Comorbidity and outcomes in geriatric rehabilitation

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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.

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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.

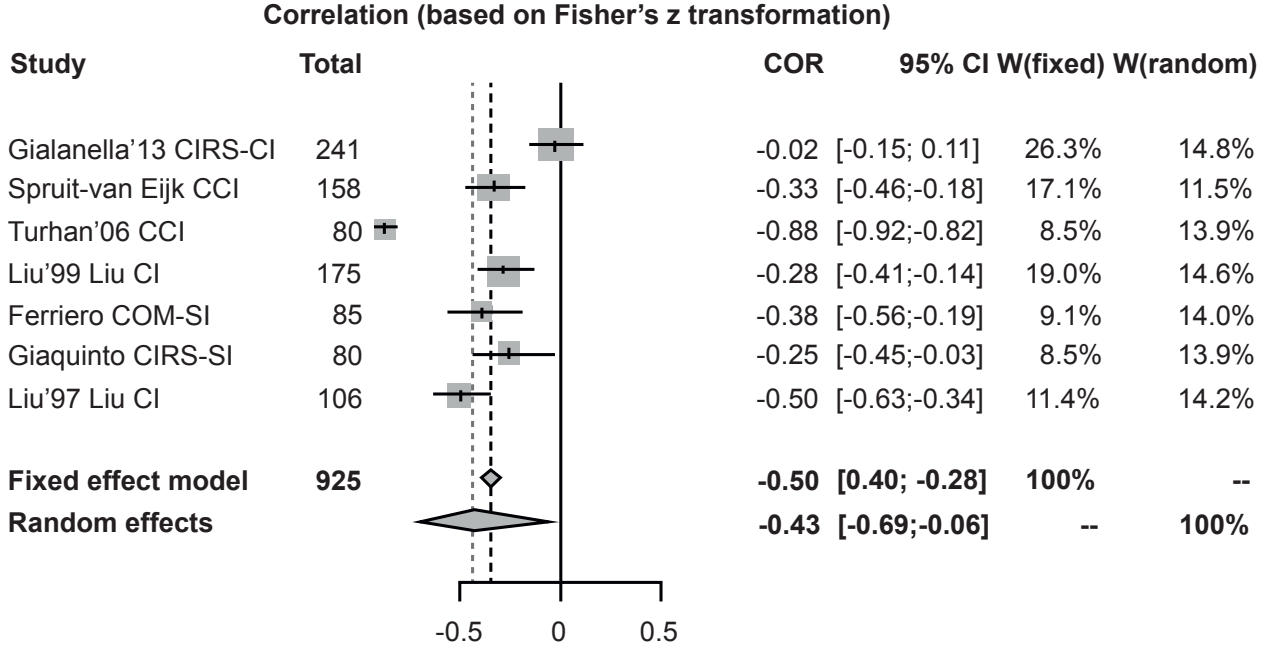
Length of stay

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.

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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

