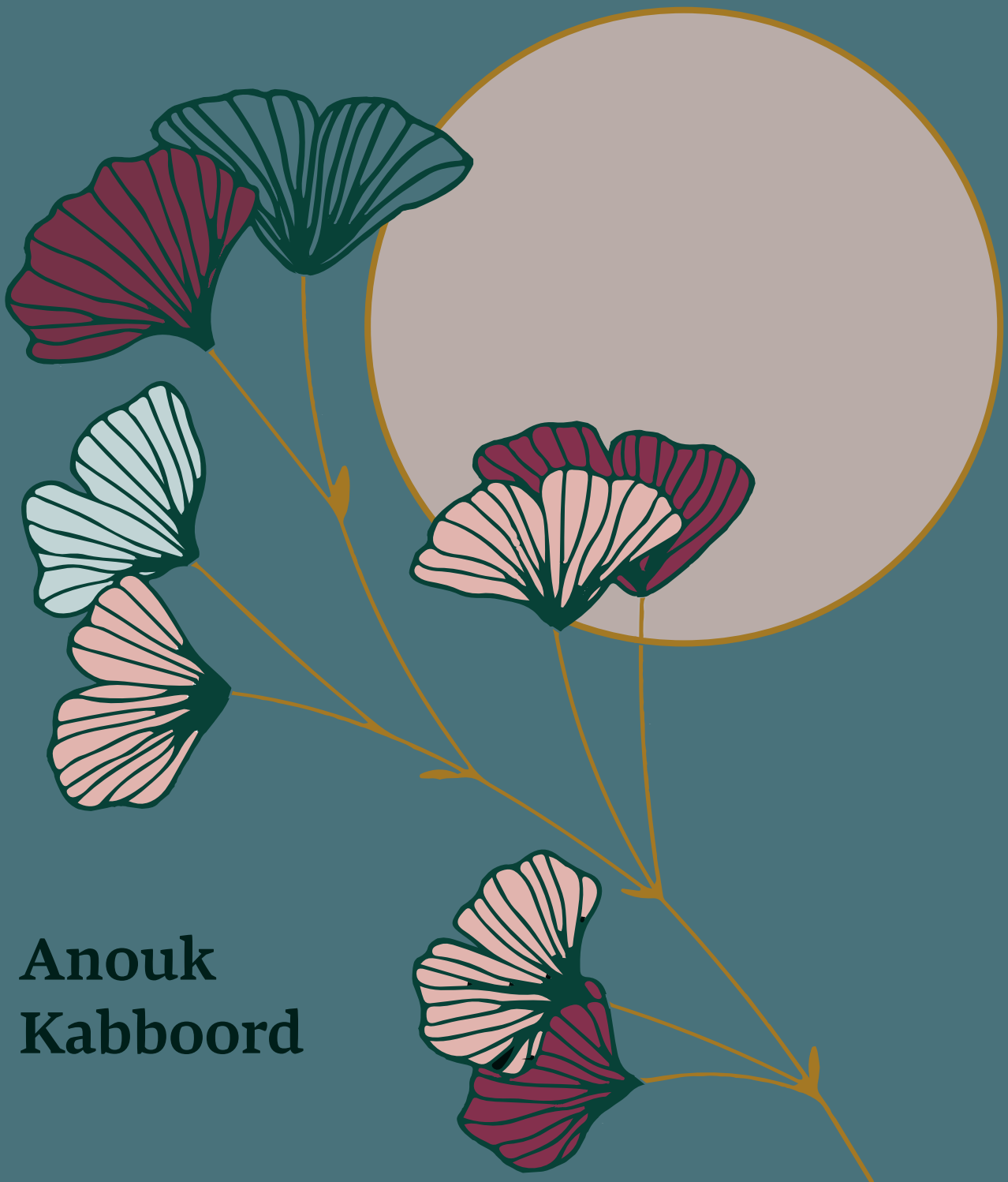
Comorbidity and outcomes in geriatric rehabilitation



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Comorbidity and outcomes in geriatric rehabilitation

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Colofon

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Academic network for research in elderly care

The studies in this thesis took place in the University Network for the Care Sector South Holland (UNC-ZH). In this network, the Leiden University Medical Center (LUMC) collaborates structurally with 12 elderly care organisations in South Holland (Marente, Pieter van Foreest, Florence, Topaz, Argos Zorggroep, Saffier, Laurens, Zonnehuisgroep Vlaardingen, Woonzorgcentra Haaglanden, Aafje, ActiVite, Haagse Wijk- en Woonzorg).

Caregivers, policy makers, researchers, students, residents and relatives work together to improve the quality of care and quality of life for vulnerable older people. The UNC-ZH is a regional platform, inspirator and learning network for innovation in long-term care. Research, education and training, and practice are closely related.

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The proof of the pudding is in the eating

Contents

Chapter 1

General introduction

Geriatric rehabilitation

Geriatric rehabilitation in the Netherlands is a post acute inpatient multidisciplinary medical treatment program, supervised by an elderly care physician.[1, 2] Geriatric rehabilitation in the Netherlands has developed and professionalized more and more in recent years. Milestones were the start of a geriatric rehabilitation specialist training for elderly care physicians in 2005, the financial reimbursement: from AWBZ (General Exceptional Medical Expenses Act) to the ZVW (Health Insurance Act) in 2013 which led to a greater focus on the aim to discharge patients to their home situation, the presentation of a research agenda and position paper in 2015, and the progression of international cooperation in recent years[3]. A European consensus statement on core principles for geriatric rehabilitation was recently published, which defined geriatric rehabilitation as *"a multidimensional approach of diagnostic and therapeutic interventions, the purpose of which is to optimise functional capacity, promote activity and preserve functional reserve and social participation in older people with disabling impairments"*.[3] Eligibility for geriatric rehabilitation in the Netherlands is not defined by age but by a combination of criteria[4, 5]:

- The patient is medically stable - not in need of acute hospital care - but is conditionally and functionally too impaired to return home.
- Frailty is present and/or the patient has 'complex multimorbidity', i.e. pre-existent comorbidities and premorbid functional impairments.
- The patient has the potential to improve his/her functional performance.
- The patient is motivated to undergo geriatric rehabilitation but has a reduced capacity to undergo intensive training.

The multidisciplinary team in geriatric rehabilitation consists of nursing staff, a physiotherapist, an occupational therapist, a speech therapist, a psychologist, a dietician, a spiritual counsellor, a social worker, and an elderly care physician. In the Netherlands, a patient can be referred for geriatric rehabilitation via two pathways: after acute hospital admission (1) and after comprehensive geriatric assessment (2) carried out by a geriatrician, an internal specialist with geriatric specialty or an elderly care physician. Reasons for admission to a geriatric rehabilitation facility vary greatly but can generally be divided into the following groups: stroke, trauma (of which +/- 50% is hip fracture), elective orthopaedic surgery, and 'other': a heterogeneous group of diagnoses[6]. In this miscellaneous group amputation, COPD, heart failure, and oncological disease are the more specific diagnoses for which specific wards and care pathways are recognized nowadays.

Multimorbidity and comorbidity

The National Institute for health and Clinical Exellence (NICE) is an independent organisation (United Kingdom) that provides national guidance on promoting good health and preventing and treating ill health.[7] NICE has developed a guideline on multimorbidity, which is defined as the presence of two or more long-term conditions in a person; most often this will be an older person. NICE recognises the importance of multimorbidity and recommends an

approach to healthcare that takes account of multimorbidity. This term is not restricted to physical conditions but it also includes mental health conditions such as cognitive problems and sensory impairments such as visual problems or hearing loss.[8] Another often used term for multimorbidity is comorbidity: the co-existence of one or more morbidities. Usually, multimorbidity is used when one speaks of disease burden of a person in general. For example in research and primary care settings or general practices: in community dwelling patients. The term comorbidity is usually used when a patient has been admitted (acute hospital or a rehabilitation facility) for a specific reason: the primary diagnosis or index disease for which the patient receives treatment or rehabilitation.[9,10,11] In addition to this index disease, a patient may have other co-existing diseases, which is then called the patients' comorbidity.

Comorbidity in research

Collecting information on chronic co-existing conditions and listing them can be useful for research and clinical practice. Many different comorbidity indices are developed to measure comorbidity.

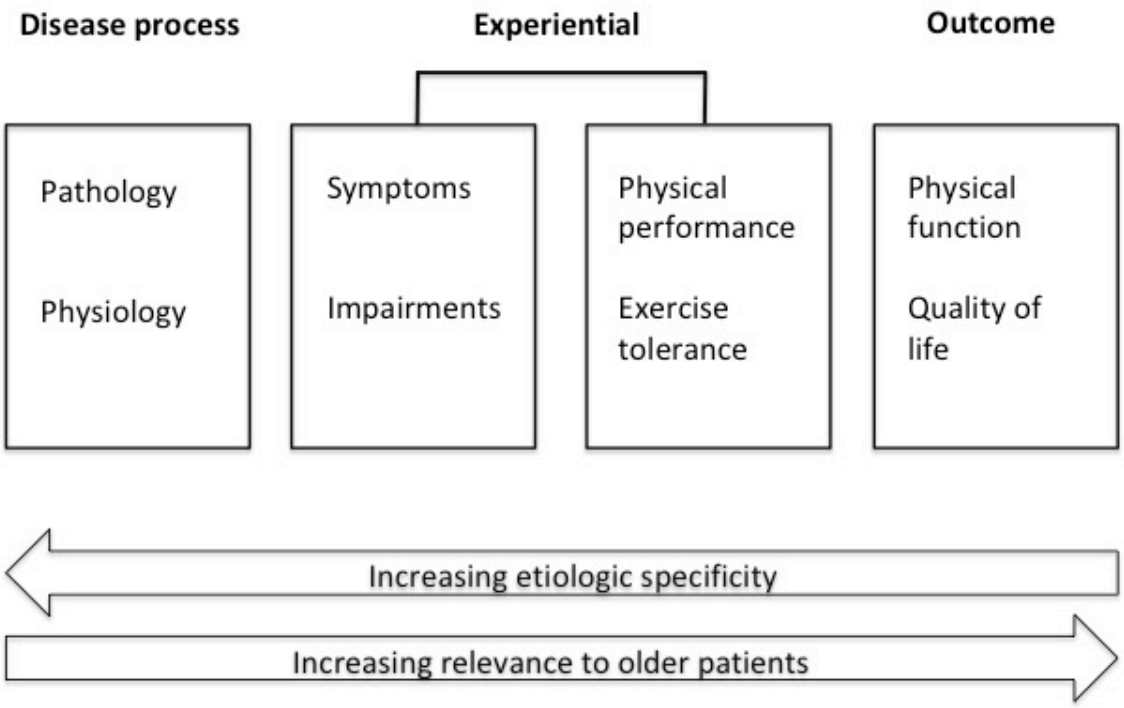
This thesis will discuss three prominent comorbidity indices. One of the most widely used comorbidity index in research is the *Charlson Comorbidity Index.*[12] This is a mortality-based weighted index in which the 19 comorbidities have an associated weight (1, 2, 3 or 6), based on the adjusted mortality risk of each condition. It is a straightforward and easy tot use index and has been investigated and validated in many studies, which makes it a popular index to use.[13] It has been designed for studies - particularly to adjust for comorbidity in big database studies - where survival and/or mortality are outcomes of interest. However, in research with older people other outcome measures are often much more interesting and important, such as quality of life and functional capacity. These kinds of studies are mostly applied clinical studies where comorbidity is directly relevant for the patient outcomes.

Another well-known comorbidity index is the *Cumulative Illness Rating Scale* (CIRS), which was one of the first comorbidity indices.[14,15] This index was designed for use in (clinical) practice and research and incorporates a severity weight based on a combination of physiological parameters and physical impairment. The latest version is adapted for use in older patients and consists of 14 organ systems in which any condition can be scored in combination with a severity rating (0-4). Although it was designed to be brief and comprehensive, completing the CIRS in a reliable way requires training and the use of a manual, which can be time-consuming. Furthermore, organ systems must be scored and not specific conditions. A final noteworthy comorbidity index is the *Functional Comorbidity Index* (FCI), which consists of 18 conditions.[16] The composition of this index is based on the associations between the comorbidities and physical function, and was specifically designed for use in studies where functional capacity is an outcome of interest. The comorbidities can be scored as present or absent (0 or 1). This index is brief and is easy to use.

Severity of comorbidity

When assessing comorbidity in a patient, not only the number of conditions can be looked at but also the severity of the comorbidities can be considered. Severity of a disease has different aspects, which are presented in figure 1: physiological severity (e.g. glucose levels, glomerular filtration rate), severity of symptoms (e.g. pain, dyspnoea), and functional severity (e.g. exercise tolerance, physical performance, mobility). This figure is adopted from a review on the evaluation of disease severity measures.[17] It states that the impact of disease on physical performance and physical function is more relevant to the older patient than physiological components.

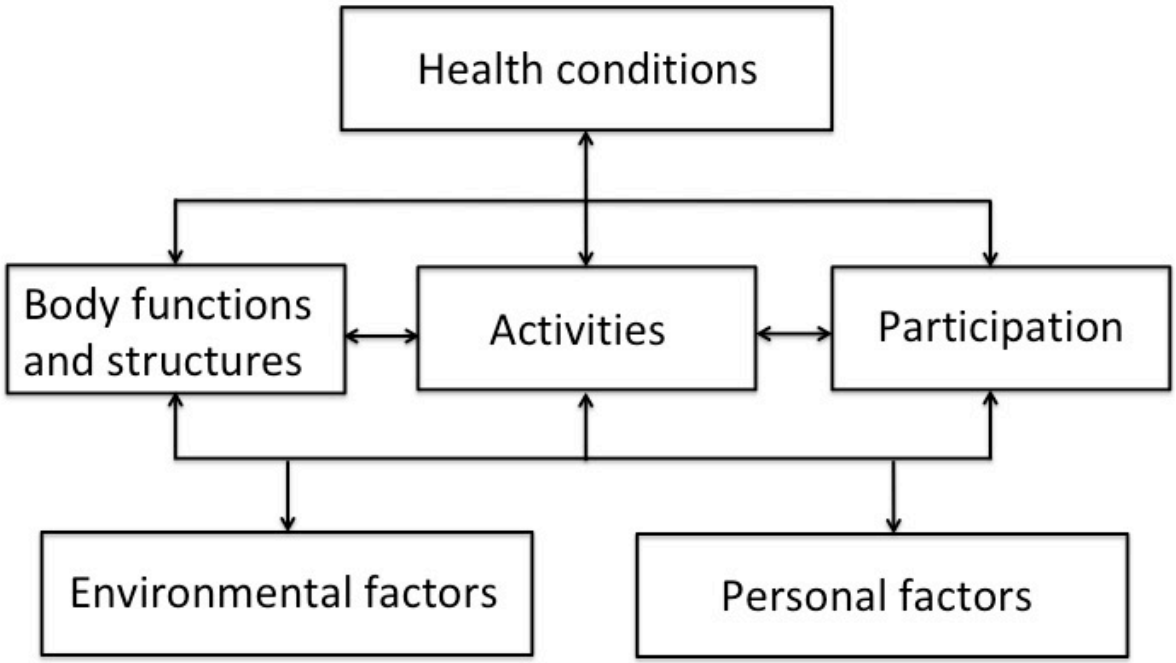
Figure 1. Components for assessing disease severity



Functioning and functional recovery

During geriatric rehabilitation, the patient receives treatment that primarily focuses on the index disease but also intercurrent diseases will be treated if they occur. However, health conditions are only part of a greater whole of aspects that are targeted during rehabilitation. This set of aspects is nicely summarized in the ICF framework: the International Classification of Functioning, Disability, and Health, which is displayed in Figure 2.

Figure 2. The ICF framework



As presented, all aspects are related to one another: health conditions, body functions & structures, activities, participation, environmental factors and personal factors. The following example will elaborate on this: a person falls and breaks his/her hip (index disease: hip fracture). Furthermore, other health conditions may be present or occur: this could be pre-existent comorbidity or an intercurrent disease during rehabilitation, such as a wound infection or subluxation of the hip prosthesis. This causes a reduced function of the affected leg and hip, even after surgery. The patient has to learn to walk again and will need physiotherapy and nursing support to be able to perform activities. A personal factor could be the presence of anxiety (e.g. fear of falling) and/or reduced therapy adherence, for which a psychological intervention may be indicated. A practical example of an environmental factor is the presence of stairs at home, inside or at the front door. This makes it necessary to train walking up and down the stairs or - if this rehabilitation goal is not realistic to be achieved - adjustments to the house on the advice of an occupational therapist could be made. If all these aspects have been addressed during rehabilitation and the patient is able to walk, free from reluctance and fear of falling, than the patient is able to participate in social activities again. This example also applies to other index diseases, such as stroke or myocardial infarction & heart failure.

The terms function, functioning, functional recovery were mentioned but what is the meaning of function? Human functioning using the ICF model is described from three different perspectives: 1) the human organism: the function of body structures, 2) human activities, and 3) the human as a participant in social life.[18] When we look at the conditions that need to be met in order to be discharged home after inpatient geriatric rehabilitation, several aspects of functioning can be considered essential: mobilising, toileting (unplanned

care), and especially when living alone the possibility to alarm in case of emergency. Other aspects are also important, but could be performed with aid of home care or an informal caregiver, such as bathing, grooming, dressing and eating/drinking (planned care).
In research, the centre perspective from the ICF model is commonly called 'activities of daily living' (ADL). Several indices that measure ADL exist, in which different aspects of functioning are composed together. The most widely used index in research is the Barthel index, but other examples are the Utrecht Scale for Evaluation of clinical Rehabilitation (USER), the elderly mobility scale (EMS), the Katz ADL, the Nottingham extended ADL, and others.[19-23] The fact that many of these indices exist shows that functioning is a complex concept consisting of different components of ADL. Moreover, as can be seen in Figures 1 and 2, health conditions (comorbidity) and functioning are related. Still, they both are different concepts.

Comorbidity in geriatric rehabilitation

Patients in a geriatric rehabilitation facility are mostly older persons but not necessarily. Premorbid physical impairments and comorbidity play a role in defining biological age, which is more important than calendar age in selecting for geriatric rehabilitation. The vast majority of patients have comorbidities in addition to their index disease and the occurrence of intercurrent diseases during geriatric rehabilitation is also common.[24,25] A higher comorbidity burden may enhance the risk of intercurrent diseases and the presence of an intercurrent disease probably affects functional outcome.[25-27]
Besides the mentioned comorbidity indices in research and the expected importance of comorbidity severity in older persons, another issue on comorbidity is interesting when investigating comorbidity assessment and its impact on geriatric rehabilitation outcome: comorbidity profiles or clustering. A study investigating the clustering of comorbidities in community dwelling older patients in combination with their associations with health outcomes (hospitalisations and mortality) was recently published.[28] The authors found that specific comorbidities formed clusters or comorbidity profiles. Some of these clusters showed stronger associations with health outcomes than others.
On admission to a geriatric rehabilitation facility, geriatric assessment will be performed by the attending physician, which includes gathering information on the medical history of the patient. However, a structural method of comorbidity assessment to incorporate into the rehabilitation plan (monitor, treatment or follow up) is currently not common practice. It is unknown to what extent comorbidity enhances the risk of intercurrent diseases during geriatric rehabilitation and affects functional recovery and other geriatric rehabilitation outcomes, such as discharge destination. Finally, it is unknown whether comorbidity clusters can be recognized in patients admitted for geriatric rehabilitation and whether specific profiles may enhance the risk of successful or unsuccessful rehabilitation.

Aims and outline of this thesis

The overall aim of this thesis was to investigate whether the presence of comorbidity in patients admitted for geriatric rehabilitation impacts successful rehabilitation outcome. To this end five research questions were formed: 'what is the association between comorbidity, its assessment and functional outcome after geriatric rehabilitation, and which methods best reveals this association?' (1), 'what is the usability and reliability of a severity-weighted version of the functional comorbidity index? (w-FCI)' (2), 'what is the predictive performance (in relation to functional outcome after geriatric rehabilitation) of this w-FCI compared to other comorbidity indices?' (3), 'what is the association between comorbidity and intercurrent diseases during rehabilitation?' (4), and 'what comorbidity clusters can be determined in a geriatric rehabilitation setting and what is the association between comorbidity (clusters) and geriatric rehabilitation outcome?' (5).

The first three chapters focus on comorbidity assessment and describe how the association between comorbidity and functional rehabilitation outcome is best reflected. **Chapter 2** presents the results of a systematic review and meta-analysis of existing literature on comorbidity - assessed using different comorbidity indices – and its relation with functional outcome in patients that received rehabilitation after stroke or hip fracture. Stroke and hip fracture were chosen because this is the index disease of about half of the patients in geriatric rehabilitation[6]. In **chapter 3**, the usability and reliability of a modified version of the FCI are described. This weighted version of the FCI incorporates a severity rating to each of the comorbidities of the FCI, and scores how severely each comorbidity affects daily functioning. The results of this usability and reliability study are presented, which includes both qualitative and quantitative results. The proposed version of the FCI, the weighted FCI (w-FCI), is further studied in **chapter 4**. In this chapter, the results of the COOPERATION study are presented. Data were collected in a cohort of patients admitted to a geriatric rehabilitation facility in Nottingham (UK). The predictive performance - predicting functional outcome - of the w-FCI was compared to that of the original FCI and the Charlson index.
The following two chapters investigate the occurrence of comorbidities in patients that underwent geriatric rehabilitation and examine the relationship between comorbidity and different rehabilitation outcomes. **Chapter 5** describes the relation between comorbidity and the development of one or more intercurrent diseases during geriatric stroke rehabilitation. For this study, patient data of the GRAMPS (Geriatric Rehabilitation in AMPutation and Stroke) study were used. Both the Charlson comorbidity index score as well as separate comorbidities are studied. Also, the role of functional status on admission in relation to comorbidity and intercurrent diseases is described. Whereas in this chapter the index score and separate comorbidities are taken into account, in **chapter 6** the clustering of comorbidities is described. Data from the SINGER (Synergy and INnovation in GEriatric Rehabilitation) study were used to investigate how comorbidities cluster together in a cohort of patients admitted to one of the participating geriatric rehabilitation facilities. In the SINGER study, patients could have any possible index disease and comorbidity was

assessed using functional comorbidity index (FCI). Furthermore, associations between comorbidity (cluster) and intercurrent diseases, unsuccessful functional recovery (a gain of less than 4 points on the Barthel index) and unsuccessful discharge (discharge to a nursing home) were analysed.

Finally, **chapter 7** provides the summary and general discussion of this thesis. The main findings obtained from this work are summarised and it reflects on the results described in the previous chapters.

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Chapter 2

Assessment of comorbidity burden and its association with functional rehabilitation outcome after stroke or hip fracture: a systematic review and meta-analysis.

Kabboord AD, van Eijk M, Fiocco M, van Balen R, Achterberg WP.
J Am Med Dir Assoc. 2016; 17(11): 1066.e13-1066.e21.

ABSTRACT

Background

A well-grounded functional prognosis during triage for rehabilitation is important, especially in older patients who experience the burden of comorbidity. However, it remains unclear what impact comorbidity has on functional outcome after rehabilitation.

Aim

To investigate the associations between comorbidity indexes and functional outcome after inpatient stroke or hip fracture rehabilitation. Furthermore, to identify which method of comorbidity assessment best reveals this relationship.

Design

A systematic review and meta-analysis.

Methods

An extensive search in PubMed, EMBASE, COCHRANE, Web of Science, and CINAHL of cited references and gray literature was carried out on March 4, 2016. This meta-analysis was conducted in agreement with the guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses. Studies were included if participants were adult patients with a stroke or hip fracture, participants received inpatient rehabilitation, comorbidity was assessed with a valid index, and functional status was an outcome measure. Two reviewers independently extracted data; according to the predefined data extraction plan, included studies were independently evaluated on risk of bias.

Results

Twenty studies were eligible for review, and 7 studies were included in the meta-analysis. The pooled correlation between comorbidity and functional status at discharge was -0.43 [-0.69; -0.06]. Presence and strength of correlations differed between comorbidity indexes. Charlson index: range = 0.0 to -0.88 and 0-1% of explained variance (%var). Cumulative illness rating scale (CIRS) total or cumulative: range = -0.02 to -0.34 and unknown %var. CIRS-severity index: range = 0.25 to -0.40 and 12-16 %var. Comorbidity-severity index: range = -0.39 and -0.47 and 5 %var. Liu index: range = -0.28 to -0.50 and 4-7 %var. When the index contained a severity weighting, the associations were more evident.

Conclusions

An association between comorbidity burden and functional outcome exists, albeit modest. Assessment of severity-weighted comorbidity is preferred for estimating the functional prognosis after stroke and hip fracture rehabilitation.

INTRODUCTION

In an aging population, the number of older patients who need rehabilitation after acute illness, such as stroke or hip fracture is growing. Sufficient functional recovery to return home after such a debilitating event is an important rehabilitation outcome that may be influenced by individual factors including age, disease severity, premorbid functional status, and pre-existing comorbidity.[1] A call has recently been made for more research on factors that can help in predicting the likelihood of a successful rehabilitation outcome and allocating appropriate rehabilitation resources to those that might benefit most.[2] Comorbidity can be expected to play a considerable role in the prediction of functional rehabilitation outcome because it may impede physical, occupational, and rehabilitation therapy. In addition, comorbidity could be a risk factor in developing intercurrent illnesses, which could hinder optimal functional recovery.[3,4] However, the role of comorbidity and its impact on functional outcome is not well understood, and studies report contradictory results.[5-10] Studies investigating the impact of comorbidity use a variety of indexes or other methods, which might explain these contradictory results. Different methods to assess comorbidity are available, but selecting a specific comorbidity index for use in clinical practice or research requires knowledge on the ability of a particular index to predict a specific outcome.[11-14] Especially in older patients, it is essential to know to what extent the burden of comorbidity impacts functional outcome. However, there is no clear evidence concerning which assessment tool is suitable to aid in making a functional prognosis in rehabilitation. Therefore, this meta-analysis examines the association between comorbidity assessment and functional rehabilitation outcome of patients with stroke or hip fracture and for that purpose it explores which comorbidity indexes are used and which method best reveals this relationship between comorbidity and functional outcome.

METHODS

Search Strategy

This meta-analysis was conducted following A MeaSurement Tool to Assess systematic Reviews (AMSTAR) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), see also Appendices A and B.[15-17] A systematic search of publications was carried out in the following electronic databases: PubMed (Medline), Embase, The Cochrane Library (CENTRAL), Web of Science, and CINAHL from the earliest record to March 4, 2016. The search strategy was designed under the supervision of an experienced medical information specialist (Appendix C). A secondary electronic search was conducted by searching grey literature: Open GREY (openSIGLE), Greylit, GLIN, ProQuest Theses&Dissertations, and NTIS. In addition, we scrutinized the cited references of eligible articles. Two reviewers (AK, MvE) independently assessed all potentially relevant publications that were identified from the systematic search. Decisions of this reviewers about inclusion and exclusion were compared and, in case of disagreement, were resolved by counselling 2 other reviewers (WA, RvB) to reach consensus.

Selection Criteria

Studies were included if the study (1) included adult patients that received inpatient rehabilitation after treatment for stroke or hip fracture; (2) reported comorbidity assessment using a valid scale or index; (3) investigated functional rehabilitation outcome, measured <6 months after the acute event; (4) reported associations between comorbidity and functional outcome; and (5) was published in English, French, German or Dutch (PRISM Flowchart, Appendix D). Studies were excluded if the study (1) included participants with other diagnoses, "chronic stroke" or elective hip surgery; (2) applied comorbidity assessment using simple presence/absence or number of comorbidities or single comorbid diseases; or (3) was a cross-sectional study, case report, review, opinion or letter.

Data Extraction

A data extraction plan was developed before undertaking independent extraction (AK, MvE) of the following data: study characteristics (author, year of publication, country of origin, study design, sample size), inclusion and exclusion criteria, patient characteristics (age, sex, diagnosis), comorbidity assessment and mean score, functional outcome measurement length of rehabilitation stay (LOS), associations between comorbidity and functional outcome, and information about covariates from multivariate analyses or other adjustments made for confounding. Corresponding authors were contacted to obtain additional data.

Risk of Bias Assessment

The Methods Guide for Comparative Effectiveness Reviews from the Agency for Healthcare Research and Quality was used to assess the risk of bias (RoB) of each included study, using the key points from the Agency for Healthcare Research and Quality.[18] Included articles were independently judged by 2 reviewers (A.K., M.vE.). The risk in each domain was defined as low (+) or high (-). An overall RoB was defined as low (≥4+), moderate (3+), or high (≤2+). Details of this assessment are available in Appendix E.

Data Synthesis and Meta-Analysis

A meta-analysis was performed to provide an overall correlation between comorbidity and functional status at discharge from rehabilitation. A random effects model was employed to pool study specific correlation to estimate an overall correlation and its confidence intervals. Before pooling these effect-size measures, the Fisher r-to-Z transformation was employed, and a weighted average of these transformed scores was computed. An overall test on heterogeneity between studies was performed (value I-squared). To estimate the between-study variance, which is represented as tau in the forest plots, the DerSimonian-Laird method was employed.[19] The overall effect corresponding to a random effects model is reported in the forest plots, together with their confidence intervals. All statistical analyses were performed using R version 2.18, and graphic design of the forest plots was optimized using Comprehensive Meta-Analysis software.

RESULTS

Study Selection

The database search identified 2910 articles, and 1514 articles were identified by using other sources. After removing the duplicates, 2551 articles were screened for eligibility of which 20 met all criteria. Reasons for exclusion are reported in the PRISMA flowchart (Appendix D). Studies that assessed comorbidity using the Tier ranking system were excluded after discussion with 2 other reviewers (WA and RvB).[20,21] This system was developed by the Centers for Medicare and Medicaid Services and is a comorbidity coding system for matching payment to costs. One study used similar methods: the Adjusted Clinical Group and the Diagnostic Cost Group. Outcomes related to the Charlson index were included from this study.[22] Finally, 1 study included a prospective cohort and a retrospective cohort, of which the latter is identical to that in another study.[23,24] Outcomes of this duplicate retrospective cohort were left out to prevent reporting double data.

Study Characteristics

Included studies were prospective (13) or retrospective (7) observational cohorts published between 1997 and 2015. Physical functioning after rehabilitation was the primary outcome in all studies.[25,26] Five studies focused primarily on the following determinants: functional status on admission, aphasia, neglect, or rehabilitation site.[27-31] However, in all studies comorbidity was a covariate or primary determinant. One study included both stroke and hip fracture patients[32]. Three studies reported data from 1 study cohort, but used slightly different selection criteria in each separate article.[29-31] Mean age of the study participants was >65 years, except in 2 studies.[23,24] On average, mean age was higher in hip fracture studies than in stroke studies. All participants received inpatient rehabilitation treatment and the mean length of rehabilitation stay ranged from 11.0 to 36.2 days in hip fracture studies and from 23.5 to 109.2 days in stroke studies. Characteristics of the included studies are presented in Table 1.

Risk of Bias Assessment

Nine studies were rated at low[25,27-31,33,34,38], 5 at moderate[4,22,23,36,42], and 6 at high RoB[24,32,35,39-41]. Thirteen studies were rated at risk of selection bias because of missing reporting inclusion or exclusion criteria or applying criteria that could lead to the exclusion of participants with high comorbidity burden. Ten studies were rated at risk of performance bias because no description of the rehabilitation protocol was provided. Two studies were rated at risk of detection bias because the functional outcome measurement was not a validated list. To prevent attrition bias, only 1 study applied techniques to appropriately handle missing data. Ten studies underreported the relation between comorbidity and functional outcome and/or lacked statements about conflicts of interest and funding sources. Four studies did not report any adjustments for possible confounding. An overview of the RoB assessment is presented in Appendix E.

