenting to the EDs of two different hospitals in the Netherlands.

METHODS

Study design and setting

We analysed the data from the Acutely Presenting Older Patient (APOP) study. The full study design and methods are published previously [4]. In short, this was a prospective follow-up study at the ED of the Leiden University Medical Center (LUMC) and Alrijne Hospital in the Netherlands performed between September to November 2014 (LUMC) and March to June 2015 (Alrijne Hospital). Patients aged 70 years and older and presenting for the first time in the study period were considered eligible. The following patients were excluded: being triaged with highest urgency (code red), patients who were not able to approach due to an unstable medical condition, when there was lack of permission of the nurse or physician to enter the room for any reason, an impaired mental status without an authorised relative to provide informed consent. Also, patients with a language barrier and patients who left the waiting room were not eligible. Written informed consent was obtained from all participants. The medical ethics committee of the LUMC waived the necessity for formal approval of the present study as it was part of the routine care.

Data collection

Completion of the questionnaire was ideally 30 to 45 minutes after arrival because by then the patients were no longer occupied, the questionnaire took 5 to 10 minutes. A representative was permitted to answer the questions when the patient was unable to provide answers, with exception for the cognition test and the self-reported quality of life questions.

Baseline

Collected demographics were age, gender, living arrangement and level of education. Living arrangement could be independent alone or with others, or living in a nursing or residential care home. High education level was defined as university or higher vocational training and low education is defined as elementary school, community college and secondary education. Disease specific includes three items: reference by ambulance, the triage category by the Manchester Triage System and chief complaint, representing the disease severity. Chief complaint was classified as minor trauma, cardiopulmonary symptoms (chest pain and dyspnea), abdominal pain, malaise, collapse and other (e.g. major trauma, psychiatric complaints and other). Geriatric measurements were the Katz Index of Independence in Activities of Daily Living (Katz ADL)[13] and the 6 Item Cognitive Impairment Test (6CIT). The Katz ADL score ranges from 0-6 and a higher score corresponds with more dependency, and gives an impression of the level of functioning two weeks prior to the ED visit. The 6CIT is a short cognition test and is validated in a

Dutch population against the Mini Mental State Examination (MMSE)[14], the 6CIT has a maximum score of 28 points and with a cut-off ≥ 11 indicating cognitive impairment (MMSE <24). In our analysis we defined an impaired cognition as an abnormal score on the 6CIT and/or a diagnosis of dementia. The number of different medications, a history of diagnosed dementia and the use of a walking aid were assessed by questioning the patient or representative.

Self-reported health related quality of life questionnaire (SRH)

To assess SRH a modified numeric rating scale was used, compared to the Cantril's Ladder, in which patients self-rate their health related quality of life. Participants were asked to score their general health during the last month excluding the reason of their visit to the ED, with zero being the worst and ten being the best imaginable situation. Three months after the ED visit, the participants were contacted by phone and asked to score their general health during the last month. At baseline only the patient was asked to give a score, but during follow-up also a proxy was allowed to give a score in case the patient was unable to provide an answer. During follow-up there were 131 (n=8.7%) proxy's providing a SRH score on behalf of the included patients.

Outcome

The main outcome was a decline in SRH defined as the transition of a sufficient SRH ≥6 at baseline to a SRH <6 three months after the visit to the ED. The reason for this distinction is that in some European countries, including the Netherlands, grading scales range from 0-10 and a 6 or higher is considered as sufficient. Secondary outcome was functional decline which was defined as an increase of one or more points in Katz ADL score or new institutionalisation defined as a higher level of living arrangement at three months after the ED visit. Three months after the ED visit the patient was contacted by telephone. In case of no response a letter with the follow-up questions was sent.

Statistical methods

Baseline characteristics are presented as mean with standard deviation (SD) in case of normal distribution, median with interquartile range (IQR) in case of skewed distribution or as numbers with percentages (%). Different groups were compared using the t-test for continuous normally distributed data, chi-square test for categorical data and the Mann-Whitney U test for skewed data. To investigate the association between baseline characteristics and a decline in SRH we used univariable and multivariable regression. Odds ratios with 95% confidence intervals (CI) were calculated and a p-value of <0.05 was considered significant. Two sensitivity analysis were performed, one in which we defined a decline in SRH as a decrease of 2 or more points three months after an ED

visit. In the other sensitivity analysis we assumed all patients with no SRH at 3 months as having a decline in SRH. All analyses were performed using SPSS (IBM, version 23).

RESULTS

During the inclusion period a total of 2192 older patients presented to one of the two ED's, 227 patients were excluded, resulting in 1965 eligible patients. Of these, 188 patients were missed for inclusion, 145 refused informed consent and from 130 there was no baseline SRH available. This led to a study population of 1502 patients (see Figure, Supplemental Digital Content 1, which demonstrates the flowchart). Figure 1 shows the different groups used in the analyses. At baseline, we divided the groups in patients with sufficient to good SRH (SRH ≥6; n=1219, 81.2%) and patients with an insufficient SRH (SRH <6; n=283, 18.8%).

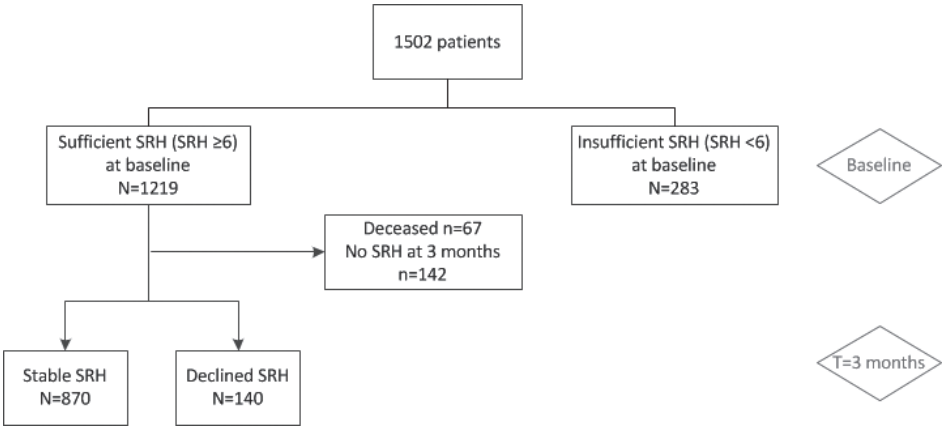

Fig 1: Flowchart of distribution of groups for analysis.
SRH: Self-rated health. Stable SRH: a SRH ≥6 after three months and a declined SRH: a SRH <6 after three months.