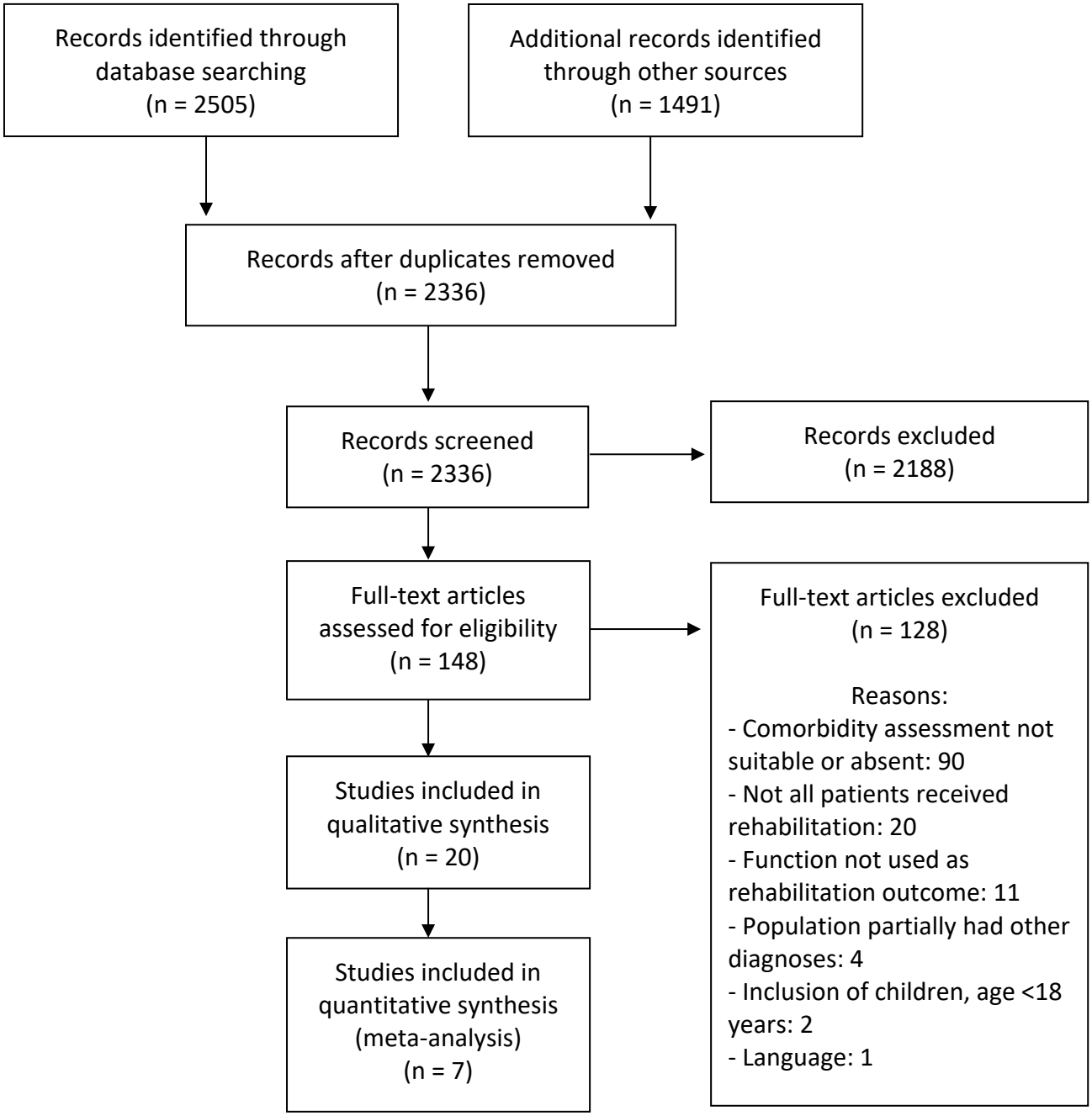
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	X Yes
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements 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



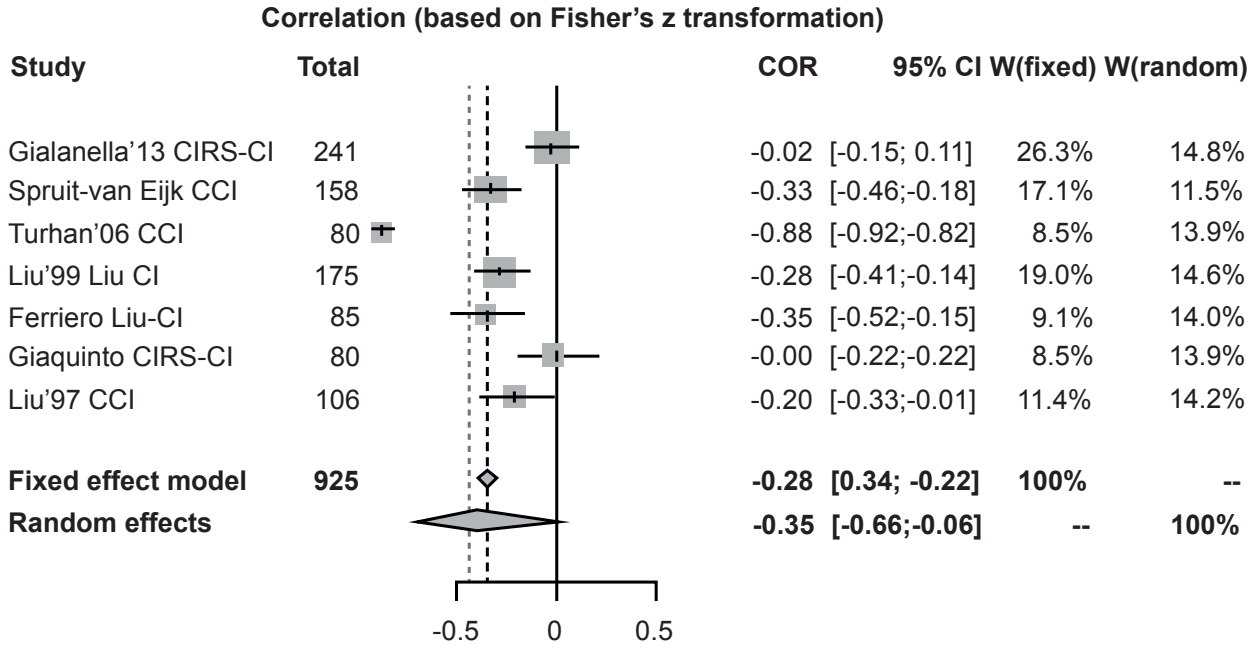
Appendix E. Risk of Bias

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