Table 1. Characteristics of included studies

First author Country	Design, sample size (n)	Study population	Age (years) mean	Gender (male %)	LOS (days) mean	Comorbidity index (mean score)	Functional measurement
Schnitzler et al[28], 2014; France	Retrospective cohort: 28,201	Stroke patients	74.8	unknown	46	*Stroke adjusted* CharlsonCI (-)	Change in Physical Dependence Score (ambulation, dressing, feeding, continence) between baseline and discharge.
Radosavljevic et al[33], 2013; Serbia	Prospective cohort: 203	First hip fracture	77.7	26.6	31.7	CIRS(G)-SI (1.74)	Berg Balance Scale (balance, transferring)
Gialanella et al[29], 2013; Italy	Prospective cohort: 260	First stroke, no dementia or ongoing neurological state.	71.1	47.5	49.4	CIRS-CI (3.3)	FIMtotal; FIMmotor; FIMeffectiveness%
Torpilliesi et al[34], 2012; Italy	Retrospective cohort: 76	Single hip fracture, non-pathologic. Age≥90. No terminal illness, no nursing home patient.	93.2	15.8	33.2	*Dementia-adjusted* CharlsonCI (1.15)	Ability to walk
Spruit-Van Eijk et al[25], 2012; The Netherlands	Prospective cohort: 186	Stroke, rehabilitation > 2 weeks, not critically ill.	78.6	45.7	85	*Stroke adjusted* CharlsonCI (1)[a]	Barthel Index
Montalban-Quesada et al[35], 2012; Spain	Prospective cohort: 48	Single hip fracture: non-metastatic, premorbid independent, age ≥65.	83.6	10.4	11.0	CharlsonCI (1.71)	Barthel Index
Gialanella et al[31], 2011; Italy	Prospective cohort: 284	First stroke, no neglect or ongoing neurological state.	69.9	51.5	48.6	CIRS-CI (3.3)	FIMmotor; FIMeffectiveness%
Gialanella et al[30], 2010; Italy	Prospective cohort: 320	First stroke, no ongoing neurological state.	70.3	49.8	50	CIRS-CI (3.3)	FIMmotor; FIM daily gain
Turhan et al[36], 2009; Turkey	Prospective cohort: 129	First stroke, rehabilitation > 1 week.	66.5	46.5	36.7	*Stroke adjusted* CharlsonCI (1.06)	FIMtotal
Berlowitz et al[22], 2008; USA	Retrospective cohort: 2402	Stroke	67.7	98.1	24.3	*Deyo version*[37] CharlsonCI (2.5)	FIMtotal gain
Press et al[38], 2007; Israel	Prospective cohort: 102	Hip fracture, age ≥ 65.	79.2	29.4	19.6	CharlsonCI (1.87); CIRS(G) total (9.9); CIRS(G)-CI (0.76); CIRS(G)-SI (1.88)	MRFS & MRFS-R

Ferriero et al[4], 2006; Italy	Prospective cohort: 85	Stroke, premorbid independent. No bilateral hemiplegia, no brainstem or cerebellar stroke.	70.0	48.2	45	LiuCI (-); COM-SI (0.55)	FIMtotal; FIMtotal daily gain
Turhan et al[39], 2006; Turkey	Retrospective cohort: 80	First stroke	72.6	56.6	32.8	CharlsonCI (3.0)	FIMtotal; FIMtotal gain
Munin et al[27], 2005; USA	Prospective cohort: 76	Hip fracture, age > 60, premorbid independent. No metastatic cancer.	80.2[b]; 83.9[c]	16.7[b]; 20.6[c]	12.8 [b]; 36.2 [c]	CIRS total (9.2)[b]; (10.2)[c]	FIM: attaining 95% of prefracture FIM
Giaquinto et al[40], 2003; Italy	Prospective cohort: 93	First stroke, not subarachnoidal hemorrhage.	71.1	37	60	CIRS-CI (2.6); CIRS-SI (1.56)	FIMtotal; FIMtotal gain
Kelly et al[41], 2001; USA	Retrospective cohort: 58	Cerebellar stroke	69.2	63.8	24	CharlsonCI (1.09)	FIMtotal; FIMtotal gain
Johnson et al[32], 2000; USA	Prospective cohort: 429	Stroke, age ≥65, only 1-year survivors. Not comatose.	77.4	44	23.5	CharlsonCI (1.75)	ADL recovery (bathing, toileting, walking, dressing, transferring) between baseline and discharge scale.
	Prospective cohort: 336	Hip fracture, age ≥65, only 1-year survivors. Not comatose.	81.1	21.3	21.7	CharlsonCI (1.33)	ADL recovery (bathing, toileting, walking, dressing, transferring) between baseline and discharge scale.
Liu et al[23], 1999; Japan	Prospective cohort: 175	Stroke	60.5	67	104.1	LiuCI (5.1)	FIMtotal
Reker et al[42], 1998; USA	Retrospective cohort: 3575	First stroke	67	98	31	CharlsonCI (0)[a]	FIMtotal gain
Liu et al[24], 1997; Japan	Retrospective cohort: 106	Stroke. No bilateral hemiplegia.	56.5	67	109.2	CharlsonCI (2)[a]; LiuCI (10)[a]	FIMtotal

[a] = median; [b] = Inpatient Rehabilitation Facility; [c] = Skilled Nursing Facility.

Abbreviations: ADL, activities of daily living; FIM, Functional Independence Measurement; FIMeffectiveness %, (FIM at discharge – FIM on admission) / (FIMmax – FIM admission); FIM gain = (discharge score – admission score); FIM daily gain = (gain)/(length of stay); MRFS(-R), Montebello Rating Factor Scale(-Revised).

Table is ordered by year of publication. Physical Dependence Score consists of ambulation, dressing, feeding, continence. ADL recovery scale consists of bathing, toileting, walking, dressing, transferring.

Table 2. Associations between comorbidity and functional outcome

First Author	Diagnosis, sample size (n)	Comorbidity index	Functional measurement	Association (p-value; 95%CI) univariate	Contribution (p-value; 95%CI) multivariate	Other Covariates
Ferriero et al[4], 2006	Stroke, 85	COM – SI	FIM at discharge	r= -0.39 (p<0.004); OR=3.57 (1.41; 8.97)	5 % of Var	**FIMadmission**, **complications**.
			FIM daily gain	r= -0.47 (p<0.001); OR=3.55 (1.39; 9.03)		
		LiuCI	FIM at discharge	r= -0.35 (p<0.001)	4 % of Var	
			FIM daily gain	r= -0.40 (p<0.002)		
Liu et al[24], 1999	Stroke, 175	LiuCI	FIM at discharge	r= -0.277 (p<0.001)		None
Liu et al[23], 1997	Stroke, 106	LiuCI	FIM at discharge	r= -0.499 (p<0.001)	6.6 % of Var	Age, **OAI**, SIAS, grip power, **deviation in bisection task**, **FIMadmission**.
		CharlsonCI	FIM at discharge	r= -0.197 (p=0.10)		
Schnitzler et al[28], 2014	Stroke, 28,201	CharlsonCI *stroke adjusted*	Change in Physical Dependence Score		score 1-4: OR=0.88 (0.81; 0.96) and when score ≥5: OR=0.67 (0.55; 0.83)	**Age**, **gender**, **rehabilitation setting**, **number of patients admitted yearly**, **stroke type**, **PDS on admission**, **behaviour score**, LOS.
Spruit-Van Eijk et al[25], 2012	Stroke, 186	CharlsonCI *stroke adjusted*	Barthel Index at discharge	r= -0.330 (p<0.001)	b= -0.13 (ns)	Age, stroke location, Motricity index arm & leg, **BBS**, FAC, **SCT**, aphasia, swallowing test, Barthel Index on admission, FAI, apraxia, GDS, FAT.
Turhan et al[36], 2009	Stroke, 129	CharlsonCI *stroke adjusted*	FIM at discharge	Unknown (p<0.05)	b= unknown (-7.0; -0.25) (p=0.035)	**Age**, **TACI**, **FIMadmission**, **optimum rehabilitation**, carotid stenosis, atrial fibrillation.
Berlowitz et al[22], 2008	Stroke, 2402	CharlsonCI *Deyo version*	FIM gain		0 % of Var	**Age**, **sex**.
Turhan et al[39], 2006	Stroke, 80	CharlsonCI	FIM at discharge	r= -0.884 (ns)		None
			FIM gain	r= -0.140 (ns)		
Kelly et al[41], 2001	Stroke, 58	CharlsonCI	FIM at discharge	Unknown	'independent predictor' (p=0.05)	Age, type of stroke, extent of stroke, **clinical syndrome at presentation**, **FIMadmission**, **arterial territory**.

Reker et al[42], 1998	Stroke, 3575	CharlsonCI	FIM gain		<1 % of Var	Age, **age/FIMadmission**, year of discharge, marital status, race, **OAI**, **referral source**, **FIMadmission**.
Johnson et al[32], 2000	Stroke, 429	CharlsonCI	ADL recovery scale	Unknown	b= unknown (ns)	Age, gender, **cognition**, premorbid ADL difficulty, pressure ulcer, **incontinence**, **depression**.
	Hip fracture, 336	CharlsonCI	ADL recovery scale	Unknown	b= unknown (ns)	Age, gender, **cognition**, **premorbid ADL difficulty**, **pressure ulcer**, incontinence, depression.
Torpilliesi et al[34], 2012	Hip fracture, 76	CharlsonCI *Dementia adjusted*	Ability to walk at discharge	Unknown (p=0.002)	OR= 2.62 (1.12; 6.14)	Age, gender, dementia, **premorbid ADL**.
Montalban-Quesada et al[35], 2012	Hip fracture, 48	CharlsonCI	Barthel Index, 3 months after discharge	r = unknown (p<0.001)		None
Press et al[38], 2007	Hip fracture, 102	CharlsonCI	MRFS	r = 0 (ns)		Age, residency, cognition, GDS, LOS, premorbid FIM, FIMadmission.
			MRFS-R	r = 0 (ns)		
		CIRS(G) total	MRFS	r= -0.2 (p<0.05)		
			MRFS-R	r= -0.18 (ns)		
		CIRS(G) - CI	MRFS	r= -0.34 (ns)		
			MRFS-R	r= -0.33 (p<0.01)		
		CIRS(G) - SI	MRFS	r= -0.3 (p<0.01)	12 % of Var	
			MRFS-R	r= -0.39 (p<0.01)	16 % of Var; b= -0.411 (p<0.001)	
Radosavljevic et al[33], 2013	Hip fracture, 203	CIRS(G) - SI	BBS at discharge	b= -0.397 (p<0.001)	15 % of Var	**Age**
			BBS 3 months after discharge	b= -0.164 (p=0.43)		
Munin et al[27], 2005	Hip fracture, 76	CIRS total	Attaining 95% of prefracture FIM	Unknown (ns)	OR= 1.22 (0.93; 1.59)	Age, sex, **rehabilitation SNF vs. IRF**, premorbid FIM motor, **participation**.

Gialanella et al[29], 2013	Stroke, 260	CIRS - CI	FIMmotor at discharge	b= -0.05 (ns)		Age, sex, stroke type, stroke size, aphasia, **neglect**, **NIHSS**, **Fugl Meyer**, TCT, **FIMadmission**.
			FIMmotor effectiveness%	b= -0.04 (ns)		
Gialanella et al[31], 2011	Stroke, 284	CIRS - CI	FIMmotor at discharge	b= -0.03 (ns)		Age, sex, stroke type, stroke size, OAI, LOS, **aphasia**, bladder catheter, **Fugl-Meyer**, TCT, **FIMadmission**, caregiver.
			FIMmotor effectiveness%	b= -0.02 (ns)		
Gialanella et al[30], 2010	Stroke, 320	CIRS - CI	FIMmotor at discharge	b= -0.06 (ns)		Age, sex, stroke type, stroke size, OAI, aphasia, **neglect**, bladder catheter, **NIHSS**, TCT, **FIMadmission**, caregiver.
			FIMmotor daily gain	b= -0.02 (ns)		
Giaquinto et al[40], 2003	Stroke, 93	CIRS - CI	FIM at discharge	r = 0 (ns)		None
			FIM gain	r= +0.5 (ns)		
		CIRS - SI	FIM at discharge	r= -0.25 (p=0.03)		
			FIM gain	r= +0.7 (ns)		

Table is ordered by comorbidity assessment and clustered by diagnosis.
Abbreviations: ADL, Activities of Daily Living; BBS, Berg Balance Scale; FAC, Functional Ambulation Categories; FAI, Frenchay Activity Index; FAT, Frenchay Arm Test; FIM, Functional Independence Measure; FIM gain = (discharge score – admission score); FIM daily gain = (gain / length of stay); FIMeffectiveness %, (FIM at discharge – FIM on admission) / (FIMmax – FIM admission); GDS, Geriatric Depression Scale; IRF, Inpatient Rehabilitation Facility; LOS, Length Of Stay; MRFS(-R), Montebello Rating Factor Score (-Revised); NIHSS, National Institutes of Health Stroke Scale; OAI, Onset to Admission Interval; PDS, Physical Dependence Score; SCT, Star Cancellation Test; SIAS, Stroke Impairment Assessment Set; SNF, Skilled Nursing Facility; TACI, Total Anterior Circulation Infarct; TCT, Trunk Control Test. Effect measures: r, correlation coefficient; b, regression coefficient; ns, not significant; % of Var, percentage of explained variance; OR, Odds Ratio.
BOLD = independently associated.

Functional Outcome

All functional measurements were scales that registered activities of daily living, except for the Berg Balance Scale and walking ability. The majority of studies used the functional independence measure as outcome measurement. The total score of the FIM ranges from 18 to 126. Mean FIM scores at rehabilitation admission ranged from 53.3 to 83.2 and at discharge from 80.7 to 108.1, which indicates that the study populations were different from each other in functional level on admission as well as at discharge. Mean FIM gain or absolute functional gain (AFG) between admission and discharge ranged from 13.5 to 29.5. However, AFG depended also on the length of stay (LOS), which is illustrated by the following example: mean AFG of 13.5 was reached after a mean LOS of 19.6 days and mean AFG of 29.5 was reached after a mean LOS of 48.6 days.[31,38] This also makes clear that functional rehabilitation outcome can be represented in different ways: functional status at discharge (FSD), AFG between admission and discharge and daily functional gain (AFG divided by LOS). One study took the premorbid functional level into account as a maximum achievable individual level of function, to calculate the relative functional gain, which was called the Montebello Rating Factor Score (MRFS). Functional outcome measurements used for each study are outlined in Tables 1 and 2. The majority of studies used FSD as outcome.

Comorbidity Assessment

Four comorbidity indexes were extracted. The Charlson comorbidity index (CharlsonCI) was found in 12 studies[22,23,25,28,32,34-36,38,39,41,42], the comorbidity index of Liu (LiuCI) in 3 studies[4,23,24], the comorbidity severity index (COM-SI) in 1 study[4], and the Cumulative Illness Rating Scale (CIRS) for geriatrics or CIRS(G) in 7 studies.[27,29-31,33,38,40] Four studies compared 2 or more comorbidity assessment tools in their outcome analyses.[4,23,38,40]. The characteristics of these indexes are summarized in Table 3.

Associations Between Comorbidity and Functional Outcome

Associations between comorbidity and functional outcome using univariate analysis were expressed by odds ratio (OR)[4], regression coefficients (b)[29-31,33], or correlation coefficients (r).[4,23-25,38-40] Contributions of comorbidity to the prediction of functional outcome, analysed in a multivariate analysis, were expressed by OR (logistic regression)[27,28,34], beta (linear regression)[25], or percentage of explained variance (var %).[4,22,23,33,38,42] The extracted data are summarized in Table 2.

The Charlson comorbidity index

The CharlsonCI was assessed in different ways. Three studies applied a stroke-adjusted version.[25,28,36] Another study applied the Deyo version, and 1 study removed dementia from the index.[22,34,37] Seven studies reported univariate associations, of which 3 reported negative correlations between the CharlsonCI and functional outcome: r = -0.140; not significant (ns), -0.197; ($p = 0.104$), -0.330 ($p < 0.001$), and -0.884 (ns)[23,25,39]; 3 reported an association of unknown effect size and the seventh reported no correlation: r = 0 (ns).[34-36,38] Eight studies

reported multivariate results: 4 reported a non-significant or minor contribution of the CharlsonCI to functional outcome (var = 0% and <1%).[22,25,32,42] Four studies reported a significant contribution of comorbidity. One of these studies reported an increasing negative effect on activities of daily living recovery with a higher CharlsonCI score: OR = 0.88 (95% CI 0.81-0.96) if the score was 1-4 and OR = 0.67 (95% CI, 0.55 - 0.83) if the score was >4).[28] One study reported a decrease in FSD of 3.6 per 1 unit increase of comorbidity (p = 0.035).[36] Another reported an OR = 2.62 (95% CI 1.12 - 6.14) on walking inability.[34] From 1 study, the effect size could not be extracted.[41]

The Liu comorbidity index

Three stroke studies used the LiuCI.[4,23,24] This index was developed in a retrospective cohort followed by a cross-validation in a prospective cohort of patients who had a stroke 2 years later.[23,24] Subsequently, the index was used in a prospective stroke study.[4] All 3 studies reported significant correlations (r = -0.28 to -0.50; p< 0.002) with and contributions (%var = 4% and 6.6%) to functional outcome.

The COMorbidity Severity Index

One stroke study developed the COM-SI to assess comorbidity in patients with a stroke.[4] It reported a significant association with FIM at discharge (r = -0.39; p < 0.004 and OR = 3.57; 95% CI 1.41-8.97) and daily FIM gain (r = -0.47; p < 0.001 and OR = 3.55; 95% CI 1.39-9.03). The COM-SI explained 5% of the variance.

The Cumulative Illness Rating Scale

CIRS total score. Two hip fracture studies used the CIRS as total score. One of them reported a non-significant contribution to functional recovery (OR = 1.22; 95% CI 0.93-1.59).[27] The other used 2 functional outcomes, the MRFS and the MRFS-Revised (MRFS-R), and reported a significant (r = -0.2; p < 0.05) and non-significant correlation (r = -0.18; ns).[38] No multivariate effects of the CIRS total score could be extracted.

CIRS-cumulative index. Five studies used the CIRS as a cumulative index (CIRS-CI), which implies a count of severe comorbidities. Mainly non-significant associations were reported.[29-31,38,40] Three studies reported associations ranging from b = -0.02 to -0.06 (ns).[29-31] Another reported no significant correlation with FSD (r = 0; p = unknown) or AFG [r = 0.5 (ns)].[40] The fifth study reported 1 significant negative correlation (r = -0.33; p < 0.01) and 1 non-significant negative correlation [r = -0.34 (ns)], depending on the functional measurement used (MRFS or MRFS-R).[38] No multivariate effects of the CIRS-CI could be extracted.

CIRS-severity index. Three studies used the CIRS as a severity index (CIRS-SI), which indicates the overall severity of comorbidities.[30,32,35] These studies reported significant associations between the CIRS-SI and functional outcome at discharge (r= -0.25; p = 0.03 to -0.39; p < 0.01). The CIRS-SI explained 12% - 16% of the variance.[33,38] Taking also the functional outcome measure into account, no significant correlation was found with AFG (r = 0.7; ns)

and with balance at 3 months after discharge (b = -0.164; p = 0.43).[33,40] Although significant associations with, and contributions to both functional outcomes were reported in 1 study.[38]

Table 3. Properties of the four comorbidity indices

Comorbidity index	**Description**
Charlson index	The index was developed to predict mortality, by calculating the relative risks of comorbid conditions in a patient cohort. It consists of a list of 19 comorbid conditions in which present comorbidities receive a score of 1, 2, 3 or 6. The weight of these scores is based on its 1-year mortality risk. Range (theoretical): 0-37.
Liu index	The index was developed to have a better validity for use in a rehabilitation setting than the Charlson index and to predict functional outcome instead of mortality. It consists of a list of 38 diseases in which present diseases receive a weighted score ranging from 0 to 5, based on the influence on activities and therapeutic exercises during rehabilitation. Range (theoretical): 0-190.
COMorbidity Severity index COM-SI	The index was developed to be more practical in use than the Liu index. It consists of 10 categories (organ systems) in which diseases can be scored. A weighted score of 0, 1 or 2 is allocated to diseases that cause no, moderate or severe functional limitation as measured by the FIM. The scored disease with the highest weight per category is counted. Range (theoretical): 0-20.
Cumulative Illness Rating Scale (Geriatrics) CIRS(G)	The index was developed for prognostic purposes in a clinical setting. It consists of 13 (or 14) organ systems. A weighted score of 0 to 4 can be assigned to the comorbidities. This weight is based on the influence on activities of daily living and urgency for treatment. The scored disease with the highest weight per organ system is counted. Range (theoretical): 0-56. Three different final scores can be used: CIRS total score: assessed by taking the highest score from each organ system and summing them up. Range: 0-56. CIRS-Cumulative Index (CIRS-CI): assessed by counting the more severe diseases, with score 3 and 4. Range: 0-14. CIRS-Severity Index (CIRS-SI): assessed by dividing the CIRS-total score by the number of scored diseases. Range: 0-4.

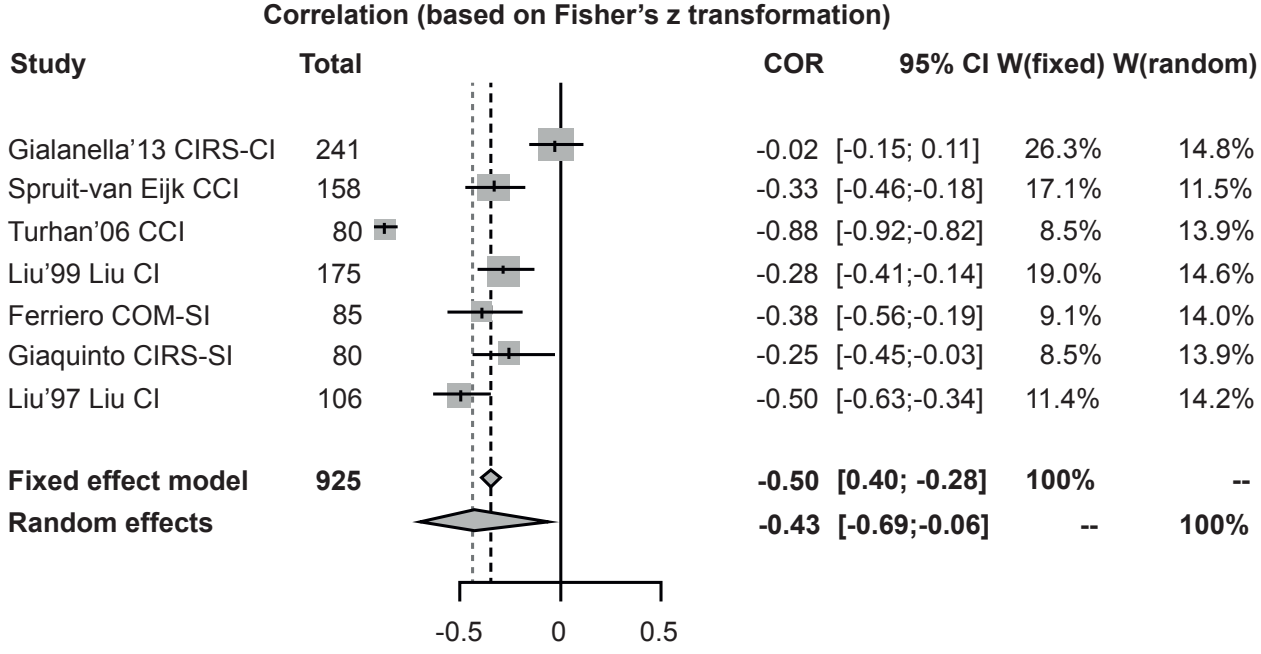
Length of stay

Besides functional outcome, 4 studies also investigated whether comorbidity burden is related to a longer length of rehabilitation stay. Three univariate correlations were extracted: r = 0.455 (p = 0.002)[23]; r . 0.352 (p = 0.0001)[24]; r = 0.013 (p < 0.05)[39]; indicating that a higher comorbidity burden is related to a longer LOS. The fourth study found that comorbidity was not independently associated with LOS.[42]

Meta-Analysis: Correlation Between Comorbidity and Functional Status at Discharge

Because of a between-study variety of functional outcome measurements, a meta-analysis could only be performed with data derived from studies that used FSD measured by the FIM or Barthel index. Seven studies were eligible to be included in the meta-analysis[4,23-25,29,39,40]. All eligible studies investigated stroke patients; comorbidity assessments varied between studies. Three studies used 2 different comorbidity assessment tools; therefore, 2 forest plots were composed.[4,23,40] From these 3 studies, correlation coefficients that showed the strongest correlation were included in the first analysis (Figure 1). In the second analysis, correlation coefficients that showed the weakest correlation were included (Appendix F). In the first forest plot CIRS-CI, CharlsonCI (2), LiuCI (2), COM-SI and CIRS-SI were included and in the second forest plot CIRS-CI (2), CharlsonCI (3) and LiuCI (2) were included. Heterogeneity between studies was high (I^2 = 94.7%). Therefore, pooled correlations of the random effects models are presented. This correlation between comorbidity and FSD in patients with a stroke was significant in the first combination of comorbidity indexes: -0.43 (95% CI -0.69, -0.06) and not significant in the second combination: -0.35 (95% CI -0.66, - 0.06).

Figure 1. Forest plot (Random effects) comorbidity and FIM at discharge



Heterogeneity: I-squared=94.7%; tau-squared=0.1423, p <0.0001

DISCUSSION

Main Findings

This review supports the hypothesis that pre-existing comorbidity is negatively associated with functional rehabilitation outcome. This relation becomes more evident when comorbidity is assessed by indicating the severity of present comorbidities. In the studied patient populations, we detected 4 comorbidity indexes: the CharlsonCI, the LiuCI, the COM-SI, and the CIRS(G) scored as total, cumulative, or severity index. The LiuCI and COM-SI were specifically designed for use in a rehabilitation setting and were uniquely developed to contribute to the prediction of function.[4,23,24] The meta-analysis showed a significant, but quite modest total correlation between comorbidity and functional outcome [-0.43 (-0.69; -0.06)] and the pooled correlation in the second analysis did not reach statistical significance [-0.35 (-0.66; 0.06)] because of other included comorbidity indexes that showed clearly weaker correlations (CIRS-SI / CIRS-CI and LiuCI / CharlsonCI). This also supports that comorbidity is a complex concept and should not arbitrarily be represented by any index or scale.[14] When examining these different comorbidity assessment tools, our results suggest a stronger relation between functional outcome and assessment tools that emphasize the severity of present comorbid diseases, like the LiuCI, the COM-SI, and the CIRS-SI. These indexes are constructed by allocating a severity weight to each comorbid disease. This weight aims to reflect the degree of impact on the patients daily activities but does not measure function itself. Two studies that compared the LiuCI (stroke) or CIRS(G) (hip fracture) with the CharlsonCI, stated that the CharlsonCI is clearly less sensitive in showing this relation.[23,38] The CharlsonCI emphasizes lethality of diseases but hardly identifies the severity of comorbidities. In addition, comparing the CIRS total score and the CIRS-CI with the CIRS-SI, the latter shows a stronger association with functional outcome (both stroke and hip fracture).[38,40] Studies that did not compare different comorbidity assessments support these findings: no significant association was found with the CIRS total score (hip fracture) or the CIRS-CI (stroke)[27,29-31], whereas another study designates a significant association between functional outcome and the CIRS-SI.[33]

The degree of contribution to the prediction of functional outcome varied between studies. Two studies (stroke and hip fracture) reported contribution of an adjusted CharslonCI in a logistic regression model.[28,34] Contribution to the explained variance was absent in studies using the CharlsonCI[22,25,27,32,42], but was contributory in studies using the COM-SI, LiuCI, or CIRS-SI, albeit small.[4,23,33,38] These main findings apply to both stroke and hip fracture patients, although caution is required when comparing the data of stroke and hip fracture studies because of divergent functional outcome measurements, mainly in hip fracture studies.

Interpretation of Findings

The most frequently reported covariate contributing to the prediction of functional outcome was “initial functional status.” This is not surprising because the premorbid level of functioning predetermines the upper limit of the individual magnitude of functional level

after rehabilitation, whereas the functional level on admission predetermines the lower limit. Somewhere within these limits lies functional status at discharge (FSD) and FSD minus the lower limit (functional status on admission) defines AFG. A thinkable explanation that associations were relatively weak is because LOS is also an important factor to consider. The positive correlations found by 3 studies suggest a relation between comorbidity and longer LOS. Longer rehabilitation LOS gives room to more rehabilitation time and may lead to a higher AFG and FSD. Translated into practice this means that a patient with a higher comorbidity burden may be admitted for a longer period of time, receiving more total time of therapy to reach an adequate level of function at discharge. Only 2 studies also took daily functional gain as an outcome.[4,30] Another explanation may be that functional outcome measurements were not sensitive enough to fully reflect functional recovery.
Elaborating on the previous explanation, a difference exists between FSD and AFG. To illustrate this, one can imagine a patient who functions at a maximum premorbid level and still has a relatively high level on admission; a small AFG is enough to regain successful FSD. In other words, a low AFG does not necessarily imply poor recovery. Two studies (stroke and hip fracture) that compared comorbidity indexes, attempted to better reflect this individual recovery by using "daily functional gain" or the MRFS-R.[4,38] It is striking that both studies concluded that assessing severity is the best prognostic content of a comorbidity index.
In a cohort study that investigated community-dwelling older patients, it was demonstrated that multimorbidity and disability were distinct, but partly overlapping concepts.[43] A simple disease count, the CharlsonCI and the CIRS were compared in this study. They were similar in identifying functional disability, but only the CIRS was found to be independently associated. A relation between comorbidity and pre-existent functional status apparently exists, but it remains a challenge to capture individual patient characteristics in a reliable assessment tool, valid for use in predicting function in clinical and research settings. Although our results reported only small contributions of comorbidity to prediction models, we assume that comorbidity could add individual information in making a personalized functional prognosis if a severity weighted comorbidity assessment is performed.
Defining and assessing comorbidity remains a complex concept. In a validation study of the CharlsonCI, the authors came to different conclusions about comorbidity and the prediction of functional outcomes in patients with a stroke.[44] They stated that the CharlsonCI predicted functional status just as well as specific comorbidity indexes, such as the functional comorbidity index (FCI). The FCI consists of a list of comorbidities that are related to functional decline and has been specifically designed to predict function.[45] However, their study did not take place in a rehabilitation setting, the patient cohorts were probably healthier and more independent than a rehabilitation population. In addition, the FCI is still a cumulative index that scores only presence of comorbid diseases and does not allocate any severity weighting.

Strengths and Limitations

To our knowledge, this review and meta-analysis is the first that specifically focuses on

analysing the impact of comorbidity on functional rehabilitation outcome. We aimed to investigate functional outcome in an older patient population by including both patients with a stroke or hip fracture who were admitted in a rehabilitation facility. As we know, these 2 diagnoses are very common among older persons, and both cause an abrupt and tremendous drop in functional abilities. Studying 2 diagnoses enabled evaluating the impact of comorbidity in a wider extent.

Another strength of our study is the comprehensive and profound literature search, which included screening grey literature. It seems unlikely that we missed relevant publications on the topics of our interest and extracted studies originated from a widespread area: Europe, Asia, and the United Sates. Although we applied language restrictions to our inclusion criteria; we think that it is likely that important studies were published in English. Moreover, 2 excluded studies because of Spanish language support the finding that the CharlsonCI is less predictive for functional outcome in a rehabilitation setting.[46,47]

Some limitations also need to be considered. First, the study may be subject to publication bias. However, only 7 studies were included in the meta-analysis, which is too few to make a reliable funnel plot for testing.[48] Also, other forms of bias should be considered. We found that studies rated at a high overall risk of bias were predominantly studies that used the CharlsonCI. The only 3 studies that used the CharlsonCI rated at low risk of bias, did report some significant effect of comorbidity.[25,28,34] However, these studies made adjustments to the CharlsonCI, which suggests that a well- performed accomplishment of study design in combination with implemented adjustments of the CharlsonCI results in stronger associations between comorbidity and functional outcome.

We narrowed our inclusion criteria by excluding studies using “disease count,” “single comorbid diseases,” or cost-weighted systems such as “Tier ranking.” Therefore, we cannot draw conclusions about these methods of assessing comorbidity.

Finally, we were not able to include all data into the meta-analysis because of divergent functional outcome measurements. This diversity allows us to draw only tentative conclusions about hip fracture study outcomes. Nonetheless, the results contain useful data from 6 hip fracture studies that are in line with the findings from stroke studies. Despite our effort to retrieve additional information by contacting all authors, we lack some data. Mainly studies using the CharlsonCI did not report full data on the size and strength of the associations. Nonetheless, this review is unique in analysing associations between different comorbidity indexes and functional outcome in an older patient population admitted for rehabilitation and answers to the call “to improve understanding of the role of multiple comorbid conditions in the health of older adults”.[49] Assessing severity-weighted comorbidities may enable to make a more personalized functional prognosis. Therefore, special attention should be paid to the impact of present comorbidities to provide optimal conditions and treatments leading to successful recovery after acute illness, especially in an older patient population.

CONCLUSIONS

There seems to be insufficient evidence that assessing comorbidity helps predicting the functional prognosis if current comorbidity indexes are used. This review adds new insights in emphasizing the severity of comorbidity to assist in estimating their functional prognosis after acute illnesses such as stroke or hip fracture. More research is needed to investigate whether a brief and practical index that captures individual impact of comorbidity, is feasible, reliable, and valid for use in research, clinical practice, and triage for rehabilitation.