Table 1 shows the baseline characteristics of the study population. The median age was 79 years (interquartile range (IQR) 74-83) and 732 patients (48.7%) were male. More than half of the patients lived independently with others (n=854, 56.9%) and 545 patients (36.3%) lived alone. The median Katz ADL score at baseline was 0 (IQR 0-1) and 267 (17.8%) patients had an impaired cognition. As shown in Table 1, the patients with a sufficient to good SRH (SRH ≥6) at baseline, differed significantly from the patients with an insufficient SRH (SRH <6) at baseline. Compared to the patients with a sufficient SRH at baseline, the patients with an insufficient SRH at baseline more often had the need of hospitalisation (56.9% vs 43.2%; p<0.001), used more medication (median 5 (IQR 3-7) vs

7 (IQR 4-10); p<0.001), used a walking device more often (36.3% vs 55.5%; p< 0.001), had a higher Katz-ADL score (median 0 (IQR 0-1) vs 1 (IQR 0-2); <0.001) and more patients had an impaired cognition (16.2% vs 24.7%; p<0.001). Independent factors associated with an insufficient SRH at baseline are: age, presentation with abdominal pain or malaise, number of different medications, the use of a walking device and a higher Katz-ADL score. (see Table, Supplemental Digital Content 2; available online)

Table 1: Baseline characteristics

Patient characteristics	All patients n= 1502	Sufficient SRH ≥ 6 (n=1219)	Insufficient SRH < 6 (n= 283)	p-value
Age, median (IQR)	79 (74-83)	79 (74-83)	78 (74-83)	0.475
Male, n (%)	732 (48.7)	582 (47.7)	133 (47)	0.111
Living situation, n (%)				0.217
Alone	545 (36.3)	447 (36.7)	98 (34.6)	
Independently with others	854 (56.9)	695 (57)	159 (56.2)	
Living in residential care home or nursing home	103 (6.9)	77 (6.3)	26 (9.2)	
Educational level				0.607
Low	1198 (79.8)	969 (79.5)	229 (80.9)	
High	303 (20.2)	249 (20.4)	54 (19.1)	
Disease specific				
Triage category, n (%)				0.013
> 1 hour (green)	482 (32.1)	412 (33.8)	70 (24.7)	
< 1 hour (yellow)	784 (52.2)	619 (50.8)	165 (58.3)	
< 10 min (orange)	236 (15.7)	188 (15.4)	48 (17)	
Arrival by ambulance, n (%)	750 (49.9)	603 (49.5)	147 (51.9)	0.453
The need of hospitalisation, n (%)	688 (45.8)	527 (43.2)	161 (56.9)	<0.001
Chief complaint, n (%)				0.001
Minor trauma	415 (27.6)	360 (29.5)	55 (19.4)	
Cardiopulmonary symptoms	453 (30.2)	366 (30)	87 (30.7)	
Abdominal pain	168 (11.1)	121 (10)	47 (16.6)	
Malaise	279 (18.6)	217 (17.8)	62 (22)	
Collapse	84 (5.6)	73 (6)	11 (3.9)	
Other	103 (6.9)	82 (6.7)	21 (7.4)	
Geriatric measurements				
Number of different medications, median (IQR)	5 (3-8)	5 (3-7)	7 (4-10)	<0.001
Using a walking device, n (%)	599 (39.9)	442 (36.3)	157 (55.5)	<0.001
Katz-ADL, median (IQR)	0 (0-1)	0 (0-1)	1 (0-2)	<0.001
Impaired cognition, n (%)*	267 (17.8)	197 (16.2)	70 (24.7)	<0.001

Abbreviations: IQR=interquartile range, n=number

Data incomplete for: educational level (n=1501), the use of a walking device (n=1497), Katz ADL (n=1480), abnormal cognition (n=1442).

* An impaired cognition is considered as an abnormal 6CIT score (≥ 11) or a diagnosis of dementia.

As shown in Figure 1, three months after follow-up 870 patients had a stable SRH (71.4%), 140 patients declined in their SRH (11.5%), 67 patients died (5.5%) and in 142 patients there was no follow-up SRH available (11.6%). Patients who were not able to provide a SRH at three months were older, more institutionalized, use a walking device more often, have a higher Katz ADL score and have more often an impaired cognition (see Table, Supplemental Digital Content 3; available online). Table 2 shows the association between baseline characteristics and a declined SRH three months after an ED visit in a multivariable analysis. As shown in Supplemental Digital Content 3 the patients who

Table 2: The association between baseline characteristics and a declined SRH <6 three months after a ED-visit.

