Advanced insights in upper limb function of individuals with cervical spinal cord injury

Inge-Marie Velstra

ADVANCED INSIGHTS IN UPPER LIMB FUNCTION OF INDIVIDUALS WITH CERVICAL SPINAL CORD INJURY

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Contents

Chapter 1

Introduction

Spinal cord injury (SCI)

A spinal cord injury (SCI) is a damage or trauma to any part of the spinal cord. This often causes permanent changes in strength, sensation, autonomic functions and other body functions below the level of the injury. The extent of SCI depends on the level and completeness of the lesion. The lesion level is classified using the American Spinal Injury Association's (ASIA) Impairment Scale (AIS) classification according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)[1] which focusses on key muscles and key sensory points. The sensory and motor level are defined as the most caudal spinal levels demonstrating normal sensation for both pin prick (PP) and light touch (LT) and normal key muscle group strength. The neurological level of injury is the most caudal level at which both motor and sensory level are intact. The level of completeness is defined using the AIS. The ISNCSCI differentiates between AIS A, B, C, D and E. A complete SCI implies that there is no function below the level of injury: no sensation and no voluntary movement. Individuals with AIS A or B are categorized as having motor complete lesions and individuals with an AIS C or D are classified as having motor incomplete lesions. Spinal cord injury results in tetraplegia when the lesion is at or above the level of T1 and affects arms, hands, trunk, legs and pelvic organs. Paraplegia is caused by lesions below T1 and the trunk, legs and pelvic organs are affected but the upper limb is intact. Besides the neurological dysfunctions, many secondary problems like urinary tract infections, pulmonary complications, blood pressure disturbances, sexual dysfunction, spasticity or pain may develop. The combination of neurological dysfunction and secondary problems in general results in reduced functioning in activities of daily living (ADLs) and affects an individual's independence, participation and quality of life.

Epidemiology

Injuries to the spinal cord may either be traumatic (due to motor vehicle accidents, falls or sport/leisure/work related accidents) or non-traumatic (due to spinal canal stenosis, tumors, infections, myelitis or ischemia). In general, traumatic SCIs affect more commonly males than females, although large variations exist concerning the male-female ratio between different countries.[2] The mean age at injury for traumatic lesions lies between 20 and 40 in the majority of cases.[2-4] This indicates that individuals with traumatic SCI are relatively young when the injury occurs and thus they need specific care for prolonged periods of time which generates larger lifetime costs than other diseases such as stroke. In contrast, a growing number of elderly in traumatic SCI was observed in the Netherlands in 2010.[5]

Furthermore in a recent publication,[6] three age peaks were noticed in acute traumatic and non-traumatic SCI in Switzerland (e.g. 30–40, 45–55 and 60–75 years).

Nijendijk et al.[5] reported that the incidence rate of traumatic SCI in the Netherlands in 2010 was around 11.7 per million population per year. The crude annual incidence rate of traumatic SCI in Switzerland between 2005–2011 was estimated at 18 per million population.[7] The worldwide annual incidence of traumatic SCI ranged from 8 to 49 persons per million population.[2] Although incidence rates vary widely across countries, the incidence of SCI is relatively low compared with other conditions, which is a challenge for the recruitment of suitable participants for clinical studies.

Evaluation of upper limb function in cervical SCI

The upper limbs play an essential role in people's lifes, because they are fundamental for performing ADLs such as self-care, various types of work, leisure and social activities. Individuals with cervical SCI suffer from motor and sensory impairments which cause limited upper limb function and effect the performance of ADLs.[8] This ultimately leads to impaired independence[9] and restricted participation as well as decreased quality of life. Indeed, previous studies have shown that individuals with tetraplegia consider improvements in upper limb function to be one of the most significant factors in improving their quality of life.[10-12] Several upper limb outcome measures are available. However, only a few have been specifically developed for SCI and these have limited psychometric properties.[13-15] Therefore, there is a clear need for valid, reliable and responsive outcome measures in cervical SCI, in order to assess upper limb function accurately.

The ISNCSCI[1] is the current standard for evaluating the neurologic status and the recovery after SCI and includes the AIS. The AIS classifies individuals with SCI in wide-ranging categories and comprises a highly heterogeneous population in terms of level and severity of the injury with respect to the whole body.[16] Thus, the ISNCSCI was not designed to be specific to the upper limb function which undermines the effectiveness of the AIS in the assessment of upper limb neurological recovery.

The Spinal Cord Independence Measure (SCIM) is the most widely used outcome measure to assess independence in fundamental daily activities and is useful to document changes in ADLs in individuals with SCI.[17] The utilization of a global outcome measure such as the SCIM, although providing clinically meaningful categorization of functioning in ADLs, does not provide insights into the underlying sensorimotor function driving functional recovery. Accordingly, the SCIM is not suitable to discern functional improvement arising

from actual healing of damaged spinal cord tissue versus rehabilitation training, mood factors and whether the performed tasks are performed bimanually or with compensatory movements, given the SCIM's focus on gained independence.[17]

Likewise, assessments such as the Tetraplegia Hand Activity Measure (THAQ),[18] the Van Lieshout test (VLT)[19, 20] and the Capability of Upper Extremity Test (CUE)[21,22] provide important information regarding the overall arm and hand usage. They are not designed to provide detailed and reliable information about changes in specific sensory and motor impairments affecting upper limb function. Also assessments like the Grasp Release Test (GRT)[23] and the Motor Capacity Scale(MCS)[24,25] are specifically designed to assess the effect of neuroprosthetic interventions or upper limb surgery and have not been adopted universally. Furthermore, they do not provide information how changes in impairment contribute to complex upper limb functional tasks.

Moreover, as a result of a wide range of recovery[26,27] after cervical SCI and the state of upper limb restoration research in SCI, it is of paramount importance to evaluate upper limb function in cervical SCI comprehensively. The widely used International Classification of Functioning, Disability and Health (ICF)[28] provides a useful framework to improve the appreciation of clinical recovery.

Considering the aforementioned limitations, the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) was developed as a clinical outcome measure specific to upper limb function in cervical SCI. The items of the GRASSP were generated from existing tests and measures which were reviewed by researchers and clinicians to determine suitability. The initial GRASSP[29] combined parts of the preexisting Link Hand Function Test[30] (LiHFT) which is a modification of the Sollerman Hand Function Test[31] (SHFT), the Tetraplegia Hand Measure (THM) and sensory testing instruments for peripheral hand injury.[32] It incorporated three domains: strength, sensibility and prehension, which is the basis for the name of the measure. GRASSP – strength is assessed using manual muscle testing (MMT) of 10 muscles of both upper limbs (3 in the arm, 7 in the hand). GRASSP – sensibility is assessed with the pocket version of the Semmes and Weinstein monofilament (SWM) at 3 dorsal and palmar sensory test locations of each hand. GRASSP – qualitative grasping (QIG) assesses three predefined grasp forms (cylindrical grasp, lateral key pinch, and tip-to-tip pinch) in both hands and does not require the ability to actually grasp an object. Quantitative grasping (QtG) assesses 6 prehension tasks (e.g. grasping or moving a coin) in a standardised way for each arm separately. Each domain can be tested individually or in conjunction with another domain. Therefore, the GRASSP

covers different aspects of upper limb function for evaluating changes within the motor and sensory systems. Furthermore, it reflects impairment changes that fall into the ICF[28] component "body structure and body function". These changes contribute to complex upper limb tasks, which refer to the ICF component "activity and participation".

In individuals with chronic cervical SCI (i.e. more than 6 months post injury), the GRASSP has shown high validity and excellent overall inter- and intra-rater reliability.[33] An important criterion for a clinical outcome measure, such as the GRASSP, is its sensitivity to detect changes in upper limb function over time.[34-37] This facilitates the evaluation of recovery patterns and treatment efficacy of experimental interventions in cervical SCI. The use of the GRASSP is recommended in the very early acute phases after injury to approximately one year post injury. However, responsiveness has not yet been investigated and is therefore one of the aims within this thesis. In general, little has been published on prediction of functional outcome following SCI,[38-40] and in particular, data on prediction and stratification of upper limb function and self-care after incomplete cervical SCI is lacking.[41]

Aims

The overall aim of this PhD thesis is therefore to study the assessment, evaluation and prediction of upper limb function up to one year post injury using the GRASSP in individuals with cervical SCI.

The specific aims of this thesis are:

a. To provide information regarding the (1) responsiveness and reliability of different outcome measures used with persons who have impairments in upper extremity function and (2) their content validity based on the International Classification of Functioning, Disability, and Health (ICF).
b. To investigate the internal and external responsiveness and recovery profiles of the GRASSP instrument in revealing changes in upper limb function within the first year following cervical SCI.
c. To compare the epicritic sensation assessed by Ligth Touch (LT), Semmes-Weinstein monofilament (SWM), and electrical perception threshold (EPT) across cervical dermatomes (C3-C8) in individuals with cervical SCI.
d. To evaluate the value of GRASSP in predicting upper limb function and self-care outcomes in individuals with cervical SCI.
e. To determine which single or combined upper limb muscles as defined by the ISNCSCI upper extremity motor score (UEMS) and the GRASSP,

best predict upper limb function and independence in ADLs, and to assess the predictive value of qualitative grasp movements (QIG) on upper limb function in individuals with acute tetraplegia.

Outline of this thesis

This thesis contains five papers, which were originally written as separate manuscripts and presented as chapters in logical order. Below, a brief description of the content of these chapters is given.

First, **chapter 2** reports the results of a systematic literature review on current outcome measures regarding upper limb function in individuals with (1) peripheral upper extremity conditions, (2) rheumatologic diseases, (3) stroke, and (4) tetraplegia. All outcome measures have been classified according to the ICF. For each outcome measure a description of the concept, operationalisation into variables and instruments as well as psychometric properties was given to determine the availability of preferably objective upper limb function outcome measures within each health condition that are relevant for research and rehabilitation.

Chapter 3 focuses on responsiveness and recovery profiles of the GRASSP in a longitudinal multi-center study. While it was shown that the GRASSP is a valid and reliable measure of upper limb function cross-sectionally, its responsiveness[34-37] was still unknown. Measures that are valid cross-sectionally are not necessary responsive.[42] The GRASSP should be able to determine subtle neurological changes in the upper limb and provide information concerning the rehabilitation progress, in order to be able to evaluate the efficacy of rehabilitation and experimental interventions. Therefore, it should be sensitive to detect changes in upper limb function up to 1 year after cervical SCI. In addition, the responsiveness of GRASSP subtests is compared to other clinical outcome measures as well as to a clinician-rated outcome measure (CROM) in order to explore clinical relevance.

Chapter 4 addresses the comparison of epicritic sensation assessed by Light Touch (LT), Semmes-Weinstein monofilament (SWM) and electrical perception threshold (EPT) across cervical dermatomes (C3-C8) in individuals with cervical SCI. The LT assessment of sensation roughly grades the ability of detecting a light touch in the affected dermatome by “absent”, “impaired”, or “normal”. It was not yet known, if the segmental assessment of epicritic sensation in cervical SCI can be improved by additional semiquantitative sensory measures like the SWM and EPT complementary to LT. These findings are required to evaluate, if LT testing is sensitive enough in interventional studies.