ACKNOWLEDGEMENTS

The authors thank J.W. Schoones, medical information specialist from the Leiden University Medical Center (LUMC) for his supervision regarding the design of the search strategy. The corresponding author (AK) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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APPENDICES

Appendix A. The PRISMA checklist

Section/topic		Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5, 6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Appendix C
Study selection	9	State the process for selecting studies (i.e. screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, 7

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7, 8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7, 8

Appendix B. The AMSTAR checklist

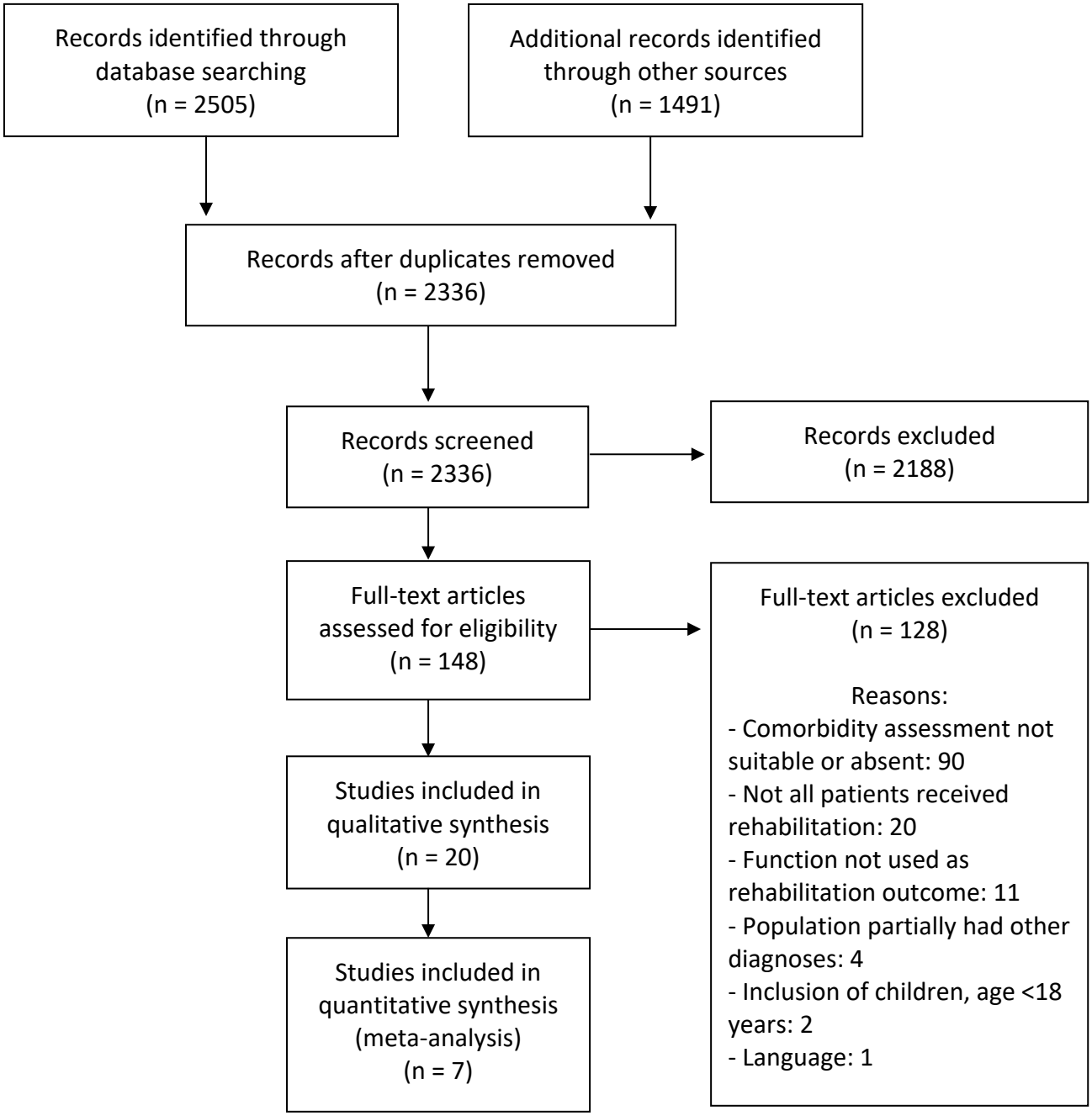
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	X Yes
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	X Yes
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	X Yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	X Yes
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	X Yes
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	X Yes
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	X Yes

8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	X Yes
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	X Yes
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	X No
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	X Yes

Appendix C. The search strategy

(("Stroke"[Mesh] OR "Stroke"[tiab] OR "Strokes"[tiab] OR "CVA"[tiab] OR "CVAs"[tiab] OR "Cerebrovascular Accident"[tiab] OR "Cerebrovascular Accidents"[tiab] OR "Cerebrovascular Stroke"[tiab] OR "Cerebrovascular Strokes"[tiab] OR "Brain Vascular Accident"[tiab] OR "Brain Vascular Accidents"[tiab] OR "Cerebral Stroke"[tiab] OR "Cerebral Strokes"[tiab] OR "Acute Stroke"[tiab] OR "Acute Strokes"[tiab] OR "Femoral fractures"[Mesh] OR "Femoral fracture"[tiab] OR "Femoral fractures"[tiab] OR "Femur fracture"[tiab] OR "Femur fractures"[tiab] OR "Hip fracture"[tiab] OR "Hip fractures"[tiab] OR "Subtrochanteric Fractures"[tiab] OR "Trochanteric Fractures"[tiab] OR "Intertrochanteric Fractures"[tiab] OR "Subtrochanteric Fracture"[tiab] OR "Trochanteric Fracture"[tiab] OR "Intertrochanteric Fracture"[tiab] OR "Arthroplasty, Replacement, Hip"[Mesh] OR "Hip Arthroplasty"[tiab] OR "Hip Prosthesis"[mesh] OR "Hip Prosthesis"[tiab] OR "Hip Replacement"[tiab] OR "total hip"[tiab]) **AND** ("rehabilitation"[Subheading] OR "Rehabilitation"[Mesh] OR "rehabilitation"[all fields] OR rehabilitat*[all fields] OR "Physical Therapy Modalities"[Mesh] OR "Physical therapy"[all fields] OR "Motion therapy"[all fields] OR "Movement exercise"[all fields] OR "Activities of Daily Living"[all fields] OR "Activity of Daily Living"[all fields] OR "Animal Assisted Therapy"[all fields] OR "Equine-Assisted Therapy"[all fields] OR "Art Therapy"[all fields] OR "Bibliotherapy"[all fields] OR "Correction of Hearing Impairment"[all fields] OR "Total Communication Methods"[all fields] OR "Total Communication Methods"[all fields] OR "Lipreading"[all fields] OR "Manual Communication"[all fields] OR "Sign Language"[all fields] OR "Dance Therapy"[all fields] OR "Early Ambulation"[all fields] OR "Exercise Therapy"[all fields] OR "Continuous Passive Motion Therapy"[all fields] OR "Muscle Stretching"[all fields] OR "Plyometric Exercise"[all fields] OR "Plyometric Exercises"[all fields] OR "Resistance Training"[all fields] OR "Music Therapy"[all fields] OR "Myofunctional Therapy"[all fields] OR "Occupational Therapy"[all fields] OR "Recreation Therapy"[all fields] OR "Language Therapy"[all fields] OR "Myofunctional Therapy"[all fields] OR "Speech Therapy"[all fields] OR "Alaryngeal Speech"[all fields] OR "Esophageal Speech"[all fields] OR "Oesophageal Speech"[all fields] OR "Voice Training"[all fields] OR "Supported Employment"[all fields] OR "Self Care"[all fields]) **AND** ("Functional prognosis"[all fields] OR "Recovery of Function"[Mesh] OR "Recovery of Function"[all fields] OR "Functional outcomes"[all fields] OR "Functional outcome"[all fields] OR "Functional improvement"[all fields] OR "Functional status"[all fields] OR "Functional decline"[all fields] OR "Functional capacity"[all fields] OR "Functional assessment"[all fields] OR "Rehabilitation outcome"[all fields] OR "Rehabilitation outcomes"[all fields] OR "FIM"[all fields] OR "Barthel Index"[all fields]) **AND** ("Comorbidity"[Mesh] OR "comorbidity"[all fields] OR "co-morbidity"[all fields] OR comorbid*[all fields] OR co-morbid*[all fields] OR "polymorbidity"[all fields] OR "multi-morbidity"[all fields] OR "multimorbidity"[all fields] OR multimorbid*[all fields] OR multi-morbid*[all fields] OR "Chronic Disease"[Mesh] OR "chronic disease"[all fields] OR "chronic diseases"[all fields] OR "disease characteristics"[all fields] OR "disease characteristic"[all fields] OR "multiple diseases"[all fields] OR "multiple disease"[all fields] OR "multiple morbidity"[all fields] OR "coexisting disease"[all fields] OR "coexisting diseases"[all fields] OR "co-existing disease"[all fields] OR "co-existing diseases"[all fields] OR "medical history"[all fields] OR "ASA"[all fields] OR "BOD Index"[all fields] OR "Burden Of Disease index"[all fields] OR "Charlson Index"[all fields] OR "Charlson Comorbidity Index"[all fields] OR "CCI"[all fields] OR "Deyo"[all fields] OR "Romano"[all fields] OR "Manitoba"[all fields] OR "D'Hoores"[all fields] OR "Cumulative Illness Rating Scale"[all fields] OR "CIRS"[all fields] OR "Cumulative Illness Rating Scale for Geriatrics"[all fields] OR "CIRS-G"[all fields] OR "Cornoni-Huntley index"[all fields] OR "Disease count"[all fields] OR "Number of comorbidities"[all fields] OR "Duke Severity Of Illness index"[all fields] OR "Hallstrom Index"[all fields] OR "Hurwitz Index"[all fields] OR "ICED"[all fields] OR "Index of Coexisting Disease"[all fields] OR "Incalzi index"[all fields] OR "Kaplan Index"[all fields] OR "Liu Index"[all fields] OR "Liu comorbidity Index"[all fields] OR "Shwartz Index"[all fields] OR "Elixhauser"[all fields] OR "FCI"[all fields] OR "Functional Comorbidity Index"[all fields] OR "GIC"[all fields] OR "Geriatric Index of Comorbidity"[all fields] OR "Total Illness Burden Index"[all fields] OR "TIBI"[all fields] OR BOD[tw] OR Burden Of Disease index OR D'Hoores[tw] OR Cornoni-Huntley[tw] OR (duke[tw] AND "Severity Of Illness index") OR Hallstrom[tw] OR Hurwitz[tw] OR Index of Coexisting Disease OR Incalzi[tw] OR Liu[tw] OR Shwartz[tw] OR Geriatric Index of Comorbidity))

Appendix D. PRISMA Flow Diagram



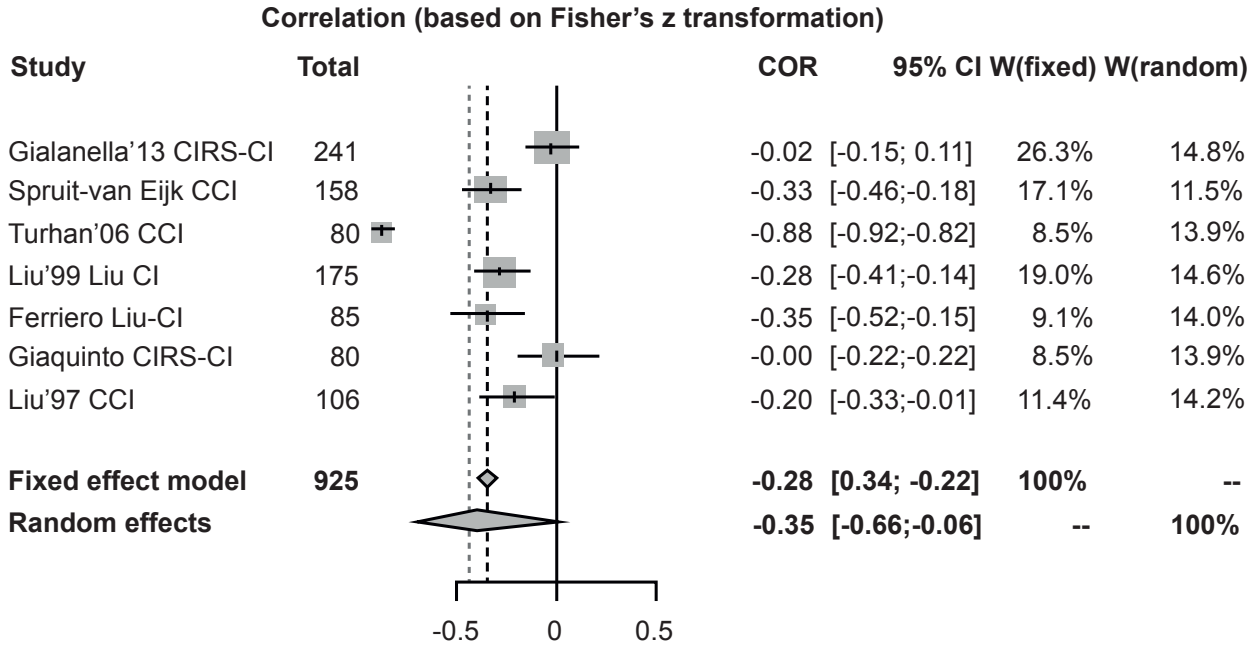
Appendix E. Risk of Bias

Source	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Inclusion/ exclusion criteria	Rehabilitation program description	Validity of measure-ments	Missing data handling	Under reporting	Adjustments
Schnitzler	+	-	+	-	+	+
Radosavljevic	-	+	+	-	+	+
Gialanella 2013	-	+	+	-	+	+
Torpilliesi	+	+	-	-	+	+
Spruit - Van Eijk	+	+	+	-	+	+
Montalban - Quesada	+	-	+	-	-	-
Gialanella 2011	-	+	+	-	+	+
Gialanella 2010	+	+	+	-	-	+
Turhan 2009	-	+	+	-	-	+
Berlowitz	-	-	+	-	+	+
Press	+	+	+	-	+	+
Ferriero	-	+	+	-	-	+
Turhan 2006	-	-	+	-	-	-
Munin	+	+	+	+	-	+
Giaquinto	-	-	+	-	-	-
Kelly	-	-	+	-	-	+
Johnson	-	-	-	-	-	+
Liu 1999	-	-	+	-	-	-
Reker	-	-	+	-	+	+
Liu 1997	-	-	+	-	+	+

+ Low risk of bias
- High risk of bias

Selection bias	1.Did the study apply inclusion/exclusion criteria uniformly to all participants?
Performance bias	2. Did the study describe the rehabilitation program, supporting reliability of uniformly implemented therapy and treatment?
Detection bias	3. Are comorbidity and functional status defined using valid and reliable measures, implemented consistently across all study participants?
Attrition bias	4. If attrition (overall or differential non-response, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?
Reporting bias	5. Was there any sign of under reporting of outcome data? Were there any conflicts of interest stated?
Other bias	6. Does the design or analysis apply any adjustments for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?

Appendix F. Forest plot 2 (Random effects) comorbidity and FIM at discharge



Heterogeneity: I-squared=94.8%; tau-squared=0.1471, p< 0.0001

Chapter 3

Reliability and usability of a weighted version of the functional comorbidity index.

Kabboord AD, van Eijk M, van Dingenen L, Wouters M, Koet M, van Balen R, Achterberg WP. Clin Interv Aging. 2019; 14: 289-299.

ABSTRACT

Aims

To investigate the reliability of a weighted version of the Functional Comorbidity Index (w-FCI) compared with that of the original Functional Comorbidity Index (FCI) and to test its usability.

Patients and methods

Sixteen physicians collected data from 102 residents who lived in 16 different nursing homes in the Netherlands. A multicentre, prospective observational study was carried out in combination with a qualitative part using the three-step test interview, in which participants completed the w-FCI while thinking aloud and being observed, and were then interviewed afterward. To analyse inter-rater reliability, a subset of 41 residents participated. The qualitative part of the study was completed by eleven elderly care physicians and one advanced nurse practitioner.

Measurements

The w-FCI was composed of the original FCI supplemented with a severity rating per comorbidity, ranging from 0 (disease absent) to 3 (severe impact on daily function). The w-FCI was filled out at baseline by 16 physicians and again 2 months later to establish intra-rater reliability (intraclass correlations; ICCs). For inter-rater reliability, four pairs of raters completed the w-FCI independently from each other.

Results

The ICCs were 0.90 (FCI) and 0.94 (w-FCI) for intra-rater reliability, and 0.61 (FCI) and 0.55 (w-FCI) for inter-rater reliability. Regarding usability of the w-FCI, five meaningful themes emerged from the qualitative data: 1) sources of information; 2) deciding on the presence or absence of disease; 3) severity of comorbidities; 4) usefulness; and 5) content.

Conclusion

The intra-rater reliability of the FCI and the w-FCI was excellent, whereas the inter-rater reliability was moderate for both indices. Based on the present results, a modified w-FCI is proposed that is acceptable and feasible for use in older patients and requires further investigation to study its (predictive) validity.

INTRODUCTION

Chronic diseases and their interaction – as in multimorbidity – have an impact on a person's functional abilities and may delay recovery after acute diseases, or complicate rehabilitation.[1-4] With an aging population, clinicians and therapists are increasingly confronted with multimorbidity in their patients. However, assessment of comorbidity is complex and should include more than simply the accumulation of single diseases.[5-8] The NICE guideline Multimorbidity: Clinical Assessment and Management confirms this, stating that: "... multimorbidity involves personalized assessment and the development of an individualized management plan".[9]

Indices such as the Cumulative Illness Rating Scale, the Index of Co-Existing Diseases (ICED), or the Geriatric Index of Comorbidity include disease severity but are complex, time-consuming, and require training and access to a comprehensive manual.[5,10-12] A brief and practical method may support clinicians in assessing individual multimorbidity as part of comprehensive geriatric assessment and, subsequently, in making a functional prognosis when acute diseases occur.

In 2005, the FCI became available.[13] The FCI was specifically designed for use in studies investigating physical function, and included 18 prevalent diagnoses related to physical function. Although the authors discussed whether "... severity ratings are likely to provide better adjustment..." the available FCI does not include severity evaluation.[13] This original FCI was developed in a community-dwelling adult population. However, severity-weighted comorbidity might be more strongly related to functional status in older vulnerable patients, such as nursing home residents. In addition, a survey study (2013) showed that most practitioners agreed that the severity of disease affected physical function following hip fracture. The authors concluded that the FCI needs modification to be useful in older patient populations, such as patients with hip fracture.[14] Therefore, we investigate an FCI that is supplemented with a severity-weighted rating scale.

The present study aims to examine the reliability of this weighted FCI (w-FCI) by analysing the intra-rater and inter-rater reliability of the original FCI and the w-FCI. A second aim is to test the usability of the w-FCI by examining its feasibility, acceptability, and completeness in clinical practice. Based on the results, a w-FCI is presented that is ready to be evaluated in both geriatric practice and prognostic research.

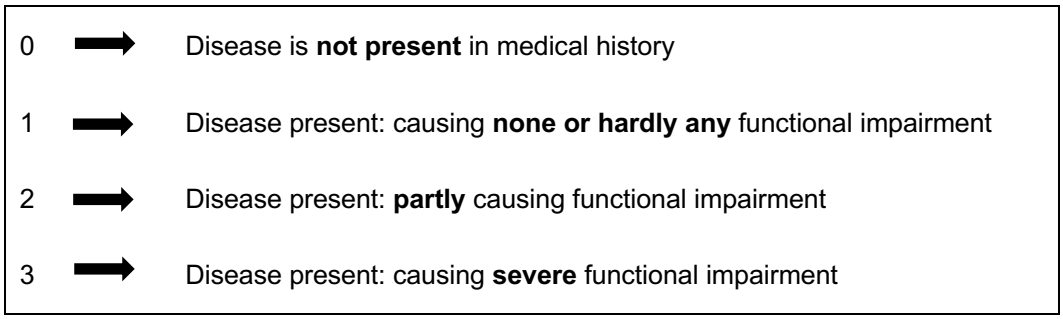
PATIENTS AND METHODS

Weighted FCI

The initial w-FCI was composed of the original index (Appendix A) supplemented with a severity rating for each of the 18 comorbidities, based on the physician's knowledge about the comorbidities of their patients and their impact on functioning.[13] This rating had four categories (Figure 1).[8-12] In item 8, an extra example was included, i.e. neurodegenerative disorder such as dementia was added after Parkinson's disease, because dementia is prevalent among nursing home residents and this addition was also recommended in an

earlier study.[14] A three-page manual was appended as a guide in case of doubt when completing the w-FCI.

Figure 1. Rating scale for functional severity



Reliability

Data collection and measurements

The present study is part of the BeCaf study, a prospective multicentre cohort study.[15] Sixteen physicians in training to be an elderly care physician (ECP), working in 16 nursing homes, collected data on patients under their responsibility.[16,17] Eligible participants were selected when diabetes mellitus had been diagnosed. All eligible participants, their proxy, and the educational nursing homes received adequate oral and written information about the study and were given reasonable time to opt-out. Data collection included anonymous patient data and complied with the Personal Data Protection Act and the Medical Treatment Agreement Act. The study was conducted in accordance with the Declaration of Helsinki and the Medical Ethics Committee of Leiden University Medical Centre approved its protocol.
To analyse ICCs for intra-rater reliability, comorbidity indices were completed by the same physicians at baseline and again 2 months later. This 2-month interval was considered optimal because it was short enough for the comorbidities to be stable, but long enough for physicians to have forgotten the baseline measurements.[11,18-20] The Barthel index was completed by a nurse and was used to assess functional status.[21] Furthermore, four different pairs of raters scored the w-FCI in a subset of patients (Appendix B). The w-FCI was completed in duplicate, first by an ECP trainee and subsequently by the supervising ECP, independently from each other.[16]

Usability

Data collection and measurements

To test usability of the w-FCI, the three-step test interview (TSTI) was conducted.[22] The TSTI combines the "think aloud" and "probing" methods and "is a powerful tool with which to establish whether a measurement is filled out in a consistent way and whether the questions and tasks are understood".[23] Qualitative data were collected by four researchers (AK, LvD, MK, and MW), while interviewing experienced ECPs who worked in various types of nursing

homes (Appendix C). An ECP is “a medical practitioner who has specialized as a primary care expert in geriatric medicine”.[16,17]
Per TSTI session, an ECP filled out the index and exchanged thoughts with the researcher. The ECP was asked to verbally express all thoughts while filling out the w-FCI.[22] The researchers recorded all observations, i.e. the verbally expressed thoughts as well as nonverbal expressions (step 1). This was followed by a retrospective interview during which the observations were discussed (step 2), and an in-depth discussion addressed any difficulties concerning the comorbidities, the descriptions, the understanding of the content, and highlighted further considerations or opinions (step 3).
All data were processed anonymously. Inclusion of ECPs continued until data saturation was achieved. Data were recorded ad verbum for further analysis.

Statistical analysis

A statistician specialized in reliability studies advised on the appropriate sample size and assisted in analysing the ICCs; at least 40 participants were necessary to ensure statistical power.[24] The SPSS version 23 was used for the analyses. The ICCs were calculated for the FCI and the w-FCI sum scores, calculating the ratio of case variance to total variance using a linear mixed model with the Barthel index as a fixed factor. This model adjusted for nested data and for true functional decline due to intercurrent disease. An ICC of <0.50 was deemed to represent poor, 0.50–0.74 moderate, 0.75–0.89 good, and >0.90 excellent agreement.[25] The scores of the two different rater groups were tested for significant difference ($p<0.05$) using a paired *t*-test. Finally, the relation between FCI and w-FCI sum scores and the Barthel index were studied by calculating the correlation coefficients (Spearman’s rho). For the qualitative part, data from the TSTIs were summarized in a table to keep track of data saturation. The content was discussed and analysed by two researchers (AK, MK) who combined, analysed, and structured the data into meaningful themes.

RESULTS

The study population consisted of 102 residents who had lived in a nursing home for (on average) 21 months (Table 1) their mean age was 82.5 years and 60% was female. The Barthel index was (median) 8, the mean FCI score was 5.0, and the mean w-FCI score was 8.6. The mean time interval between T1 and T2 was 2.4 months. During the study, 7 patients died and 12 patients were lost to follow-up.

Table 1. Characteristics of included patients

Variables	n = 102
Age on admission (years)	
Median (IQR)	82.5 (14)
Min - max	48 – 95
Gender, n (%)	
Male	41 (40%)
Female	61 (60%)
Months in nursing home	
Median (IQR)	21 (39)
Min - max	0 – 351
Type of care home	
Psychogeriatric care (predominantly dementia)	56 (55)
Nursing care (chronic physical conditions)	46 (45)
Barthel index	
Median (IQR)	8.0 (10)
Min - max	1 – 20
Original Functional Comorbidity Index	
Mean (SD)	5.0 (1.9)
Weighted Functional Comorbidity Index	
Mean (SD)	8.6 (3.7)
Comorbidity at baseline, n (%)	
Arthritis	23 (23%)
Osteoporosis	15 (15%)
Asthma	2 (2%)
COPD	17 (17%)
Angina pectoris	20 (20%)
Heartfailure	35 (34%)
Myocardial infarction	17 (17%)
Neurological	71 (70%)
Stroke	50 (49%)
Peripheral vascular disease	7 (7%)
Diabetes mellitus I or II	102 (100%)
Gastrointestinal disease	13 (13%)
Depression	19 (19%)
Anxiety	15 (15%)
Visual impairment	41 (40%)
Hearing impairment	25 (25%)
Degenerative disc disease	15 (15%)
Obesity	23 (23%)
Deceased, n (%)	7 (7)

Abbreviations: IQR, interquartile range; SD, standard deviation.

Reliability

The ICCs (intra-rater) were 0.94 for the w-FCI and 0.90 for the FCI. Duplicate comorbidity indices from a subset of 41 patients were completed and the resulting ICCs (inter-rater) were 0.55 for the w-FCI and 0.61 for the FCI. Although the mean FCI was 4.7 in both groups of raters, the mean w-FCI differed between the raters, i.e. the ECP trainees assessed a mean of 8.0 and the supervising ECPs 9.3; this difference was significant (p = 0.021). Spearman's rho was -0.103 (p = 0.307) between FCI and Barthel index and was -0.240 (p = 0.015) for the w-FCI.

Usability

After interviewing 12 participants, data saturation was achieved and five themes were extracted.

Discrepancies due to various sources of information

Essential information was collected to decide on whether a disease was present or absent. ECPs used various sources for this, i.e. medical history (general practitioner), specialist letters, (electronic) patient records, and the list of actual medication, and also considered the results of recent interviews and physical examinations. Clinical knowledge of the patient was used to decide on the severity of present comorbidities. However, the sources did not always correspond with each other. Furthermore, when a patient has been admitted to a care home or geriatric rehabilitation facility, ECPs experienced that it could take days or weeks until the full medical history was received. One question they raised was: *"What is an appropriate moment in time to complete a comorbidity index?"*

Inconsistency in interpretation and deciding on presence or absence

Information from the different sources was sometimes confusing: Sometimes the medication list includes a particular medication, whereas no matching indication can be retrieved from the medical history. Many COPD patients have clinical symptoms of anxiety but don't have an official diagnosis; in this case: *"should I decide present or absent"*? Furthermore, information was sometimes interpreted in different ways. For example, if a patient had had a disease many years ago, without any residual symptoms, it was considered as currently not invalidating and therefore scored as "absent", whereas other participants scored this as "present without causing any functional impairment".

Experienced difficulties during the rating of functional severity

To complete the w-FCI, ECPs needed to know the patient's medical, physical, and functional situation: i.e. comorbidities and their impact. Various problems were experienced when rating the severity: *"Who determines what causes functional impairment: the patient or the doctor?"* and *"I only see the more severely impaired patients – one can imagine that scoring severity depends on my frame of reference"*.

Severity of a disease is not static, but changes from day to day. Also, the impact on function can depend on the availability of supportive aids. Some noted that different diseases may have the same symptoms and cause similar functional impairment, thereby affecting the choice of a rating: *"How do we determine whether functional disabilities are caused by disease A or B?"* and *"Exacerbation of heart failure and COPD both cause shortness of breath, which causes functional impairment irrespective of the underlying pathophysiological aetiology"*. In this case, ECPs were inclined to choose “the happy medium”, i.e. "partly causing functional impairment". Others did not experience this difficulty and indicated that physicians are trained to evaluate symptoms and diagnose diseases; thus, a physician is the appropriate professional to decide what symptom belongs to what disease.

Acceptability and usefulness of the w-FCI

Depending on the availability of information, the conscientiousness of the ECP and the complexity of the patient’s conditions, the time spent on filling out the w-FCI ranged from 4 to 13 minutes. None of the participants used the manual. ECPs who took the most time were positive about the usefulness of the w-FCI, whereas ECPs who needed the least time referred to themselves as “quick deciders” and experienced few problems. Others indicated that the w-FCI would need several adaptations to be useful in the care of older patients (see section “Considerations regarding the content and layout”). Finally, there were doubts about the usefulness of the w-FCI in long-term care practice, when gradual and progressive functional decline is expected. However, the index was seen as being potentially useful in the practice of geriatric rehabilitation, where functional recovery is expected.

Considerations regarding the content and layout

Dementia was considered an important cause of functional impairment in an older patient population. The following conditions were also suggested: fractures, liver and kidney failure, malignancies, chronic wounds, alcohol/substance abuse, and/or other psychiatric diseases. Furthermore, it was unclear whether or where diseases such as atrial fibrillation and valve dysfunction should be scored. Regarding the layout: the w-FCI did not allow scoring the primary diagnosis (main reason why the patient was admitted in the nursing home) separately from the co-existing morbidities, whereas this distinction is commonly made. Finally, because some experienced difficulty with the rating of severity, a threefold rating was suggested: (0) absent or present in medical history without any residual symptoms, (1) partly impairing function, and (2) severe impact.

The w-FCI and the considerations that led to the amendments are presented in Figure 2A and B. Major amendments were: COPD and asthma combined into one pulmonary item, dementia was added to the index as a separate comorbid condition, upper gastrointestinal disease was changed into gastrointestinal disease (also the lower intestinal tract was considered important in older persons), some of the additional explanations or examples below the items were adjusted, supplemented, or removed, and some items were reordered (degenerative disc disease and obesity).

Figure 2A. The proposed weighted Functional Comorbidity Index.

Primary diagnosis (if applicable):
_____

No: this disease is NOT present in medical history.
Yes: this disease is PRESENT in medical history.

No score = 0
Yes score depends on how severely it affects daily functioning →

Score = 0 if: NO influence
Score = 1 if: Partially of influence
Score = 2 if: Severe influence

			Score
1. Arthritis (rheumatoid and/or osteoarthritis)	No	Yes	☐
Also gout or autoimmune disorders causing arthritis, e.g. Sjögren.			
2. Osteoporosis and/or fractures	No	Yes	☐
3. Degenerative disc disease	No	Yes	☐
(e.g. back disease, spinal stenosis or severe chronic back pain)			
4. COPD, Asthma, emphysema or other pulmonary disease	No	Yes	☐
5. Angina pectoris	No	Yes	☐
6. Myocardial infarction	No	Yes	☐
7. Heart failure	No	Yes	☐
Any disease causing heart failure, e.g. atrial fibrillation or valve problems.			
8. Neurological disease	No	Yes	☐
(e.g. multiple sclerosis, Parkinson's disease)			
9. Dementia or other neurocognitive disorder	No	Yes	☐
10. Cerebrovascular accident (stroke)	No	Yes	☐
11. Peripheral vascular disease	No	Yes	☐
12. Diabetes mellitus type I or II	No	Yes	☐
13. Gastrointestinal disease	No	Yes	☐
14. Obesity and/or body mass index (BMI) > 30?	No	Yes	☐
Height: ____ cm weight: ____ kg			
(BMI = weight/ (height in meters)^2			
15. Depression	No	Yes	☐
(or other psychiatric diagnoses causing mood disturbances, e.g. bipolar disorder)			
16. Anxiety or panic disorder	No	Yes	☐
17. Visual impairment	No	Yes	☐
(e.g. cataracts, glaucoma, macular degeneration)			
18. Hearing impairment	No	Yes	☐
		Total score	☐

Figure 2B. Amendments

1	**Arthritis**	Additional examples are provided, such as gout
2	**Osteoporosis**	ECPs discussed this item. Osteoporosis affects function only when it leads to deformation of the spine and/or (vertebral) fractures. Therefore, fractures were added to this item.
3	**Degenerative disc disease**	An ECP mentioned that, logically, this item should be placed next to the other musculoskeletal comorbidities.
4	**COPD, asthma and other pulmonary**	The prevalence of asthma was low in our cohort and ARDS was absent. Besides, ECPs mentioned that it can be difficult to distinguish symptoms of asthma or COPD. We decided to merge the pulmonary comorbidities into one item.
5	**Angina pectoris**	No changes other than adding 'pectoris'.
6	**Myocardial infarction**	We changed 'heart attack' into 'myocardial infarction', because in the original index the latter was written in parenthesis. The term 'heart attack' caused some discussion about its meaning, which is broad and open to multiple interpretations.
7	**Heart failure**	We changed 'congestive heart failure' into 'heart failure' and added examples of cardiac diseases that can cause heart failure, because ECPs got confused about this.
8	**Neurological disease**	No changes made.
9	**Dementia**	Dementia was added to the index. Firstly, because ECPs frequently mentioned this as an important comorbidity and secondly, because a study by Hoang-Kim et al stressed the importance of adding dementia(14).
10	**Cerebrovascular accident**	TIA was removed; it is also considered to be a cerebrovascular accident.
11	**Peripheral vascular disease**	No changes made.
12	**Diabetes mellitus**	No changes made.
13	**Gastrointestinal disease**	Upper gastrointestinal disease was changed into 'gastrointestinal disease'. This includes comorbidities of the lower intestine, which are prevalent in older persons(29). Hoang-Kim et al showed that practitioners expected that upper gastrointestinal disease has no influence on functional abilities.
14	**Obesity**	Obesity was moved up four items.
15	**Depression**	Additional suggestions are provided, because ECPs mentioned that they regularly see patients with other psychiatric diagnoses. Comorbidities that cause mood disturbances, similar to depression, can be scored.
16	**Anxiety**	No changes made.
17	**Visual impairment**	No changes made.
18	**Hearing impairment**	The extra suggestion 'very hard of hearing, even with hearing aids' was removed, because the rating scale provides the possibility to distinguish between 'hearing impairment with well functioning hearing aids' (yes, no impact = 0) and 'hard of hearing, even with hearing aids' (yes, severe = 2).

DISCUSSION

Main findings

In this population of vulnerable nursing home residents characterized by diabetes, multimorbidity, and high functional dependency, the intra-rater reliability of the FCI and w-FCI was excellent, whereas the inter-rater reliability was moderate. Based on these results, we present a modified and weighted version of the FCI (Figure 2A).