Variables	**Multivariable analysis**		
	OR	**95% CI**	**p-value**
Age (per 5 years)	1.04	0.87-1.25	0.642
Male gender	1.83	1.18-2.84	0.007
Living situation			
Independently with others	ref		
Alone	1.56	1.00-2.45	0.050
Living in residential care or nursing home	2.75	1.21-6.28	0.016
Educational level			
High	ref		
Low	0.91	0.56-1.49	0.717
Triage category			
> 1 hour (green)	ref		
< 1 hour (yellow)	1.30	0.82-2.09	0.267
< 10 min (orange)	1.49	0.81-2.77	0.204
Arrival with ambulance	0.98	0.64-1.53	0.954
The need of hospitalisation	1.14	0.75-1.72	0.530
Chief complaint, n (%)			
Minor	ref		
Cardiopulmonary symptoms	1.41	0.82-2.41	0.215
Abdominal pain	1.49	0.74-3.03	0.266
Malaise	0.69	0.35-1.40	0.307
Collapse	1.60	0.72-3.54	0.246
Other	1.59	0.73-3.46	0.244
Number of different medications	1.08	1.03-1.13	0.003
Using a walking device	1.70	1.04-2.80	0.035
Katz-ADL	1.22	1.02-1.47	0.034
Impaired cognition, n (%)*	0.67	0.37-1.22	0.187

Abbreviations: IQR=interquartile range, n=number. The multivariable analysis was done with complete data for 964 patients, 255 were missing. * An impaired cognition is considered as an abnormal 6CIT score (≥ 11) or a diagnosis of dementia.

declined in SRH and the patients who had a stable SRH three months after the ED visit differed from each other at baseline in several respects. They had a higher age, lived in residential care or a nursing home, a higher triage category, presentation with a collapse, a higher number of medications and using a walking device. Also higher Katz-ADL scores were associated with a declined SRH after three months. All single items of the Katz ADL score were significantly associated with a decline in SRH three months after a ED-visit. The OR of these single items were between 1.57 (the use of incontinence material) and 4.25 (needing help with transfers). In the multivariable model, the independent factors associated with a decline in SHR were: male gender (OR 1.84, 95 % CI 1.19-2.85), living alone (OR 1.58. 95 % CI 1.01-2.47), living in residential care or a nursing home (OR 2.76, 95 % CI 1.21-6.27), number of different medications (OR 1.08, 95 % CI 1.03-1.13), using a walking device (OR 1.72, 95 % CI 1.05-2.82) and the Katz-ADL score (OR 1.23, 95 % CI 1.02-1.48).

Figure 2 shows the difference in mean SRH at baseline and after three months in patients with functional decline (n=216, 18.3%) and no functional decline (n=963, 81.7%) three months after an ED visit. Patients who experienced functional decline during three months after an ED visit, show a steeper decline in mean SRH by 0.68 (SD 2.02) compared to patients who did not experienced functional decline 0.12 (SD 1.61), p< 0.001.

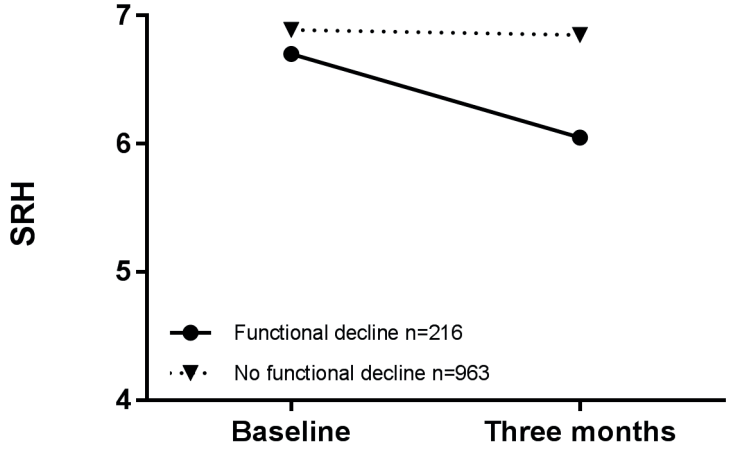

Fig 2: Difference in mean Self-Rated Health (SRH) on baseline and after three months in two groups: patients with functional decline and no functional decline after an ED visit.

We performed a sensitivity analysis in which we defined a decline in SRH as a decrease of 2 or more points three months after an ED visit. The univariable analysis shows that a higher age, living in residential care or a nursing home and Katz-ADL scores were significant associated with a declined SRH with two or more points after three months.

However, none of the determinants were independent factors associated with a decline in SHR with two of more points after three months (see Table, Supplemental Digital Content 4; available online). When assuming that the patients who were not able to provide a SRH at three months would have a decline in SRH, living situation, number of different medications, using a walking device and Katz-ADL remain independently associated with a decline in SRH at three months (see Table, Supplemental Digital Content 5; available online).

DISCUSSION

This prospective study has three main findings. First, determinants of insufficient SRH at presentation at the ED were number of medications, using a walking device, Katz-ADL score and 6CIT-score. Second, predictors of decline to an insufficient SRH during three months were male gender, living situation and number of medications. Third, the patients with functional decline show a steeper decline in SRH three months after follow-up.

Our results are in line with previous literature. Wong et al., described 741 patients aged 75 years and older attending the ED, made a comparison with the baseline characteristics and the different groups of SRH (poor, fair, good, very good and excellent), showing that those who rated their health fair/poor at baseline had a lower ADL and cognitive functioning than those rating their health excellent [12]. Furthermore, Chin et al. described 983 patients aged 65 years and older, and reports that deficiencies in activities of daily living at baseline, reports of needing more help with everyday tasks, increasing Charlson Comorbidity Index Score and requiring a proxy for the initial survey are predictors of poor recovery of Health-Related Quality of Life after an ED visit [15]. The relationship between SRH and a decline in functional status is already shown in community dwelling older adults [16], in older adults presenting at the emergency department [12] and in medical outpatients [17].

Our study shows that patients with a SRH <6 on baseline were significantly different than the patients with a SRH ≥6 at baseline. Patients with a SRH <6 were more dependent in the daily activities, had a higher 6CIT-score and had a higher number of medication. It is imaginable that, when experiencing impairments on multiple domains, the self-rated health is also low. This is also shown in Spanish institutionalized older persons in which chronic conditions, functional status, depressive symptoms and socioeconomic factors were the main determinants of self-perceived health [18]. We also show that three months after an emergency department visit, patients with a sufficient to good

SRH and patients with an insufficient SRH are significantly different with regard number of medication, reflecting multiple chronic conditions, and geriatric conditions. In the univariable analysis all the geriatric conditions had a significant association with a decline in SRH, and in the multivariable analysis only gender, living in a nursing home or residential care home and number of different medications were significantly associated with a decline in SRH. We also showed that not the baseline determinants, but a decline in functional status is associated with a decline in SRH after three months. This is not surprising, since a decline in functional status is usually a reflection of the severity of the disease. This is also described in literature that each chronic condition had a significant independent effect in a poor SRH and poor QOL [19].