Chapter 5 presents a study on the prediction of upper limb function and self-care following cervical SCI within 1 year of injury. After cervical SCI, arm and hand function outcomes vary significantly and are not only dependent on the level and completeness of the lesion but also on the degree of recovery, motivation, and performance of the individual. This inherent heterogeneity within individuals following cervical SCI[25,26] renders early prediction of upper limb function and self-care challenging.[43] A thorough and adequate clinical assessment of upper limb function in cervical SCI is important to predict potential functional outcome after rehabilitation. In this longitudinal multi-center cohort study, outcome of upper limb function and self-care measured by subtests of GRASSP and SCIM and predicted by subtests of GRASSP, ISNCSCI and SCIM, is described in individuals with cervical SCI. **Chapter 6** describes the influence of individual muscles or muscle groups defined by GRASSP and ISNCSCI on the prediction of upper limb function and ADLs. Furthermore, the effect of specific grasp patterns, described in the GRASSP, on the prediction of upper limb function in individuals with acute tetraplegia is identified.

The last chapter, **chapter 7**, provides a general discussion and reflects on the findings from the various studies. Conclusions are translated into clinical implications and methodological considerations as well as recommendations for future research are formulated.

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Chapter 2

A systematic literature review of outcome measures for upper extremity function using the international classification of functioning, disability, and health as reference

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PM&R 2011;3(9):846-860
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Abstract

Objective: To provide information regarding the (1) responsiveness and reliability of different outcome measures used with persons who have impairments in upper extremity function and (2) their content validity based on the International Classification of Functioning, Disability, and Health (ICF).

Data sources: MEDLINE, CINAHL, PsycINFO, and EMBASE databases were systematically searched for studies on outcome measures used to evaluate upper extremity function; only studies written in English and published between July 1997 and July 2010 were considered.

Study selection: One investigator reviewed titles and abstracts of the identified studies to determine whether the studies met predefined eligibility criteria (e.g., study design, age < 18 years). Another investigator did the same for 70% of the studies.

Data extraction: All types of outcome measures in the included studies were extracted, and the information retrieved from these outcome measures was linked to the ICF by 2 independent investigators who used standardized linking rules. In addition, studies reporting the clinical responsiveness, interrater reliability, and test-retest reliability of the outcome measures were identified.

Data synthesis: From among the 894 studies that were included in this review, 17 most frequently used outcome measures in the different study populations were identified. Five were patient-reported outcome measures and 12 were clinical outcome measures. The outcome measures show large variability with regard to the areas of functioning and disability addressed. Reliability and responsiveness data are missing for a few outcome measures or for certain populations for which they have been used.

Conclusion: This systematic review provides an overview of the outcome measures used to address functioning and disability as they are related to the upper extremity. The results of this study may help clinicians and researchers select the most appropriate outcome measure for their clinical population or research question according to ICF-based content validity, and additional information on the reliability and responsiveness of the measures is provided. Our findings also can provide directions for further research.

Introduction

The upper extremities play an essential role in people's lives because they are integral to performing activities of daily living such as self-care, various types of work, leisure, and social activities. Impairment of the upper extremity can affect other body functions such as sleep or emotional functions[1-4] and can influence the individual's experience of autonomy and independence.[3,5-7] Impairment of an upper extremity (e.g., finger amputations or carpal tunnel syndrome) is not only related to peripheral upper extremity conditions but also to other health conditions, such as rheumatologic diseases (e.g., rheumatoid arthritis), stroke, and tetraplegia.

Other investigators report that approximately 70–80% of persons with stroke have upper extremity impairment[8] and that more than 75% of persons with rheumatoid arthritis[9] show impairments in body functions and limitations in activities associated with upper extremity function. In addition, restoration of upper extremity function is reported to be a major priority for people with tetraplegia.[10,11]

Considering the significant consequences that result from upper extremity impairments,[3,4,12-15] efforts during the last 2 decades have focused on developing condition-specific outcome measures to assess bodily impairments, activity limitations, and participation restrictions. With the exception of the tetraplegic population, for which few outcome measures specific to upper extremity function have been applied,[16] a proliferation of outcome measures has been seen in the fields of peripheral upper extremity conditions,[17-20] rheumatologic diseases[17,18] and stroke.[21]

Thus it is worthwhile to study the areas of functioning, disability, and health that are addressed by different outcome measures that focus on the upper extremity. A comparative examination would allow researchers and health professionals to select the best outcome measure to address the impairments and needs of a specific population in research or practice. The International Classification of Functioning, Disability, and Health (ICF)[22] is a useful tool for performing such a comparison.[23] The ICF provides a comprehensive framework for classifying and describing functioning, disability, and health in people with various types of diseases or conditions. The ICF is composed of 4 components—Body Functions, Body Structures, Activities and Participation, and Environmental Factors—that are organized into a hierarchical structure (Figure 2.1). Chapters are related to each component, and each chapter is divided into different levels of categories.[23,24] For example, the third-level ICF category "d4452 Reaching" is one element of the second-level category "d 445 Hand and Arm Use", which in turn is an element of the chapter "d4 Mobility", which is part of the ICF component "d Activities and Participation".

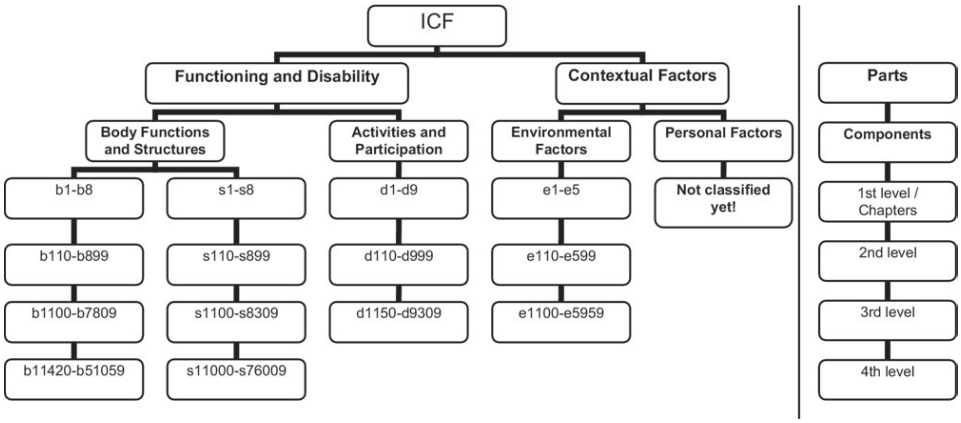

Figure 2.1 The structure of the International Classification of Functioning, Disability and Health (ICF).

An ICF-based comparison also enables the selection of outcome measures that best address the functioning domain in relation to an intervention, which may be at the level of Body Function or Structure, Activities and Participation, or the Environment. Thus the objective of this literature review is to provide an overview of different outcome measures used to address functioning and disability by focusing on persons with impairments in upper extremity function. Our specific aims are to (1) identify outcome measures that address functioning and disability in studies that involve persons with impairments in upper extremity function; (2) compare the content of the identified outcome measures with the ICF as a reference; and (3) report the reliability and responsiveness data of the identified outcome measures when these data are available.

Reliability means “repeatability” or “consistency”. An outcome measure can be considered reliable if it provides the same result with repeated applications. Interrater reliability is used to assess the degree to which different raters are consistent on ratings with the same outcome measure. The test-retest reliability is used to find the consistency of a measure over time. Responsiveness describes the ability of an outcome measure to detect clinically important change.[25]

Methods

Study design

A systematic review encompassing 3 steps was performed. The first step was selection of studies. The second step was identification of outcome measures and extraction of information on the reliability and responsiveness of the extracted outcome measures. The third step was linkage of the information contained within the outcome measures to the corresponding categories of the ICF.

Search strategy and eligibility criteria

In step 1, the MEDLINE, CINAHL, PsycINFO, and EMBASE databases were used to select interventional and observational studies. We selected studies published from July 1997 to July 2010 and used specific terms related to upper extremity function, such as “hand”, “arm”, “upper extremity”, “function”, “activity”, “activities”, “performance”, or “skill”. The Boolean operator AND was used to combine these terms with the following terms: “assessment”, “measure”, “measurement”, “instrument”, “test”, “evaluation”, “questionnaire”, “interview”, or “outcome”. The following exclusion criteria were used: nonhuman population, language other than English, patient age < 18 years, review or meta-analysis, case report/case series, phase 1 or 2 study, ecological study, economic-evaluation study or decision analysis, comment, letter, editorial, guideline, conference report, book chapter, or dissertation. An initial search was developed for Medline, and this search was then adapted to the other 3 databases.

We checked the abstracts by applying the same general and specific eligibility criteria. Study populations with no impairment in upper extremity function and studies with a sample size < 10 were excluded. The full text was ordered for selected studies, and the same criteria were used to review the text. Studies that did not provide any reference or information about the psychometric properties of any of the outcome measures used also were excluded.

Data extraction procedure

In step 2, outcome measure extraction, all types of outcome measures with a reference or information about psychometric properties were extracted. Outcome measures included were categorized according to the study population for which they were used. The following groups were differentiated: (1) peripheral upper extremity conditions, (2) rheumatologic diseases, (3) stroke, and (4) tetraplegia, all of which affect the upper extremity. Because the number of retrieved outcome measures turned out to be very large, the 5 (arbitrary)

most frequently used outcome measures in each of the study populations were selected for further analysis (Figure 2.2).

In our study the selected outcome measures were categorized into 2 different types of measures: (1) patient-reported outcome measures and (2) clinical outcome measures observed or rated by health professionals. Patient-reported outcome measures contained items reported by the patients or proxy respondents, such as “Are you able to shampoo your hair?” from the Health Assessment Questionnaire (HAQ).[26] Clinical outcome measures observed or rated by health professionals contained items such as “Wash/dry upper body” from the Quadriplegia Index of Function Scale (QIF),[27,28] parameters such as “joint range of motion”, or tasks such as “Picking up wooden pegs and dropping them in a box” from the Grasp Release Test (GRT).[29]

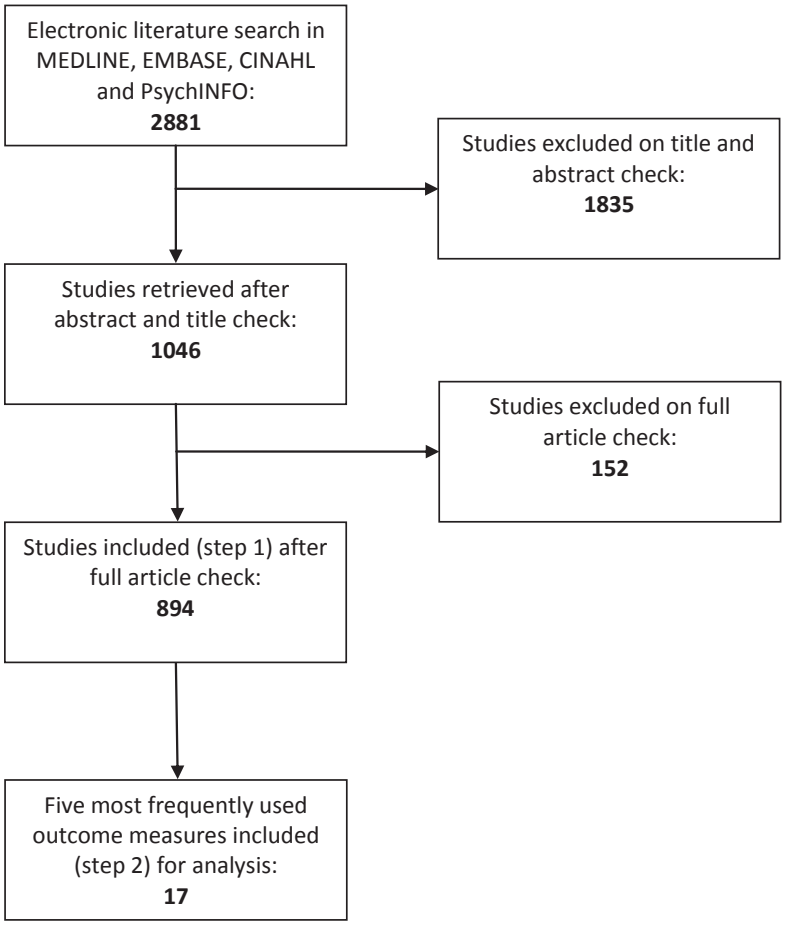

Figure 2.2 Flow chart of the study selection process.