Strengths and limitations

The present study has several strengths: this is the first study to add a rating to the FCI based on functional impact, where few of the available comorbidity indices integrate the impact of disease. Another strength is the addition of a qualitative part to gain insight into actual clinical practice and decision- making, and to extract information on factors that may have caused reduced reliability. To our knowledge, the TSTI method has not been used before to collect qualitative data when investigating comorbidity indices. Furthermore, this study provides insight into the clinical practice of assessing comorbidity, which enhances its external validity. However, this strength also has some limitations: the ECPs were not trained in completing the w-FCI but received a brief explanation only and although a manual was available it was not used by any participant. Furthermore, deciding on "impact on function" is a relatively intuitive process and depends on the opinion of the clinician and his/her knowledge of the patient. Although providing decision rules (as in the New York Heart Association classification of heart failure) might improve reliability, such classifications are lacking for most of the diseases included in the FCI. Another limitation may be that we included only nursing home residents with diabetes, which was decided to create a more homogeneous group among a rather heterogeneous group of nursing home residents.[15] We believe that it is unlikely that this has influenced the reliability or usability results and the w-FCI could be used in all older patients according to us. Finally, an unexpected finding was that the ECP-group scored a higher overall w-FCI sum score than the trainees. However, a difference of 1.3 does not necessarily indicate a clinical difference.[26] In this context the following limitation needs to be considered: the raters for inter-rater reliability that completed the w-FCI could only be the ECP trainee and the supervising ECP in our study, because the w-FCI needs to be completed by someone who has insight in the patients' diseases and functioning. This condition limits who is eligible to fill out the w-FCI. A possible explanation for the significant difference might be that trainees usually focus on discussing the medical problems with their supervisor and less often the patients' successful recovery or positive well-being. As a result, supervisors may have scored a more severe impact.

Interpretation of findings

The reason why both indices had moderate inter-rater reliability is probably related to our study design, i.e. using a variety of sources from which comorbidities were extracted rather than related to the severity-weighted rating. Our reliability results are in line with those of an earlier study that investigated the reliability of the ICED (a comparable comorbidity

index).[11] Completion of the ICED requires training; however, in that study, despite using a 20-page manual, the ICCs still ranged from 0.35 to 0.71. Moreover, no improvement in reliability was achieved after extra training of the raters.[11] In the present study, none of the physicians used the three- page manual, which may be understandable bearing in mind that: "an index has to be simple to use and not be stressful in any ... time consuming way, to be useful in practice".[27]

The inter-rater reliability of the FCI was lower than that in a study investigating patients with acute lung injury (ICC: 0.91).[26] However, these two studies clearly differ in design and population, e.g., comorbidity and age differed widely (in the present study the mean FCI was 5, compared with 1 in the earlier study). Furthermore, the comorbidities were extracted from one retrospective record: an electronic hospital discharge summary.[26] Although using one record as the sole source of information may improve reliability (higher ICCs), it is less representative of clinical practice. The present study aimed to investigate reliability in the practice of a nursing home. The results of the correlation analysis support that the w-FCI is more strongly correlated with function than the FCI, although the effect sizes are rather small. This result is in line with some studies but a higher correlation between comorbidity and function was found in other studies.[19,28-30]

Our second aim was to study the feasibility, acceptability, and completeness of the w-FCI. The five themes that emerged provided insight into its usability, i.e. the ability to complete the index, its usefulness, and its imperfections.

Sources of information: Information from different sources did not always fully match or provided conflicting information on the presence/absence of diseases. This may lead to different scores on the index, for both the FCI and w-FCI. This difficulty applies to all comorbidity assessments when various sources of information are used. Moreover, in daily practice a patient file always consists of different medical sources (e.g., medication list, specialist letters, GP medical history, and recent laboratory results).

Presence of comorbidity: Even when the medical history was conclusive, the ECPs could differ in their opinion, mainly when residual symptoms were absent. To address this, some ECPs suggested that a threefold rating would be more practical: i.e. rating "zero" for disease absence as well as for diseases without impact on function (i.e. without residual symptoms).

Severity rating: Completing the w-FCI requires knowledge of the patient's medical and functional status. Some inconsistencies emerged that may complicate rating the impact of a disease on function and, therefore, contribute to disagreement. First, severity may be dynamic and change over time, e.g., due to the nature of the disease progress, or due to the relief of symptoms after successful treatment. In addition, severity can also depend on the environment, e.g., the availability of effective supportive aids and social support. Furthermore, who should decide on severity: the doctor or the patient? Originally, the FCI was designed as a self-report index. However, in another study (by the same author) the FCI was completed by research nurses.[13,31] In the present study, due to the high prevalence of cognitive impairment in the study population, the w-FCI was not self-reported but was completed by a physician. Finally, some ECPs experienced difficulty in distinguishing

between different diseases that may cause similar symptoms and/or impairments. However, the opinion of others was that a physician is specifically trained to recognize diagnoses and to differentiate between symptoms and diseases and thus, a physician seems to have the necessary skills to fill out the w-FCI. Although rating severity of disease is more complex than registering its presence, physicians recognize the importance in relation to functional recovery. In a study, the opinions of various experts in the area of hip fracture and functional recovery were surveyed. In 11 out of the 18 FCI comorbidities a consensus of >85% on the importance of severity was observed.[14] Furthermore, the concept of "functional severity" was already published in 1987 being "the impact of a disorder on an individual's ability to perform age-appropriate activities". This publication stresses that "persons with equal physiological or morphological disorders may vary widely in the impairments they experience" and "functional severity relates to a person rather than to an organ system".[32] Acceptability, usefulness, and content: We consider the amount of time needed to complete the w-FCI acceptable. Although the majority found completing the list to be feasible, they thought the content needed to be adapted to be useful with an older patient population. Dementia is probably the most important comorbidity to be added to the modified index, because it affects functional abilities and is prevalent in older persons. Another study also stressed the importance of dementia in the FCI.[14] The authors also reported that the majority of practitioners suggested that "upper gastrointestinal disease" was not related to physical function (neither its presence nor severity). We argue that changing "upper gastrointestinal" into "gastrointestinal" would be more suitable, since bowel disease (eg, constipation) is prevalent in older patients.[33] Combining COPD and asthma together was based on the prevalence in the cohort. A declining prevalence of asthma with advancing age and an increasing prevalence of COPD with advancing age has been described.[34] Furthermore, we could not find convincing supportive literature while processing the other suggestions (kidney and liver failure, malignancies, substance abuse, and chronic wounds). At least kidney failure and chronic wounds can be considered in the severity-rated part of the w-FCI when they are a consequence of peripheral vascular disease or diabetes, but further research will be needed to determine whether additional comorbidities, in relation to function, should be included in the index. This could be conducted using a survey method or Delphi procedure that focuses on this specific question.

CONCLUSION AND IMPLICATIONS

In this study, the intra-rater reliability of the FCI and w-FCI was excellent, whereas the inter-rater reliability was moderate. We modified the investigated initial w-FCI into a definitive w-FCI, to be acceptable and feasible for use in a vulnerable older patient population, based on the results of this study. This w-FCI is presented, which allows evaluating the impact of comorbidities in older patients and may be used for comprehensive geriatric assessment, e.g., in post-acute care and geriatric rehabilitation. However, the predictive validity of this modified index needs further investigation.

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APPENDICES

Appendix A. The original Functional Comorbidity Index

Please indicate whether a co-morbid condition is present (YES) or absent (NO):
YES: this comorbidity is present
NO: this comorbidity is absent

1. Arthritis (rheumatoid and osteoarthritis)	☐ YES	☐ NO
2. Osteoporosis	☐ YES	☐ NO
3. Asthma	☐ YES	☐ NO
4. Chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), or emphysema	☐ YES	☐ NO
5. Angina	☐ YES	☐ NO
6. Congestive heart failure (or heart disease)	☐ YES	☐ NO
7. Heart attack (myocardial infarct)	☐ YES	☐ NO
8. Neurological disease (such as multiple sclerosis or Parkinson's)*	☐ YES	☐ NO
9. Stroke or transient ischemic attack (TIA)	☐ YES	☐ NO
10. Peripheral vascular disease	☐ YES	☐ NO
11. Diabetes mellitus types I and II	☐ YES	☐ NO
12. Upper gastrointestinal disease (ulcer, hernia of the diaphragm, reflux)	☐ YES	☐ NO
13. Depression	☐ YES	☐ NO
14. Anxiety or panic disorders	☐ YES	☐ NO
15. Visual impairment (such as cataracts, glaucoma, macular degeneration)	☐ YES	☐ NO
16. Hearing impairment (very hard of hearing, even with hearing aids)	☐ YES	☐ NO
17. Degenerative disc disease (back disease, spinal stenosis or severe chronic back pain)	☐ YES	☐ NO
18. Obesity and/ or body mass index (BMI) > 30? Height: ____ m Weight: ____ kg (BMI = weight/ (height in meters)^2	☐ YES	☐ NO

* Added to these examples was: "or neurodegenerative disease such as dementia".

Appendix B. Characteristics of the rater pairs.

	Profession	Type of nursing home
Pair 1, rater 1	ECP trainee	Specialized 'Korsakov' and psychogeriatric long term care home
Pair 1, rater 2	ECP, supervisor	Specialized 'Korsakov' and psychogeriatric long term care home
Pair 2, rater 1	ECP trainee	Specialized 'Acquired Brain Injury' and long term care home
Pair 2, rater 2	ECP, supervisor	Specialized 'Acquired Brain Injury' and long term care home
Pair 3 , rater 1	ECP trainee	Combined nursing home: short (rehabilitation and palliative) and long term care (dementia).
Pair 3, rater 2	ECP, supervisor	Combined nursing home: short (rehabilitation and palliative) and long term care (dementia).
Pair 4, rater 1	ECP trainee	General long term care home (both psychogeriatric and physical indications)
Pair 4, rater 2	ECP, supervisor	General long term care home (both psychogeriatric and physical indications)

Appendix C. Characteristics of participants in the TSTI.

	Profession	Gender	Type of care home and subspecialty
1	Elderly Care Physician, PhD	Male	Geriatric rehabilitation, SNF
2	Elderly Care Physician, PhD	Male	Geriatric rehabilitation, SNF
3	Elderly Care Physician	Male	Long-term care
4	Elderly Care Physician	Male	Short stay recovery
5	Elderly Care Physician	Female	Long-term care
6	Elderly Care Physician, PhD	Male	Specialized Korsakov and psychogeriatric care home
7	Elderly Care Physician	Male	Psychogeriatric care
8	Elderly Care Physician	Female	Short stay recovery
9	ECP trainee	Female	Long-term care
10	Elderly Care Physician	Female	Geriatric rehabilitation and palliative care
11	Elderly Care Physician	Female	Long-term care and psychogeriatric care
12	Advanced Nurse Practitioner	Female	Geriatric (COPD) rehabilitation, SNF

Abbreviations: TSTI, Three-step Test Interview; ECP, elderly care physician; SNF, skilled nursing facility; COPD, chronic obstructive pulmonary disease.

Chapter 4

The modified functional comorbidity index performed better than the Charlson index and original functional comorbidity index in predicting functional outcome in geriatric rehabilitation: a prospective observational study.

Kabboord AD, Godfrey D, Gordon AL, Gladman JRF, van Eijk M, van Balen R, Achterberg WP. BMC Geriatr. 2020; 20(1): 114.

ABSTRACT

Background

In the inpatient rehabilitation of older patients, estimating to what extent the patient may functionally recover (functional prognosis), is important to plan the rehabilitation programme and aid discharge planning. Comorbidity is very common in older patients. However, the role of comorbidity in making a functional prognosis is not clearly defined. The aim of this study was to investigate a modified and weighted Functional Comorbidity Index (w-FCI) in relation to functional recovery and compare its predictive performance with that of the Charlson comorbidity index (CCI) and the original Functional Comorbidity Index (FCI).

Methods

The COOPERATION study (Comorbidity and Outcomes of Older Patients Evaluated in RehabilitATION) is a prospective observational cohort study. Data of patients that were admitted in an inpatient geriatric rehabilitation facility in the UK between January and September 2017, were collected. The outcome measures were: the Elderly Mobility Scale (EMS) and Barthel index (BI) at discharge, EMS gain/day and BI gain/day. Baseline comorbidity was assessed using the CCI, the FCI and the w-FCI. Correlations, receiver operating curves (ROC), and multiple linear regression analyses were performed. The models were adjusted for age, gender and EMS or BI on admission.

Results

In total, 98 patients (mean age 82 years; 37% male) were included. The areas under the ROC curves of the w-FCI (EMS at discharge: 0.72, BI at discharge: 0.66, EMS gain/day: 0.72, and BI gain/day: 0.60) were higher than for the CCI (0.62, 0.53, 0.49, 0.44 respectively) and FCI (0.65, 0.59, 0.60, 0.49 respectively). The w-FCI was independently associated with EMS at discharge (20.7% of variance explained (PVE), $p < 0.001$), EMS gain/day (11.2 PVE, $p < 0.001$), and BI at discharge (18.3 PVE, $p < 0.001$). The FCI was only associated with EMS gain/day (3.9 PVE, $p < 0.05$). None of the comorbidity indices contributed significantly to BI gain/day (w-FCI: 2.4 PVE, $p > 0.05$).

Conclusions

The w-FCI was predictive of mobility & function at discharge and mobility gain per day, and outperformed the original FCI and the CCI. The w-FCI could be useful in assessing comorbidity in a personalised way and aid functional prognosis at the start of rehabilitation.

INTRODUCTION

Making a functional prognosis - estimating to what extent a patient is able to functionally recover at the start of rehabilitation - is important for adequate planning of rehabilitation therapy and timely preparation for discharge. The degree to which recovery can be achieved varies between patients. This is particularly true for older patients after an acute and debilitating illness, for example a hip fracture, sepsis or delirium. Achieving an adequate functional level that enables the patient to perform activities of daily living (ADL), with or without aids and/or home care, is necessary prior to discharge home. Therefore, mobility and functional recovery are important outcomes in the rehabilitation of older people.
Many patient-related factors may contribute to successful or unsuccessful rehabilitation outcomes. These can be medical (multimorbidity, disease severity), functional (premorbid ADL, baseline function) and social (access to formal care, caregiver availability).[1]
The role of assessing comorbidity in functional prognosis in older patients is not well understood and different comorbidity indices exist.[2-4] Comorbidity can be expected to contribute to the prediction of functional outcome because it may increase the risk of intercurrent illnesses and therefore impede rehabilitation therapy.[4-6] The Charlson index (CCI) is one of the most widely used comorbidity indices.[7,8] It includes 19 conditions, each assigned a weight based on their hazard ratio; the total score is the sum of these weighted scores. The index, however, was initially developed to predict mortality and not functional outcome. A number of measures have been designed that may be better associated with functional outcome. Some of these are severity weighted, such as the Cumulative Illness Rating Scale and the Index of Co-Existing Diseases, but they are complex, require specific training, and the use of a comprehensive manual.[9,10] The Functional Comorbidity index (FCI) has been designed specifically in relation to physical function and is easier and more intuitive to use.[11] It includes 18 diagnoses, counting their presence or absence, resulting in a cumulative sum score: the number of comorbidities. A major limitation is that it does not incorporate a severity weighting which could help improve its accuracy in predicting functional outcome.[12] Furthermore, the index does not include dementia, which is a prevalent condition that influences functional abilities among older patients.[13] To investigate a comorbidity index that is both brief and feasible for use in older patients, a severity-weighted rating scale was added to the original FCI and also dementia was added. As such, this modified and weighted FCI (w-FCI) assesses pre-existent comorbidity (chronic conditions) in combination with its impact on present function.
The present study aims to compare the performance of the w-FCI in an older patient population with that of the original FCI and the CCI in predicting mobility and functional recovery at discharge from geriatric rehabilitation.[8]

METHODS

Setting and design

A prospective observational cohort study was carried out as a service improvement project: COOPERATION, Comorbidity and Outcomes of Older Patients Evaluated in RehabilitATION.

The setting was a community hospital based intermediate care facility that provides inpatient rehabilitation services for older people: Lings Bar Hospital in Nottingham, UK. The multidisciplinary team consisted of an advanced nurse practitioner (ANP), nursing staff, a physician, a speech therapist, a physiotherapist, an occupational therapist, and a social worker.

Patients

Patients studied were older adults that were referred for inpatient geriatric rehabilitation. No strict age criterion was applied, but all patients had multimorbidity, complex medical problems or were ≥ 65 years old. Formal research consent was not required because this study was conducted as a service improvement project under clinical governance. A sample size of 90 was calculated based upon a minimum sample size of 50 + 8 k (where k = the number of predictors), including four predictors into a linear regression model and assuming a dropout rate of 10%.[14] Other than the open application of these prognostic indices, which were known to the clinical team, patients received care as usual with no additional intervention.

Comorbidity assessment

Pre-existent comorbidity was assessed by the physician or the ANP within the first week of admission using three different indices: the CCI (Appendix A), the FCI (Appendix B) and the w-FCI (Figure 1).[15] The sum score of the indices represented pre-existent comorbidity and not the actual disease for which the patient had been admitted to the facility.

Outcome measures

Data from routine clinical assessments were collected on admission and at discharge from the rehabilitation facility. A physiotherapist completed the two outcome measures. These measures from routine clinical data were mobility at discharge as measured with the Elderly Mobility Scale (EMS), range 0–20 (where higher scores denote greater mobility, Appendix C), from which EMS gain/day was calculated by subtracting EMS on admission from EMS at discharge and dividing the outcome by the total length of stay in days. The other outcome was functional dependency at discharge measured with the Barthel index (BI), range 0–20 (where higher scores denote greater independence in personal ADL, Appendix D), from which BI gain/day was calculated.[16,17] The EMS measures mobility and the ability to carry out transfers that are necessary for ADL activities while the patient performs 7 different tasks. The total score depends on the level of help the patient requires to succeed in the tasks. The BI determines the degree of (physical or verbal) help that a person needs to perform ADL activities. Gain/day is a measure that takes account of the fact that the length of stay of each patient varied, leading to a variable time of recovery to which the patient is 'exposed'.

Figure 1. The weighted FCI

Primary diagnosis (if applicable):
_____

No: this disease is NOT present in medical history.
Yes: this disease is PRESENT in medical history.

No score = 0
Yes score depends on how severely it affects daily functioning →

Score = 0 if: NO influence
Score = 1 if: Partially of influence
Score = 2 if: Severe influence

			Score
1. Arthritis (rheumatoid and/or osteoarthritis)	No	Yes	☐
Also gout or autoimmune disorders causing arthritis, e.g. Sjögren.			
2. Osteoporosis and/or fractures	No	Yes	☐
3. Degenerative disc disease	No	Yes	☐
(e.g. back disease, spinal stenosis or severe chronic back pain)			
4. COPD, Asthma, emphysema or other pulmonary disease	No	Yes	☐
5. Angina pectoris	No	Yes	☐
6. Myocardial infarction	No	Yes	☐
7. Heart failure	No	Yes	☐
Any disease causing heart failure, e.g. atrial fibrillation or valve problems.			
8. Neurological disease	No	Yes	☐
(e.g. multiple sclerosis, Parkinson's disease)			
9. Dementia or other neurocognitive disorder	No	Yes	☐
10. Cerebrovascular accident (stroke)	No	Yes	☐
11. Peripheral vascular disease	No	Yes	☐
12. Diabetes mellitus type I or II	No	Yes	☐
13. Gastrointestinal disease	No	Yes	☐
14. Obesity and/or body mass index (BMI) > 30?	No	Yes	☐
Height: ____ cm weight: ____ kg			
(BMI = weight/ (height in meters)^2			
15. Depression	No	Yes	☐
(or other psychiatric diagnoses causing mood disturbances, e.g. bipolar disorder)			
16. Anxiety or panic disorder	No	Yes	☐
17. Visual impairment	No	Yes	☐
(e.g. cataracts, glaucoma, macular degeneration)			
18. Hearing impairment	No	Yes	☐
		Total score	☐

Other variables

Besides comorbidity, the ANP collected the following data from routine clinical records in the first week after admission: age, gender, admission domicile, premorbid BI, primary diagnosis, cognition measured using the Montreal Cognitive Assessment (MoCA; range 0–30 where higher scores denote greater cognitive function).[18] At discharge, the ANP noted the discharge date (length of stay), intercurrent diseases and discharge destination.

Statistical analysis

The outcomes were used as continuous variables, except for ROC analysis. Correlations (Spearman's rho) were calculated to test the relation between comorbidity indices and the functional outcome measures. Correlations of 0.1-0.3, 0.3-0.5 and > 0.5 were considered small, medium and large effect sizes respectively.[19] Receiver operating characteristic curve (ROC) analyses were performed in order to create a plot to visualize the differences of predictive performance of the comorbidity indices. To create the ROC plot, the outcomes were dichotomized: the cut off point for the BI was set at 15 and for the EMS at 13 on the base of literature.[20-22] The clinical interpretation of a BI = 15 is mildly disabled to independent, and EMS = 13 is mildly ADL dependent to independent. For "gain/day" no clinical interpretation of a cut off score is available and therefore was set at their median. Additional ROC curves with different thresholds (cut-off values at 25th, 50th, and 75th percentiles) were created to analyse the robustness of these results. These were performed because AUC's may vary when different cut-off scores are used. Finally, three multiple linear regression models per outcome were created to compare the R-squared value and percentage of variance explained (PVE) of the w-FCI with that of the other indices. At first, simple models were created (comorbidity index only), age and gender were then added to the second models and function on admission was added to the full models. The areas under the ROC curves (AUCs), R squared values and PVEs were used to compare the performance of the comorbidity indices in relation to the four outcome measures.

RESULTS

Characteristics of patients

Ninety-eight patients were included in the study, between January and September 2017. Two patients were admitted directly from home but the remainder was admitted after acute hospitalisation. Fiftyfive (56%) patients were admitted following presentation with a fall with a fracture (n = 38) or without fracture (n = 17). Patients' ages ranged from 57 to 99 years and 38 (39%) were male. The median functional level on admission was 5.5 (EMS) and 9 (BI) and this improved to 11 (EMS) and 14 (BI). The median length of stay in the rehabilitation facility was 24 days and functional gain/day was 0.19 (EMS) and 0.18 (BI). In total, 68 (69%) were discharged home. All characteristics are presented in Table 1.

Table 1. Patient characteristics on admission and at discharge

On admission (n = 98)	Median (IQR, Q1-Q3) or n (%)
Age	82 (11, 77-88)
Gender (male), n (%)	38 (39)
Admission domicile, n (%)	
- Own home (alone)	40 (41)
- Own home with informal caregiver	31 (32)
- Own home, with formal care assistance	25 (26)
- Other	2 (2)
Premorbid BI	17 (5, 15-20)
CCI	1 (2, 1-3)
Original FCI	3 (2, 2-4)
Weighted FCI	2 (2, 1-3)
MoCA score (baseline)	20 (10, 14-24)
EMS on admission	5.5 (4, 4-8)
BI on admission	9 (5, 6-11)
Primary diagnosis category, n (%)	
- Fall with fracture(s)	38 (39)
- Fall without fracture	17 (17)
- Infectious disease	15 (15)
- Neurological	7 (7)
- Deconditioning	6 (6)
- Other	15 (15)
At discharge	
Length of stay (days)	24 (26, 17-43)
EMS at discharge	11 (6, 8-14)
EMS gain/day	0.20 (0.27, 0.11-0.38)
BI at discharge	14 (5, 11-16)
BI gain/day	0.18 (0.22, 0.08-0.30)
Discharge destination, n (%)	
- Own home (alone)	7 (7)
- Own home with informal caregiver	6 (6)
- Own home, with formal care assistance	47 (48)
- Home with health reablement	8 (8)
- Care home	17 (17)
- Transfer to acute hospital (lost to follow up)	3 (3)
- Unknown (missing)	5 (5)
Patients died, n (%)	5 (5)

Abbreviations: MoCA, Montreal Cognitive Assessment; EMS, Elderly Mobility Scale.

Comorbidity and functional outcome

The most prevalent comorbidities were arthritis (47%) and osteoporosis (41%). The median scores were 1 for the CCI (range: 0–8), 3 for the FCI (range: 0–9) and 2 for the w-FCI (range: 0–7). The FCI correlated with both the CCI (ρ: 0.376, $p < 0.001$) and the w-FCI (ρ: 0.497, $p < 0.001$), but the CCI and the w-FCI were not significantly correlated (ρ: 0.180, p: 0.076). The FCI correlated only with EMS at discharge (ρ: -0.245, p: 0.023). The w-FCI correlated with EMS at discharge (ρ: -0.469, $p < 0.001$), EMS gain/day (ρ: -0.385, $p < 0.001$) and BI at

discharge (ρ: -0.415, p < 0.001), but did not significantly correlate with BI gain/day (ρ: -0.125, p: 0.250). The CCI did not correlate significantly (p > 0.10) with any of the outcomes.

Predictive performance

The ROC curves and corresponding AUCs - with their 95% confidence intervals - are presented in Fig. 2.The AUCs of the w-FCI were larger than those of the CCI and the FCI, which applied to all functional outcomes. This remained true for different cut-off scores, except for BI gain/day (Appendix E). In the linear regression analyses, the CCI did not significantly contribute to the simple or to the full models (p > 0.05), the FCI only contributed to EMS gain/day (p = 0.037) but was not independently associated in the full models. The w-FCI independently contributed to the prediction of EMS & BI at discharge (p < 0.01) and EMS gain/day (p < 0.001) but not to BI gain/day (p = 0.082). These associations were also statistical significant in the full models. The PVE's of included variables - with their 95% confidence intervals - are presented in Table 2.

Figure 2. The ROC curves of the four different outcomes

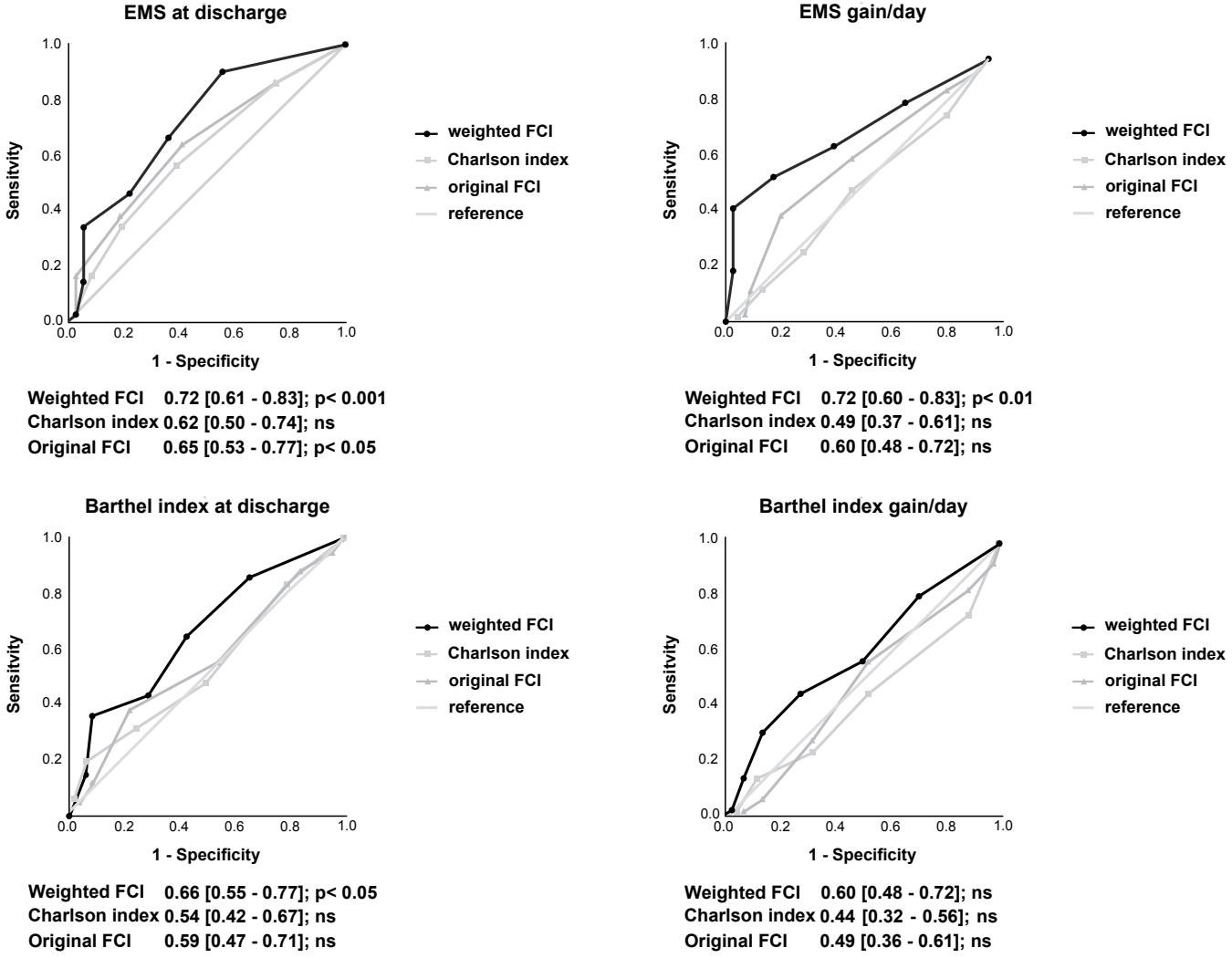

Table 2. R squared values and percentages of variance explained per comorbidity index

Simple linear regression	EMS at discharge R^2 (% of variance)	EMS gain/day R^2 (% of variance)	BI at discharge R^2 (% of variance)	BI gain/day R^2 (% of variance)
CCI	0.042 [-0.034–0.118] (4.2%)	0.006 [-0.024–0.036] (0.6%)	0.037 [-0.035–0.109] (3.7%)	0.001 [-0.011–0.013] (0.1%)
Original FCI	0.043 [-0.034–0.120] (4.3%)	0.051 [-0.032–0.134] (5.1%)	0.008 [-0.026–0.042] (0.8%)	0.007 [-0.025–0.039] (0.7%)
Weighted FCI	0.216 [0.075–0.357] (21.6%)	0.122 [0.003–0.241] (12.2%)	0.192 [0.055–0.329] (19.2%)	0.036 [-0.035–0.107] (3.6%)
Multiple linear regression model				
CCI + age & gender	0.094 [-0.011–0.199] (9.4%)	0.177 [0.046–0.308] (17.7%)	0.107 [-0.004–0.218] (10.7%)	0.125 [0.008–0.242] (12.5%)
Original FCI + age & gender	0.082 [-0.018–0.342] (8.2%)	0.184 [0.051–0.317] (18.4%)	0.080 [-0.019–0.179] (8.0%)	0.126 [0.008–0.244] (12.6%)
w-FCI + age & gender	0.246 [0.104–0.388] (21.8%)	0.242 [0.101–0.383] (24.3)	0.227 [0.087–0.367] (22.7%)	0.137 [0.016–0.258] (13.7%)
CCI + age, gender & function on admission	0.423 [0.282–0.564] (42.3%)	0.199 [0.065–0.342] (19.9%)	0.460 [0.323–0.597] (46.0%)	0.131 [0.013–0.249] (13.1%)
Original FCI + age, gender & function on admission	0.423 [0.282–0.564] (42.3%)	0.207 [0.072–0.342] (20.7)	0.463 [0.326–0.600] (46.3%)	0.132 [0.014–0.250] (13.2%)
w-FCI + age, gender & function on admission	0.487 [0.353–0.621] (48.7%)	0.291 [0.148–0.434] (29.1%)	0.470 [0.334–0.606] (47.0%)	0.160 [0.034–0.286] (16.0%)

Abbreviations: EMS, elderly mobility scale; FCI, functional comorbidity index.

DISCUSSION

Main findings

Our key finding was that the modified FCI had a better predictive performance than the CCI and the original FCI with regard to EMS and BI at discharge and EMS gain/day in older patients that underwent geriatric rehabilitation. The w-FCI had a larger AUC and stronger correlation with these three outcomes (medium effect size) than the CCI and FCI. Results were not significant for BI gain/day. Furthermore, the w-FCI was independently associated with EMS and BI at discharge and EMS gain/day, whereas the CCI and FCI were not.

Strengths and limitations

This study has several strengths: we did not apply any restrictions or exclusion criteria except that all patients had to be referred for rehabilitation. The study cohort was characterised by a high age, prevalent comorbidity and a large drop in mobility and functional capacity after acute illness: it was a typical population and the study was conducted in a normal clinical setting.[23] However, no stroke patients were admitted in the facility: stroke rehabilitation usually is provided in specific post-acute stroke rehabilitation facilities.

Furthermore, the design of the w-FCI and its rating scale is function-based and involves the clinical judgement of the clinician. This is in contrast to many studies that used an administration-based method of assessing comorbidity. Therefore, this prospective study gives insight in the clinical assessment of severity-weighted comorbidity and its potency in making a functional prognosis. Finally, we used two different rehabilitation impact indices per outcome measure: function/mobility at discharge and function/mobility gain/day.[24] Function at discharge is an important rehabilitation outcome that indicates the functional independence of a patient, which is necessary for discharge planning. However, other factors than functional status alone may influence discharge planning such as availability of informal caregivers and home situation (stairs or ground floor). That is why EMS and BI gain/day - which is a measure of rehabilitation efficiency - are also important outcomes with regard to the functional prognosis and duration of stay.

There were also several limitations. The study cohort was relatively small and the study was carried out in one facility where the clinicians that completed the measurements were not blinded to clinical practice and the course of a patient. To minimize potential bias, the therapists that performed the EMS and BI were not aware of the comorbidity indices and its scores. Therefore, we think it is unlikely that it has affected our results to any major degree. We also did not take therapy type, duration and intensity into account. Patients likely received customized therapy, on the basis of their capacity and general condition. A larger multicentre study that takes account of therapy differences across patients would be needed to investigate whether the predictive validity of the w-FCI can be confirmed. It is also important to realise that our findings apply to vulnerable older patients but may not be generalizable to younger patients with less comorbidity. One last limitation concerning the study design: our study did not investigate outcomes like quality of life or other indicators of wellbeing, which are also important outcomes of rehabilitation.

Furthermore, a limitation of the w-FCI may relate to what we have stated above as one of its strengths: the w-FCI assesses comorbidity on the base of the clinician's opinion and quantifies this into a rating scale. This may reduce the reliability and reproducibility due to variability of opinions about the impact of a comorbid condition. Lastly, for the ROC analyses of BI or EMS gain/day we have used the medians as the cut-off. A clinical interpretation of these cut off values is lacking in literature, therefore these results have to be interpreted with caution. However, to give a better insight in all the results from the ROC analyses plots and AUC's with different thresholds are presented in the appendices (Appendix E).