There is a growing interest in quality of life as an outcome in older patients and also to maintain quality of life as long as possible. Besides, several literature describes that older adults give more importance to quality of live than length of life [20, 21]. Our study reports the determinants of an insufficient SRH three months after the ED visit. Future research should be focused on ways to intervene on maintaining SRH after an ED visit. Recently, a prediction tool was developed for older emergency patients and is usable to predict functional decline after an ED visit [4]. When a physician is able to predict functional decline, which goes hand in hand with a decline in SRH as our results show, physicians should also be able to use preventive interventions and maintain functional status and SRH. However, more research is needed to implement this tool and prove its use in maintaining functional status and hopefully therewith also SRH.

There are some limitations to our study. First, this study used a modified numeric rating scale to assess SRH. Ideally we would have used a more comprehensive assessment for SRH, for example the EQ-5D exploring five different dimensions (mobility, self-care, usual activities, pain and anxiety/depression)[22]. Also other aspects, such as depression, which is also strongly linked to SRH in different studies [23, 24]have not been investigated in our study. However, the limited time at the ED restricts the extent to which health status can be assessed. Second, during follow-up the proxies were allowed to grade the SRH of the patient, which could have made the answer less reliable. However, when excluding the SRH giving by a proxy, the overall results did not change, implying that the results would not have been different if all patients would have answered the questions themselves. In this study the Charlson Comorbidity Index (CCI) is not available for most of the patients, as a reflection of comorbidity the number of different medications is used. The major strength is the unselected representative study population presenting at the emergency department. A second strength is the fact that demographics, severity of disease and geriatric vulnerability of the patient were taken into account as a

reflection of the condition of the patient. And finally, this is the first study reporting on determinants associating with a decline in SRH three months after an emergency visit.

CONCLUSION

In conclusion, decline in SRH after an ED visit in older patients is at least partly dependent on factors of functional capacity and functional decline. Preventive interventions to maintain functional status may be the solution to maintain SRH, but more research is needed to further improve and firmly establish clinical usability of these findings.

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8 GENERAL DISCUSSION

KEY FINDINGS

This thesis has three key findings. First, only a small proportion of the randomized controlled trials (RCTs) specifically included older adults, and the geriatric characteristics in these RCTs are underreported. Second, we show that geriatric impairments, such as cognitive impairment and functional dependency, are prevalent, and associate with adverse health outcomes in older patients with head and neck cancer and in patients with esophageal cancer. Third, self-rated health is partly dependent on factors of functional capacity and functional decline. This chapter reviews these key findings, discusses the implications for research and for clinical practice, and provides perspectives for future research.

IMPLICATIONS FOR RESEARCH

Increasing the number of representative older adults in research

In **chapter 2** we report that only a small proportion of the published RCTs targeted older adults. RCTs and meta-analyses are generally considered to provide the highest 'level of evidence', and the results of these RCTs or meta-analyses are used to compose clinical guidelines. Since older adults are underrepresented in these trials and the included participants are often not representative for the older adults seen in clinical practice, it is questionable whether these clinical guidelines are applicable for older adults. Because of the ageing population and the increasing prevalence of multiple (chronic) diseases at higher age [1], there will be a need of improving the scientific evidence in older adults. To achieve this, several steps should be taken.

Researchers should start to systematically report the geriatric characteristics of older patients in all RCTs. In **chapter 2** we show that geriatric characteristics are underreported, even in the RCTs specifically designed for older adults. Consequently, this results in a low external validity; i.e. it is unclear to which older adults the results can be applied. Since older patients are very heterogeneous with respect to for example, cognitive functioning and/or physical capacity, extrapolating research outcomes based on chronological age or disease stage alone may lead to undertreatment as well as overtreatment [2, 3]. So, when older adults are participating in research, in my opinion, geriatric characteristics should always be reported. Ideally a guideline is available which includes a standard set of geriatric characteristics, and that imposes for example, that at least one aspect of each geriatric domain should be reported. There is already a guideline available addressing 'physical frailty' [4]. This could be helpful in characterising older adults in research and therewith make the participants comparable between the diverse studies.

To increase the representative number of older adults participating in RCTs, the RCTs should be conducted differently. For instance, by applying less stringent exclusion criteria or by making RCTs more accessible for older adults to participate. One suggestion could be to plan home visits, so older (vulnerable) adults are more willing to participate. There is already a guideline available on how to perform an RCT in older adults. This guideline suggests to combine research activities with routine hospital visits, to plan research visits at home or to provide telephone follow up [5]. However, these adaptions make RCTs more complex and more expensive, while resources are limited.

Other research methods, like observational studies, may be valuable alternatives to consider. Observational studies can generate a large amount of reliable data, are easily accessible and often cheaper than an RCT since randomization is unnecessary [6]. Besides, observational studies often have less exclusion criteria, and the included participants may therefore more broadly represent patients seen in daily practice [7, 8]. Furthermore, (international) databases, originally established for improving the quality of care, can also be used for research purposes. An example from the Netherlands is the Dutch Institute of Clinical Auditing (DICA), which is a registry with information on patients and disease characteristics as well as outcomes relevant for patients, such as functional performance in the period after a hip fracture. Data from these (international) databases may even be combined with local study data. For example, when studying geriatric characteristics in patients with esophageal cancer, the study data can be combined with disease and treatment specific information registered in the Netherlands Cancer Registry (NCR) database. When studying diseases in older adults, collaboration with other institutions in order to increase inclusion rates can be necessary. Major challenges in these collaborations are the standardization of clinical care and to facilitate the systematic registration and collection of data for research purposes. In the future perspectives we describe such an initiative.