After having identified the outcome measures, we searched for articles in which investigators examined the reliability and responsiveness of these measures in the populations in which they had been used. The number of patients included in the psychometric study, their health condition, the method applied to study the reliability or responsiveness, the corresponding results, and references were extracted from the identified investigations. Validations of cultural adaptations or translations of the selected outcome measures were not considered in the psychometric properties search. Qualitative studies of the outcome measures of interest performed on subjects with another health condition, from the general population, or with adolescents or children were not included.

Linking to the ICF

Step 3 was linkage of the information contained in the outcome measures. In this step, each item of the patient-reported outcome measures and each item, aim of each task, or aim of the clinical outcome measure was extracted and linked to the ICF by 2 independent investigators according to a set of linking rules.[23,24] An item could be linked to one or more ICF categories, depending on the number of concepts contained in that item.[30] If specific information could not be linked to the ICF, this was documented and classified in 2 ways. First, if the information was not sufficiently specified to make a decision as to which ICF category or categories should be selected, the option “not definable” was chosen (linking rule 9). For example, the item “My health is excellent” found in the Short Form-36 Health Survey Questionnaire (SF-36)[31,32] was considered “not definable” for linking. Second, if the information was not represented in the ICF, the option “not covered” was chosen (linking rule 10). For example, the item “How satisfied are you with your HEALTH NOW” of the Arthritis Impact Measurement Scale (AIMS II)[33,34] was considered to be “not covered” by the ICF. If the information referred to a determined diagnosis or disease, “health condition” was used. Personal factors are not yet classified in the ICF. However, when information was considered to address personal factors per definition in the ICF, “personal factor” was used. For example, the item “I seem to get sick a little easier than other people” of the SF-36 was considered a personal factor.

Consensus between the 2 investigators was reached to decide which ICF categories should be linked to the different items or aims. To resolve disagreements between the 2 investigators, a third person trained in the linking rules was consulted. In a discussion led by the third person, the 2 investigators who linked the outcome measures stated their pros and cons for the linking of the information by taking a specific ICF category

into consideration. The third person made an informed decision on the basis of these statements. The application of the predefined linking rules has been shown to yield high agreement between raters (i.e., 91% at the second level of the classification).[23]

Quality assurance

In the abstract checking phase, one investigator reviewed all abstracts for eligibility. Approximately 70% of abstracts were screened by another investigator. In case of disagreement, the 2 investigators discussed the reasons for inclusion or exclusion of a study. All included articles were examined by one investigator for outcome measure extraction. The linking of the outcome measures selected for further analyses was performed by 2 investigators. Finally, the search of the literature to find the psychometric studies of the selected outcome measures and the corresponding data extraction was performed by one investigator.

Analyses

Descriptive statistics were used to document the most frequently used outcome measures (Table 2.1)[35-49] in the 4 different populations. Descriptive statistics also were used to analyze the areas of functioning and disability (i.e., ICF categories) in the most frequently used patient-reported and clinical outcome measures. In addition, the frequency with which an ICF category was being used in the measures was documented.

The degree of agreement between the 2 investigators at the first, second, and third ICF levels was calculated by means of the K statistic and bootstrapped intervals.[50,51] These analyses were performed with SAS for Windows V 9.1 (SAS Institute, Cary, NC).

Results

In step 1, the electronic literature searches in MEDLINE, CINAHL, PsycINFO, and EMBASE yielded 2881 hits. One thousand forty-six studies were included after the abstracts were checked for eligibility. The 2 investigators who together checked approximately 70% of the abstracts (69.15%; 2881/100*69.15 = 1992) agreed on 1746 of them (87.65%). Of the 2881 studies identified, 894 studies contained a reference or information on the psychometric properties of at least one of the outcome measures used and were definitely included. Figure 2.2 provides an overview of the selection process.

In step 2, the 5 most frequently used outcome measures in each of the study populations were determined, which resulted in a total of 17 outcome measures.

Table 2.1 Overview of the 17 most frequently used outcome measures on upper extremity function in the different populations studied and the frequency with which they were used in those populations

Outcome measures	Tetraplegia	Rheumatologic diseases	Peripheral upper extremity conditions	Stroke
Clinical outcome measures				
Modified Ashworth Scale (MAS)[44, 45]			1	61
Action Research Arm Test (ARAT)[39]				61
Motor Activity Log (MAL)[46]				52
Wolf Motor Function Test (WMFT)[47]		1		40
Functional Independence Measure (FIM)[36, 37]	2			40
Jebsen Hand Function Test (JHFT)[48, 49]		13	17	22
Grasp-Release Test (GRT)[29]	4			
Quadriplegia Index of Function (QIF)[27, 28]	3			
Van Lieshout Test Short Form (VLT SF)[42, 43]	3			
Fugl-Meyer Assessment (FMA)[40]		1		97
Assessment of Strength[35]	6	57	46	42
Assessment of Range of Motion[35]	2	15	10	9
Patient-reported outcome measures				
Short Form 36 Health Survey Questionnaire (SF36)[31, 32]		9	24	7
Health Assessment Questionnaire (HAQ)[26]		63	2	1
Disability of the Shoulder, Arm and Hand Questionnaire (DASH)[38]		22	64	1
Severity of Symptoms and Functional Status of the Boston Carpal Tunnel Questionnaire (BCTQ)[41]		1	27	
Arthritis Impact Measurement Scale II (AIMSII)[33, 34]		31	2	1

Numbers in columns indicate the frequency of the outcome measure used in the respective population; blank spaces indicate no entry in this field.

Table 2.1 presents the 17 outcome measures and the frequency with which they were used in the different populations. Five of these outcome measures were patient-reported outcome measures and 12 were clinical outcome measures.

Forty-four publications were identified that included information about the reliability and responsiveness of 15 of the 17 identified outcome measures. Table 2.2 presents the populations for which reliability and responsiveness studies for those outcome measures have been reported, the number of patients included in the studies, the method applied to study the reliability or responsiveness, and the corresponding results and references.[52-87] For 2 clinical outcome measures (assessment of muscle strength and assessment of joint range of motion), we did not provide information on reliability and responsiveness in Table 2.2. Various devices are available to measure strength (e.g., the dynamometer, the vigorimeter, or the microFET [The Trigenics Institute of Functional Neurology, Toronto, Canada]) and joint range of motion (e.g., the goniometer or the inclinometer), and their assessment corresponds to an objective measurement. The complexity of the resulting psychometric data with different populations and different experimental settings could not be integrated in the analysis of the quality of outcome measures.[35]

The results of step 3 are presented in Tables 2.3–2.5, which show the coverage of ICF categories for the components Body Functions and Structures, Activities and Participation, and Environmental Factors, respectively, by the selected outcome measures. The tables display the linkage results at all levels of the ICF hierarchy, including the frequency with which the ICF categories were covered in the outcome measures. The first column represents the list of ICF categories (first, second, third, and fourth level) addressed in at least one of the measures, whereas the following columns represent the outcome measures. The numbers in each of the columns indicate which of the ICF categories were represented and how often the category was used in the outcome measure.

The outcome measures cover 33 ICF categories of the component Body Function. Eleven outcome measures refer to Chapter b1, Mental Functions; 6 refer to Chapter b2, Sensory Functions and Pain; 3 refer to Chapter b5, Functions of the Digestive, Metabolic, and Endocrine Systems; 1 refers to Chapter b6, Genitourinary and Reproductive Functions; and 12 refer to Chapter b7, Neuromusculoskeletal and Movement-Related Functions.

Two outcome measures cover 8 ICF categories of the component Body Structure, and they belong to Chapter s7, Structures Related to Movement. Fourteen of the 17 outcome measures cover 96 ICF categories of the component Activities and Participation. All ICF chapters of this ICF component are represented.

Table 2.2 The interrater and test-retest reliability, internal consistency and responsiveness of the most frequently used outcome measures of upper extremity function in the different populations

Outcome measures	Health condition	Sample size	Interrater reliability	Test-retest reliability	Internal consistency	Respon-siveness	First author, year, reference no.
Clinical outcome measures							
Modified Ashworth Scale	Stroke	36	±[1]				Blackburn, 2002[52]
	Stroke	9	± to +[1]				Brashear, 2002[53]
	Stroke	35	± to ++[2]				Gregson, 2000[54]
	Stroke	18	++[1]				Bodin, 1991[55]
	Peripheral upper extremity conditions			NA			
Action Research Arm Test	Stroke	40	++[4]		++		Nijland, 2010[56]
	Stroke	33				±[7]	Beebe, 2009[57]
	Stroke	20	++[4]	++[3]			Lyle, 1981[39]
Motor Activity Log	Stroke	30				±[7] to +[7,8]	Hammer, 2010[58]
	Stroke	41	±[4]	+[5]	++		Uswatte, 2005[59]
Wolf Motor Function Test	Stroke	40	++[4]				Nijland, 2010[56]
	Stroke	24	++[4]	++[5]	++		Morris, 2001[60]
	Rheumatologic diseases			NA			
Functional Independence Measure	Stroke	163				± to +[7]	Schepers, 2006[61]
	Stroke	25	++[4]				Fricke, 1993[62]
	Tetraplegia	57	± to ++[5]				Segal, 1993[63]
Jebsen Hand Function Test	Stroke	33				±[7]	Beebe, 2009[57]
	Rheumatologic diseases	50	++[5]				Vliet Vlieland, 1996[64]
	Peripheral upper extremity conditions	26		+ to ++[5]			Jebsen, 1969[48]
Grasp-Release Test	Tetraplegia	60				- to ±[7] & - to +[8]	Spooren, 2006[43]
	Tetraplegia	19		++[4]			Mulcahey, 2003[65]

Table 2.2 continues on next page

Table 2.2 *Continued*

Outcome measures	Health condition	Sample size	Interrater reliability	Test-retest reliability	Internal consistency	Respon-siveness	First author, year, reference no.
Quadriplegia Index of Function	Tetraplegia	60				± to +[7,8]	Spooren, 2006[43]
	Tetraplegia	30	+ to ++[5]				Gresham, 1986[28]
	Tetraplegia	18	+ to ++[5]				Labi, 1981[66]
Van Lieshout Test Short Form	Tetraplegia	60				- to +[7] & ± to +[8]	Spooren, 2006[43]
	Tetraplegia	12	++[5]		++		Post, 2006[42]
Fugl-Meyer Assessment	Stroke	377		++[4]			Woodbury, 2008[67]
	Stroke	12	++[4]				Sanford, 1993[68]
	Stroke	19	++[5]				Duncan, 1983[69]
	Rheumatologic diseases			NA			
Patient-reported outcome measures							
Short Form 36 Health Survey Questionnaire	Stroke	188			+ to ++	-[7]	Almborg, 2009[70]
	Stroke	124			± to +	-[8]	Hagen, 2003[71]
	Stroke	1128		- to +[2]	± to +		Dorman, 1998[72]
	Stroke	90			+		Anderson, 1996[73]
	Rheumatologic diseases	168			+		Leung, 2010[74]
	Rheumatologic diseases	1552			+ to ++		Kvien, 1998[75]
	Rheumatologic diseases	113			++		Husted, 1997[76]
	Peripheral upper extremity conditions	99		++[4]		- to +[8]	Beaton, 1998[77]
Health Assessment Questionnaire	Rheumatological diseases	110		++[5]	++		Lautenschläger, 1997[78]
	Rheumatological diseases	20	± to ++[3]				Fries, 1980[26]
	Peripheral upper extremity conditions			NA			
	Stroke			NA			