Findings in context

With regard to mobility, the w-FCI showed higher AUCs than the other indices and independently contributed to the prediction of mobility and function at discharge and mobility gain/day. This finding supports the conclusion of other studies that severity of disease should be included in comorbidity assessment.[12,25-29] The w-FCI contains information on the impact of disease in the patient's individual situation and therefore quantifies severity of comorbidity: a clinical severity weight. This is in contrast to the method of the

design studies of the CCI and FCI.[8,11] In these studies a statistical weight (relative risk and/or beta coefficient) was used and no clinical severity was added to the index. The statistical weighted count in the original FCI study did not perform much better, but the authors discuss the issue that de FCI does not take the severity of diagnoses into consideration. They agree that severity ratings are likely to provide a better performance, but discuss the practical problems of severity rating. We believe that it is an important part of assessing comorbidity in older patients.
In our study, the w-FCI explained almost half of the variance in three out of the four models (not in BI gain/day). For research purposes in older patients, the w-FCI seems to be preferable compared to the CCI and the FCI when functional outcomes are of interest. The CCI has proven to be a sufficient predictor of mortality and we think that the use of it should be restricted to studies that investigate mortality and survival. The FCI has been designed in relation to function, but has not yet been validated in older patients (e.g. absence of dementia), which may explain the lower predictive performance in our study.[13]
Regarding the BI, the w-FCI performed sufficiently (AUC > 0.60) and the other indices were poor. An explanation for the overall stronger associations with mobility (EMS) than with the BI (Table 2) could be that the EMS is sensitive in detecting change (improvement), which was found to be stronger compared to that of the BI.[30] In addition, our study cohort was specifically characterized by reduced mobility (Table 1).

Interpretation of findings

The present study demonstrated that clinicians were able to estimate functional impact of comorbid conditions in such a way that it proved to be an independent factor in predicting mobility and function at discharge and EMS gain/day. Assessing functionally weighted comorbidity using the rating scale distinguishes the w-FCI from the CCI and the FCI. It resembles usual clinical rehabilitation practice, in which a clinician evaluates disease severity, functional impairments and the potential for successful functional recovery. Using the w-FCI, this could be carried out in a brief and structured way, for example as part of comprehensive geriatric assessment. Finally, the w-FCI seems to fit well into the concept of the International Classification of Functioning, Disability and Health, the ICF framework.[1] This framework defines health by the interactions between conditions, body functions and structures, activities and participation, including environmental and personal factors (Appendix F).

CONCLUSIONS

The w-FCI had higher predictive performance in relation to functional recovery and efficiency of recovery than the CCI and the original FCI, especially when measured using the EMS. The w-FCI may aid in assessing comorbidity in a personalised way and could be incorporated into routine triaging and discharge planning in the rehabilitation practice of older patients. However, further research is required to investigate whether the predictive validity of the w-FCI can be confirmed.

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APPENDICES

Appendix A. The Charlson Comorbidity Index

Condition	**Score** (weight)
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes without end organ damage	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes with end organ disease	2
Any tumor / malignacy	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6

Appendix B. The original Functional Comorbidity Index

Please indicate whether a co-morbid condition is present (YES) or absent (NO):

YES: this comorbidity is present
NO: this comorbidity is absent

1. Arthritis (rheumatoid and osteoarthritis)	☐ YES	☐ NO
2. Osteoporosis	☐ YES	☐ NO
3. Asthma	☐ YES	☐ NO
4. Chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), or emphysema	☐ YES	☐ NO
5. Angina	☐ YES	☐ NO
6. Congestive heart failure (or heart disease)	☐ YES	☐ NO
7. Heart attack (myocardial infarct)	☐ YES	☐ NO
8. Neurological disease (such as multiple sclerosis or Parkinson's)	☐ YES	☐ NO
9. Stroke or transient ischemic attack (TIA)	☐ YES	☐ NO
10. Peripheral vascular disease	☐ YES	☐ NO
11. Diabetes mellitus types I and II	☐ YES	☐ NO
12. Upper gastrointestinal disease (ulcer, hernia of the diaphragm, reflux)	☐ YES	☐ NO
13. Depression	☐ YES	☐ NO
14. Anxiety or panic disorders	☐ YES	☐ NO
15. Visual impairment (such as cataracts, glaucoma, macular degeneration)	☐ YES	☐ NO
16. Hearing impairment (very hard of hearing, even with hearing aids)	☐ YES	☐ NO
17. Degenerative disc disease (back disease, spinal stenosis or severe chronic back pain)	☐ YES	☐ NO
18. Obesity and/ or body mass index (BMI) > 30? Height: ____ m Weight: ____ kg (BMI = weight/ (height in meters)^2	☐ YES	☐ NO

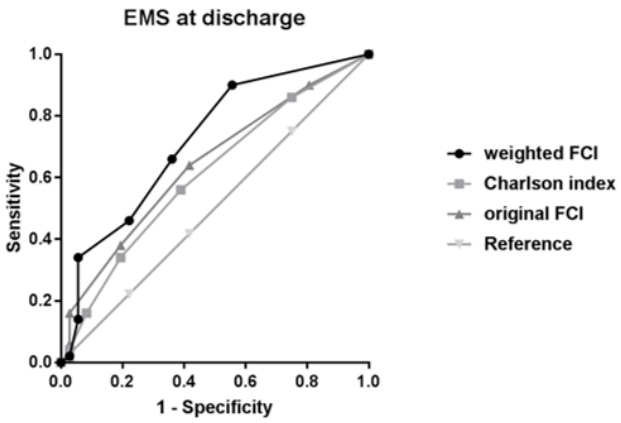
Appendix C. The Elderly Mobility Scale

ELDERLY MOBILITY SCALE	
Lying to sitting **2** Independent **1** Needs help of 1 person **0** Needs help of 2+ people	**Gait** **3** Independent (incl. use of sticks) **2** Independent with frame **1** Mobile with walking aid but erratic/ unsafe turning **0** Requires physical assistance or constant supervision
Sitting to lying **2** Independent **1** Needs help of 1 person **0** Needs help of 2+ people	**Timed walk** **3** Under 15 seconds **2** 16-30 seconds **1** over 30 seconds
Sit to stand **3** Independent in under 3 seconds **2** Independent in over 3 seconds **1** Needs help of 1 person (verbal or physical) **0** Needs help of 2 + people	**Functional Reach** **4** Over 20cm **2** 10-20cm **0** Under 10cm or unable
Standing **3** Stands without support & reaches within arm's length **2** Stands without support but needs help to reach **1** Stands, but requires support **0** Stands, only with physical support (1 person)	
Total score:	Support = uses upper limbs to steady him / herself.

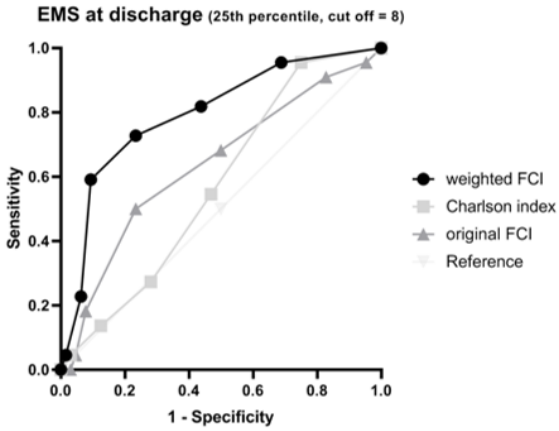
Appendix D. The Bartel index

Activity
Grooming 0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Bathing 0 = dependent 1 = independent (or in shower)
Dressing 0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Feeding 0 = unable 1 = needs help cutting spreading butter, etc., or requires modified diet 2 = independent
Toilet use 0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Bowels 0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder 0 = incontinent, or catheterized and unable to manage alone 1 = occasional accident (max. once in 24 hour) 2 = continent, or catheterized and manages this alone
Transfers (bed to chair and back) 0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces) 0 = immobile or < 50 yards 1 = wheelchair independent, including corners, > 50 yards 2 = walks with help of one person (verbal or physical) > 50 yards 3 = independent (but may use any aid; for example, stick) > 50 yards
Stairs 0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent
Total score

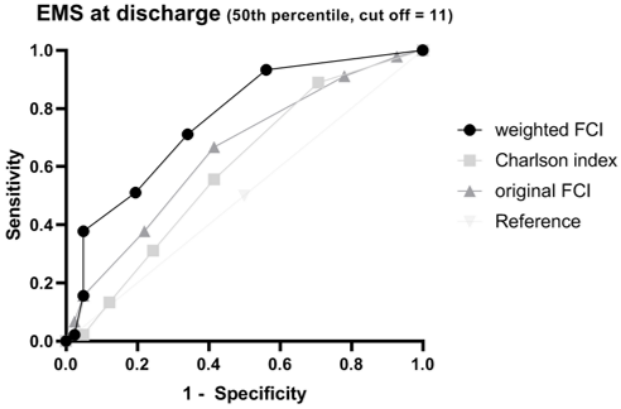
Appendix E. Robustness of ROC curves



Weighted FCI 0.72 [0.61 – 0.83]; p< 0.001
Charlson index 0.62 [0.50 – 0.74]; ns
Original FCI 0.65 [0.53 – 0.77]; p< 0.05



Weighted FCI 0.80 [0.69 – 0.91]; p < 0.001
Charlson index 0.57 [0.50 – 0.78]; ns
Original FCI 0.64 [0.45 – 0.70]; ns



Weighted FCI 0.76 [0.66 – 0.86]; p < 0.001
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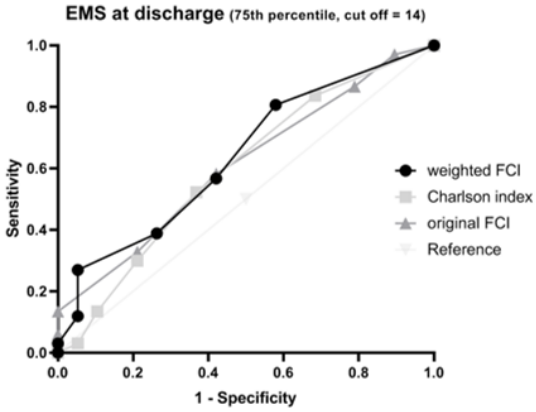
Original FCI 0.65 [0.53 – 0.77]; p < 0.05



Weighted FCI 0.64 [0.50 – 0.78]; ns
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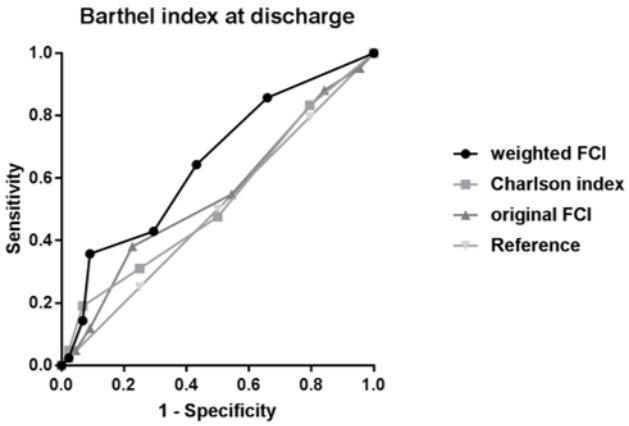
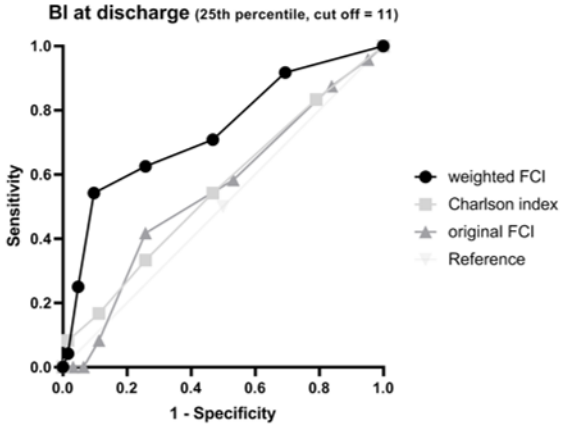
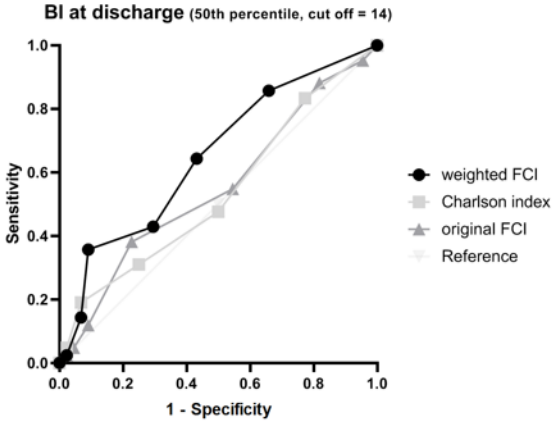
Original FCI 0.61 [0.47 – 0.75]; ns



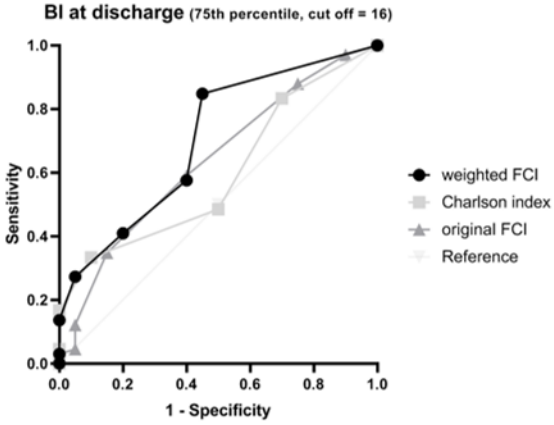
Weighted FCI 0.66 [0.55 – 0.77]; p < 0.05
Charlson index 0.53 [0.42 – 0.67]; ns
Original FCI 0.59 [0.47 – 0.71]; ns



Weighted FCI 0.74 [0.61 – 0.86]; p < 0.001
Charlson index 0.56 [0.41 – 0.69]; ns
Original FCI 0.55 [0.42 – 0.69]; ns



Weighted FCI 0.65 [0.55 – 0.77]; p < 0.05
Charlson index 0.54 [0.41 – 0.66]; ns
Original FCI 0.55 [0.43 – 0.67]; ns



Weighted FCI 0.70 [0.57 – 0.84]; p < 0.05
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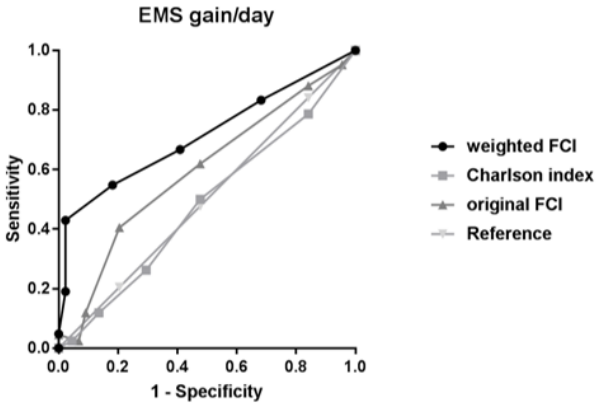
Original FCI 0.64 [0.50 – 0.77]; ns



Weighted FCI 0.72 [0.60 – 0.83]; p < 0.01
Charlson index 0.49 [0.37 – 0.61]; ns
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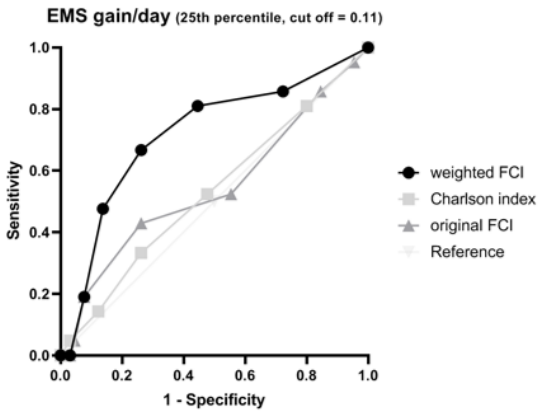
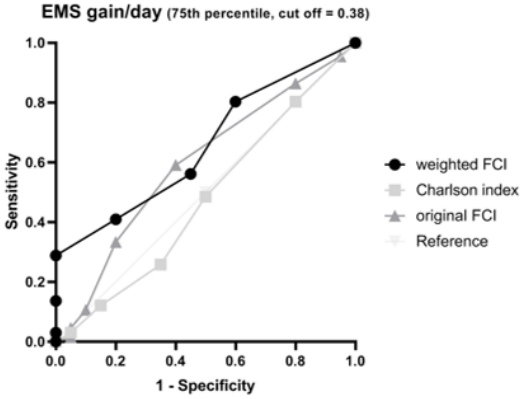
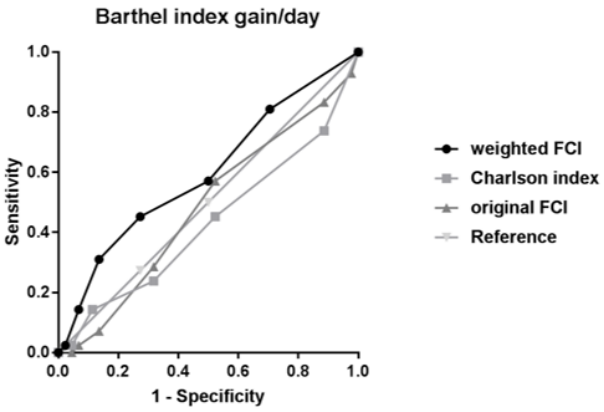


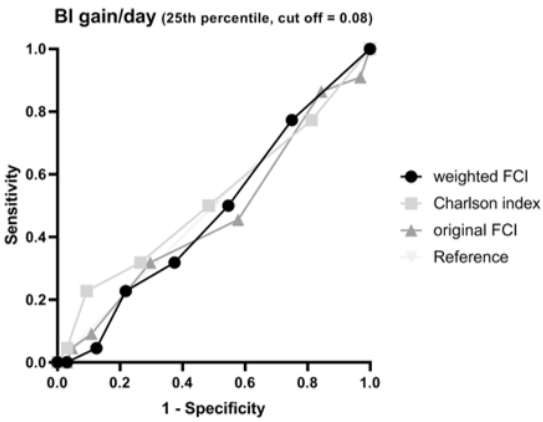
Weighted FCI 0.72 [0.59 – 0.85]; p < 0.001
Charlson index 0.53 [0.39 – 0.68]; ns
Original FCI 0.55 [0.39 – 0.70]; ns



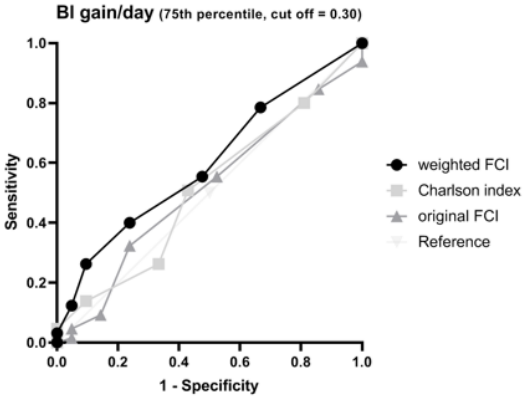
Weighted FCI 0.65 [0.53 – 0.78]; p < 0.05
Charlson index 0.48 [0.33 – 0.63]; ns
Original FCI 0.60 [0.45 – 0.74]; ns



Weighted FCI	0.60 [0.48 – 0.72]; ns
Charlson index	0.44 [0.32 – 0.56]; ns
Original FCI	0.49 [0.36 – 0.61]; ns

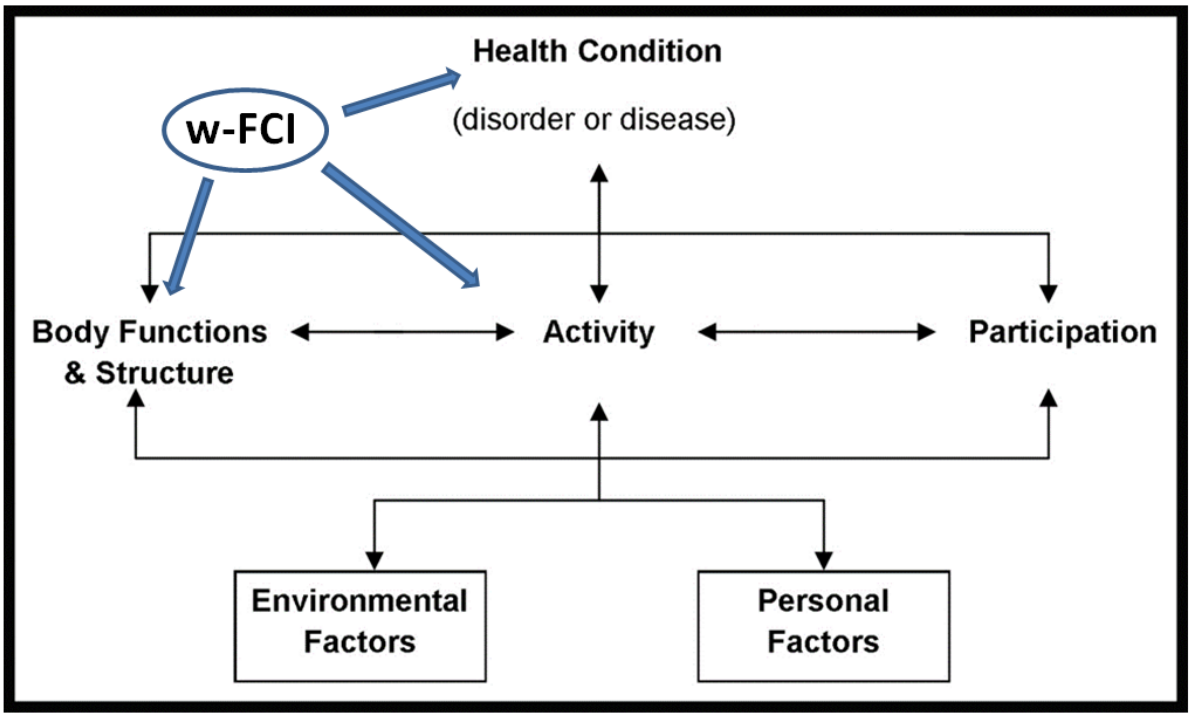


Weighted FCI	0.48 [0.34 – 0.62]; ns
Charlson index	0.52 [0.37 – 0.67]; ns
Original FCI	0.47 [0.33 – 0.61]; ns



Weighted FCI	0.60 [0.47 – 0.73]; ns
Charlson index	0.51 [0.37 – 0.66]; ns
Original FCI	0.51 [0.37 – 0.65]; ns

Appendix F. The ICF framework



Chapter 5

Comorbidity and intercurrent diseases in geriatric stroke rehabilitation: a multicentre observational study in skilled nursing facilities.

Kabboord AD, van Eijk M, Buijck BI, Koopmans RTCM, van Balen R, Achterberg WP. Eur Geriatr Med. 2018; 9(3): 347-353.

ABSTRACT

Background

Older patients often have multiple comorbidities and are susceptible to develop intercurrent diseases during rehabilitation. This study investigates intercurrent diseases and associated factors in patients undergoing geriatric stroke rehabilitation, focussing on pre-existing comorbid conditions, overall comorbidity and baseline functional status.

Materials and Methods

This multicentre prospective cohort study included 15 skilled nursing facilities. Data were collected at baseline and at discharge. The primary outcome measures were presence and number of intercurrent diseases, and secondary their impact on change in rehabilitation goals or length of stay was examined. Comorbidity was assessed with the Charlson index, and functional status with the Barthel index (BI).

Results

Of the 175 included patients, 51% developed an intercurrent disease. A lower baseline BI, a higher Charlson index, presence of diabetes mellitus (DM) and kidney disease were related to the occurrence of an intercurrent disease ($p<0.05$). Moreover, a lower BI, a higher Charlson index, and particularly the presence of DM were independently associated. If both comorbidity and a lower baseline functional status were present, the odds ratio (95%CI) of developing intercurrent diseases was 6.70 [2.33-19.2], compared to 1.73 [0.52-5.72] (comorbidity only) and 1.62 [0.53-4.94] (only BI ≤14).

Conclusions

On admission, functional impairments and comorbidity (particularly diabetes) independently contribute to developing intercurrent diseases during geriatric stroke rehabilitation. Therefore, routine evaluation of comorbidity and functional status at the start of rehabilitation helps to identify patients at risk. Particular attention should be paid to patients with DM to prevent the occurrence of intercurrent diseases and support optimal functional recovery.

INTRODUCTION

Following acute hospitalisation, rehabilitation helps patients to regain functional independency that enables them to be discharged home. However, during hospitalisation, the risk of functional decline and complications is particularly increased in older patients.[1] In the Netherlands, about one-third of all stroke patients are referred to a skilled nursing facility (SNF) that provides geriatric rehabilitation. These patients are usually relatively older, have a longer length of stay (LoS) in the acute hospital, and have more complex problems (Appendix A).[2] Also, during inpatient rehabilitation, intercurrent diseases may occur that interfere with therapy and could negatively impact rehabilitation outcome.[3,4]

Studies investigating complications during inpatient stroke rehabilitation found that 30–96% of the patients developed complications; this wide range could be due to different definitions of a complication and the methods of measurement.[5–12] The present study investigates intercurrent diseases, i.e. any disease that occurs during the progress of another disease, during rehabilitation. Factors related to intercurrent diseases can include age, gender[9,13], time interval between stroke and rehabilitation[7,10,12], severe stroke[7,11] or functional impairment[6, 9,12,13] and comorbidity[5–7,13,14], although it is unknown which specific comorbidities are related. Particularly, older patients are at risk of functional decline and often have multiple comorbidities. However, few studies have investigated associations with intercurrent diseases in the older, vulnerable group of patients receiving geriatric stroke rehabilitation.[5,13] Furthermore, intercurrent diseases may impede successful functional recovery.[5,14] Therefore, to better understand the relations between comorbidity, functional impairment and intercurrent diseases, and to identify associated pre-existing comorbid conditions, this study explores: (i) the presence, and number of intercurrent diseases and their impact on older patients admitted to an SNF, recovering after stroke, and (ii) factors associated with the presence and number of intercurrent diseases, focusing on functional status and comorbidity.

METHODS

Participants

Data were obtained from the Geriatric Rehabilitation in AMPutation and Stroke (GRAMPS) study. Data collection took place between January 2008 and July 2010; details on the study design are already published.[15] A total of 15 SNFs located in the southern part of the Netherlands participated. All stroke patients admitted to one of these SNFs were eligible for inclusion. Patients were excluded if they refused participation, were unable to give informed consent, were critically ill, or were expected to have a stay of ≤ 2 weeks. The medical ethics committee of the region Nijmegen-Arnhem approved the study protocol.

Outcome measures

For the present study, the outcome measures were: the presence and number of intercurrent diseases that occurred during rehabilitation. Intercurrent diseases were coded using the 10th revision Clinical Modification ICD-10CM. At discharge, the attending physician registered intercurrent diseases that affected the course of the rehabilitation: impact was classified according to (i) whether the disease had prolonged the LoS or (ii) whether the rehabilitation goals needed adjustment. Four categories were formed: (1) no intercurrent disease, (2) 'No impact', (3) 'With impact', and (4) intercurrent disease that directly caused death.

Data collection

The participating multidisciplinary teams consisted of a physician[16], a physiotherapist, an occupational therapist, a psychologist, a speech therapist, a dietician and skilled nurses; all received the same instructions regarding performance of the assessments. Data were collected within the first 2 weeks after admission (T0) and at discharge (T1) from the SNF or (at the latest) 1 year after admission, if a patient was still in the SNF at that time.

Measurements

The following patient characteristics and data were collected: age, gender, home situation, comorbidity, LoS in acute hospital, LoS in the SNF, and discharge destination.[5–14,17]
Functional assessment was performed at baseline and at discharge using the modified Barthel index (BI) to assess activities of daily living (ADL).[18] Premorbid BI was assessed on admission, using information on the patient's situation prior to the acute stroke, based on interview and collateral history. Functional recovery was defined in two ways: BI at discharge and 'relative functional gain', which was calculated as follows: (BI-discharge minus BI-admission)/(BI-premorbid minus BI-admission) × 100.[19,20] Relative functional gain expresses the achieved percentage of potential functional gain.
Pre-existing comorbidity was assessed using the Charlson comorbidity index (Charlson-CI). This index consists of 19 diagnoses and was adjusted for stroke.[21–23] The Charlson-CI was categorised as: 0 (no comorbidity), 1 (single comorbidity) or ≥ 2 (multiple comorbidities), unless otherwise specified. Comorbidities were recorded if present in medical history, e.g. chronic diseases and conditions that required ongoing use of (preventive) medication. Conditions that had completely resolved without any residual symptoms or need for treatment were not noted (e.g. childhood asthma). Finally, if myocardial infarction in the past had led to heart failure, only heart failure was recorded.

Statistical analysis

Data were processed and analysed using the Statistical Package for Social Science version 23. Means with standard deviations (normal distribution), medians with interquartile ranges (skewed data), or absolute numbers with percentages (categorical data) are reported.
A Chi-Squared test (categorical data), ANOVA or Kruskal–Wallis test, depending on their distribution, were used to detect mean differences in characteristics between the four

intercurrent disease categories and to identify comorbid conditions related to the occurrence of intercurrent diseases. A p-value of ≤ 0.05 was considered statistically significant.
Multivariate analyses were performed using binary logistic regression with the presence of intercurrent diseases and Poisson regression with number of intercurrent diseases as the dependent variable. Rehabilitation LoS (log) was added as the 'offset'. Factors included in the multivariate model were age and gender. Significant baseline variables ($p < 0.10$) were added as a continuous variable if applicable.
Before performing the analyses, data were tested for the required assumptions, such as multicollinearity, interaction and effect modification. To investigate comorbidity and baseline functional status, separate and combined relations with the presence of intercurrent diseases were analysed. For this purpose, variables were dichotomized. Odds ratios (OR) were calculated with the absence of both factors as reference category.[24]
Sensitivity analyses were performed, i.e. with and without deceased patients.

RESULTS

Characteristics

Of the 378 eligible patients, 186 were included in the GRAMPS study; the excluded patients did not differ with regard to age, gender or LoS.[25] The present study included 175 patients because 11 patients were lost to follow-up, mainly due to translocation to another SNF (Supplement material Appendices B and C). Table 1 presents the baseline characteristics of the study population, and the intercurrent disease categories. Mean age was 78.8 years and 46% were males. On average, LoS in the acute hospital was 19 days, the premorbid BI was 20, baseline BI was 12, and BI at discharge was 17. LoS in the SNF was 12 weeks, the (average) relative functional gain was 67, and 56% of these patients was discharged home. Of the 89 (51%) patients that developed an intercurrent disease, 49% developed one disease, 33% ≥ 2 diseases, and 18% died. Comorbidity was present in 116 (62%) patients: 40 (21%) scored 1 and 76 (41%) scored ≥ 2. The most prevalent pre-existing comorbidities were myocardial infarction (18%), diabetes mellitus (18%) and congestive heart failure (16%).

Characteristics related to intercurrent diseases

Patients without any intercurrent disease had a BI on admission of at least 4 points higher than those with intercurrent diseases. The proportion of patients without comorbidity was largest in the category 'no intercurrent disease' (52%), whereas in the category 'With impact', the proportion of patients with multiple comorbidities was the largest (54%), $p = 0.007$. Patients that developed intercurrent diseases were less often discharged home, had a longer LoS, a lower BI at discharge, and a lower relative functional gain. This also applied to the category that was considered as having 'No impact'. Multivariate analyses showed that: BI on admission (OR 0.87 [0.82–0.92]) and comorbidity (OR 1.43 [1.13–1.81]) were independently associated with the presence of intercurrent diseases, but

only the Charlson-CI was significantly associated with number of intercurrent diseases (incidence rate ratio: 1.14 [1.03–1.25], p= 0.008). This means that with every extra point on the Charlson-CI, a 14% increase in the number of intercurrent diseases is expected (Supplement material Appendix D).

Comorbidity and intercurrent diseases

Having diabetes and/or kidney disease was significantly related to the occurrence of an intercurrent disease (Table 2). Logistic regression analysis showed that only diabetes was independently associated (OR: 3.50 [1.32–9.26]). No clear patterns or relations between comorbidities and specific intercurrent diseases were observed: a wide variety of different diseases occurred in patients with pre-existing comorbidity. The intercurrent diseases that most frequently occurred were cardiovascular (13%), psychiatric (12%) such as depression and delirium, and genitourinary (11%), predominantly urinary tract infections. An overview of intercurrent diseases, per comorbidity (the five most prevalent only), is presented in Supplement material Appendix E.

Comorbidity and baseline functional status

Table 3 shows the cumulative effect of the combination of a lower functional status on admission (BI ≤ 14) and the presence of comorbidity (CharlsonCI ≥ 1) in relation to the occurrence of an intercurrent disease. On admission, when comorbidity and lower functional status on admission were present separately, ORs were 1.73 [0.52–5.72] and 1.62 [0.53–4.94] respectively. However, if both were present, the OR was 6.70 [2.33–19.2].

Table 1. Patient characteristics classified by intercurrent disease impact category.