The importance and the specific aspects of conducting research in older adults should firstly be recognized by researchers, clinicians, research grant providers and sponsors. This can be achieved by providing more education. One of our initiatives is the development an e-learning for medical professionals, but also accessible for non-medical professionals, about evidence-based medicine in the older patient. All the aspects described above (i.e. the importance of conducting research in older adults, the current gaps and the needs) are discussed in this e-learning, see also www.iemo.nl/elearning.

Including relevant endpoints for older adults in research

With increasing age, treatment goals are changing. Compared to younger patients, older patients give more importance to quality of life and maintaining functional dependency than to length of life [9-11]. Endpoints relevant for patients can be measured using patient reported outcome measurements (PROMs). In **chapter 7** we show that self-rated health, one example of a PROM, is partly dependent on factors as functional capacity and functional decline. Until now, PROMs are not structurally taken into account as relevant outcome in research. One reason is the lack of a "golden instrument" for measuring PROMS in older adults. It is not desirable that older adults, often suffer from multiple diseases, have to fill several overlapping disease-specific questionnaires. A solution could be one standard set of health outcome measures specific for older persons, regardless of the disease. The International Consortium for Health Outcomes Measurement (ICHOM), an international consortium with goal to increase value-based healthcare, recently developed such a standard set [12]. It is debatable if this set is usable in the Netherlands, but it can be a good starting point for further investigation of outcome measures that would be relevant for clinicians, health care policies and researchers.

IMPLICATIONS FOR CLINICAL PRACTICE

In **chapter 3, 4 and 5** we report that geriatric impairments are prevalent in patients with head and neck cancer and esophageal cancer. The finding that geriatric impairments are so prevalent stresses the importance to a more holistic approach of the patient, rather than only taking their disease into consideration. Furthermore, geriatric impairments might influence the shared decision process. For example, cognitive impairment can directly influence the patients' shared decision making capacity by limiting the amount and speed of information processing [13]. The association of geriatric impairments with adverse health outcomes is described in diverse patient groups in **chapter 3, 4 and 5.** This finding is in line with literature in other diseases where it has been described that geriatric impairments predict several health outcomes including mortality, disability and cognitive functions[14].

The discussion above endorses that geriatric characteristics are important to consider when making personalized clinical treatment decisions. However, it is remains unclear which instrument or tests to explore the geriatric characteristics are the most helpful in treatment decision making or in predicting successful outcomes relevant for older adults. It is doubtful that there will ever be one perfect instrument usable and suitable for all different diseases and settings. From this thesis it is recommended to start exploring the geriatric characteristics as part of routine clinical care instead of waiting for the 'best' assessment

without taking geriatric characteristics into account at all. Importantly, it is not necessary to administer a complete comprehensive geriatric assessment (CGA) to all patients. Several two-stepped models have been described in literature, in which all patients undergo a short simple screening, and only those with abnormal test scores undergo a complete CGA [15]. For example, the geriatric-8 (G8) has a good sensitivity for detecting geriatric impairments and for identifying the patients who will benefit most from a complete CGA [16]. Taken together, I recommend that all older patients needing an intensive treatment should undergo some geriatric screening for example by using a two-stepped model.

FUTURE PERSPECTIVES

We have described several steps that can be taken to improve evidence-based medicine and personalized treatment decision making in older adults. The 'Triage of Elderly Needing Treatment' (TENT)-study is a good example combining all the described steps. In four hospitals in the Netherlands a routine clinical care pathway is implemented for older patients (aged 70 years or older), who possibly need intensive treatment (e.g. surgery, chemotherapy or radiation therapy or a combination). These patients receive a geriatric screening and on indication a comprehensive geriatric assessment prior to the start of treatment. We designed the TENT-study based on this routine clinical care pathway. All patients are followed for complications of treatment, mortality, functional status and quality of life up to 12 months after treatment. The TENT-study has several aims. First, to describe the prevalence of geriatric impairments in diverse patient populations needing invasive treatment and to explore the association with outcomes after treatment. Second, to develop a tool which can help in making informed treatment decisions and to, ultimately, increase the rate of favourable outcomes after treatment and increase the quality of care for older patients. The TENT-study started in January 2016 in the LUMC and since July of 2018 has been extended into a multicentre study. The first results of the TENT-study are expected mid-2019.

The TENT-study exemplifies how geriatric screening can be integrated into the daily practice and how to use clinical data in a large multicentre observational study focussing on the older adult needing intensive treatment. This also demonstrates the opportunities when collaborating with other institutions, standardizing routine clinical care and combine it with research. We hope that in the future the format of the TENT-study may serve as a template for implementing standardized routine clinical care pathways for older adults needing intensive treatment. Ultimately, we hope that the evidence gathered by the TENT-study can be used to improve research and evidence-based care for older adults needing intensive treatment.

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9

ENGLISH SUMMARY

Introduction

The world's population is ageing: almost every country in the world is experiencing growth in the number older persons in their population (Eurostat Statistics 2017). With increasing age, the prevalence of disease increases, resulting in a high proportion of older adults suffering from multiple (chronic) diseases (also called multimorbidity) [1]. Higher age is accompanied with multimorbidity, ageing-associated diseases and is also associated with the presence of geriatric conditions. Examples of geriatric conditions are: a decreased ability to perform activities of daily living (or functional impairment), cognitive impairment, delirium and falls [2, 3]. A way of phenotyping older patients is the use of a geriatric assessment. A geriatric assessment is used to explore the different domains of somatic status, mental functioning, physical functioning and social functioning.

Because of the multimorbidity and the complex interaction between the different domains, clinical decision making in older patients can be challenging for clinicians, patients and caregivers. It is known that a higher age and multimorbidity are associated with many adverse health outcomes such as disability, institutionalization, poorer quality of life and higher rates of side effects after treatment [4, 5]. However, only few studies have assessed the association of a geriatric assessment with outcomes in vulnerable older patients with severe diseases, such as head and neck cancer, esophageal cancer or end-stage renal disease [5]. Especially in these vulnerable older patients with severe treatments can have major impact on outcomes such as disability and quality of life.