Disability of the Shoulder, Arm and Hand Questionnaire	Peripheral upper extremity conditions	32		++	-[7]	Hobby, 2005[79]
	Peripheral upper extremity conditions	57	+[5]		+[8]	Greenslade, 2004[80]
	Peripheral upper extremity conditions	109		++	± to +[7,8]	Gummesson, 2003[81]
	Peripheral upper extremity conditions	34			± to +[7,8]	Gay, 2003[82]
	Peripheral upper extremity conditions	68	++[4]			Beaton, 2001[83]
	Peripheral upper extremity conditions	50	+[2] to ++[5]	++		Veehof, 2002[84]
	Rheumatologic diseases	106		++	-[7]	Christie, 2009[85]
	Stroke		NA			
Severity of Symptoms and Functional Status of the Boston Carpal Tunnel Questionnaire	Peripheral upper extremity conditions	57	+ to ++[5]		± to +[8]	Greenslade, 2004[80]
	Peripheral upper extremity conditions	34			+[7,8]	Gay, 2003[82]
	Peripheral upper extremity conditions	102	+[5]	++	+[7,8]	Atroshi, 1998[86]
	Peripheral upper extremity conditions	67	++[5]	++	+[7]	Levine, 1993[41]
	Rheumatologic diseases		NA			
Arthritis Impact Measurement Scale II	Rheumatologic diseases	25	++[4]		- to ±[7]	Goossens, 2000[87]
	Rheumatologic diseases	104		+ to ++		Meenan, 1980[33]
	Peripheral upper extremity conditions		NA			
	Stroke		NA			

Reliability (Correlation, Kappa, Cronbach's alpha): -- indicates poor; -, fair; ±, moderate; +, good; ++, very good; [1] Kendall's Tau; [2] Kappa; [3] Spearman correlation; [4] Intraclass correlation coefficient (ICC); [5] Pearson correlation.
Responsiveness: - indicates small; ± moderate; +, large; [7] Effect size (ES); [8] Standardized response mean (SRM).
Blank field indicates no information found.
NA = not available.

Table 2.3 The frequency of the number of different second, third, and fourth ICF categories for the component Body Functions and Body Structures represented in the examined outcome measures on upper extremity function

Body Functions and Body Structures	Patient-reported outcome measures					Clinical outcome measures											
ICF category	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
b1 CHAPTER 1 MENTAL FUNCTIONS																	
b114 Orientation functions							1										
b1265 Optimism					2												
b1266 Confidence	1																
b134 Sleep functions					1												
b1342 Maintenance of sleep				2													
b144 Memory functions							1										
b147 Psychomotor functions					2												
b152 Emotional functions			9		16												
b16710 Expression of spoken language							1										
b16711 Expression of written language							1										
b16712 Expression of sign language							1										
b2 CHAPTER 2 SENSORY FUNCTIONS AND PAIN																	
b260 Proprioceptive function													1				
b265 Touch function	3			6									1				
b270 Sensory functions related totemperature and other stimuli	3			6									1				
b280 Sensation of pain		1	2	1	6												
b28014 Pain in upper limb	8			4													
b28016 Pain in joints	4			4	4												

b5 CHAPTER 5 FUNCTIONS OF THE DIGESTIVE, METABOLIC AND ENDOCRINE SYSTEMS												
b5102 Chewing					1							
b5105 Swallowing					1							
b5253 Faecal continence					1							
b6 CHAPTER 6 GENITOURINARY AND REPRODUCTIVE FUNCTIONS												
b6202 Urinary continence					1							
b7 CHAPTER 7 NEUROMUSCULOSKELETAL AND MOVEMENT - RELATED FUNCTIONS	12											
b710 Mobility of joint functions											1	
b7101 Mobility of several joints	5		12	17					7	21		
b7151 Stability of several joints		2								2		
b730 Muscle power functions												1
b7300 Power of isolated muscles and muscle groups	3	2						4				
b7350 Tone of isolated muscles and muscle groups							5					
b7502 Reflexes generated by other exteroceptive stimuli										4		
b760 Control of voluntary movement functions										1		
b7602 Coordination of voluntary movements										1		
b7603 Supportive functions of arm or leg						1						
b7800 Sensation of muscle stiffness			1									

Table 2.3 continues on next page

Table 2.3 *Continued*

Body Functions and Body Structures	Patient-reported outcome measures					Clinical outcome measures										
ICF category	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
s7 STRUCTURES RELATED TO MOVEMENT																	
s720 Structure of shoulder region	4														1		
s730 Structure of upper extremity	4																
s73001 Elbow joint															1		
s73002 Muscles of upper arm															2		
s7301 Structure of forearm															1		
s73011 Wrist joint															1		
s7302 Structure of hand	4														1		
s73022 Muscles of hand															1		

Numbers indicate the frequency of the ICF category covered by the respective outcome measure on upper extremity function; blank spaces indicate no entry in this field.
AIMS II = Arthritis Impact Measurement Scale II; ARAT = Action Research Arm Test; BCTQ = Boston Carpal Tunnel Questionnaire; DASH = Disability of the Shoulder, Arm and Hand Questionnaire; FIM = Functional Independence Measure; FMA = Fugl-Meyer Assessment; GRT = Grasp-Release Test; HAQ = Health Assessment Questionnaire; ICF = International Classification of Functioning, Disability, and Health; JHFT = Jebsen Hand Function Test; MAL = Motor Activity Log; MAS = Modified Ashworth Scale; QIF = Quadriplegia Index of Function; SF-36 = Short Form-36 Health Survey Questionnaire; VLT = Van Lieshout Test; WMFT = Wolf Motor Function Test.

Table 2.4 The frequency of the number of different second, third, and fourth ICF categories in the component Activities and Participation represented in the examined outcome measures on upper extremity function

Activities and Participation	Patient-reported outcome measures					Clinical outcome measures											
ICF category	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
d1 CHAPTER 1 LEARNING AND APPLYING KNOWLEDGE																	
d155 Acquiring skills							1										
d166 Reading				1													
d170 Writing	1			1	1				2	1			1				
d175 Solving problems							1										
d2 CHAPTER 2 GENERAL TASKS AND DEMANDS																	
d2200 Carrying out multiple tasks													2				
d230 Carrying out daily routine	1		2														
d3 CHAPTER 3 COMMUNICATION																	
d310 Communicating with-receiving-spoken messages							1										
d315 Communicating with-receiving-nonverbal messages							1										
d3601 Using writing machines										1							
d4 CHAPTER 4 MOBILITY			1		4												
d410 Changing basic body position		2					1										
d4100 Lying down		1			1							1					
d4102 Kneeling			1														
d4103 Sitting		1										2					
d4104 Standing							2										
d4105 Bending		1	1		4												

Table 2.4 continues on next page

Table 2.4 *Continued*

Activities and Participation	Patient-reported outcome measures					Clinical outcome measures										
ICF category	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
d4153 Maintaining a sitting position												1					
d4154 Maintaining a standing position										1							
d4200 Transferring oneself while sitting							1					6	1				
d4201 Transferring oneself while lying							1					3					
d430 Lifting and carrying objects	1		1														
d4300 Lifting			1		2			3	2	1			3	1			
d4301 Carrying in the hands	1			1						1			2				
d4302 Carrying in the arms																	
d4305 Putting down objects		1															
d440 Fine hand use	7			2	1	1			2	2			6				
d4400 Picking up								2	1	2			1	2			
d4401 Grasping		1		3		6		1		2			4		5		
d4402 Manipulating		1		1	6		2		2	1			1	3			
d4403 Releasing								2					1				
d445 Hand and arm use	10	1											5				
d4450 Pulling													1				
d4451 Pushing	1		1										3				
d4452 Reaching	1	1			1								1	1			
d4453 Turning or twisting the hands or arms	3	3		1	1	1				1			2	1			

d450 Walking		1			4							
d4500 Walking short distances			1		1							
d4501 Walking long distances			2		1							
d4551 Climbing		1	2		5	2						
d4552 Running			1		1							
d4600 Moving around within the home						1						
d4601 Moving around within buildings other than home						1						
d4602 Moving around outside the home and other buildings		1			2							
d465 Moving around using equipment						1			6	1		
d470 Using transportation	1				1							
d4702 Using public motorized transportation	1											
d475 Driving	1											
d4751 Driving motorized vehicles					1							
d5 CHAPTER 5 SELF-CARE		2			3							
d510 Washing oneself					5							
d5100 Washing body parts	2	1				2			4			
d5101 Washing whole body		2	1	1		4						
d5102 Drying oneself	1	1					1		4			
d5200 Caring for skin						1	1					
d5201 Caring for teeth						1	1		1			
d5202 Caring for hair					5	2	2		3			
d530 Toileting		1			1	2						
d5300 Regulating urination						1						
d5301 Regulating defecation						1						
d5302 Menstrual care									1			

Table 2.4 continues on next page

Table 2.4 *Continued*

Activities and Participation	Patient-reported outcome measures					Clinical outcome measures											
ICF category	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
d540 Dressing		1	1	1	1		2					1					
d5400 Putting on clothes	1	1		1	2					1		3					
d5401 Taking off clothes				1	1					1		3					
d5402 Putting on footwear		1										2					
d5403 Taking off footwear												2					
d550 Eating	1	2					4		1	1		4					
d560 Drinking		2				1	1		2			2		1			
d6 CHAPTER 6 DOMESTIC LIFE	1			1													
d620 Acquisition of goods and services		2			4												
d6200 Shopping					1												
d630 Preparing meals	1				4							1					
d6300 Preparing simple meals												1					
d640 Doing housework	2		1		9		1										
d6400 Washing and drying clothes and garments					1												
d6402 Cleaning living area	2				1												
d6403 Using household appliances		1															
d6505 Taking care of plants, indoors and outdoors	1	1															
d7 CHAPTER 7 INTERPERSONAL INTERACTIONS AND RELATIONSHIPS							1										
d750 Informal social relationships	1		1														

d7500 Informal relationships with friends	1	1	1	
d7501 Informal relationships with neighbours	1	1		
d760 Family relationships	1	1		
d7702 Sexual relationships	1			
d8 CHAPTER 8 MAJOR LIFE AREAS	1			
d820 School education			2	
d850 Remunerative employement		6	11	
d855 Non-remunerative employment			1	
d9 CHAPTER 9 COMMUNITY, SOCIAL AND CIVIC LIFE		1	3	
d910 Community life			1	
d920 Recreation and leisure	3			
d9200 Play	1			
d9201 Sports	6	2	1	
d9202 Arts and culture	1			
d9203 Crafts	2			1
d9204 Hobbies				1
d9205 Socializing		1	6	

Numbers indicate the frequency of the ICF category covered by the respective outcome measure on upper extremity function; blank spaces indicate no entry in this field.
AIMS II = Arthritis Impact Measurement Scale II; ARAT = Action Research Arm Test; BCTQ = Boston Carpal Tunnel Questionnaire; DASH = Disability of the Shoulder, Arm and Hand Questionnaire; FIM = Functional Independence Measure; FMA = Fugl-Meyer Assessment; GRT = Grasp-Release Test; HAQ = Health Assessment Questionnaire; ICF = International Classification of Functioning, Disability, and Health; JHFT = Jebsen Hand Function Test; MAL = Motor Activity Log; MAS = Modified Ashworth Scale; QIF = Quadriplegia Index of Function; SF-36 = Short Form-36 Health Survey Questionnaire; VLT = Van Lieshout Test; WMFT = Wolf Motor Function Test.