	Total baseline n = 175	ID absent n = 86	ID no impact n = 22	ID with impact n = 46	ID deceased n = 16	ID impact unknown n = 5
Variables at baseline						
Age (years), mean (SD)	78.8 (8.0)	78.2 (8.3)	78.8 (5.6)	78.9 (8.5)	81.2 (8.4)	82.6 (7.8)
Gender (male), n (%)	80 (46)	45 (52)	11 (50)	16 (35)	7 (44)	1 (20)
CharlsonCI score, median (IQR)	1 (2)*	0 (2)	1 (2)	2 (2)	2 (2)	2 (3)
CharlsonCI = 0, n (%)	68 (39)#	45 (52)	8 (36)	10 (22)	3 (19)	2 (40)
CharlsonCI = 1, n (%)	38 (22)#	19 (22)	6 (27)	11 (24)	2 (13)	0 (0)
CharlsonCI ≥ 2, n (%)	69 (39)#	22 (26)	8 (36)	25 (54)	11 (69)	3 (60)
Premorbid Barthel Index, median (IQR)	20 (3)	20 (2)	20 (2)	19 (3)	17 (7)	18 (3)
LoS acute hospital in days, median (IQR)	19 (14)	19 (11)	19 (13)	19.5 (18)	22 (18)	21 (21)
Barthel Index on admission, median (IQR)	12 (10)*	14 (7)	9 (12)	9 (8)	8 (9)	10 (6)
Variables at discharge						
LoS rehabilitation in weeks, median (IQR)	12 (15)*	8 (6)	16 (23)	22 (26)	-	16 (6)
Barthel Index at discharge, median (IQR)	17 (8)*	18 (4)	16 (9)	11 (10)	-	15 (4)
Relative functional gain, median (IQR)	67 (90)*	85 (84)	67 (76)	24 (79)	-	71 (42)
Discharge home, n (%)	88 (56)#	62 (73)	9 (43)	13 (28)	-	4 (80)

Abbreviations: ID, intercurrent disease; SD, Standard Deviation; Charlson CI, Charlson comorbidity index; IQR, interquartile range; LoS, length of stay. Note: statistical significance at $p<0.05$: * Kruskal-Wallis test; # Chi-Square test. Equal statistical significance was found when deceased patients were excluded

Table 2. Associations between comorbid conditions and presence of ≥ 1 intercurrent disease.

	Total	ID absent	ID present
Charlson comorbidity index, median (IQR)	1 (2)	0 (2)[#]	2 (3)[#]
Myocardial infarction, n (%)	31 (18)	13	18
Heart failure, n (%)	29 (17)	**10***	**19***
Peripheral vascular disease, n (%)	23 (13)	9	14
Dementia, n (%)	1 (1)	1	0
Chronic pulmonary disease, n (%)	18 (10)	8	10
Musculoskeletal/connective tissue, n (%)	9 (5)	**2***	**7***
Ulcers, n (%)	8 (5)	2	6
Mild liver disease, n (%)	3 (2)	1	2
Kidney disease (moderate) , n (%)	16 (9)	**3[#]**	**13[#]**
Diabetes mellitus, n (%)	31 (18)	**9[#]**	**22[#]**
Malignancy, n (%)	10 (6)	3	7
Leukaemia, n (%)	1 (1)	1	0
Lymphoma, n (%)	2 (1)	0	2
Moderate liver disease, n (%)	0 (0)	0	0
Metastasis of solid tumour, n (%)	3 (2)	1	2
Any malignancy (of the above mentioned), n (%)	13 (7)	4	9

Abbreviations: ID, intercurrent disease; IQR, interquartile range.
Note: Chi Square test: * p<0.10, [#] p<0.05. Comorbidities included in the logistic regression analysis are presented in **bold**.

Table 3. Comorbidity and baseline function: the separate and combined effect on developing an intercurrent disease in geriatric stroke rehabilitation (n=170).

CharlsonCI score ≥ 1	BI ≤ 14 on admission*	Intercurrent disease: YES	NO	Odds ratio [95% CI]
NO	NO	6	17	Reference 1.00
NO	YES	16	28	1.62 [0.53 – 4.94]
YES	NO	11	18	1.73 [0.52 – 5.72]
YES	YES	52	22	6.70 [2.33 – 19.2]

Abbreviations: Charlson CI, Charlson Comorbidity Index; BI, Barthel index; CI, confidence interval.
Note: *Assessing the BI on admission was not possible in 5 patients. Sensitivity analysis showed similar results: when deceased patients were excluded (n=154) ORs were 1.32 [0.42-4.11], 1.42 [0.42-4.83] and 5.54 [1.91-16.0] respectively.

DISCUSSION

Main findings

To our knowledge, this is the first study to focus on comorbidity and intercurrent diseases during geriatric stroke rehabilitation. The study cohort was characterised by a large drop in functional status after acute stroke, often with multiple comorbidities and a higher age compared to the majority of studies on stroke patients.[5–10,12–14,26] Although this subgroup had been triaged for inpatient geriatric rehabilitation, and selected as a vulnerable subgroup of patients on the base of medical complexity and functional dependency, discriminant factors were still present. Lower baseline functional status, higher pre-existing comorbidity burden in general and specifically the presence of diabetes mellitus were independent determinants of developing intercurrent diseases. Furthermore, patients with multiple comorbidities (higher Charlson-CI) had an increased risk to develop a higher number of intercurrent diseases. Finally, the odds of developing an intercurrent disease were substantially higher if a patient had both comorbidity and functional impairment than if only one of these factors was present.

Intercurrent diseases

The percentage of patients (51%) that developed intercurrent diseases is comparable to that of studies using an assessment method similar to ours (i.e. 30–54%).[5,8,9,13,14,17] However, although other studies found a higher rate (60–100%), there was a clear difference in the methods used. For example, shoulder pain, limb spasticity, dysphagia or aphasia were categorised as a complication, whereas in the present study (and similar studies) these were considered to be symptoms and not diseases.[6,7,10-12,26] In this study, we were specifically interested in intercurrent diseases that occurred during the inpatient rehabilitation period, and physicians retrospectively registered the intercurrent diseases. Nevertheless, our incidence rates were similar to those in studies using prospective assessment and similar prevalent diseases were found, i.e. genitourinary (urinary tract infections) and psychiatric diseases (depression and delirium).[6-12,14,17] However, in the present study intercurrent cardiovascular disease was more prevalent, presumably because pre-existing cardiovascular comorbidities were highly prevalent in our subgroup of vulnerable geriatric patients.

Intercurrent diseases and their associations

The presence of intercurrent diseases was related to rehabilitation impact indices (longer LoS, less functional recovery and less often being discharged home). Despite that physicians registered intercurrent diseases retrospectively according to their influence on rehabilitation, it was striking that this relation also applied to the category ‘No impact’. This underlines the impact that intercurrent diseases can have on rehabilitation outcomes. Besides baseline functional status and comorbidity in general, diabetes mellitus was found to be a significant determinant of the occurrence of an intercurrent disease. Diabetes affects various organ systems (e.g. vascular, skin, eyes, nervous system) and might be the (underlying) cause of a variety of intercurrent diseases. However, the present study had

insufficient power to further investigate different comorbidities and their associations with specific intercurrent diseases.

Comorbidity and functional impairment

The last aim was to focus on comorbidity and functional impairment, as both seem to play an important role in relation to the occurrence of intercurrent diseases. Moreover, our results suggest that the combination of these factors increases the risk of developing intercurrent diseases, even more than would be expected (i.e. the ORs from the separate factors multiplied or summed up). This may indicate that the evaluation of comorbidity and functional status should be integrated, preferably taking into account the functional severity of each comorbid condition. It should be noted that some ORs were not significant due to the small size of the subgroups. A larger study is needed to further investigate this combined effect on developing intercurrent diseases during rehabilitation.

Strengths and limitations

The strength of the GRAMPS study is its multidisciplinary and multicentre prospective design in a relatively large study population. Whereas most studies on stroke rehabilitation investigated mainly younger patients, the present study represents the older, geriatric stroke patient population relatively well and, therefore, strengthens external validity.[27] The study investigated two outcomes: presence and number of intercurrent diseases. Diseases were recorded using the ICD-10 coding system, and only diseases were scored (i.e. not symptoms such as pain or dysphagia). We believe this prevents confusion regarding definitions and elucidates the role of functional activities (functional status), medical health conditions (comorbidity and intercurrent diseases) and their interactions in the complex setting of rehabilitation and recovery, using the ICF model as a framework.[28]

Another strength is the use of a Poisson regression that allowed analysing the 'number of intercurrent diseases'. Furthermore, we presented the classifications 'No impact' and 'With impact'. The intercurrent diseases found in this study might be a selection of the more severe diseases, due to the retrospective design of registering the diseases; however, analysing the impact classification as separate groups provided extra information and insight.

Some limitations of the study need to be considered. This study can be considered a secondary analysis, because the GRAMPS study sample size (power) estimation was originally based on the dichotomous outcome measure 'home discharge', and a minimum group size of 70 was considered to be appropriate (15). However, in the present study, the groups with and without intercurrent disease were of sufficient size (n = 89 and n = 86, respectively). Furthermore, the cohort was a specific subgroup of older and vulnerable stroke patients as presented in Appendix A, and data collection for the GRAMPS study ended some years ago (in 2010). The mean LoS in this study was longer (i.e. ± 4 weeks) compared with recent clinical practice in similar SNFs. Nevertheless, we believe that these data reflect

the current situation of geriatric stroke rehabilitation well enough, since no important changes regarding comorbidities or intercurrent diseases are expected.
Finally, comorbidity was assessed using the CharlsonCI in relation to outcomes other than mortality, although the index was specifically designed to predict mortality. Nevertheless, all detected relations showed similar results after performing sensitivity analyses in which deceased patients were excluded.

CONCLUSIONS

Intercurrent diseases frequently occur during geriatric stroke rehabilitation and have a detrimental effect on rehabilitation outcome, such as functional recovery and length of stay. The present study emphasises that comorbidity and functional status need to be integrated and are important factors associated with intercurrent diseases. In particular, diabetes mellitus showed a strong independent association; therefore, this should be a focus for screening, early detection of dysregulation and treatment, to target prevention of various intercurrent diseases. The impact of specific comorbidities and the usefulness of routinely assessing comorbidity combined with integrated functional severity should be further investigated.

ACKNOWLEDGEMENTS

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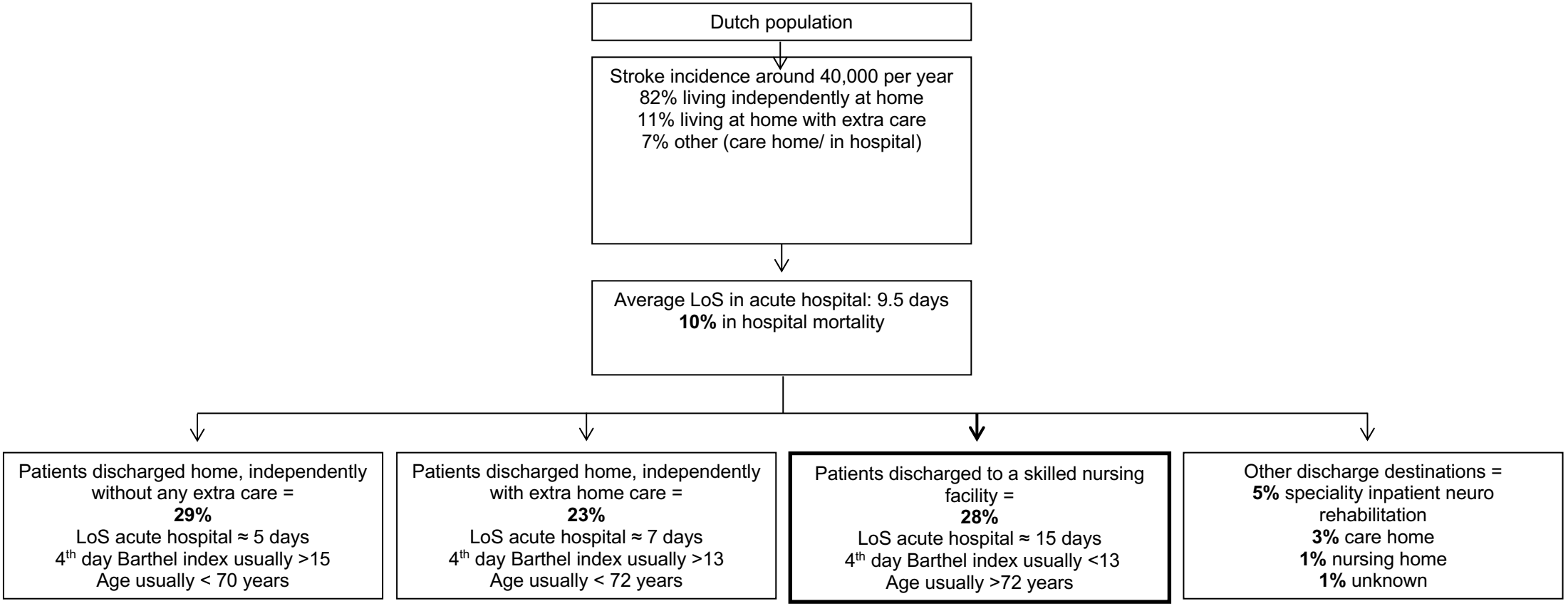
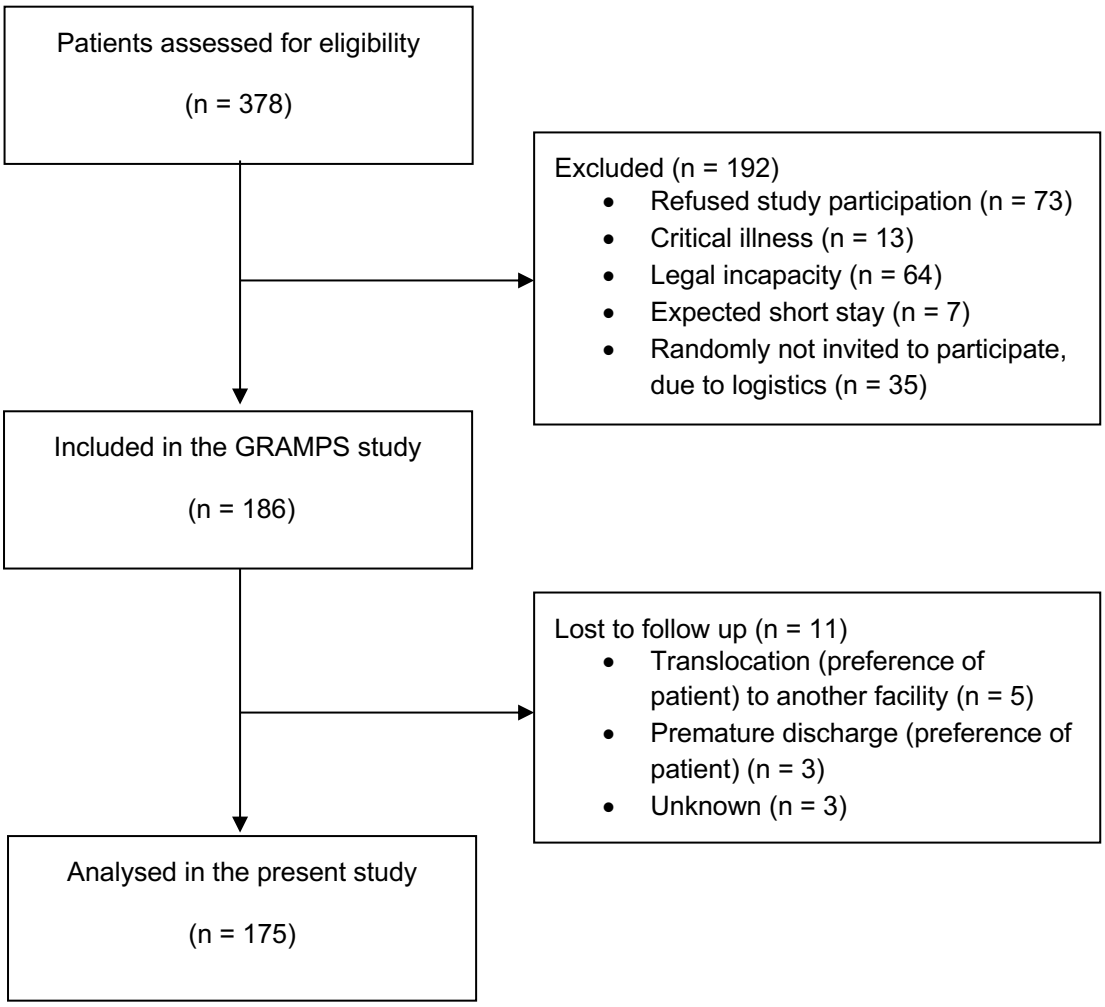
APPENDICES

Appendix A. Flow chart: characteristics of the Dutch stroke population (2008-2012)(2)



Note: characteristics of the subgroup in the highlighted frame **(bold)** are similar in the present study. Abbreviations: LoS, length of stay.

Appendix B. Flow Diagram of the present study cohort



Appendix C. Characteristics of the patients that were lost to follow up

	Missing (n=11)	Cohort (n=175)
Age in years, mean (SD)	74.8 (10.8)	78.8 (8.0)
Gender, male (n, %)	5 (46)	79 (46)
LoS in acute hospital, median (IQR)	18 (9)	19 (13)
Independent living before event (n, %)	11 (100)	153 (89)
Charlson-CI score, mean (SD)	2.0 (1.8)	1.5 (1.8)
BI premorbid, median (IQR)	20 (2)	20 (3)
BI on admission, median (IQR)	3 (9)	12 (10)

Abbreviations: SD, standard deviation; IQR, Interquartile range; LoS, length of stay; Charlson-CI, Charlson comorbidity index; BI, Barthel index.

Appendix D. Characteristics independently associated with intercurrent diseases during geriatric stroke rehabilitation.

Variable	Presence of ID OR [95% CI]*	Number of ID IRR [95% CI]#
Age	1.01 [0.97 – 1.05]	1.01 [0.98 – 1.04]
Gender (male)	0.70 [0.36 – 1.39]	1.19 [0.78 – 1.82]
Barthel index on admission	0.87[c] [0.82 – 0.92]	0.99 [0.96 – 1.03]
Charlson comorbidity index	1.43[a] [1.13 – 1.81]	1.14[b] [1.03 – 1.25]

Abbreviations: ID, intercurrent disease; OR, odds ratio; CI, confidence interval; IRR, incident rate ratio. Note: * logistic regression analysis; # Poisson regression analysis. Statistical significance: [a] $p < 0.05$; [b] $p < 0.01$.; [c] $p < 0.001$. Equal statistical significance when deceased patients were excluded.

Appendix E. Number of intercurrent diseases and their impact on rehabilitation goals or length of stay.

ICD 10 code	Intercurrent Disease	Total n = 175	MI and ID n = 18	HF and ID n = 19	PVD and ID n = 14	KD and ID n = 13	DM and ID n = 22	Deceased n = 16
I A00-B99	Generalised infection	6	0	3	0	0	2	2
II C00-D48	Neoplasm	4	1	1	1	1	1	0
III D50-D89	Haematological	3	0	2	1	3	0	0
IV E00-E90	Endocrine	4	0	1	1	0	1	0
V F00-F99	Psychiatric/ delirium	21	3	4	2	2	2	0
VI G00-G90	Neurological	8	2	1	2	0	2	5
VII H00-H59	Ocular	4	1	1	1	1	1	0
VIII H60-H95	Ear/nose/throat	0	0	0	0	0	0	0
IX I00-I99	Cardiovascular	22	4	7	4	2	4	6
X J00-J99	Pulmonary	15	2	3	0	1	2	3
XI K00-K93	Gastrointestinal	14	1	2	3	2	2	0
XII L00-L99	Dermatological	5	0	1	0	2	2	0
XIII M00-M99	Musculoskeletal	9	1	2	2	2	3	0
XIV N00-N99	Genitourinary	19	9	5	4	6	6	0
XVIII R00-R99	Not otherwise specified	4	2	0	2	1	3	0
XIX S00-T98	Iatrogenic injury or intoxication	1	0	0	0	0	0	0

Abbreviations: ICD, International Classification of Diseases; ID, intercurrent disease; MI, myocardial infarction; HF, heart failure; PVD, peripheral vascular disease; KD, kidney disease; DM, diabetes mellitus.
Note: a patient could have multiple comorbidities and intercurrent diseases.

Chapter 6

Comorbidity clusters and their association with unsuccessful geriatric rehabilitation: discharge destination and functional recovery.

Submitted as: Kabboord AD, van Eijk M, van Balen R, Achterberg WP.

ABSTRACT

Objectives: To investigate whether comorbidities from patients that were admitted for geriatric rehabilitation (GR) form clusters, and whether these clusters are associated with unsuccessful GR outcomes.

Design: The SINGER study is a prospective cohort study. It was part of a national program, aiming to improve the quality of GR by stimulating self-organizing capacity to develop integrated care. Data collection took place in March–June 2011, September–December 2011, and March–June 2012.

Setting: Sixteen skilled nursing facilities providing GR, situated across the Netherlands.

Participants: All admitted patients were asked to participate. Patients with severe dementia were excluded.

Methods: Professional caregivers collected patient characteristics: age, gender, primary diagnosis, and length of stay. Comorbidity was assessed using the functional comorbidity index including the presence of dementia. Function on admission and at discharge was measured using a modified Barthel index (BI). A two-step cluster analysis was performed. Logistic regression analyses were performed to examine the independent associations between comorbidity (clusters) and the outcomes.

Main outcome measures: occurrence of intercurrent diseases, less than 4 points gain on the BI, and discharge to a nursing home.

Results: Six clusters were identified. The cardiovascular (OR:1.66 [1.05–2.62]) and degenerative&mental (OR:1.87 [1.13–3.11]) clusters were associated with intercurrent diseases. The cardiovascular (OR:1.87 [1.18–2.97]) and osteoarthritis (OR:1.83 [1.14–2.93]) clusters were associated with BI gain<4. The cardiovascular (OR:1.93 [1.04–3.59]), degenerative&mental (OR:2.97 [1.52–5.79]), and the rest group (OR:2.07 [1.12–3.82]) clusters were associated with discharge to a nursing home.

Conclusions: Patients in the cardiovascular cluster had a high risk of all the unsuccessful rehabilitation outcomes. Comorbidity is an important factor related to rehabilitation outcomes and the clusters specifically indicated a negative impact of cardiovascular comorbidity. Interventions that focus on comorbidity assessment and treatment during GR should be further investigated.

INTRODUCTION

Many countries face the challenges of providing adequate post-acute care for older patients who need to recover after acute illness and hospitalization before being discharged home.[1] In the Netherlands, specialized geriatric rehabilitation is provided by skilled nursing facilities and is supervised by an elderly care physician.[2, 3] In patients that are referred for geriatric rehabilitation, comorbidity is common. Studies have shown that comorbidity may hamper or delay successful functional recovery and increase the risk of intercurrent diseases during rehabilitation.[4-8] However, much is still unclear about whether comorbidities in the patient population admitted for geriatric rehabilitation cluster and form patterns and furthermore, whether these comorbidity clusters are associated with rehabilitation outcome, such as functional recovery and being discharged home after rehabilitation.

In a community dwelling population in the Netherlands the prevalence of one or more chronic diseases was 75% and that of multimorbidity (coexistence of 2 or more chronic diseases) was 47% in persons above 65 years old.[9] The authors found that comorbidity included many different combinations of diseases that clustered, especially depression and anxiety, coronary heart disease and heart failure, and COPD and heart failure. This study did not, however, investigate the associations of comorbidity clusters with one or more outcomes. Recently, a study was carried out in New Zealand which investigated clusters of comorbidities in persons above 80 years old and the authors also studied the relation with different outcomes: medication use, mortality and hospitalizations.[10] The following comorbidity clusters (in non-Maori) were discovered: 1) 'well', a cluster with low comorbidity prevalence, 2) 'heart failure', 3) 'arthritis and depression', 4) 'cancer', 5) 'respiratory and diabetes', and 6) 'stroke'. They also found that patterns of multimorbidity differed between ethnic groups (Maori and non-Maori) and concluded that profiles of conditions (multimorbidity clusters) were associated with longitudinal outcomes: hospitalizations and mortality. Both studies were carried out in the community[9,10]. In the patient population admitted for geriatric rehabilitation, an analysis of comorbidity clusters and their relation with rehabilitation outcome has not yet been published. The present study aims to determine clusters of comorbidities in older patients admitted for geriatric rehabilitation and to describe the cluster characteristics. Furthermore, it aims to investigate whether comorbidity and clusters of comorbidities are associated with unsuccessful rehabilitation outcomes.

METHODS

Design and participants

Data were obtained from the Synergy and INnovation in GEriatric Rehabilitation (SINGER) study. Details of this study have previously been published.[11-13] Sixteen skilled nursing facilities in the Netherlands participated and professional caregivers (physiotherapists, nurses and medical specialists) collected data of patients that were referred for geriatric rehabilitation after acute hospital admission. Eligibility criteria were: admission for geriatric

rehabilitation for any reason. Exclusion criteria: severe dementia, no informed consent, and for this study duplicate participants (those who were readmitted in a later cohort) were included once. The SINGER study had a prospective observational design in which three cohorts were formed. Each cohort had an inclusion period of 4 months. Data collection took place in March – June 2011 (cohort 1), September – December 2011 (cohort 2), and March – June 2012 (cohort 3). The local Medical Ethics Committee approved the study protocol with a waiver of informed consent. However, it was decided to still ask for informed consent during the study.

Data collection and measurements

The following patient characteristics and data were selected on admission: age, gender, pre-existent comorbidity, primary diagnosis, functional status on admission. At discharge from rehabilitation: duration of stay, intercurrent diseases, readmissions to acute hospital, and discharge destination.

Four categories of primary diagnoses were distinguished: stroke, traumatic fracture(s), elective orthopedic surgery (knee or hip joint replacement), and a heterogeneous group 'miscellaneous'. To assess pre-existent chronic conditions 19 comorbidities were selected: the 18 comorbidities from the Functional Comorbidity Index (FCI) and dementia (Appendix A). The FCI has specifically been designed to assess comorbidities that are related to function.[14] An Elderly Care Physician completed the index. Functional status was measured on admission and at discharge using the modified Barthel index (BI).[15] This index scores the degree of (physical or verbal) help that a person needs to perform ADL activities. The index consists of 10 items where the actual performance is assessed (items cover the last 24-48 hours). A high score on the BI corresponds to a high degree of functional independence. Finally, intercurrent diseases were registered (Appendix B).

Outcome measures

The outcome measure was unsuccessful rehabilitation, using three different outcome measures: the occurrence of intercurrent diseases, unsuccessful functional recovery defined as 'improvement of less than 4 on the BI' (BI gain < 4), and unsuccessful discharge (discharge to a more dependent living arrangement in a long term care setting) defined as 'discharge to a nursing home'. Patients that reached a maximum of 20 on the BI but had a BI gain of less than four (ceiling effect) were considered successful. The cut-off point was set at 4 because this is the smallest real difference (SRD) of the BI and 3.6 was the patient-based minimal important change (MIC).[16, 17]

Statistical analysis

To identify clusters of comorbidities, a two-step cluster analysis was performed[18]. In step one, the log-likelihood distance measure was used to measure distance between clusters and form a cluster feature tree. In step two, the Schwarz's Bayesian Criterion was used as a clustering criterion to determine the number of clusters. Participants were assigned to one

of the clusters based on their comorbidity profile. Cluster classification was based on the most prevalent condition(s) within the cluster in combination with the highest prevalence across the clusters. Characteristics and outcomes are presented for each of the clusters. After cluster classification, logistic regression analyses were performed with the three outcomes: occurrence of intercurrent diseases, BI gain <4, and discharge to a nursing home. Age, gender, primary diagnosis, BI on admission, and comorbidity were included as independent variables. Missing data were not imputed. Per outcome, two regression models were created: the first model included FCI total score representing comorbidity and the second model included the comorbidity clusters. Statistical analyses were performed with SPSS (Statistical Package for Social Sciences) version 25.

RESULTS

Participants

Baseline data on comorbidity were available from 1106 participants and were included in the cluster analysis. Availability of data on the outcome measures are presented in the flowchart (Figure 1 and Appendix C). Mean age was 77 (SD 11) and 693 (63%) were women. Median length of stay in rehabilitation (LOS) was 40 days (IQR 20-74). Primary diagnoses for which the participants received rehabilitation were stroke (n=412, 37%), elective orthopedic surgery (n=164, 15%), trauma (n=268, 24%), and a miscellaneous group (n=262, 24%). See also Appendix D for specific diagnoses in this last group. Median FCI score was 2 (IQR 1-3), BI on admission was 12 (IQR 7-16), BI at discharge 17 (IQR 13-20), mean total BI gain during rehabilitation was 3.7 (SD 4.1, range: -16-20), 682 (68%) had an intercurrent disease during rehabilitation, and 115 (11%) were readmitted to an acute hospital (Appendix E). Finally, 680 (61%) were discharged home, 183 (17%) were discharged to a nursing home, and 62 (6%) died during rehabilitation (Appendix E). The other participants were lost to follow up: 20 (2%) were readmitted in acute hospital without return to rehabilitation, 43 (4%) moved to another rehabilitation facility, and from 118 (11%) discharge data are missing for unknown reasons.

Figure 1. Flow chart

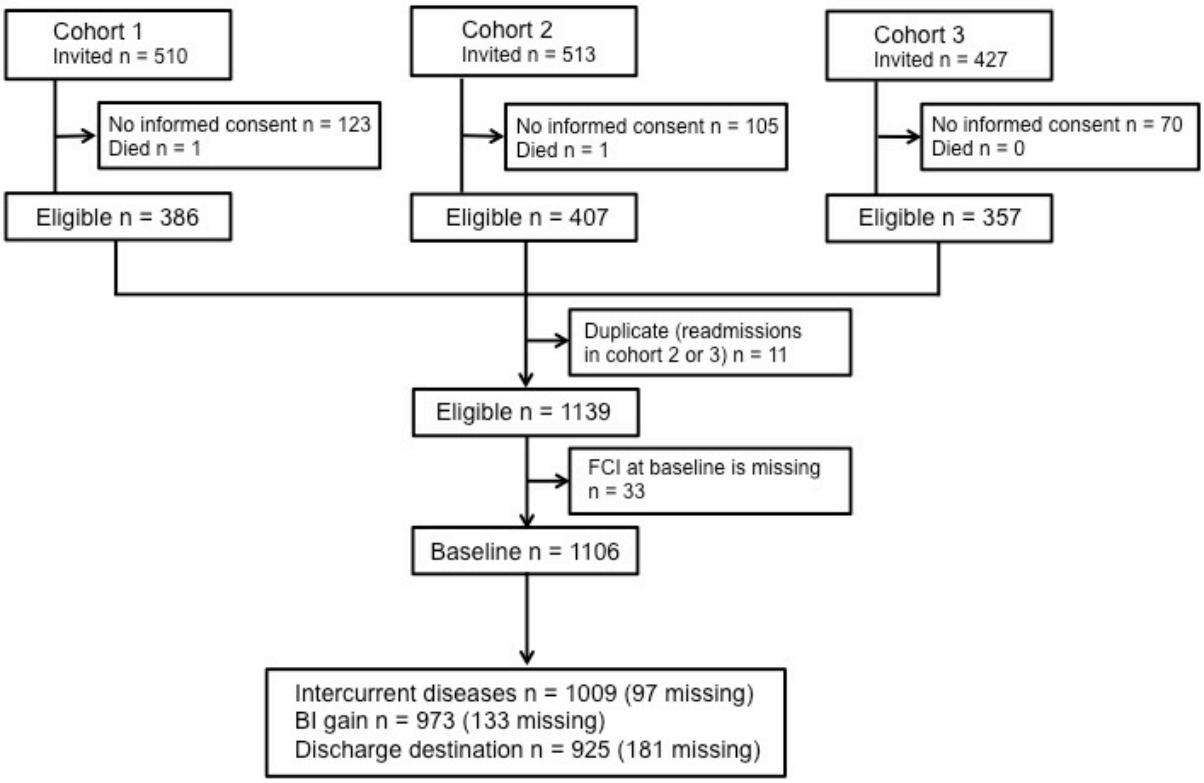
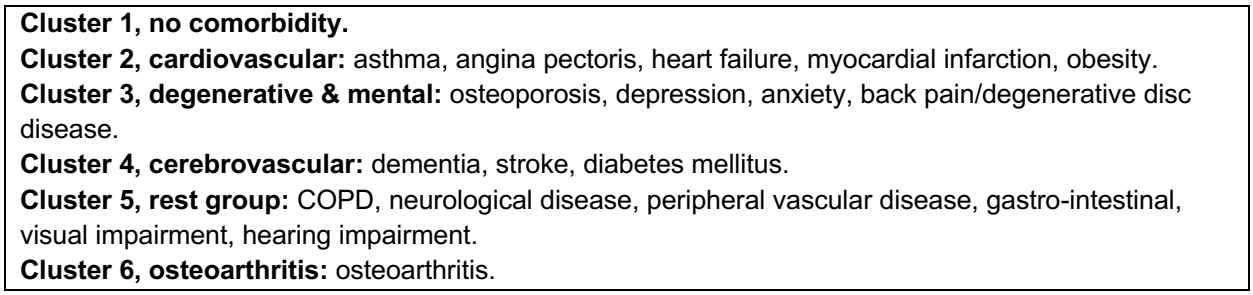


Figure 2. Cluster grouping



Cluster descriptions and characteristics

After performing a two-step cluster analysis, six clusters were identified (Figure 2). The comorbidities of the participants clustered into six different clusters: a cluster containing participants without any comorbidity (1), a cluster containing participants that mainly had cardiovascular comorbidities (2), a cluster containing participants with mainly degenerative musculoskeletal comorbidity and/or a mental disorder (3), a cluster containing participants with mainly cerebrovascular comorbidity (4), a heterogeneous rest group (5), and the last cluster mainly containing participants with osteoarthritis (6). The number of patients with diabetes and stroke were (almost) even in clusters 2 (stroke 63; diabetes 81) and 4 (stroke 63; diabetes 85). Characteristics are presented in Table 1.