Aim of the thesis

This thesis has three aims. The first aim is to quantify the lack of evidence in the literature regarding the report of elements of a geriatric assessment in older adults participating in clinical trials. The second aim is to study the association between the outcome of a geriatric assessment and adverse health outcomes in older patients with various severe diseases. The third aim is to assess the determinants of a patient reported outcome measurement in an older patient population.

Summary of the key findings

In **chapter 2**, we aimed to evaluate whether it is insightful what kind of older patients participated in randomized controlled trials (RCTs). We analysed the published RTCs in 2012 and evaluated what proportion of trials, specifically designed for older patients, reported on elements of the domains of the geriatric assessment in the patient characteristics (i.e. in the population descriptives or the in- and exclusion criteria). We found

that only 34% of all trials (participants had a mean age ≥ 60 years) report elements of the domains in the patient characteristics. The percentage of reported geriatric domains increased when the age limit was higher, however, that only presented a small percentage of all included trials.

In **chapter 3 and 4** we studied the association of functional or cognitive impairment, social environment and frailty with adverse health outcomes in patients with head and neck cancer and in patients with esophageal cancer with a review of the literature. In both patient groups we showed that impairment in functional performance, depression and social environment were highly prevalent. In patients with head and neck cancer the majority of the studies reported a statistically significant association of impairment in functional and cognitive performance, mood or social environment with a higher risk of adverse outcome. In patients with esophageal cancer, functional or cognitive impairment or frailty were associated with adverse health outcomes, but the studies were relatively small.

In **chapter 5** we studied the association of geriatric assessment and one-year mortality in older patients with cancer in the head and neck region. We analysed the data of a cohort study in which all patients aged 70 years and older, diagnosed with head and neck cancer, received a geriatric assessment prior to their treatment. We showed that geriatric impairments were highly prevalent. Furthermore, we found that the mortality rate was high, even in the patient treated with a curative intention. Malnutrition and mobility were independently associated determinants with one-year mortality.

In **chapter 6** we aimed to describe in detail the patterns of cognitive functioning and identifies nephrologic, geriatric and neuroradiologic determinants associated with an impaired cognitive function in older patients reaching end-stage renal disease (ESRD) and who have not started with renal replacement therapy (yet). We analysed the data from the Cognitive decline in Older Patients with End stage renal disease (COPE) study. All patients with end-stage renal disease received a full nephro-geriatric work-up. We showed that older patients reaching ESRD have a high prevalence of impaired memory, executive function and psychomotor speed. High age, low education, low functional status, frailty, higher burden of white matter hyperintensities on MRI and a history of vascular disease were determinants. The patterns of cognitive impairment and brain changes on MRI are suggestive of vascular cognitive impairment.

In **chapter 7**, we aimed to identify the determinants associated with self-rated health in an older population visiting the Emergency Department (ED). We used the data of the Acutely Presenting Older Patients (APOP) study in which a patient reported outcome

measurement was described in older patients visiting the emergency department (ED) of the LUMC or the Alrijne Hospital. As patient reported outcome measurement we used self-rated health. We found that a decline in SRH after an ED visit in older patients is at least partly dependent on factors of functional capacity and functional decline.

DISCUSSION

As mentioned previously, only a small proportion of the randomized controlled trials (RCTs) specifically included older adults, and the geriatric characteristics in these RCTs were underreported. This finding supported our hypothesis that for clinicians it is unclear to which older patients the results can be applied. Because of the ageing population and the increasing prevalence of multiple (chronic) diseases at higher age [1], there will be a need of improving the scientific evidence in older adults. To achieve this, several steps should be taken. Researchers should start to systematically report the geriatric characteristics of older patients in all RCTs and make RCTs more accessible for older adults to participate. Furthermore, alternative research methods, like observational studies, should be considered. However, the importance and the specific aspects of conducting research in older adults should firstly be recognized by researchers, clinicians, research grant providers and sponsors.

In this thesis we describe that aspects of the geriatric assessment are associated with adverse health outcomes. This finding endorses the importance of taking geriatric characteristics into account in patients who possibly need intensive treatment (e.g. surgery, chemotherapy or radiation therapy or a combination). Importantly, it is not necessary to administer a complete geriatric assessment to all patients. A two-stepped model, in which all patients undergo a short simple screening, and only those with abnormal test scores undergo a complete geriatric assessment, is suggested[6].

An example where all the above described aspects are combined is the 'Triage of Elderly Needing Treatment' (TENT)-study. In this study all patients who possibly need intensive treatment (e.g. surgery, chemotherapy or radiation therapy or a combination), the geriatric characteristics are taken into account and all patients are followed for complications of treatment, mortality, functional status and quality of life up to 12 months after treatment.

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NEDERLANDSE SAMENVATTING

Introductie

De wereldpopulatie veroudert; bijna ieder land krijgt te maken met een toename van het aantal oudere mensen in de samenleving (Eurostat Statistics 2017). Met de toename van de leeftijd stijgt ook de prevalentie van ziekten, resulterend in een groter aandeel ouderen met meerdere (chronische) ziekten, ook wel multimorbiditeit genoemd [1]. Hogere leeftijd gaat samen met verouderingsziekten, multimorbiditeit, en is gerelateerd aan geriatrische condities. Voorbeelden van geriatrische condities zijn een verminderd fysiek functioneren, geheugenklachten, verwardheid en vallen [2, 3]. In een geriatrisch onderzoek worden verschillende domeinen (lichamelijke gezondheid, psychologisch functioneren, fysiek functioneren en sociaal functioneren) in kaart gebracht. Hiermee kan een inschatting gemaakt worden van het algeheel functioneren van de patiënt.