Table 2.5 The frequency of the number of different second, third, and fourth categories in the component Environmental Factors represented in the examined outcome measures on upper-extremity function

Environmental Factors	Patient-reported outcome measures					Clinical outcome measures											
ICF category	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
e1 CHAPTER 1 PRODUCTS AND TECHNOLOGY		2															
e1101 Drugs					2		2										
e1151 Assistive products and technology for personal use in daily living		8					5										
e1201 Assistive products and technology for personal indoor and outdoor mobility and transportation		4			3												
e1250 General products and technology for communication					1												
e1650 Financial assets					1												
e3 CHAPTER 3 SUPPORT AND RELATIONSHIPS					2												
e310 Immediate family					9												
e315 Extended family					9												
e320 Friends					3												
e355 Health professionals					1												

e4 CHAPTER 4 ATTITUDES		
e410 Individual attitudes of immediate family members	1	
e415 Individual attitudes of extended family members	1	
e420 Individual attitudes of friends	1	

Numbers indicate the frequency of the ICF category covered by the respective outcome measure on upper extremity function; blank spaces indicate no entry in this field.
AIMS II = Arthritis Impact Measurement Scale II; ARAT = Action Research Arm Test; BCTQ = Boston Carpal Tunnel Questionnaire; DASH = Disability of the Shoulder, Arm and Hand Questionnaire; FIM = Functional Independence Measure; FMA = Fugl-Meyer Assessment; GRT = Grasp-Release Test; HAQ = Health Assessment Questionnaire; ICF = International Classification of Functioning, Disability, and Health; JHFT = Jebsen Hand Function Test; MAL = Motor Activity Log; MAS = Modified Ashworth Scale; QIF = Quadriplegia Index of Function; SF-36 = Short Form-36 Health Survey Questionnaire; VLT = Van Lieshout Test; WMFT = Wolf Motor Function Test.

Table 2.6 The frequency of items not linked to the International Classification of Functioning, Disability and Health (ICF)

	Patient-reported outcome measures					Clinical outcome measures										
	DASH	HAQ	SF-36	BCTQ	AIMSII	ARAT	FIM	GRT	JHFT	MAL	MAS	QIF	VLT	WMFT	FMA	Assessment of range of motion	Assessment of strength
NC					2		2					1					
ND	4	1	15		7	1									4		
HC	3			3	4												
PF	1		2		12												

Numbers indicate the frequency of the ICF category covered by the respective outcome measure on upper extremity function; blank spaces indicate no entry in this field.
AIMS II = Arthritis Impact Measurement Scale II; ARAT = Action Research Arm Test; BCTQ = Boston Carpal Tunnel Questionnaire; DASH = Disability of the Shoulder, Arm and Hand Questionnaire; FIM = Functional Independence Measure; FMA = Fugl-Meyer Assessment; GRT = Grasp-Release Test; HAQ = Health Assessment Questionnaire; ICF = International Classification of Functioning, Disability, and Health; JHFT = Jebsen Hand Function Test; MAL = Motor Activity Log; MAS = Modified Ashworth Scale; QIF = Quadriplegia Index of Function; SF-36 = Short Form-36 Health Survey Questionnaire; VLT = Van Lieshout Test; WMFT = Wolf Motor Function Test, NC = not covered; ND = not defined; PF = personal factor; HC = health condition.

The number of ICF categories from the different chapters represented in the outcome measures ranged from 39 in Chapter 4, Mobility, to 2 in Chapter d2, General Tasks and Demands.

Fourteen ICF categories of the component Environmental Factors are covered in 3 of the 17 outcome measures. Six belong to Chapter e1, Products and Technology, 5 belong to Chapter e3, Support and Relationships; and 3 belong to Chapter e4, Attitudes.

Three outcome measures had content that was considered not covered in the ICF. These measures were the AIMS II, Functional Independence Measure (FIM),[36,37] and QIF. Six outcome measures had content considered not sufficiently specified to be assigned to a specific ICF category. These measures were Disability of the Shoulder, Arm and Hand Questionnaire (DASH),[38] HAQ, SF-36, AIMS II, Action Research Arm Test (ARAT),[38] and the Fugl-Meyer Assessment (FMA).[40] Three outcome measures addressed personal factors. These measures were the DASH, SF-36, and AIMS II. Two outcome measures cover 2 health conditions, and they were the Severity of Symptoms and Functional Status of the Boston Carpal Tunnel Questionnaire (BCTQ)[41] and AIMS II. This information is shown in Table 2.6.

The K statistic (with bootstrapped confidence intervals) was 0.52 (0.48–0.55) at the first level, 0.47 (0.44–0.50) at the second level, and 0.45 (0.41–0.48) at the third level of the classification. No confidence interval includes the value zero, which indicates that the level of agreement is beyond chance.

Discussion

This literature review provides an overview of outcome measures used to address functioning and disability in persons with impairment in upper extremity function. Moreover, it presents an overview of the content addressed in these outcome measures when the ICF is used as a reference. It was possible to identify outcome measures from a comprehensive perspective rather than from just one specific patient population. We also present information on the reliability and responsiveness of the outcome measures and the populations in which these psychometric properties were studied. Thus this investigation provides clinicians and researchers with a guide for selecting the most appropriate outcome measure for their clinical population or research question, taking ICF-based content validity (“what do the outcome measures address?”), reliability, and responsiveness into consideration.

Patient-reported outcome measures for the upper extremities are most frequently used in rheumatologic diseases and peripheral upper extremity-specific conditions,

whereas clinical outcome measures are most frequently used in persons who have had a stroke. Outcome assessment in rheumatologic diseases with use of patient-reported outcome measures has a long tradition. In 1993, the Outcome Measures in Rheumatology[88] emphasized the importance of including patient-recorded outcome measures in rheumatoid arthritis clinical trials. In peripheral upper extremity-specific conditions, the patient's view also is considered an important outcome measure.[89-92] In persons who have had a stroke, clinicians are still reluctant to use patient-reported outcome measures, which usually reflect the patient's own perception, because of cognitive impairments frequently associated with this health condition.[93]

This review shows that only a few upper extremity-specific measures are used in studies of persons with tetraplegia, and none of them is a patient-reported outcome measure. Information on psychometric properties of outcome measures is lacking for this specific population.[16] This defiency can be a hindrance for rehabilitation and research in the tetraplegic population because relevant outcome measures are not validated and consequently are not used. For example, the DASH has not yet been validated for tetraplegia, even though it could provide great insight into activity limitations and participation restrictions of persons with tetraplegia. Further research should be performed to study the psychometric properties of the DASH when it is used in the tetraplegic population.

Regarding the content comparison of the specific outcome measures analyzed in this review, different issues require special annotation. In the component Body Functions, all patient-reported outcome measures address mental functions (e.g., maintenance sleep), sensory functions, and pain. Mental functions in upper extremity impairment are major concerns.[1-4] However, only the FIM as a clinical outcome measure addresses both mental functions and pain. In addition, the FIM also includes body functions that are not related to impairment of upper extremity function such as chewing, swallowing, and fecal and urinary continence.[94] The Van Lieshout Test[42,43] exclusively addresses sensory functions. Our work shows that almost all the patient-reported and clinical outcome measures address body functions related to the musculoskeletal system. This finding is consistent with the literature.[35,95-97]

In the Activities and Participation component, all outcome measures comprehensively address Chapter d4, Mobility, except for the Modified Ashworth Scale.[44,45] However, the HAQ and the AIMS II address not just aspects of mobility of the upper extremities alone but also of the lower extremities. This finding reflects the fact that both outcome measures were originally developed for patients with rheumatoid arthritis whose lower extremities

also were affected.[9] Several outcome measures address ICF category d170, Writing, and the BCTQ also addresses category d166, Reading. It must be considered that the content of outcomes addressing writing was not linked only to the mentioned ICF category d170 but also to the category d440, Fine Hand Use, and d445, Arm Hand Use, because the definition of "writing" provided by the ICF refers exclusively to the cognitive components of this Activity and Participation domain. The same scenario applies to items such as "Holding a Book While Reading" (BCTQ), which was linked to both d166, Reading, and d445, Hand and Arm Use.

Chapter d5, Self-care, is covered by all patient-reported outcome measures, whereas the HAQ and the AIMS II address self-care in a comprehensive way. These 2 measures not only address washing and dressing, as do the other patient-reported measures, but also toileting. In the case of clinical outcome measures, only 3 address self-care, namely the FIM, Motor Activity Log,[46] and QIF. All of them also cover this chapter in a comprehensive way because they include washing, dressing, toileting, eating, and drinking.

Only 3 patient-reported outcome measures in the component Activity and Participation cover Chapter 8, Major Life Areas, and Chapter 9, Community, Social, and Civic Life, with the exception of the MAL, which covers d9203, Crafts, and d9204, Hobbies. This situation indicates that few outcome measures related to the upper extremity can be used to cover these relevant areas of life, which are usually restricted in the studied populations considered in this review.[6,98,99]

In the component Environmental Factors, only 3 outcome measures, the HAQ, AIMSII, and FIM, address to some extent the influence of the environment. However, although the HAQ and FIM exclusively address medication and assistive devices, the AIMS II also addresses the social environment and its attitudes, which can have a very relevant positive or negative influence on the lives of persons with upper extremity problems.[5,15,100-105] Attitudes and support of health professionals, family members, and friends or colleagues are essential in a person's ability to cope with the consequences of the disability.[102-105] Our results show that current outcome measures lack information on Environmental Factors. Therefore it would be worthwhile to either increase the coverage of Environmental Factors when developing upper extremity function outcome measures or add domains to existing measures.

An important finding of this study is that most information related to patient-reported and clinical outcome measures could be linked to the ICF. The linking option "not covered" was seldom used, which indicates that the ICF is a potentially useful tool for describing

the problems of functioning and disability associated with the upper extremities with the outcome measures we found. In contrast, the option “not definable” was more frequently used. In particular, this option was used 17 times in the SF-36, because the information “general health” and “physical health” contained in its items were linked to that option. The same situation applies to the items of the AIMS II. It also is apparent that the AIMS II is the outcome measure that contains the most personal factors such as race, age, and gender.

The information regarding reliability and responsiveness shows that for a number of outcome measures, no data are available on responsiveness for different populations, and reliability data also are lacking for different outcome measures and populations (Table 2.2). Thus this overview table can be used to facilitate the selection process of outcome measures for investigations or clinical practice and provides an indication of the areas of upper extremity outcome measures in which future research is needed.

Limitations

The current review is subject to some limitations. We excluded case series; the minimum sample size was 10; and the minimum age of subjects was 18 years. These exclusions must be considered when interpreting the results of this review. An additional limitation is that we considered only outcome measures for which a reference or information on the psychometric properties were provided. This approach could have biased the frequency with which the outcome measures were identified. However, it may encourage authors of scientific publications to always properly reference the outcome measures used in their studies. Furthermore, we included the 5 most frequently used outcome measures in each of the study populations. Outcome measures developed in recent years that have not yet been frequently used, such as the Graded and Redefined Assessment of Strength, Sensibility and Prehension,[106] were not considered in this review. On the basis of the K coefficient and the lower limits of the confidence intervals, the degree of agreement between health professionals is acceptable.