Table 1. Characteristics of patients and clusters

Variable	Number (n)	Cluster 1 No comorbidity n = 224	Cluster 2 Cardiovascular n = 219	Cluster 3 Degenerative & mental n = 146	Cluster 4 Cerebrovascular n = 135	Cluster 5 Rest group n = 216	Cluster 6 Osteoarthritis n = 166
Age, mean (SD)	1102	73.9 (12.5)	78.0 (9.8)	75.6 (11.2)	75.5 (11.7)	77.7 (10.1)	78.2 (9.4)
Female, n (%)	1106	141 (63)	121 (55)	111 (76)	71 (53)	115 (53)	134 (81)
Primary diagnosis on admission	1106						
Stroke, n (%)		90 (40)	99 (45)	37 (25)	64 (47)	83 (38)	39 (24)
Elective orthopedic surgery, n (%)		41 (18)	24 (11)	12 (8)	12 (9)	20 (9)	55 (33)
Trauma, n (%)		54 (24)	39 (18)	59 (40)	25 (19)	44 (20)	47 (28)
Miscellaneous		39 (17)	57 (26)	38 (26)	34 (25)	69 (32)	25 (15)
BI on admission, median (IQR)	1066	12 (8)	11 (10)	13 (8)	11 (8)	11 (7)	13 (7)
Number of comorbidities	1106						
FCI score, median (IQR)		0	3 (2-4)	2 (2-3)	1 (1-2)	2 (1-2)	2 (1-3)
0, n (%)		224	0	0	0	0	0
1, n (%)		0	45 (21)	35 (24)	97 (72)	79 (37)	47 (28)
2, n (%)		0	63 (29)	44 (30)	23 (17)	85 (39)	60 (36)
≥ 3, n (%)		0	111 (50)	67 (46)	15 (11)	52 (24)	59 (36)
Comorbidities (n)	1106						
Arthritis		0	30	11	6	0	**166**
Osteoporosis		0	5	**75**	2	4	18
Asthma		0	**15**	1	0	3	4
COPD		0	51	22	0	**70**	18
Angina pectoris		0	**56**	7	0	7	0
Heart Failure		0	**108**	19	0	19	16
Myocardial infarction		0	**108**	11	0	2	3
Neurologic disease		0	0	12	1	**39**	12
Stroke		0	63	29	**63**	58	29

Peripheral vascular disease		0	19	8	1	**53**	8
Diabetes mellitus		0	81	24	**85**	37	18
Gastrointestinal disease		0	12	25	4	**39**	23
Depression		0	6	**51**	1	1	10
Anxiety disorder		0	4	**25**	0	5	3
Visual impairment		0	11	3	0	**61**	31
Hearing impairment		0	1	2	2	**26**	4
Degenerative disc disease		0	6	**47**	2	2	13
Obesity		0	**30**	1	1	0	8
Dementia		0	6	5	**24**	4	7
Outcome variables							
Length of stay in days, median (IQR)	1096	37 (54)	45 (62)	36 (59)	47 (53)	40 (47)	34 (44)
BI at discharge, median (IQR)	929	18 (5)	17 (7)	16 (8)	17 (9)	17 (7)	18 (7)
BI gain, mean (SD)	912	4.5 (4.0)	3.4 (4.1)	2.8 (3.9)	3.8 (4.4)	3.7 (4.6)	3.5 (3.4)
BI gain <4, n (%)	912	89 (45)	101 (59)	65 (55)	54 (52)	84 (49)	84 (56)
Intercurrent disease, n (%)	1009	129 (60)	145 (75)	96 (73)	81 (68)	133 (68)	98 (65)
Readmissions, n (%)	1007	17 (8)	22 (11)	16 (12)	17 (14)	26 (13)	17 (11)
Discharge to a nursing home, n (%)	925	26 (15)	40 (24)	32 (28)	20 (20)	42 (26)	23 (16)
Deceased, n (%)	1106	10 (4.5)	17 (7.8)	9 (6.2)	7 (5.2)	16 (7.4)	3 (1.8)

Notes: inclusion in the cluster was based on the comorbidity numbers in **bold**.

Abbreviations: BI, Barthel index; IQR, interquartile range; COPD, Chronic Obstructive Pulmonary Disease.

Associations with the outcomes

The results (odds ratios or ORs) of the logistic regression analyses are presented in table 2. The FCI was significantly associated with all outcome measures. All ORs from the significantly associated clusters are higher than the ORs of the FCI. Clusters 2 and 6 were associated with unsuccessful functional recovery (BI gain <4); clusters 2, 3, and 5 were associated with unsuccessful discharge, and clusters 2 and 3 were associated with the incidence of intercurrent diseases. Cluster 2 was associated with all outcomes. See also Appendix F for the results with deceased patients included in the models.

Table 2 Logistic regression analyses with comorbidity and comorbidity clusters

	Intercurrent diseases OR [95% CI]	**BI gain < 4 OR [95% CI]**	**Discharge to a nursing home OR [95% CI]**
Comorbidity			
Functional Comorbidity Index	**1.15 [1.03 – 1.27]**	**1.22 [1.10 – 1.34]**	**1.27 [1.13 – 1.44]**
Comorbidity cluster			
Cluster 1 (no comorbidity)	Reference	Reference	Reference
Cluster 2 (cardiovascular)	**1.66 [1.05 – 2.62]**	**1.87 [1.18 – 2.97]**	**1.93 [1.04 – 3.59]**
Cluster 3 (degenerative/mental)	**1.87 [1.13 – 3.11]**	1.49 [0.89 – 2.48]	**2.97 [1.52 – 5.79]**
Cluster 4 (cerebrovascular)	1.13 [0.69 – 1.87]	1.47 [0.87 – 2.47]	1.22 [0.60 – 2.48]
Cluster 5 (rest group)	1.08 [0.70 – 1.86]	1.25 [0.80 – 1.97]	**2.07 [1.12 – 3.82]**
Cluster 6 (osteoarthritis)	1.31 [0.82 – 2.10]	**1.83 [1.14 – 2.93]**	1.35 [0.68 – 2.67]

Bold = statistical significant (p<0.05). Note: adjusted for age, gender, primary diagnosis and BI on admission. Abbreviations: OR = odds ratio, 95% CI = 95% confidence interval.

DISCUSSION

Main findings

On the basis of comorbidity presence in the study participants six different clusters were formed: no comorbidity (1), cardiovascular (2), degenerative and mental disorder (3), cerebrovascular (4), a rest group (5), and osteoarthritis (6). A relation was found between comorbidity cluster and the study outcomes. Specifically the degenerative and mental disorder cluster was independently associated with unsuccessful discharge and intercurrent diseases and the cardiovascular cluster had the highest comorbidity rate, the highest percentage of intercurrent diseases, and was independently associated with all outcome measures.

Interpretation of findings

The cluster without comorbidity was overall younger and performed generally well with regard to the outcome measures. This cluster and the osteoarthritis cluster had the highest BI at discharge. The osteoarthritis and degenerative and mental disorder clusters had the

highest BI on admission. Furthermore, the osteoarthritis cluster was independently associated with a BI gain < 4 (adjusted for primary diagnosis and BI on admission). Osteoarthritis seems to affect functional recovery. However, this cluster still had a high BI at discharge. The ceiling effect of the BI may be an underlying factor why many patients in this cluster had a lower BI gain.

Furthermore, patients in the degenerative and mental disorder cluster had a low BI at discharge, a low BI gain, they were often discharged to a nursing home, and this cluster was also independently associated with discharge to a nursing home and to the incidence of intercurrent diseases. Osteoporosis and degenerative disc disease (chronic back pain) clustered together with depression and anxiety. An explanation could be the relation between chronic pain and depression/anxiety.[19, 20] This combination of physical (chronic pain) and mental problems seems to be unfortunate, leading to higher risk of being unable to return back home after rehabilitation. However, this cluster was not associated with BI gain <4. This was probably due to the adjustment for BI on admission in the regression models: this cluster had a high BI on admission.

Furthermore, the cardiovascular was independently associated with all the outcomes. Patients with cardiovascular problems have a higher risk of unsuccessful rehabilitation outcome: they had a higher risk of intercurrent diseases during rehabilitation, a lower functional gain, and a higher risk of being discharged to a nursing home. This cluster also had the highest FCI score. Teh et al. also found that cardiovascular disease (CVD) rarely occurred in isolation and that 96% of those with CVD had comorbidities.[10] Furthermore, stroke and diabetes were comorbidities that were almost evenly spread in the cardiovascular and the cerebrovascular clusters. Teh et al. also found that diabetes was present in different clusters.[10] Diabetes is a disease that affects many organ systems and can be expected to relate to different comorbid conditions (e.g. visual disorder, kidney dysfunction, vascular problems). Another study found that diabetes was associated with intercurrent diseases during geriatric stroke rehabilitation.[4] We did not investigate the impact of separate comorbidities on the outcomes measures in the present study but a large proportion (one third) of diabetes patients were included in the cardiovascular cluster. Diabetes is prevalent in patients with cardiovascular diseases and different studies demonstrated that diabetes and/or cardiovascular comorbidity is related to worse patient outcomes in general.[21-24] The cerebrovascular cluster was not associated with any of the outcomes. This is remarkable, knowing that diabetes was also highly prevalent in this cluster. Patients with severe cerebrovascular disease (including dementia) as a pre-existent comorbidity were less likely to be considered eligible for geriatric rehabilitation due to cognitive impairment. This could be a reason why the cerebrovascular cluster showed no associations with the outcomes (selection bias), whereas an association with discharge to a nursing home would be expected in patients with dementia or cerebrovascular problems.

Finally, cluster 5 - the rest group - was independently associated with discharge to a nursing home only. This cluster is very heterogeneous, which makes it difficult to interpret the

associations of this cluster and its comorbidities. Overall, associations appeared to be stronger (higher ORs) when comorbidity was represented by comorbidity clusters.

Strengths and limitations

To our knowledge, this is the first study that performed cluster analysis in combination with regression analyses to investigate the associations with unsuccessful geriatric rehabilitation outcomes. Comorbidity is usually studied by using 'number of comorbidities' or a comorbidity index total score in the analyses. This study provides insight into the coherence of specific comorbidities and the impact of these comorbidity patterns on different rehabilitation outcomes. This study had several other strengths: participating rehabilitation facilities were located across the country and the study sample size is relatively large, which enabled performing a meaningful cluster analysis in combination with analyzing the associations with different study outcome measures.

Some limitations of the study need to be considered. At first, participants with dementia may be underrepresented in this study because patients with a more severe dementia will not be admitted in a rehabilitation facility. Furthermore, by using the FCI, comorbidities that are specifically related to function are collected but the severity of comorbidities could not be determined, as the weighted FCI at the time of this data collection was not yet developed.[25, 26] Professionals that filled out the FCI did not receive specific training, which could have led to measurement error. For example, a distinction between osteoporotic back disease and degenerative disc disease may not be well made while completing the FCI, which could play a role in the clustering of these two diagnoses. Considering the disease combinations in the clusters, some things are noticed of which some were already discussed: the remarkable combination of degenerative skeletal disease and mental disease, and the rather evenly spread of stroke and diabetes. Furthermore, asthma and COPD did not appear in the same cluster; asthma was included in the cardiovascular cluster. The total number of patients with asthma was very low (n=23, 2%), so this classification could be due to chance. Another possibility could be that some data collectors may have noted asthma instead of cardiac asthma/heart failure. Lastly, the residual group cluster contains a very diverse group of diagnoses. An additional cluster analysis of this separate group revealed that no new clusters could be discriminated, unfortunately.

Finally, not all participants could be analyzed (Appendix 2). The group that could not be analyzed was characterized by younger male patients admitted after stroke, with a lower BI on admission and a longer length of stay. However, the main objective in this study - comorbidity - did not differ between the groups. It is uncertain whether or how this may have affected the results.

CONCLUSION AND IMPLICATIONS

Comorbidities from older patients in geriatric rehabilitation generally formed meaningful clusters. Specifically patients in the cardiovascular cluster and the degenerative and mental disorder cluster had a higher risk of intercurrent diseases and were more often discharged

to a nursing home. Patients in the cardiovascular cluster also had a risk of unsuccessful functional recovery. These results demonstrate that comorbidity and comorbidity clusters are an important factor in relation to rehabilitation outcomes. Therefore, a comprehensive geriatric assessment including comorbidity assessment should be carried out in all patients admitted for geriatric rehabilitation with a special attention for cardiovascular comorbidities. Subsequently, a geriatric rehabilitation care plan should not only be focused on the primary diagnosis for which the patient is admitted but comorbidity should also be included. In the future, an intervention that focuses on assessment and treatment of comorbidities in these patients should be further investigated.

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APPENDICES

Appendix A. The Functional Comorbidity Index

Please indicate whether a co-morbid condition is present (YES) or absent (NO):

YES: this comorbidity is present
NO: this comorbidity is absent

1. Arthritis (rheumatoid and osteoarthritis)	☐ YES	☐ NO
2. Osteoporosis	☐ YES	☐ NO
3. Asthma	☐ YES	☐ NO
4. Chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), or emphysema	☐ YES	☐ NO
5. Angina	☐ YES	☐ NO
6. Congestive heart failure (or heart disease)	☐ YES	☐ NO
7. Heart attack (myocardial infarct)	☐ YES	☐ NO
8. Neurological disease (such as multiple sclerosis or Parkinson's)	☐ YES	☐ NO
9. Stroke or transient ischemic attack (TIA)	☐ YES	☐ NO
10. Peripheral vascular disease	☐ YES	☐ NO
11. Diabetes mellitus types I and II	☐ YES	☐ NO
12. Upper gastrointestinal disease (ulcer, hernia of the diaphragm, reflux)	☐ YES	☐ NO
13. Depression	☐ YES	☐ NO
14. Anxiety or panic disorders	☐ YES	☐ NO
15. Visual impairment (such as cataracts, glaucoma, macular degeneration)	☐ YES	☐ NO
16. Hearing impairment (very hard of hearing, even with hearing aids)	☐ YES	☐ NO
17. Degenerative disc disease (back disease, spinal stenosis or severe chronic back pain)	☐ YES	☐ NO
18. Obesity and/ or body mass index (BMI) > 30? Height: ____ m Weight: ____ kg (BMI = weight/ (height in meters)^2	☐ YES	☐ NO

Appendix B. List of possible intercurrent conditions

Organ system	Condition
Urinary tract system	Urinary tract infection
	Bladder retention
	Incontinence
	Kidney dysfunction
Gastro intestinal system	Incontinence (fecal)
	Other gastro intestinal disorder
Endocronological system	Diabetic disorder/ disregulation
Pulmonic system	Pneumonia
	Pulmonary embolism
Cardiovascular system	Myocardial infarction
	Heart failure
	Heart rhythm disorder
	Deep venous thrombosis
Cerebrovascular/ neurologic	Stroke
Skin	Wound infection
	Pressure ulcer
Psychiatric/ cognitive	Delirium
	Depression
	Anxiety disorder
Musculoskeletal	Fracture
	Other musculoskeletal disorder
Hematological	Anemia
General	Sepsis
	Other infection
	Dehydration
	Other

Appendix C. Baseline characteristics of patients that were analyzed versus not analyzed

1) Outcome: intercurrent disease

Variable	Analyzed participants (n=1009)	Participants not analyzed (n=97)
Age, mean (SD)	77 (11)	77 (10)
Male gender, n (%)	374 (37%)	39 (40%)
Primary diagnosis, n (%)		
Elective orthopedic surgery	157 (16%)	7 (7%)
Stroke	376 (37%)	36 (37%)
BI on admission	12 [8-16]	9.5 [5-13]
FCI score, median [IQR]	2 [1-3]	2 [1-3]
Length of stay, median [IQR]	37 [20-68]	100 [43-169]

2) Outcome: BI gain

Variable	Analyzed participants (n=973)	Participants not analyzed (n=133)
Age, mean (SD)	77 (10)	76 (11)
Male gender, n (%)	359 (37%)	54 (41%)
Primary diagnosis, n (%)		
Elective orthopedic surgery	153 (17%)	9 (7%)
Stroke	333 (36%)	57 (43%)
BI on admission	12.5 [8-16]	9 [4-13]
FCI score, median [IQR]	2 [1-3]	2 [1-3]
Length of stay, median [IQR]	37 [20-69]	62 [34-128]

3) Outcome: discharge destination

Variable	Analyzed participants (n=925)	Participants not analyzed (n=181)
Age, mean (SD)	77 (10)	73 (13)
Male gender, n (%)	332 (36%)	81 (45%)
Primary diagnosis, n (%)		
Elective orthopedic surgery	153 (17%)	11 (6%)
Stroke	333 (36%)	79 (44%)
BI on admission	12.5 [8-16]	9 [3-13]
FCI score, median [IQR]	2 [1-3]	2 [1-3]
Length of stay, median [IQR]	38 [20-69]	50 [23-108]

Appendix D. Diagnoses in the group 'miscellaneous'

Diagnosis	N (%)
Amputation upper leg	7 (3)
Amputation lower leg/foot	11 (4)
Cardiac disease	27 (10)
Neuromuscular disorder	2 (1)
Spinal disorder	16 (6)
Vascular disease	10 (4)
Musculoskeletal disorder	12 (5)
Brain / cerebral disorder	14 (5)
Neurological disorder	20 (8)
Problems in any organ system	82 (31)
Respiratory disorder	59 (22)
Rheumatic disorder	2 (1)
Total	262

Appendix E. Reasons for hospital readmissions and causes of death

Reason for readmission	n =	Cause of death	n = 62
Fracture in osteosynthesis material	4	Deydration	4
Infection of osteosynthesis material	4	Acute cardiac arrest	4
Joint luxation (luxation of prosthesis)	4	GI carcinoma	3
Other problem of osteosynthesis material	10	GI bleeding	4
Wound infection	6	Anorexia-cachexia syndrome	3
Pneumonia	7	Cardial decompensation	7
Sepsis	9	Pneumonia	13
Other infection	9	GI infection	4
Stroke	8	COPD end stage	1
Myocarcial infarction	3	Serious stroke (for example swallowing problems)	4
Heart failure	5	Delirium	1
Anemia (transfusion)	7	Recurrent stroke	4
Kidney dysfunction/ dehydration	3	Euthanasie	1
Chemo therapy	3	Epileptic convulsion	1
Delirium	6	Metastatic cancer	4
Catheter dysfunction	3	Myocardial infarction	2
Other (miscellaneous)	9	Respiratory insufficiency eci	1
Unknown diagnosis	15	Refusal of food and drink	1
Total	115	Total	62

Appendix F. Logistic regression results with deceased patients included

	Intercurrent diseases or died during rehabilitation OR [95% CI]	BI gain < 4 or died OR [95% CI]	Discharge to a nursing home or died OR [95% CI]
Comorbidity			
Functional Comorbidity Index	**1.16 [1.05 – 1.29]**	**1.22 [1.10 – 1.34]**	**1.23 [1.10 – 1.24]**
Comorbidity cluster			
Cluster 1 (no comorbidity)	Reference	Reference	Reference
Cluster 2 (cardiovascular)	**1.77 [1.11 – 2.81]**	**1.92 [1.25 – 2.52]**	**1.84 [1.06 – 3.22]**
Cluster 3 (degenerative/mental)	**1.99 [1.19 – 3.32]**	1.53 [0.95 – 2.47]	**2.62 [1.42 – 4.85]**
Cluster 4 (cerebrovascular)	1.17 [0.71 – 1.94]	1.40 [0.86 – 2.29]	1.13 [0.60 – 2.15]
Cluster 5 (rest group)	1.10 [0.71 – 1.71]	1.33 [0.87 – 2.02]	**1.84 [1.06 – 3.21]**
Cluster 6 (osteoarthritis)	1.31 [0.82 – 2.10]	**1.61** [1.03 – 2.52]	1.06 [0.56 – 2.02]

Bold = statistical significant (p<0.05). Note: adjusted for age, gender, primary diagnosis and BI on admission.

Chapter 7

General discussion

Reflections on the results

The purpose of comorbidity assessment

In research, comorbidity can be assessed and included in statistical models as a possible confounder, effect modifier or predictive factor.[1,2] Knowing how to reliably and validly measure comorbidity for different purposes is important. This will be elaborated on in the next paragraph. The purpose of using comorbidity as a confounder or effect modifier was not our intention. In this thesis, comorbidity is the subject under study as a predictive factor in relation to geriatric rehabilitation outcome, mainly functional outcome. We focussed on its relevance in predicting rehabilitation outcome, or with other words: its clinical relevance in a population of older patients admitted for geriatric rehabilitation and its potential in helping the physician make a functional prognosis of the patient. This is important, for example when evaluating patients for the appropriate post-acute care setting. After acute hospital admission a patient can be directly discharged home (with or without formal home care and outpatient physiotherapy), be referred for intermediate care: temporary care in a nursing home (in Dutch: eerstelijnsverblijf) or multidisciplinary rehabilitation with the purpose to return home as soon as possible, or be admitted into a nursing home or other long term care setting permanently.[3] Deciding what is the best follow up for a patient is not always a simple and straightforward task for the clinician. For example, deciding to discharge the patient home too early - without considering rehabilitation - could lead to worse patient outcomes, such as less functional recovery, a higher chance to be admitted into a nursing home or hospital and higher mortality.[4]

In the Netherlands, a distinction is made between two types of inpatient rehabilitation: rehabilitation in a rehabilitation clinic and geriatric rehabilitation in a skilled nursing facility. Although it is possible, and sometimes even a good option, to be transferred between a rehabilitation clinic and a skilled nursing facility, this may be burdensome for the patient. Therefore, a well-developed and well-founded selection in advance is important.[5]

For a patient to be considered eligible for geriatric rehabilitation he/she has to have 'complex multimorbidity'.[6] The presence of multimorbidity often leads to a reduced capacity to undergo high-intensity training and therapy, in particular reduced exercise tolerance[6].

This thesis confirms that assessing comorbidity plays an important role in the selection for the appropriate rehabilitation trajectory: a higher comorbidity burden may lead to a longer length of stay in rehabilitation (chapter 2) and enhances the risk of intercurrent diseases during rehabilitation (chapter 5 and 6), less functional recovery during rehabilitation (chapter 4 and 6), a lower functional status at the day of discharge from rehabilitation (chapter 2 and 4), and being discharged to permanent residing in a nursing home instead of returning home (chapter 6). Therefore, assessing comorbidity for the purpose of evaluating a patient's clinical course and prognosis of successful rehabilitation is a relevant part of the evaluation and geriatric assessment for geriatric rehabilitation. It may support setting realistic rehabilitation goals and aid in managing expectations from the patient and his/her family, such as expected length of stay or risk of complications and readmissions in to hospital.[7-9]

Comorbidity assessment methods

Several different comorbidity indices are described in chapter 2. In this thesis, a limited number of indices were discussed (CharlsonCI, CIRS, COM-SI, LiuCI, FCI and w-FCI), but there are many more methods to assess comorbidity[1]. Examples are: counting the number of comorbidities, weighted indices consisting of statistical weights based on the risk of an outcome of interest (mortality/survival like in the CharlsonCI), Tier comorbidities (inpatient rehabilitation facility prospective payment system of the United States of America), and indices that incorporate impairments (index of coexistent disease, geriatric index of comorbidity), physiological or clinical severity weighted ratings of comorbidities (the Duke severity of illness checklist), and comorbidity profiles (clusters).[1, 10-19]

Summing up the number of comorbidities is a simple and straightforward method but leaves no room for additional information about these comorbidities, such as a weighted classification based on their severity. Also, studies sometimes use a limited number of specific conditions of interest or in other cases an endless list of comorbidities. Therefore, 'counting diseases' cannot be considered as one sort of method, as it may have many different phenotypes. For example, the FCI consists of a list of 18 diagnoses, but the index is composed of conditions that specifically relate to functional outcome: the sum score contains more information than just the simple count. Furthermore, comorbidity assessed with the Tier comorbidities system is an economic-based proxy of disease severity and cannot be considered to be a form of clinical disease severity.[18] A study that investigated two methods for prostate surgery also compared the impact of different comorbidity assessment methods and the influence on the results.[20] The authors concluded that both comorbidity count and cost-related severity (Tier) of comorbidities lead to different and inadequate mortality results compared to a weighted index (CharlsonCI and Kaplan Feinstein severity grades). Another study investigated comorbidity count in a cohort of older patients in the community and compared its performance with the CharlsonCI and the in relation to disability and frailty.[21] In contrast to the CIRS, disease count and the CharlsonCI were not independently associated with disability. The CIRS is an index that incorporates clinical severity of disease in which three categories are integrated: impairment (impact on activities), treatment and prognosis.

This thesis investigated the relation between severity weighted comorbidity and functional outcome. The results support the hypothesis that comorbidity assessment that includes a functionally weighted severity rating is preferred when functional outcome is the outcome of interest (chapter 2 and 4). In both chapters this remained true when function on admission was included in de statistical models. With other words: functionally weighted comorbidity contributes to the prediction of functional outcome in addition to separate functional measurement (chapter 2, table2 and chapter 4, table 2). Functional outcome is one of the most important outcomes in the setting of geriatric rehabilitation, and therefore the use of a functionally weighted comorbidity assessment, such as the w-FCI, in geriatric

rehabilitation is recommended. However, this method of comorbidity assessment could be rather complex (chapter 3). This issue is discussed in the next paragraph.

Assessing comorbidity

In both research and in clinical practice, several pitfalls may be encountered when assessing comorbidity. In chapter 3, some of these problems were discussed. De Groot et al. describe how data on comorbidities can be collected: by interview or questionnaire with the patient, using complete medical chart reviews and/or patient files, and code based administrative databases such as International Classification of Primary Care (ICPC) codes in General Practice databases or International Classification of Disease (ICD-10) codes.[1] Each source of information has its advantages and disadvantages.

The reliability of patient reported data (interviews) depends on the ability of the patient to know and recall his/her medical history, chronic and recent diagnoses. An adequate understanding and memory is required. A correlation of 0.45-0.63 between patient report and medical records as source of information was found.[1] Especially in an older patient population where cognitive problems are prevalent, this method may not be preferable due to a higher risk of recall bias. However, from a clinical perspective, information from the patient and his/her actual situation is very valuable.

Complete medical chart review is a method that probably provides the most complete information on the patient's comorbidities and medical history. Medical charts contain detailed information on the patient: laboratory results, specialist letters, medical history, and so on. However, gathering the information can be time-consuming. Also, reliability is at stake when so many sources of information must be evaluated.[12]

Finally, the use of coded databases may enhance reliability, but detailed information can easily be missed.[22,23] A combination of these three methods of data collection would be ideal from a research perspective. In nursing homes and skilled nursing facilities in the Netherlands a list of diagnoses from the past medical history (inactive diagnoses) in combination with an up to date episode list (current diagnoses) must be made when constructing the electronic patient file. These two lists have to be kept up to date and be supplemented with every new diagnosis or disease episode by the attending physician. Such an electronic patient record - accessible by any attending physician - could be introduced for every person nationwide. This would provide up to date and complete information on chronic and acute diseases. In research and clinical practice, patients can be asked to provide additional information on how severe he/she experiences each of the present diseases and on the impact on daily activities. However, until now serious privacy and legal issues arose about plans to implement a nationwide electronic patient record.[24]

In this thesis, the w-FCI was constructed and evaluated. This comorbidity index is limited to 18 specific conditions, which makes the index brief and less time consuming to complete and enhances its clarity. To fill out the index, information on complete past and recent medical history in combination with the actual impact on daily functioning is required. Thus, both complete medical charts/patient files and knowledge of the patient's actual situation

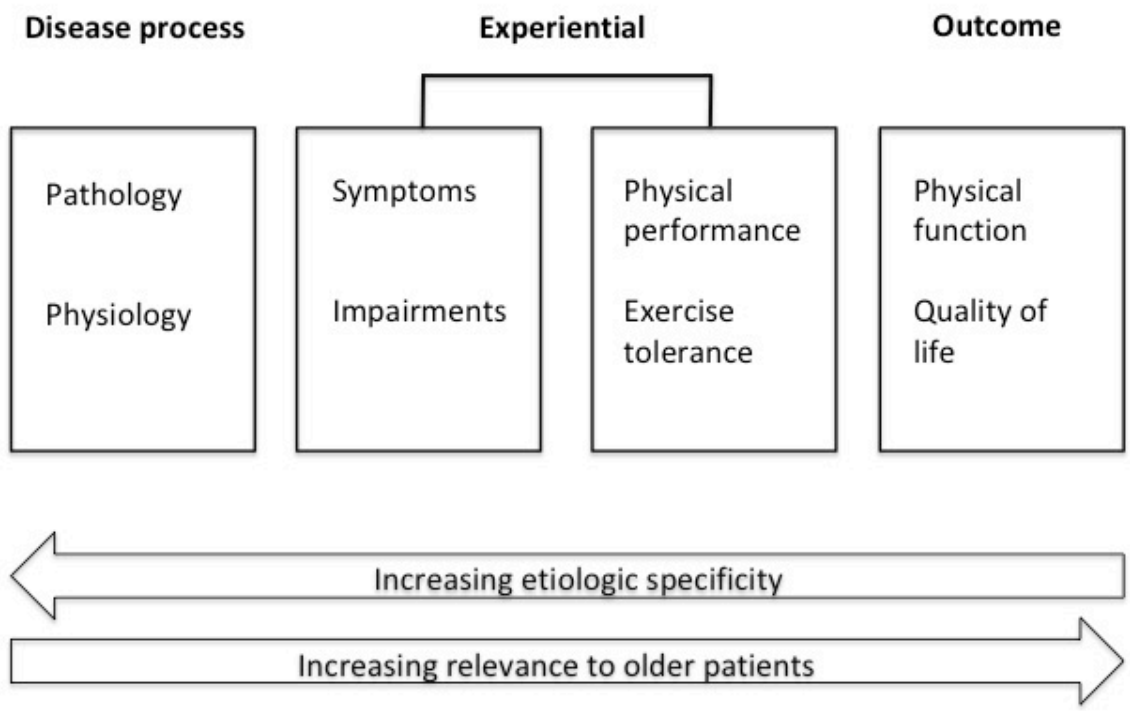
(interview and/or observation) need to be collected in order to complete the w-FCI. To do this sufficiently, the time frame in which the index is completed should not be too soon after the admission of a new patient; otherwise the information on past medical history will not yet be complete (chapter 3). A gold standard of comorbidity assessment in general is not available and all methods meet potential problems. Despite the mentioned disadvantages of such comprehensive data collection, assessing comorbidity using the w-FCI is a method that strives to fully reflect the relevant comorbidity burden with regard to function. Especially when assessing patients for the appropriate post acute care setting and for making a functional prognosis, this leads to prognostic information, which is relevant in that process. Another aspect - which is part of the w-FCI - is how to rate the severity of comorbidity in a patient. The meaning of 'severity' will be further explained in the next paragraph but the practice of rating severity needs some more attention. The person that completes the w-FCI decides which scores are rated. Inter-rater reliability of the index depends on how well different persons agree with each other on the scores.[25] Because the w-FCI does not relate objective measures (e.g. glucose levels for diabetes or ventricle ejection fraction for heart failure) but a clinical judgement of severity, raters may disagree more easily on the severity scores. We observed physicians when completing the w-FCI and found out that none of them used the provided manual. Also, a 20-page manual, used in a reliability study of the ICED did not lead to high agreement between the raters.[7] Therefore, a manual seems to reduce the practicability and feasibility of the w-FCI, and probably without enhancing its inter-rater reliability. We also interviewed professionals to reflect on comorbidity assessment and rating its severity. Some issues were mentioned that should be thought of when completing the w-FCI. In summary:

- Disease severity and its impact change over time. The w-FCI is filled out at one point in time (cross-sectional comorbidity measurement) and a possible change is not reflected by this index. Scoring the impact in the w-FCI should be the actual situation of the patient.
- Symptoms (as a manifestation of severity) should be related to the right comorbidity causing the symptom.[26,27]

The first version of the w-FCI had a moderate reliability (intraclass correlation: 0.55). The later version was improved, based on the experiences but we did not investigate the reliability of the final version of the w-FCI in a geriatric rehabilitation setting (chapter 3). Our hypothesis is that the reliability of this final version will be higher, because some problems have been addressed in this last w-FCI to improve its reliability. This should, however, be confirmed by further research.

Severity of comorbidity

Figure 1. Components for assessing disease severity



Intuitively, one would think that severity of a disease is important when considering the impact of disease in a patient. To further explain and discuss the subject 'severity of comorbidity', we will again use the figure above that was provided in the introduction of this thesis.[28] It depicts different components of disease severity: pathophysiology (1), clinical symptoms (2), physical performance/exercise (3), and functional status & quality of life (4). According to this figure, from right to left it reflects increasing aetiological specificity, whereas from left to right it reflects increasing relevance to older patients. The following example elaborates on the impact specifically in older patients. Older patients often have multimorbidity and the underlying pathophysiology of multiple comorbid conditions may overlap: atherosclerosis is the aetiological cause of different vascular diseases, such as cardiovascular, cerebrovascular, and peripheral vascular problems. This one underlying condition may cause the following conditions to occur, which are included in the w-FCI: angina pectoris, myocardial infarction, heart failure, dementia, stroke, peripheral vascular problems, depression, and visual problems.[29-31] The prevalence and the risk of developing these conditions rise with age. For the patient, the impairments that result from these conditions will have more impact on their daily life than the technically determined pathophysiological severity of atherosclerosis. With other words, functional impact of present disease is more relevant to older patients. This also applies to younger patients, but in their case the pathophysiological component will be more important in the light of preventing diseases later in life.

The w-FCI reflects the second en third component from this figure: the experiential aspect of disease severity. The results described in chapter 4 demonstrate that the w-FCI performed better than the original FCI and the Charlson index in relation to geriatric rehabilitation outcome: physical function and mobility, which are measures of the last component of the figure.