De aanwezigheid van multimorbiditeit en de complexe relatie tussen de domeinen, kan het maken van behandelbeslissing uitdagend maken voor artsen en patiënten. Het is al bekend dat onderdelen van het geriatrisch onderzoek voorspellend zijn voor uitkomsten zoals achteruitgang in functioneren, opname in een zorginstelling en een vermindering van kwaliteit van leven [4, 5]. Deze relatie is echter nog maar beperkt onderzocht in kwetsbare oudere patiënten met ernstige aandoeningen zoals kanker in het hoofd-hals gebied, de slokdarm of patiënten met eindstadium nierfalen [5]. Terwijl juist in deze patiëntencategorie de behandeling grote gevolgen kan hebben voor uitkomsten zoals achteruitgang in functioneren en kwaliteit van leven.

Doel van het proefschrift

Dit proefschrift heeft drie doelen. Allereerst om het gebrek aan bewijs, ten aanzien van het geriatrisch onderzoek en de relatie tot behandeluitkomsten, in de huidige literatuur te kwantificeren; ten tweede om te onderzoeken, in verschillende patiëntenpopulaties, wat de relatie is tussen het de uitkomst van het geriatrisch onderzoek en de uitkomsten na een behandeling en als derde om te exploreren wat de determinanten zijn van een patiënt gerelateerde uitkomstmaat in een oudere patiënten populatie.

Overzicht van het beschreven onderzoek

In **hoofdstuk 2** hadden we als doel om te evalueren of het inzichtelijk was wat voor oudere patiënten deelnamen aan gerandomiseerde studies. Hiervoor analyseerden we de gepubliceerde gerandomiseerde studies in 2012 en beoordeelden we of de domeinen van het geriatrisch onderzoek werden gerapporteerd in de patiëntkarakteristieken (d.w.z. in de populatiebeschrijving of in de in- en exclusiecriteria). We zagen dat er maar weinig studies speciaal op oudere deelnemers gericht waren. Daarnaast vonden we dat

slechts 34% van alle onderzoeken (waarvan de deelnemers een gemiddelde leeftijd van ≥60 jaar hadden) een domein van het geriatrisch onderzoek rapporteerde in de patiëntkarakteristieken. Dit percentage nam weliswaar toe naar mate de gemiddelde leeftijd van de studie-deelnemers naar boven toenam, maar het ging dan slechts om een heel klein percentage van alle onderzochte studies.

In **hoofdstuk 3 en 4** hebben we de relatie van het geriatrisch onderzoek met uitkomsten van behandeling in twee verschillende groepen onderzocht; in patiënten met hoofd-halskanker en in patiënten met slokdarmkanker. Dit deden we door middel van het bestuderen van de bestaande literatuur. We zagen in beide patiëntengroepen dat geriatrische afwijkingen, zoals een beperkt functioneren, somberheidsklachten en het hebben van geen partner, veel voorkomend waren. Daarnaast zagen we bij de patiënten met hoofd-halskanker in de meerderheid van de gevonden studies dat er een relatie was met afwijkingen op het geriatrisch onderzoek en slechtere uitkomsten na de behandeling. Dit vonden we ook bij de studies naar slokdarmkanker, maar de beschreven studies waren relatief klein.

In **hoofdstuk 5** onderzochten we de relatie tussen het geriatrisch onderzoek op de verschillende domeinen en de mortaliteit binnen één jaar bij oudere patiënten met hoofd-halskanker. We hebben de gegevens gebruikt van een zorgpad in het LUMC voor oudere patiënten met hoofd-halskanker. Al deze patiënten kregen een geriatrisch onderzoek voordat een eventuele behandeling werd overwogen. We toonden aan dat het sterftecijfer erg hoog was, zelfs bij de mensen die behandeld werden met de intentie tot genezing. Onafhankelijke voorspellers voor het overlijden binnen één jaar waren ondervoeding en mobiliteit.

In **hoofdstuk 6** wilden we het patroon van cognitief functioneren beschrijven en nefrologische, geriatrische en neuroradiologische factoren identificeren voor een verminderd cognitief functioneren in oudere patiënten met eindstadium nierfalen. Hiervoor zijn de prospectieve gegevens geanalyseerd van vier ziekenhuizen die deelnamen aan de “Cognitive decline in Older Patients with End stage renal disease” (COPE) studie. Hierbij kregen alle oudere patiënten met eindstadium nierfalen een uitgebreid nefrogeriatrisch onderzoek. We toonden aan dat er een verminderd cognitief functioneren aanwezig was in het geheugen, het executief functioneren en in de in denksnelheid. De sterkste voorspellers voor een verminderd cognitief functioneren waren geslacht, lager opleidingsniveau, meer afhankelijkheid in het dagelijks functioneren, witte stofafwijkingen op de MRI van het hoofd, en een voorgeschiedenis van vasculaire ziekten.

In hoofdstuk 7 onderzochten we factoren die geassocieerd zijn met zelf-gewaardeerde gezondheid na een SEH bezoek. We hebben de data van de "Acuut Presenterende Oudere Patiënt" (APOP) studie gebruikt waarin een patiëntgerichte uitkomstmaat beschreven werd in een oudere patiënten populatie die de Spoedeisende Hulp van het LUMC of het Alrijne Ziekenhuis bezochten. We zagen dat achteruitgang in de zelf-gewaardeerde gezondheid na een SEH bezoek op zijn minst gedeeltelijk te verklaren was door factoren zoals fysieke capaciteit en achteruitgang in functioneren.