Conclusion

In conclusion, the ICF provides a useful reference for identifying the content validity of outcome measures used to address functioning and disability in persons with impairment in upper extremity function. This overview can be helpful when planning studies, deciding which outcome measure to use in clinical practice, and determining whether development of a new outcome measure is necessary. In clinical practice, the selection of outcome

measures can properly capture change resulting from an intervention, and in research, a proper outcome measure can provide answers to a research question. For example, before deciding to develop a new outcome measure for tetraplegia, the content of outcome measures used for other specific conditions should be consulted. However, not only the content is relevant when selecting outcome measures or deciding whether the development of a new outcome measure is necessary; psychometric properties such as reliability and responsiveness also are relevant. Therefore reliability and responsiveness data of the outcome measures selected were also provided in this study.

Our results show that reliability and responsiveness data are not always available for the populations in which the outcome measures have been used. In selecting appropriate outcome measures, one needs to consider clinical and patient-reported measures with broad coverage of the domains of functioning. Such a selection will depend on the research question and study design.

The findings from our study show that research with a wider focus is needed to encompass the multifaceted problems experienced by persons with upper extremity function impairment. It is therefore important that outcome measures related to upper extremity function capture the entire spectrum of functioning and disability.

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Chapter 3

Changes in strength, sensation and prehension in acute cervical spinal cord injury: European multicenter responsiveness study of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP)

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Abstract

Objective: To investigate the internal and external responsiveness and recovery profiles of the Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) instrument in revealing changes in upper limb function within the first year following cervical spinal cord injury (SCI).

Method: A European prospective, longitudinal, multicenter study assessing the GRASSP at 1, 3, 6, and 12 months after cervical SCI. Subtests of GRASSP were compared to the upper extremity motor (UEMS) and light touch scores (LT) according to the International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI), the Spinal Cord Independence Measure self-care subscore (SCIM-SS), as well as a clinician-rated outcome measure (CROM) of clinical relevance. Data were analyzed for GRASSP responsiveness and recovery rate over time.

Results: Seventy-four participants entered the study. GRASSP subtests proved responsive (standardized response mean [SRM] ranged from 0.79 to 1.48 for strength, 0.50 to 1.03 for prehension, and 0.14 to 0.64 for sensation) between all examination time points. In comparison, UEMS and LT showed lower responsiveness (SRM UEMS ranged from 0.69 to 1.29 and SRM LT ranged from 0.30 to -0.13). All GRASSP subtests revealed significant, moderate-to-excellent correlations with UEMS, LT, and SCIM-SS at each time point, and changes in GRASSP subtests were in accordance with the CROM. GRASSP prehension and motor recovery was largest between 1 and 3 months.

Conclusion: The GRASSP showed excellent responsiveness, detecting distinct changes in strength and prehension relating to the severity of cervical SCI. It detected clinically significant changes complimentary to the ISNCSCI and SCIM-SS assessments.

Introduction

After cervical spinal cord injury (SCI), motor and sensory impairments cause limitations in upper limb function which affect performance of activities of daily living (ADLs), independence and, ultimately, restrict participation and quality of life. Previous studies have shown that individuals with tetraplegia consider improvements in upper limb function to be one of the most significant factors in improving quality of life.[1,2] Longitudinal studies in acute SCI reveal that most recovery occurs within the first months after cervical SCI[3,4] even though the degree of upper limb functional recovery is highly variable.[5,6] Nevertheless, clinical recovery assumes rather complex dimensions that are not sufficiently appreciated by a single outcome measure (such as motor scores) but stem from multiple factors following acute tetraplegia. The International Classification of Functioning, Disability and Health (ICF)[7] provides a comprehensive framework to improve the appreciation of clinical recovery.

Several upper limb outcome measures are available, however only a few have been specifically developed for SCI[8,9] and these have limited psychometric properties.[9] At present, the International Standards of Neurological Classification of Spinal Cord Injury[10] (ISNCSCI) is the current standard to assess neurological recovery and the Spinal Cord Independence Measure[11] (SCIM) is the most widely used outcome measure to document change in ADLs in individuals with SCI. A tetraplegia-specific outcome measure, the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) was developed[12] in an attempt to demonstrate how changes in impairment (i.e. neurological deficit which falls into the ICF component 'body structure and body function') may change over time and contribute to complex upper limb tasks, which refer to the ICF component 'activity and participation'. In individuals with chronic cervical SCI (i.e. more than 6 months post-injury), all subtests within the GRASSP have shown high inter-rater and test-retest reliability (0.84–0.96 and 0.86–0.98, respectively) and favorable validity[13] and it is highly predictive of upper limb function and self-care in acute cervical SCI.[14]

Responsiveness of the GRASSP, so far not yet established, may be defined as its sensitivity in detecting changes in upper limb function over time, allowing for the evaluation of patterns of recovery in cervical SCI during rehabilitation and in the assessment of treatments for SCI. For further evaluation of the clinically relevant changes it is important to also include the clinician's perception of change in upper limb function and daily functioning. The latter aims to capture clinical judgments reflecting the degree of changes in the patients' life beyond the changes as measured by a standardized clinical assessment tool.[15]

This prospective study in acute cervical SCI up to 1 year post injury thus aimed to investigate: (1) the responsiveness of the GRASSP subtests; (2) the responsiveness of the

GRASSP subtests compared and related to ISNCSCI and the spinal cord independence self-care subscore (SCIM-SS); (3) the clinical appreciation of changes in GRASSP and SCIM-SS by using a clinician-rated outcome measure (CROM), and (4) recovery profiles in GRASSP strength and prehension.

Methods

Study design

The study was designed as a prospective longitudinal multicenter study.

Study population

Participants were recruited from five European SCI centers specializing in the rehabilitation of individuals with SCI. Participants were recruited between January 2009 and June 2011. Inclusion criteria consisted of traumatic or non-traumatic tetraplegia, enrollment within 0 to 10 days post injury and assessment of the American Spinal Injury Association (ASIA) Impairment Scale (AIS grade of A, B, C, or D).[10] Individuals were included if their injury level was between C3 and T1 in the case of AIS A patients and C1-T1 in those with incomplete injuries. Excluded were those individuals with any accompanying severe neurological (e.g., traumatic brain injury) or medical disorders or those aged less than 16 years. Participants were recruited after providing written informed consent. The study was approved by the relevant local ethics committees.

Procedures

Assessors who had at least one year experience in working with individuals with SCI were trained to ensure high-quality examinations and to reduce inter-observer variability. Occupational therapists performed the GRASSP and rated the questionnaires. For organizational reasons, it was unavoidable that, in some cases, the two assessments were performed by the same therapist. Physicians performed the ASIA testing and the SCIM III was completed by physical therapists, nurses and occupational therapists. The GRASSP takes between 30–45 minutes to complete.

The assessments and clinical examination were performed during inpatient rehabilitation between 0–10 days, at 1 month (range 16–40 days), 3 months (range 70–98 days), 6 months (range 150–186 days) after cervical SCI and in outpatient clinics at 12 months (range 300–400 days) after cervical SCI. The clinician-reported outcome measure

(CROM) were performed at 3, 6 and 12 months post-injury. The AIS classifications were calculated by a computer algorithm,[16] according to the definitions in the International Standards.[10]

Outcome measures

We have included a table (Table 3.1) to explain the acronyms of outcome measures used in this study.

The GRASSP is a three-domain, upper limb clinical outcome measure for individuals with tetraplegia, contains five subtests and measures each upper limb separately. The subtests within GRASSP are:

Manual muscle testing[17] *(MMT).* Ten muscles in the arm and hand were assessed on both sides. Each item (muscle) was scored between 0 and 5, whereby score 5 represented normal strength and score 0 total paralysis. The total score for both sides is the sum of all item scores with a maximum of 100.

Semmes and Weinstein Monofilament (SWM). The touch threshold was assessed using the pocket version of SWM[18] (North Coast Medical, Inc, Campbell, CA), with four probes (monofilaments) across three dorsal and three palmar locations for each hand as described in the instructions of the SWM mini-kit[18] and the GRASSP manual. The pressure applied and sensation elicited was represented by numeric values ranging from

Table 3.1 Summary of outcome measures

Abbreviation	Outcome measure name
GRASSP	Graded Redefined Assessment of Strength, Sensibility and Prehension
MMT	Manual muscle testing
SWM	Semmes and Weinstein monofilament
SWMP	Semmes and Weinstein monofilament; palmar
SWMD	Semmes and Weinstein monofilament; dorsal
QIG	Qualitative grasping
QtG	Quantitative grasping
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
UEMS	Upper extremity motor score
LT	Light touch
SCIM	Spinal Cord Independence Measure
SCIM-SS	Spinal Cord Independence Measure; self-care subscale
CROM	Clinician-rated outcome measure
ICF	International Classification of Functioning, Disability and Health

0 (no response) to 4 (normal sensation). Three locations for the dorsal (SWMD) or palmar (SWMP) side are summed as subtest total score for both sides, ranging from 0 to 24 points.

Qualitative Grasping (QlG). Three grasps were assessed according to the grasp acquisition outlined in the GRASSP manual and developed by the GRASSP International Research and Design Team. The grasps were scored between 0 (no voluntary control of wrist and digits when grasping) and 4 (normal voluntary control of wrist and digits when generating the grasp). The sum of the grasping quality subtest scores for both upper limbs ranges from 0 to 24 points.

Quantitative Grasping (QtG). In a strictly standardized way, six prehension tasks, such as picking up a key from a table, were performed for each arm separately, as adapted from the Sollerman Hand Function Test.[19] Each task was scored on a 0 to 5 scale according to the grasp used. Details of scoring are available in the GRASSP manual. The total score was the sum of all task scores with a range of 0 to 60 for both sides.

The SCIM is a global measure of fundamental daily activities specific to individuals with SCI and focuses on gained independence.[11] The SCIM III has well-validated psychometric properties[20-22] and the SCIM-SS reflects upper limb performance.[23] In our study, the *SCIM III-SS* was therefore selected. The sum of the SCIM III-SS ranges between 0 and 20.

The *CROM* was developed by the GRASSP International Research and Design Team and consists of four questions regarding perceived physical change over time. The questions of the CROM were rated by occupational therapists, based on their perceived impressions of the change in performance of patients' (1) strength; (2) sensation; (3) fine motor tasks (ability to perform tasks such as screwing the cap from a toothpaste tube) and (4) functional tasks (ability to perform tasks such as eating independently, holding a cup and brushing one's teeth) between 1 and 3 months, between 3 and 6 months and between 6 and 12 months post-cervical SCI. The scale of the CROM has seven categories ranging from 1 (much worse) to 7 (much better).

The neurological assessment was performed according to the ISNCSCI protocol.[10] The ISNCSCI was selected to classify the neurological level of injury (NLI) and the overall AIS grade. The ISNCSCI *UEMS* and the ISNCSCI *LT (C6-C8)* were used in this study. Five key muscle groups of the upper limb in both arms were assessed and scored between 0 (total paralysis) and 5 (normal strength). The sum value of this score ranges from 0 and 50 for both sides. Sensation (LT) in three dermatomes (C6-C8) were scored as follows: 0 (absent sensation); 1 (impaired sensation) and 2 (normal sensation). The sum value of this score ranges from 0 to 12 points for both sides.

Data analysis

Descriptive statistics were used to determine the frequency, mean, standard deviation and range of the study participants' characteristics including AIS grade, lesion level, sex and age. Parameters were visually checked for normal distribution by a QQ plot.