Comorbidity clustering

Considering the results of the systematic review, we became interested in a more individualised method of comorbidity assessment, which lead to the construction and research of the w-FCI. On the other hand we also wanted to investigate whether patients could be classified into meaningful clusters on the basis of their comorbidity profile. Geriatric patients often have multiple comorbid diagnoses, some of which are interrelated and form patterns.[19,32-34] One study has shown that more differentiation in associations between comorbidity clusters and outcome measures exists when including profiles instead of numbers of comorbidities.[19] If specific comorbidity combinations can be discovered that have a particular impact on rehabilitation outcome, this information could be used to better differentiate while selecting patients for geriatric rehabilitation and indicating their care pathway; the latter specifically when the index disease unclear. To our knowledge, no other studies are published on comorbidity clusters and its predictive associations (prospective study design) with certain health outcomes. Chapter 6 describes the clustering of comorbidities. The clusters were a significant factor in relation to the rehabilitation outcome measures: intercurrent disease, functional recovery and discharge destination. The cluster without comorbidity had the best overall outcome and the cardiovascular cluster had the worst outcomes.

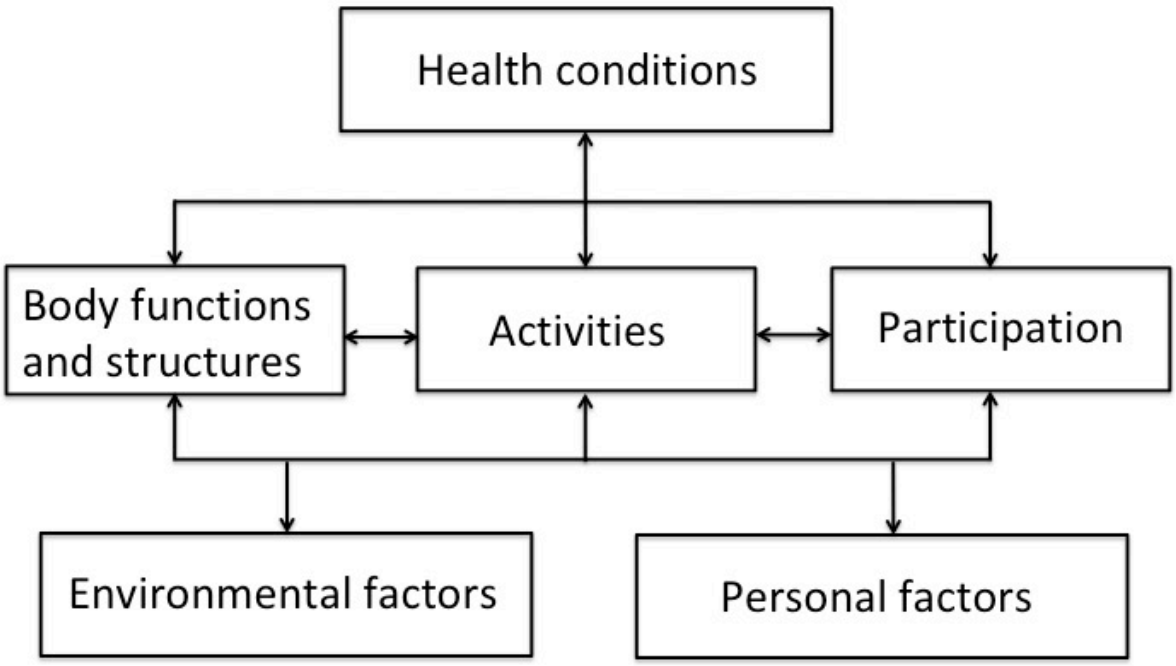
In geriatric rehabilitation, patients are generally admitted to a specific ward and receive a corresponding rehabilitation care pathway on the basis of their index disease: i.e. patients with a hip fracture on the trauma ward and stroke patients on the neurorehabilitation ward. A distinction that is based on the index disease makes sense, however the index disease is not always straightforward. Often, patients faced multiple medical problems during their stay in the acute hospital. Therefore, within such a group a second distinction could be made on the basis of their comorbidities, especially between patients without comorbidity and patients with cardiovascular comorbidity. This distinction could be made in their rehabilitation program. Patients with a higher risk of intercurrent diseases, low functional recovery and discharge to a nursing home - on the basis of their comorbidity profile - will probably benefit from a more intensive involvement of care and medical supervision (such as monitoring of vital functions and other symptoms), adapted physiotherapy intensity, psychological counselling, and support from a social worker.

Geriatric rehabilitation outcome

In the general introduction the ICF model was presented and explained (Figure 2).[35] In this thesis we investigated comorbidity and intercurrent diseases, which are part of the HEALTH

CONDITIONS component of this framework. Comorbidity and intercurrent diseases have a negative influence on functional rehabilitation outcome (chapters 2, 4, 5 and 6), which is a part of the ACTIVITIES component of this framework. Comorbidity enhances the risk of discharge to a nursing home (chapter 6). This outcome can be considered as a proxy of reduced PARTICIPATION in society. However, formal research on participation has not been carried out in this thesis. Measurements for the other components BODY FUNCTIONS & STRUCTURES, PERSONAL- and ENVIRONMENTAL FACTORS were not taken into account, except for age and gender. Personal and environmental factors may influence how disease is experienced and may affect functional outcome or other rehabilitation outcomes.[36]

Figure 2. The ICF framework



However, studying functional outcome is already a challenge. Function is a complex concept and includes different aspects, which will be elaborated on in the next paragraph. In this thesis, we used the Elderly Mobility Scale (EMS) and the Barthel index to measure function. The EMS measures different components of mobility and the Barthel index measures mobility in combination with other aspects of functioning, such as dressing, bathing, eating and continence. A certain level of functional capacity is necessary to be able to be discharged home after inpatient rehabilitation. However, this level differs from person to person and depends on factors such as home situation (e.g. single-storey house or the need to climb stairs), living alone or with an informal carer (usually partner) or having the possibility to extent the trajectory with outpatient geriatric rehabilitation. The latter is related to the access to transport facilities.

Functional outcome measures

In this thesis, the main geriatric rehabilitation outcome was function. To assess function different methods of measurement exist. In chapters 3-6, we included the Barthel index and in chapter 4 the EMS was also used as a measurement of function.[37,38] The EMS has been developed as a mobility assessment tool for specific use in frail older adults.[38] The measurement properties of the scale were investigated and its inter-rater reliability and (face, content and concurrent) validity were considered good.[39] Recently, the clinimetrical properties of the Barthel index were investigated specifically for use in a geriatric rehabilitation setting.[40] The authors considered its structural validity, reliability, and interpretability sufficient for measuring and interpreting changes in physical function of geriatric rehabilitation patients.

The outcome scores of the EMS or Barthel index are often handled as a continuous variable like we did in chapter 4, where the EMS and Barthel index were the dependent variable in linear regression analyses. However, summing up functional abilities cannot be considered to be a pure continuous scale. One point higher in transferring or mobility does not correspond with one point higher on the items eating or bladder function: the items are not equivalent. Nevertheless, we assume that no methodological problems have arisen, since one of the assumptions of a linear regression analysis is not whether the dependent variable follows a normally distributed continuous scale, but that the condition of homoscedasticity is met: the variance around the regression line is the same for all values of the predictor variable.[41] In chapter 4 this assumption was satisfied. Furthermore, for the skewed distribution of the EMS or Barthel index, correlation analyses are easily adjusted using Spearman's *rho* instead of Pearson *r*. Finally, for both indices a ceiling effect has been identified. This means that functionally recovered and highly recovered patients cannot be distinguished.

In addition to functional measurement instruments, several methods of determining function as a rehabilitation outcome exist.[42] Four methods can be extracted from literature: function at discharge (FD), absolute functional gain (AFG) = FD – function on admission, relative functional gain (RFG) = AFG/ (premorbid function – function on admission), and functional gain per day = AFG per day.[42,43]

In this thesis, we used different functional outcome measures: FD (chapters 4-6), AFG (chapter 6), RFG (chapter 5), and gain per day (chapter 4). FD was used in each study and depending on the possibilities in the study or database one of the other indices was used. Each measure has its advantages and its disadvantages. Function at discharge is an important outcome, because it is the only measure that directly relates to what the patient actually is able to perform at the end of rehabilitation. Therefore, it is an important outcome for discharge planning. The other measures indicate rehabilitation effect (AFG, RFG) and efficiency (gain per day). Out of these three, functional gain per day is probably the most straightforward and complete outcome measure (Table 1).

Table 1. Advantages and disadvantages of functional outcome methods

Functional outcome	Advantage	Disadvantage
Function at discharge	Indicator for home discharge	Does not relate to former functional status. Does not reflect the degree of recovery. Influenced by length of stay. Influenced by ceiling effect.
Absolute functional gain	Provides information on functional recovery.	Affected by function on admission*. Influenced by length of stay#. Influenced by ceiling effect.
Relative functional gain	Not influenced by a ceiling effect. Relates to premorbid function.	Influenced by length of stay#. Less reliability due to retrospective measurement of premorbid function. Less feeling with the score, it is an abstract from the real score.
Functional gain per day	Provides information on functional recovery. Length of stay is taken into account.	Affected by function on admission*.

* A patient who recovers from a Barthel index of 3 to 7 (highly dependent patient) has the same AFG as an improvement of Barthel index 16 to 20 (highly independent patient).
# When a patient receives more time to recover, a higher functional level may be achieved.

Intercurrent disease

Comorbidity is associated with the occurrence of one or more intercurrent diseases (chapter 5 and 6). The occurrence of an intercurrent disease enhances the risk of unsuccessful rehabilitation, in terms of functional recovery and readmissions in hospital.[44] In the studies described in chapters 5 and 6 we did not, however, discriminate between exacerbations from a pre-existent comorbidity (e.g. COPD exacerbation) or new diseases (e.g. wound infection). This is a limitation of the present studies and would be an interesting subject for future research, for example to investigate whether an intercurrent disease is - in some cases – a possible explanatory factor between comorbidity on the one hand and impaired functional recovery on the other.

Methodological considerations

Several limitations need to be considered when interpreting the results of this thesis.
This thesis is composed of several studies, using four different databases: two existing datasets and two new data collections. Many different data collectors have participated in the studies, all of whom may have used slightly different ways of data collection. This may reduce the internal validity of the whole thesis. Particularly, different comorbidity indices were used in the datasets (GRAMPS study (2010): Charlson index, SINGER study (2013): FCI

and BeCaf study (2018): w-FCI), and in the COOPERATION study (2020) all three indices were included and compared.[7,45,46] Finally, all studies used the Barthel index as a measure of function, which supports the homogeneity and comparability of the outcomes.
An overall problem is the external validity (generalizability) of the results described in this thesis. This issue has not yet been discussed in chapters 2 to 6. In the review, the rehabilitation settings may not be similar to Dutch geriatric rehabilitation facilities. Likewise, in the BeCaf study (chapter 3) data collection took place in different nursing home settings: predominantly long term care settings but also skilled nursing facilities. However, we expect hardly any influence on the study results, because the subject of the study was comorbidity assessment and not the patients themselves. Furthermore, this same limitation applies to the COOPERATION study. This study took place in the United Kingdom, in an intermediate care facility that provides rehabilitation for older patients. Circumstances in such a facility are not the same as in the Netherlands. Criteria for admission and discharge, therapeutic protocols and therapeutic atmosphere (in Dutch: het therapeutisch klimaat) on the wards probably differ, and more patients with dementia were admitted in the UK than is usual in the Netherlands. Due to these differences, caution must be taken to translate the results to the Dutch situation. On the other hand, the main subject of the study was comorbidity, which can be considered similar in both countries.
Finally, the GRAMPS study took place from 2008-2010 and the SINGER study in 2011-2012. In the mean time processes and methods have been further developed, which may have lead to different patient selection for geriatric rehabilitation. Again the issue of external validity arises. Examples of changes that occurred in recent years are the reduction of hospital length of stay and rehabilitation length of stay, and the proportion of patients that went home became higher.[7] Within the SINGER study, cognitive function was higher and number of comorbidities was lower in the third cohort, compared to cohort 1 and 2.[7] This may be due to stricter criteria for admission into geriatric rehabilitation in the more recent years.

A last topic of a methodological issue is the w-FCI. In the paragraph *'assessing comorbidity'* some issues of the w-FCI were already discussed: clinical judgement of severity and its reliability, distinction between an index disease and pre-existent comorbidity, change of disease severity in time, and the possible difficulty of distinguishing between different diseases that may have similar symptoms (heart failure and COPD: both cause dyspnoea). Or the other way around: one disease may lead to different problems, like diabetes may cause retinopathy (visual impairment), neuropathy (neurological disease), or peripheral vascular problems.
A possibility to increase the reliability of the w-FCI may be to change the severity rating scale into measurable scores, such as a subdivision based on the range of action or other ADL activity. For example: no influence = can walk >500 meter; partially of influence = range of action limited to 50 - 500 meter due to this comorbidity, severe influence = range of action limited to <50 meter due to this comorbidity. However, such a rating scale tries to capture a

disease into a small part of the broad concept of function. Furthermore, comorbidity assessment should not be a derivative of functional measurement. The objective of the w-FCI is to assess comorbidities which is, in essence, a different concept than measuring ADL activities. It may be true that a part of overlap of concepts between comorbidity and function probably exists.[21] To test whether this overlap is problematic for a correct statistical analysis, it is mandatory to test multicollinearity of the independent variables before running a multiple regression model. In chapter 4, no multicollinearity between the w-FCI and function and/or mobility was detected.

Implications for clinical practice and future research

On the basis of this thesis, three subjects can be extracted as a target for future research and a topic for possible changes in geriatric rehabilitation practice: comorbidity and selection for post-acute care (1), comorbidity profile and patient centeredness (2), and comorbidity assessment using the w-FCI (3).

Assessing comorbidity and its functional impact in a patient and recognizing comorbidity patterns play an important role in selecting for the appropriate post-acute care (1), indicating the rehabilitation program and discharge planning (2), and in managing expectations (3). A realistic expectation of personal rehabilitation outcomes will contribute to the satisfaction of patient and his/her family.[8,9] It would be interesting to investigate how comorbidity is currently assessed in acute hospitals and how this is used in decision making for discharge destination and post acute care. Future research on the role of comorbidity in selecting post-acute care could include the possibility of ambulatory geriatric rehabilitation as a distinct form of post-acute care. Also, the usefulness of the w-FCI for accurate post-acute care could be investigated after implementation in the evaluation of patients in acute hospitals. Outcomes could for example be patient and clinician satisfaction, length of stay in acute hospital, readmissions into hospital, functional outcomes and participation.

In this thesis several comorbidity clusters were recognized (chapter 6). These results indicate that meaningful clusters exist and that these comorbidity profiles can be associated with one or more unsuccessful outcomes in geriatric rehabilitation. If the usefulness of comorbidity profiles can be confirmed in future research and a distinction between them can be made regarding their associations with rehabilitation outcomes, then a classification of care pathways that takes these profiles into account may provide an improvement in patient-centred care. An additional distinction could be made on the basis of a patient's comorbidity profile, specifically when the index disease is unclear. Rehabilitation care pathways may then be better adjusted to the patient's possibilities and impairments.

Finally, to our knowledge, this was the first study that investigated comorbidity clusters in a geriatric rehabilitation setting. Further research into this subject is needed whether to confirm, adjust or maybe even refute the comorbidity clusters that are described and analysed in this thesis.

The current w-FCI needs to be re-investigated and maybe improved by studying the reliability of the final version of the w-FCI. The final version of the w-FCI was adjusted by

making some changes in its content on the basis of the interviews and literature.[47] In a future Delphi study, the content of the w-FCI could be re-examined: experts in the field of geriatric rehabilitation can be asked whether specific comorbidities should be removed from the index or added to it. Furthermore, the w-FCI was compared with the original FCI and the Charlson index. It would be interesting to compare its predictive validity with that of other comorbidity indices, such as the CIRS because this index also includes a form of severity rating. Finally, when the w-FCI would be improved it could be an index that moves forward to an unambiguous way of comorbidity assessment in selecting for geriatric rehabilitation and throughout the practice of geriatric rehabilitation.

Final conclusion

Many methods of comorbidity assessment exist and the concept of comorbidity is complex. When assessed in the context of geriatric rehabilitation, it should preferably be assessed in relation to function, because it enhances its predictive validity. The w-FCI assesses comorbidity in an individual way including functionally weighed severity. In this form, comorbidity seems to add important information to aid in selectiong for post-acute care and together with comorbidity profiles it may well increase the patient centeredness of geriatric rehabilitation care and care pathways. Determining comorbidity profiles and using the w-FCI in geriatric rehabilitation require further investigation to confirm and establish their usefulness.

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Chapter 8

Summary

SUMMARY

The general aim of this thesis was to study comorbidity and its assessment in patients admitted for geriatric rehabilitation and to investigate the association with rehabilitation outcomes such as intercurrent diseases, functional recovery and discharge destination.

In order to investigate the association between comorbidity and functional outcome after rehabilitation we performed a systematic review and meta-analysis (research question 1). We identified 20 studies: 14 on stroke patients, 5 on hip fracture patients, and 1 on both stroke and hip fracture. In these studies, one or more comorbidity indices were included as a determinant of functional outcome after rehabilitation. The studies included different comorbidity indices and some studies compared two or more comorbidity indices in their ability to predict functional outcome. In total, four indices were identified: the Charlson comorbidity index (CharlsonCI), the Liu comorbidity index (LiuCI), the Cumulative Illness Rating Scale (CIRS) and the Comorbidity Severity Index (COM-SI). The meta-analysis demonstrated a significant relation between comorbidity and functional outcome. However, we discovered that the effect size and statistical significance of this relation depended on which comorbidity index was included from studies that had investigated two or more indices. When indices were included that better reflected the functionally weighted severity of present comorbidities (LiuCI instead of CharlsonCI, CIRS severity index instead of CIRS cumulative index), the relation became stronger and statistically significant (**chapter 2**).
A comorbidity index that was unfortunately not detected in the literature search of the systematic review is the functional comorbidity index (FCI). Apparently, the FCI had not yet been used in studies investigating comorbidity in a rehabilitation setting. The FCI has specifically been designed in relation to functional outcome and is brief and easy to apply. However, it does not include a severity rating scale. We were interested in a severity-weighted version of the FCI (w-FCI) and its predictive validity in relation to functional outcome in geriatric rehabilitation (research questions 2 and 3). Therefore, we performed two studies: designing the w-FCI and testing its usability and reliability in order to present the new version of the w-FCI (**chapter 3**). Furthermore, we studied the predictive performance of this modified FCI in a prospective observational study (**chapter 4**).
At first, we modified the FCI by adding a functionally weighted severity rating scale based on the physician's assessment of impact on daily functioning of each comorbidity. We tested the reliability and usability of this w-FCI in a cohort of nursing home residents. The intra-rater reliability of the w-FCI was excellent (ICC: 0.94) and the inter-rater reliability was moderate (ICC: 0.55). Elderly care physicians (ECPs) were interviewed, from which five themes were extracted that helped to interpret the reliability results and provided input for the definitive version of the w-FCI. The themes 'what are the used sources of information' (1) and 'how to decide on the presence/absence of a comorbid condition' (2) apply to all comorbidity indices and not only to the w-FCI. When assessing comorbidity, inter-rater reliability of the index is related to how many different sources are used to collect data on

comorbidity. The more sources of information are used, the higher the chance of measurement error and disagreement between raters. Reliability will be higher when only one (retrospective) record, such as a hospital discharge summary, is used. ECPs suggested a threefold rating instead of a fourfold rating to increase reliability when deciding on the presence of comorbidity. Furthermore, 'rating disease severity' (3) may reduce reliability because severity is dynamic and changes over time and different diseases may cause similar symptoms and functional impairments. Nonetheless, the importance of rating functional severity was also recognized by the ECPs. Finally, some considerations regarding the 'usefulness and content' (4 and 5) were made with which the final version of the w-FCI is presented in **chapter 3**. This w-FCI was further studied in **chapter 4.** In a geriatric rehabilitation facility in Nottingham (UK) the w-FCI was compared with the original FCI and the CharlsonCI. The results of this study show that the w-FCI had a higher predictive validity than the FCI and the CharlsonCI when considering the correlations, the areas under the curve (ROC analysis) and the independent associations (multiple linear regression analyses) with function at discharge, mobility at discharge and mobility gain per day during rehabilitation.

In **chapter 5 and 6** the occurrence of comorbidities in patients admitted for geriatric rehabilitation was studied and the relationship between comorbidity and geriatric rehabilitation outcome was examined.

In a cohort of stroke patients (GRAMPS database) the relation between comorbidity (assessed using the Charlson index) and the occurrence of intercurrent diseases became evident (research question 4). Comorbidity in general and particularly diabetes mellitus was independently associated with the occurrence of one of more intercurrent diseases during rehabilitation. The higher the comorbidity total score, the higher the risk of developing more than one intercurrent disease. Finally, when comorbidity co-occurred with a lower functional level at the start of rehabilitation, a synergistic effect was found (**chapter 5**). In three consecutive cohorts of patients that were admitted for geriatric rehabilitation (SINGER database) the clustering of comorbidities (assessed using the FCI) and their relation to rehabilitation outcome was studied (research question 5). Six clusters were identified: no comorbidity (1), cardiovascular (2), degenerative & mental disorder (3), cerebrovascular (4), a rest group (5), and osteoarthritis (6). Patients in the cardiovascular cluster and the degenerative & mental disorder cluster had a higher risk of developing intercurrent diseases and were more often discharged to a nursing home instead of discharged home. Patients in the cardiovascular cluster also had a risk of unsuccessful functional recovery, i.e. an improvement of less than 4 on the Barthel index during rehabilitation. Finally, comorbidity in general was independently associated with all three outcomes although associations were more evident (higher odds ratios) when comorbidity was presented as comorbidity clusters (**chapter 6**).

Chapter 9

Samenvatting in het Nederlands

SAMENVATTING

Het algemene doel van dit proefschrift was het bestuderen van comorbiditeit en de beoordeling daarvan bij patiënten die werden opgenomen voor geriatrische revalidatie. Daarnaast werd de associatie met revalidatie-uitkomsten zoals intercurrente ziekten, functioneel herstel en ontslagbestemming onderzocht.

Om de associatie tussen comorbiditeit en functionele uitkomsten na revalidatie te onderzoeken voerden we een systematische review en meta-analyse uit (onderzoeksvraag 1). We identificeerden 20 studies: 14 over patiënten met een beroerte, 5 over patiënten met een heupfractuur, en 1 over zowel een beroerte als een heupfractuur. In deze studies werden één of meer comorbiditeitsindices meegenomen als determinant van functionele uitkomst na revalidatie. De studies includeerden verschillende comorbiditeitsindices en sommige studies vergeleken twee of meer comorbiditeitsindices betreffende hun vermogen om functionele uitkomst te voorspellen. In totaal werden vier indices geïdentificeerd: de Charlson comorbiditeitsindex (CharlsonCI), de Liu comorbiditeitsindex (LiuCI), de Cumulative Illness Rating Scale (CIRS) en de Comorbidity Severity Index (COM-SI). De meta-analyse toonde een significant verband aan tussen comorbiditeit en functionele uitkomst. Wij ontdekten echter dat de effectgrootte en de statistische significantie van deze relatie afhing van welke comorbiditeitsindex werd opgenomen in studies die twee of meer indices hadden onderzocht. Wanneer indices werden opgenomen die de functioneel gewogen ernst van aanwezige comorbiditeiten beter weergaven (LiuCI in plaats van CharlsonCI, CIRS severity index in plaats van CIRS cumulative index), werd de relatie sterker en statistisch significant (hoofdstuk 2).
Een comorbiditeitsindex die helaas niet werd gevonden in de gevonden literatuur van de systematische review is de functionele comorbiditeitsindex (FCI). Blijkbaar was de FCI nog niet gebruikt in studies die comorbiditeit in een revalidatiesetting onderzochten. De FCI is specifiek ontworpen in relatie tot functioneren, is kort en bondig en gemakkelijk toe te passen. Deze lijst bevat echter geen schaal voor het beoordelen van de ernst van de aandoening. Wij waren geïnteresseerd in een naar ernst gewogen versie van de FCI (w-FCI) en de voorspellende waarde daarvan in relatie tot functionele uitkomsten in de geriatrische revalidatie (onderzoeksvragen 2 en 3). Daarom voerden we twee studies uit: het ontwerpen van de w-FCI en het testen van de bruikbaarheid en betrouwbaarheid om de nieuwe versie van de w-FCI te kunnen samenstellen (hoofdstuk 3). Verder hebben we de voorspellende waarde van deze aangepaste FCI onderzocht in een prospectieve observationele studie (hoofdstuk 4).
In eerste instantie hebben we de FCI aangepast door een functioneel gewogen en ernst gewogen beoordelingsschaal toe te voegen, gebaseerd op de beoordeling door de arts van de impact op het dagelijks functioneren van elke comorbiditeit. We testten de betrouwbaarheid en bruikbaarheid van deze w-FCI in een cohort van verpleeghuisbewoners. De intra-beoordelaarsbetrouwbaarheid van de w-FCI was uitstekend (ICC: 0,94) en de inter-

beoordelaarsbetrouwbaarheid was matig (ICC: 0,55). Specialisten ouderengeneeskunde (SO's) werden geïnterviewd, waaruit vijf thema's werden geëxtraheerd die hielpen bij het interpreteren van de betrouwbaarheidsresultaten en die input leverden voor de definitieve versie van de w-FCI. De thema's 'wat zijn de gebruikte informatiebronnen' (1) en 'hoe beslis je over de aan-/afwezigheid van een comorbide aandoening' (2) zijn van toepassing op alle comorbiditeitsindices en niet alleen op de w-FCI. Bij de beoordeling van comorbiditeit hangt de interbeoordelaarsbetrouwbaarheid van de index samen met het aantal verschillende bronnen dat wordt gebruikt om gegevens over comorbiditeit te verzamelen. Hoe meer informatiebronnen worden gebruikt, hoe groter de kans op meetfouten en onenigheid tussen beoordelaars. De betrouwbaarheid zal hoger zijn wanneer slechts één (retrospectief) record wordt gebruikt, zoals een samenvatting van een ziekenhuisontslag. De SO's stelden een drievoudige beoordeling voor in plaats van een viervoudige beoordeling om de betrouwbaarheid te verhogen bij het beslissen over de aanwezigheid van comorbiditeit. Bovendien kan het "beoordelen van de ernst van de ziekte" (3) de betrouwbaarheid verminderen omdat de ernst dynamisch is en in de loop van de tijd verandert en verschillende ziekten soortgelijke symptomen en functionele beperkingen kunnen veroorzaken. Niettemin erkenden de SO's ook het belang van de beoordeling van de functionele ernst. Tenslotte werden enkele overwegingen met betrekking tot de 'bruikbaarheid en inhoud' (4 en 5) gemaakt waarmee de definitieve versie van de w-FCI in hoofdstuk 3 wordt gepresenteerd. Deze w-FCI werd verder bestudeerd in hoofdstuk 4. In een geriatrische revalidatie-instelling in Nottingham (UK) werd de w-FCI vergeleken met de oorspronkelijke FCI en de CharlsonCI. De resultaten van deze studie laten zien dat de w-FCI een hogere predictieve validiteit had dan de FCI en de CharlsonCI wanneer gekeken wordt naar de correlaties, de gebieden onder de curve (ROC analyse) en de onafhankelijke associaties (multiple lineaire regressie analyses) met functie bij ontslag, mobiliteit bij ontslag en mobiliteitstoename per dag tijdens de revalidatie.
In hoofdstuk 5 en 6 werd het vóórkomen van comorbiditeit bij patiënten die waren opgenomen voor geriatrische revalidatie bestudeerd en werd de relatie tussen comorbiditeit en geriatrische revalidatie uitkomst onderzocht. In een cohort van patiënten met een CVA (GRAMPS database) werd de relatie tussen comorbiditeit (beoordeeld met de Charlson index) en het vóórkomen van intercurrente ziekten duidelijk (onderzoeksvraag 4). Comorbiditeit in het algemeen en diabetes mellitus in het bijzonder waren onafhankelijk geassocieerd met het optreden van één of meer intercurrente ziekten tijdens de revalidatie. Hoe hoger de totale comorbiditeitsscore, hoe groter het risico op het ontwikkelen van meer dan één intercurrente ziekte. Tenslotte, wanneer comorbiditeit samenging met een lager functioneel niveau aan het begin van de revalidatie, werd een synergistisch effect gevonden (hoofdstuk 5). In drie opeenvolgende cohorten van patiënten die werden opgenomen voor geriatrische revalidatie (SINGER database) werd de clustering van comorbiditeiten (beoordeeld met de FCI) en hun relatie met het revalidatieresultaat bestudeerd (onderzoeksvraag 5). Er werden zes clusters geïdentificeerd: geen comorbiditeit (1), cardiovasculair (2), degeneratieve & psychische aandoening (3), cerebrovasculair (4), een

restgroep (5), en artrose (6). Patiënten in het cardiovasculaire cluster en het degeneratieve & mentale stoornis cluster hadden een hoger risico op het ontwikkelen van intercurrente ziekten en werden vaker ontslagen naar een verpleeghuis in plaats van naar huis ontslagen. Patiënten in het cardiovasculaire cluster hadden ook een risico op onsuccesvol functioneel herstel; d.w.z. een verbetering van minder dan 4 op de Barthel-index tijdens de revalidatie. Tenslotte was comorbiditeit in het algemeen onafhankelijk geassocieerd met alle drie uitkomsten, hoewel de associaties duidelijker waren (hogere odds ratio's) wanneer comorbiditeit werd gepresenteerd als comorbiditeitclusters (hoofdstuk 6).

List of publications

Curriculum vitae

Dankwoord

LIST OF PUBLICATIONS

Chapters in this thesis

Kabboord AD, van Eijk M, Fiocco M, van Balen R, Achterberg WP. Assessment of comorbidity burden and its association with functional rehabilitation outcome after stroke or hip fracture: a systematic review and meta-analysis. *J Am Med Dir Assoc. 2016; 17(11): 1066.e13-1066.e21.*

Kabboord AD, van Eijk M, van Dingenen L, Wouters M, Koet M, van Balen R, Achterberg WP. Reliability and usability of a weighted version of the functional comorbidity index. *Clin Interv Aging. 2019; 14: 289-299.*

Kabboord AD, Godfrey D, Gordon AL, Gladman JRF, van Eijk M, van Balen R, Achterberg WP. The modified functional comorbidity index performed better than the Charlson index and original functional comorbidity index in predicting functional outcome in geriatric rehabilitation: a prospective observational study. *BMC Geriatr. 2020; 20(1): 114.*

Kabboord AD, van Eijk M, Buijck BI, Koopmans RTCM, van Balen R, Achterberg *WP.* Comorbidity and intercurrent diseases in geriatric stroke rehabilitation: a multicentre observational study in skilled nursing facilities. *Eur Geriatr Med. 2018; 9(3): 347-353.*

Award

Jan Stoopprijs (2016): award of the Interfacultair Overleg Specialisme Ouderengeneeskunde for scientific article "*Assessment of comorbidity burden and its association with functional rehabilitation outcome after stroke or hip fracture: a systematic review and meta-analysis*".

Contribution to education

Kabboord AD. Ethische dilemma's in de geriatrische neurorevalidatie. Socares, maart 2021 [1].

CURRICULUM VITAE

Anouk Dorothé Kabboord is in 1983 in Goes (Zeeland) geboren. Ze behaalde haar VWO diploma aan het Calvijn College te Goes. In 2001 werd ze ingeloot voor de studie geneeskunde aan de universiteit van Leiden. Haar wetenschappelijke eindstage sloot zij af met het artikel "Risk factors for recurrence of *Clostridium difficile* infection after antibiotic treatment in relation to serum levels of antibodies against *Clostridium difficile* toxin A". Anouk heeft altijd een interesse gehad in andere landen en culturen. Haar laatste coschap heeft zij dan ook met veel plezier gelopen in het Kalafong Hospital in Atteridgeville (Pretoria) bij de afdeling Family Medicine in Zuid-Afrika.

Na het behalen van haar artsenbul in 2009 werkte zij als anios (arts niet in opleiding) bij de GGZ Rivierduinen. In haar volgende baan bracht haar interesse in de Antilliaanse cultuur haar naar Curaçao om als anios neurologie in het Sint Elisabeth Hospitaal te werken (2010/2011). Terug in Nederland ging zij in Rotterdam wonen en kon zij drie maanden overbruggen als anios interne geneeskunde in het Ikazia ziekenhuis; in de wachttijd tot de start van haar baan als anios geriatrie in het Havenziekenhuis (2012). Tijdens deze baan koos zij er voor om de opleiding tot specialist ouderengeneeskunde te gaan doen, waar zij in 2013 mee startte. Vanaf 2014 combineerde zij deze opleiding met een promotietraject als AIOTO-SO (arts in opleiding tot onderzoeker en specialist ouderengeneeskunde). Tijdens deze opleiding zette zij zich samen met SOON (samenwerkende opleidingen tot specialist ouderengeneeskunde Nederland) in voor de promotie van het vak ouderengeneeskunde onder geneeskundestudenten (Carrièrebeurs KNMG) en coassistenten (Nationaal Coassistenen Congres).
In 2016 ontving ze de Jan Stoopprijs voor haar eerste publicatie: *Assessment of comorbidity burden and its association with functional rehabilitation outcome after stroke or hip fracture: a systematic review and meta-analysis*, hoofdstuk 2 van dit proefschrift. Tenslotte studeerde zij in 2019 af als specialist ouderengeneeskunde en begon zij haar huidige baan als specialist ouderengeneeskunde bij Laurens te Rotterdam.

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