DISCUSSIE

Zoals eerder beschreven zijn er maar weinig gerandomiseerde studies specifiek op ouderen deelnemers gericht, en in de gerandomiseerde studies waar oudere patiënten wel aan deelnemen is het niet inzichtelijk wat voor type ouderen dat zijn. Deze bevinding ondersteunde onze hypothese dat het voor een arts lastig is om de resultaten van gerandomiseerde studies te vertalen en toe te passen op de individuele patiënt in de spreekkamer. Omdat er meer ouderen komen met multimorbiditeit [1], is het belangrijk om het wetenschappelijke bewijs voor deze groep te vergroten. Om dit te bereiken zouden meerdere stappen genomen kunnen worden. Allereerst, om inzichtelijk te krijgen wie er aan het gerandomiseerde onderzoek deelneemt, zouden geriatrische karakteristieken altijd gerapporteerd moeten worden wanneer er oudere patiënten aan gerandomiseerde studies deelnemen. Daarnaast zouden gerandomiseerde studies toegankelijker gemaakt kunnen worden voor oudere patiënten. Tot slot zal er nagedacht moeten worden of alternatieve onderzoeksopzetten, bijvoorbeeld observationele studies, niet meer geschikt zijn om de bewijsvoering voor oudere patiënten te vergroten. Echter, het belang van het uitvoeren van onderzoek bij oudere patiënten en de specifieke aspecten moeten in de eerste plaats worden erkend door onderzoekers, artsen en subsidieverstrekkers.

Zoals hierboven beschreven zijn verschillende domeinen van het geriatrisch onderzoek geassocieerd met slechtere uitkomsten na een behandeling. Dit benadrukt de noodzaak om bij alle oudere patiënten, die een grote behandeling krijgen (operatie, chemotherapie en/ of radiotherapie), de geriatrische domeinen in kaart te brengen. Het is echter niet nodig om bij alle oudere patiënten een geheel geriatrisch onderzoek te verrichten, er kan eerst een screening plaatsvinden en alleen op indicatie een volledig geriatrisch onderzoek [6].

Een voorbeeld waarbij alle bovenstaande aspecten aan bod komen is de 'Triage of Elderly Needing Treatment' (TENT) studie. Hierbij worden in alle oudere patiënten

die een grote behandeling krijgen (operatie, chemotherapie en/ of radiotherapie), de geriatrische domeinen in kaart gebracht. Daarnaast worden ze gevolgd in de tijd voor uitkomsten als functionaliteit en kwaliteit van leven.

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LIST OF ABBREVIATIONS

6CIT	6 Item Cognitive Impairment Test
15-WVLT	15-Word Verbal Learning Test
AC	adenocarcinoma
ADL	Activities of Daily Living
BDI	Beck Depression Inventory
CGA	comprehensive geriatric assessment
CI	confidence interval
CKD-epi	Chronic Kidney Disease Epidemiology Collaboration
COPE-study	Cognitive Decline in Older Patients with ESDR study
ECOG	Eastern Cooperative Oncology Group
ED	emergency department
e-GFR	estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
ESDR	end-stage renal disease
FFI	Fried Frailty Index
GARS	Groningen Activity Restriction Scale
GDS-15	Geriatric Depression Scale 15
GDS-SF	Geriatric Depression Scale Short Form
HADS	Hospital Anxiety and Depression Scale
HNC	head and neck cancer
HR	hazard ratio
HRQoL	health related quality of life
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases
IEMO	Institute for Evidence-based Medicine in Old Age
IPAQ	International Physical Activity Questionnaire
IQR	interquartile range
KPS	Karnofsky Performance Score
LDST	Letter Digit Substitution Test
LOS	length of hospital stay
LUMC	Leiden University Medical Center
MDRD	the Modified of Diet in Renal Disease
METC	medical ethics committee
miRNA	microRNA
MMSE	Mini-Mental State Examination
NPTB	neuropsychological test battery
OR	odds ratio

PRO	patient reported outcome
QoL	quality of life
RCT	randomized controlled trial
SCWT	Stroop Color Word Test
SGA	Subjective Global Assessment
SRH	self-rated health
RRT	renal replacement therapy
RR	relative risk
SCC	squamous cell carcinoma
SD	standard deviation
SPS	Social Provision Scale
TMT-A/B	Trail Making Test A/B
TUGT	Timed Up to Go Test
VAT	Visual Attention Test
WHO	World Health Organization
WMH	white matter hyperintensities

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CURRICULUM VITAE

Floor Johanna Adriana van Deudekom is geboren op 20 juni 1985 in Veldhoven. Ze behaalde haar atheneum diploma in 2003 aan het Van Maerlant Lyceum te Eindhoven. Nadat ze haar diploma behaalde, heeft ze een jaar Gezondheidswetenschappen gestudeerd aan de Vrije Universiteit in Amsterdam, waarna ze in 2004 werd ingeloot voor de studie Geneeskunde aan het VU Medisch Centrum Amsterdam. Gedurende haar wetenschapsstage op de afdeling geriatrie in het toenmalige MC Slotervaart, raakte zij geïnteresseerd in de oudere patiënt. Nadat zij haar artsenbul ontving, is zij gaan werken als arts-niet in opleiding bij de Interne Geneeskunde in het Spaarne Gasthuis in Haarlem (2011-2012) en later als arts-niet in opleiding bij de Klinische Geriatrie in het Westfriesgasthuis in Hoorn (2012). Per januari 2013 startte zij de opleiding tot Klinisch Geriater vanuit het toenmalige MC Slotervaart (huidig in OLVG; opleider drs. I.M.J.A. Kuper), die werd aangevangen met de vooropleiding Interne Geneeskunde in het Spaarne Gasthuis te Haarlem (opleiders prof. dr. R.W. ten Kate en dr. W. de Ronde). Van januari-maart 2015 heeft zij haar opleiding tot Klinisch Geriater gecontinueerd, tot zij besloot om haar opleiding tijdelijk te onderbreken om een promotietraject te starten. Dit promotietraject vond plaats op de afdeling Ouderengeneeskunde van het Leids Universitair Medisch Centrum onder leiding van prof. dr. G.J. Blauw en dr. S.P. Mooijaart. Per 1 maart 2019 heeft zij de opleiding hervat in het OLVG, locatie West.

Floor is getrouwd met Maarten en samen hebben zij een zoon Mink (2015) en dochter Maud (2018).

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