There are many approaches for assessing responsiveness but no general consensus has yet been reached on the best method to use.[24,25] Internal responsiveness is defined as the ability of a measure to change over a particular, specified time period.[25] External responsiveness reflects the extent to which changes in a measure over a specified time relate to corresponding changes in referential measurement of health status.[25] Both internal and external responsiveness have been used in our comparisons.

Because differences in recovery and responsiveness depending on completeness of the lesion can be expected, we performed additional subgroup analyses (motor complete AIS: A-B and motor incomplete AIS: C-D).

Internal responsiveness

For internal responsiveness, a *linear mixed model* was used to assess change of the measure controlling for time. The level of significance was set at $\alpha < 0.05$.

Paired t-tests (Bonferroni adjusted) based on the linear mixed model were performed to localize significant differences between time intervals. The following time intervals were selected: 3, 6, and 12 months to 1 month; 6 and 12 to 3 months and lastly 12 months to 6 months. 95% confidence intervals (CI) of changes between time intervals were calculated. The standardized response mean *(SRM)* is now widely used[26] to express effect size and was calculated for the six intervals mentioned above. SRM is the mean delta score between the above defined intervals divided by the standard deviation (SD) of the delta score.[26-28] Values of 0.20 indicate low responsiveness; 0.50 medium responsiveness; and above 0.80, high responsiveness.[29]

External responsiveness

The external responsiveness of the GRASSP was quantified using correlation analysis and receiver operating characteristics (ROC) analysis. The level of significance was set at $\alpha < 0.05$. UEMS, LT (C6-C8) and SCIM III-SS were used as reference measures of GRASSP and CROM was used as an external standard for GRASSP.

Correlation analysis was performed between subtests of GRASSP and the reference measures using Spearman's rho correlation coefficient to determine the relationship

between them. Correlations in the range of 0 to 0.25 were interpreted as none to poor, 0.26 to 0.50 as fair, 0.51 to 0.75 as moderate to good, and 0.76 to 1.0 as very good to excellent.[29] With respect to aim 3, *ROC analysis* was performed to analyse the area under the curve (AUC) of MMT, SWM, QtG and SCIM III-SS delta values, in order to discriminate between patients with and without improvement as rated by clinicians (CROM). Values of the AUC between 0.7 and 1.00 indicate acceptable to excellent discrimination.[30] For ROC analysis we dichotomized the four CROM questions strength, sensation, fine motor tasks and functional tasks to assign individuals into an improved or non-improved group. Individuals were allocated to the improved group if the reported outcomes were: 'somewhat better', 'better' or 'much better'. All participants with: the 'same', 'somewhat worse', 'worse' or 'much worse' reported outcomes were allocated to the non-improved group. Furthermore we calculated mean delta scores for MMT, SWM, QtG and SCIM III-SS between the assessment stages (1–3 months, 3–6 months and 6–12 months).

Recovery profile

The annualized rate of recovery was calculated by dividing the amount of recovery between two assessments by the time interval between the two assessments. This value was then multiplied by 365 to express the rate of recovery during a particular interval that would have been expected if it were to have continued over 1 year, as used by Waters et al.[3,4] All data were analyzed using SPSS version 18.0 for Windows.

Results

Of the total 74 participants included, 69 had a traumatic and 5 a non-traumatic SCI (two ischemic in origin and three cases of spinal canal stenosis). Some GRASSP data were missing for 14 participants at the 6 months assessment and for 15 participants at the 12 months assessment (due to medical (n = 2) and logistical reasons (e.g. discharge, n = 12)). Because of the lower number of participants between 0–10 days post-injury (n = 40) we excluded this baseline time point from our analyses. Data of all parameters were approximately normally distributed. There was no statistically significant difference between the sum scores of the right and left sides and, therefore, all analyses were made for the sum score of the right and left sides combined. Detailed cohort characteristics are presented in Table 3.2.

Table 3.2 Demographic and clinical characteristics of participants (n = 74)

Characteristics	n (%)
Cause of SCI	
Traumatic	69 (93.2%)
Non-traumatic	5 (6.8%)
Site	
Klinik Hohe Warte Bayreuth (D)	25 (33.8%)
Unfallklinik Murnau (D)	1 (1.4%)
Orthopädische Universitätsklinik Heidelberg (D)	9 (12.2%)
Balgrist University Hospital Zurich (CH)	14 (18.9%)
Swiss Paraplegic Center Nottwil (CH)	25 (33.8%)
Gender	
Female	23 (31.1%)
Male	51 (68.9%)
Age (mean years; SD; min/max)	49 (±18; 18–87)
AIS	
1 month (range 16–40 days) (n = 74)	A: 18 (24.3%); B: 12 (16.2%); C: 10 (13.5%); D: 34 (45.9%)
3 months (range 70–98 days) (n = 68)	A: 13 (17.6%); B: 10 (13.5%); C: 8 (10.8%); D: 37 (50.0%)
6 months (range 150–186 days) (n = 60)	A: 14 (18.9%); B: 7 (9.5%); C: 4 (5.4%); D: 35 (47.3%)
12 months (range 300–400 days) (n = 58)	A: 10 (13.5%); B: 6 (8.1%); C: 6 (8.1%); D: 36 (48.5%)
Neurological level at 1 month	
C1	4 (5.4%)
C2	6 (8.1%)
C3	11 (14.4%)
C4	26 (35.1%)
C5	17 (23.0%)
C6	7 (9.5%)
C7	1 (1.4%)
C8	1 (1.4%)
T1	1 (1.4%)

Abbreviations: n, sample size; SCI, spinal cord injury; D, Germany; CH, Switzerland; AIS, American Spinal Injury Association Impairment Scale; C2, cervical dermatome 2; C, cervical T1, thoracic dermatome 1; T, thoracic; dermatomes are indicated by numbers; SD, standard deviation.

Internal responsiveness GRASSP

Linear mixed model analysis showed that overall and in both subgroups, the GRASSP subtest mean scores MMT, SMW, SWMP, SWMD, QIG and QtG differed significantly over time ($p < 0.0001$).

Pairwise comparison showed that MMT mean score significantly improved over all time intervals, both overall and for both subgroups with exception of the AIS C-D group, in which no significant change between 6–12 months was seen. Overall and in both subgroups, SWM, SWMP, SWMD, QIG and QtG mean scores significantly improved from 1 month to 12 months, but no significant difference was found between 3–6 months and 6–12 months.

Overall and in both subgroups, the SRM for MMT was large between all intervals except for the entire group and AIS C-D group, where a moderate SRM between 6–12 months was found. For QIG, moderate-to-large responsiveness was found from 1 month to 12 months and between 3–6 months in the group as a whole and in the AIS C-D subgroup. A moderate-to-large responsiveness was observed for QtG overall and in both subgroups over all time intervals except for the AIS A-B group between 3–6 months. The SWM tests showed poorer internal responsiveness compared to the other GRASSP subtests results. Detailed results of the pairwise comparison and the SRM of all time intervals for GRASSP subtests and the different groups are presented in Table 3.3.

Internal responsiveness of GRASSP compared to internal responsiveness of the reference measures

The results of the linear mixed model showed that the UEMS, LT (C6-C8) and SCIM-SS mean scores differed significantly over time ($p < 0.0001$).

As shown in Table 3.3, the GRASSP subtests showed similar, significant differences over the same time intervals as the scores of the UEMS and SCIM-SS (Table 3.4) with exception of LT (C6-C8), where no significant differences between time intervals was found and UEMS, in which no significant difference between 6–12 months was observed.

Both overall and for both subgroups, the SRM values of the GRASSP subtests (Table 3.3) were higher compared to the reference measures (Table 3.4 and Figure 3.1) with the exception of SCIM-SS. Detailed results of the pairwise comparison and the SRM of all time intervals for the reference measures and the different groups are available in Table 3.4. Figure 3.1 shows the SRM up to 12 months for the GRASSP subtests compared to the reference measures (as visual complement with Table 3.3 and Table 3.4).

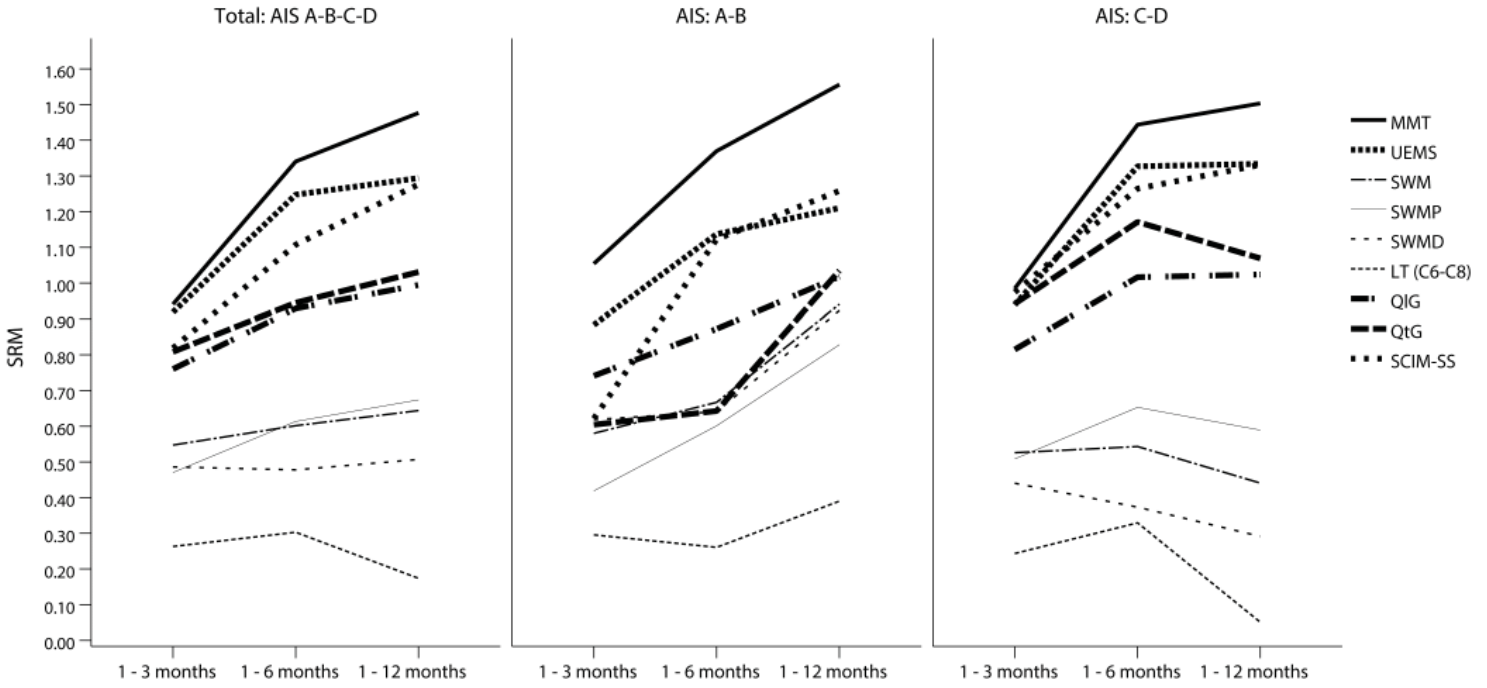

Figure 3.1 Standardized response mean GRASSP subtests and reference measures (as visual complement with Table 3.3 and Table 3.4).
Abbreviations: GRASSP, Graded Redefined Assessment of Strength, Sensibility and Prehension; AIS, American Spinal Cord Injury Association Impairment Scale; SRM, standardized response mean; MMT, manual muscle testing; UEMS, upper extremity motor score; SWM, Semmes and Weinstein Monofilament; SWMP, Semmes and Weinstein Monofilament, palmar; SWMD, Semmes and Weinstein Monofilament, dorsal; LT, light touch; C6-C8, cervical dermatom 6, 7 and 8; QIG, qualitative grasping; QtG, quantitative grasping; SCIM-SS, Spinal Cord Independence Measure self-care subscale.

Table 3.3 Internal responsiveness GRASSP subtests[a]

	AIS: A, B, C, D					AIS: A-B					AIS: C-D				
	Linear Mixed Model					Linear Mixed Model					Linear Mixed Model				
	Mean	SE	95% CI	SRM	n	Mean	SE	95% CI	SRM	n	Mean	SE	95% CI	SRM	n
GRASSP-MMT (0–100)[b]															
1–3 months	9.60***	1.24	6.29–12.90	**0.94**	70	6.68***	1.42	2.83–10.52	**1.05**	29	11.60***	1.83	6.69–16.50	**0.98**	41
1–6 months	16.14***	1.33	12.59–19.69	**1.34**	58	12.05***	1.50	7.98–16.12	**1.37**	25	19.14***	1.98	13.82–24.46	**1.44**	33
1–12 months	20.73***	1.34	17.16–24.30	**1.48**	57	16.68***	1.52	12.55–20.81	**1.56**	24	23.78***	1.98	18.46–29.10	**1.50**	33
3–12 months	11.13***	1.36	7.51–14.76	**1.27**	54	10.01***	1.54	5.82–14.19	**1.33**	23	12.19***	2.01	6.78–17.59	**1.27**	31
3–6 months	6.54***	1.35	2.95–10.13	**1.04**	56	5.37***	1.52	1.25–9.49	**0.82**	24	7.55***	2.00	2.17–12.92	**1.23**	32
6–12 months	4.59***	1.40	0.87–8.32	*0.79*	53	4.63*	1.56	0.41–8.85	**1.23**	24	4.64	2.09	-0.99–10.27	*0.68*	29
GRASSP-SWM (0–48)[b]															
1–3 months	3.68***	0.85	1.42–5.94	*0.55*	71	3.75*	1.30	0.21–7.28	*0.58*	29	3.65***	1.10	0.69–6.60	*0.53*	42
1–6 months	4.76***	0.91	2.33–7.20	*0.60*	58	5.89***	1.38	2.15–9.63	*0.67*	25	4.01***	1.20	0.78–7.24	*0.54*	33
1–12 months	5.69***	0.92	3.24–8.14	*0.64*	57	7.96***	1.40	4.16–11.75	**0.94**	24	4.10***	1.20	0.87–7.33	0.44	33
3–12 months	2.01	0.93	-0.48–4.50	**0.93**	54	4.21*	1.42	0.37–8.05	*0.58*	23	0.45	1.22	-2.83–3.73	0.23	31
3–6 months	1.08	0.92	-1.38–3.54	0.15	56	2.15	1.40	-1.64–5.93	0.41	24	0.36	1.21	-2.9–3.63	0.04	32
6–12 months	0.93	0.96	-1.63–3.49	0.14	53	2.07	1.43	-1.82–5.95	0.31	24	0.09	1.27	-3.34–3.52	0.02	29
GRASSP-SWMP (0–24)[b]															
1–3 months	1.86***	0.44	0.68–3.05	0.47	71	1.98	0.79	-0.17–4.13	0.42	29	1.79***	0.50	0.44–3.15	*0.51*	42
1–6 months	2.63***	0.48	1.36–3.91	*0.61*	58	3.16***	0.84	0.88–5.43	*0.60*	25	2.27***	0.55	0.79–3.75	*0.65*	33
1–12 months	3.00***	0.48	1.72–4.28	*0.67*	57	4.08***	0.85	1.77–6.39	**0.83**	24	2.22***	0.55	0.74–3.70	*0.59*	33
3–12 months	1.13	0.49	-0.17–2.44	0.40	54	2.10	0.86	-0.23–4.43	0.46	23	0.43	0.56	-1.08–1.93	0.36	31
3–6 months	0.77	0.68	-0.52–2.06	0.22	56	1.18	0.85	-1.12–3.48	0.44	24	0.48	0.56	-1.02–1.98	0.13	32
6–12 months	0.37	0.50	-0.97–1.71	0.12	53	0.92	0.87	-1.44–3.28	0.24	24	-0.05	0.58	-1.63–1.52	-0.01	29

GRASSP-SWMD (0–24)[b]															
1–3 months	1.82***	0.50	0.48–3.15	0.49	71	1.77*	0.65	0.00–3.53	*0.62*	29	1.84	0.72	-0.08–3.77	0.44	42
1–6 months	2.13***	0.54	0.69–3.57	0.48	58	2.72***	0.69	0.85–4.58	*0.64*	25	1.75	0.78	-0.35–3.85	0.37	33
1–12 months	2.70***	0.54	1.25–4.15	*0.51*	57	3.87***	0.70	1.97–5.76	*0.92*	24	1.92	0.78	-0.18–4.02	0.29	33
3–12 months	0.89	0.55	-0.58–2.36	0.28	54	2.10*	0.71	0.18–4.02	*0.55*	23	0.07	0.79	-2.06–2.21	0.09	31
3–6 months	0.31	0.55	-1.15–1.77	0.07	56	0.95	0.70	0.94–2.84	0.31	24	-0.09	0.79	-2.22–2.03	-0.04	32
6–12 months	0.58	0.57	-0.94–2.09	0.14	53	-2.06	2.39	0.79–3.09	0.35	24	0.17	0.83	-2.06–2.39	0.03	29
GRASSP-QIG (0–24)[b]															
1–3 months	2.90***	0.43	1.74–4.06	*0.76*	70	2.01***	0.50	0.64–3.38	*0.74*	29	3.52***	0.64	1.79–5.24	**0.81**	41
1–6 months	3.98***	0.47	2.73–5.23	**0.93**	57	2.83***	0.54	1.37–4.30	**0.87**	24	4.79***	0.70	2.92–6.66	**1.02**	33
1–12 months	4.73***	0.47	3.48–5.98	**0.99**	57	3.52***	0.54	2.05–4.98	**1.02**	24	5.66***	0.70	3.79–7.53	**1.02**	33
3–12 months	1.82***	0.48	0.56–3.09	*0.66*	54	1.50*	0.55	0.02–2.99	*0.69*	23	2.14*	0.71	0.25–4.04	*0.67*	31
3–6 months	1.08	0.47	-0.19–2.34	*0.52*	55	0.82	0.55	-0.66–2.31	0.43	23	1.28	0.70	-0.61–3.17	*0.58*	32
6–12 months	0.75	0.49	-0.56–2.06	0.34	52	0.68	0.56	-0.84–2.20	0.22	23	0.87	0.74	-1.11–2.85	0.41	29
GRASSP-QtG (0–60)[b]															
1–3 months	9.12***	1.21	5.90–12.34	**0.81**	66	5.89***	1.49	1.84–9.93	*0.60*	25	11.09***	1.70	6.52–15.65	**0.94**	41
1–6 months	11.95***	1.31	8.45–15.45	**0.94**	52	7.38***	1.61	3.01–11.76	*0.64*	20	14.88***	1.85	9.90–19.85	**1.17**	32
1–12 months	14.65***	1.31	11.16–18.13	**1.03**	52	10.94***	1.60	6.6–15.28	**1.03**	20	17.07***	1.85	12.09–22.04	**1.07**	32
3–12 months	5.52***	1.30	2.06–8.99	**0.89**	53	5.05**	1.55	0.83–9.28	**1.10**	22	5.98**	1.87	0.97–11.00	**0.83**	31
3–6 months	2.83	1.30	-0.65–6.31	*0.50*	53	1.50	1.58	-2.80–5.79	0.42	21	3.79	1.85	-1.20–8.78	*0.58*	32
6–12 months	2.70	1.34	-0.89–6.28	*0.64*	51	3.56	1.59	-0.77–7.88	*0.78*	22	2.19	1.94	-3.03–7.41	*0.55*	29

Abbreviations: GRASSP, Graded Redefined Assessment of Strength, Sensibility and Prehension; AIS, American Spinal Cord Injury Association Impairment Scale; SE, standard error; 95% CI, 95% confidence interval; SRM, standardized response mean; n, sample size; MMT, manual muscle testing; SWM, Semmes and Weinstein Monofilament; SWMP, Semmes and Weinstein Monofilament palmar test location; SWMD, Semmes and Weinstein Monofilament dorsal test location; QIG, qualitative grasping; QtG, quantitative grasping.

[a] **Bold** indicates large responsiveness; *italic* indicates moderate responsiveness.

[b] Range of sum score for both sides: SRM values indicate: 0.2, small; 0.50 medium; > 0.80 large responsiveness.[29]

*** $p < 0.0001$, ** $p < 0.01$; * $p < 0.05$ (Bonferroni adjusted p value).

Table 3.4 Internal responsiveness reference measures[a]

	AIS: A, B, C, D					AIS: A-B					AIS: C-D				
	Linear Mixed Model					Linear Mixed Model					Linear Mixed Model				
	Mean	SE	95% CI	SRM	n	Mean	SE	95% CI	SRM	n	Mean	SE	95% CI	SRM	n
ISNCSCI-UEMS (0–50)[b]															
1–3 months	5.14***	0.70	3.28–7.00	**0.92**	64	4.78***	1.03	1.98–7.57	**0.88**	28	5.44***	0.96	2.87–8.01	**0.94**	36
1–6 months	8.70***	0.72	6.77–10.62	**1.25**	58	8.03***	1.06	5.16–10.91	**1.14**	26	9.28***	0.99	6.61–11.95	**1.33**	32
1–12 months	10.2***	0.73	8.28–12.18	**1.29**	56	9.66***	1.12	6.61–12.71	**1.21**	22	10.66***	0.97	8.04–13.28	**1.33**	34
3–12 months	5.09***	0.75	3.10–7.08	**0.96**	52	4.88***	1.14	1.80–7.97	**1.08**	21	5.21***	1.00	2.53–7.90	**1.06**	31
3–6 months	3.56***	0.74	1.59–5.53	**0.99**	54	3.25*	1.07	0.34–6.17	**0.83**	25	3.83***	1.02	1.09–6.57	**1.14**	29
6–12 months	1.53	0.75	-0.47–3.54	*0.69*	53	1.63	1.14	-1.46–4.72	*0.79*	22	1.38	1.01	-1.34–4.10	*0.63*	31
ISNCSCI-LT (C6-C8) (0–12)[b]															
1–3 months	0.62	0.29	-0.15–1.38	0.26	65	0.50	0.37	-0.51–1.50	0.30	28	0.71	0.41	-0.40–1.82	0.24	37
1–6 months	0.66	0.30	-0.13–1.45	0.30	60	0.49	0.38	-0.54–1.53	0.26	26	0.81	0.43	-0.34–1.96	0.33	34
1–12 monhts	0.43	0.30	-0.37–1.23	0.17	57	0.91	0.40	-0.19–2.01	0.39	22	0.14	0.42	-1.00–1.27	0.05	35
3–12 months	-0.19	0.31	-1.01–0.63	-0.08	53	0.41	0.41	-0.69–1.52	0.22	21	-0.57	0.43	-1.73–0.60	-0.24	32
3–6 months	-0.15	1.38	-0.76–0.85	0.02	56	0.00	0.39	-1.05–1.04	0.02	25	0.10	0.44	-1.07–1.28	0.01	31
6–12 months	-0.23	0.31	-1.06–0.59	-0.13	54	0.42	0.41	-0.69–1.53	0.24	22	-0.67	0.44	-1.85–0.51	-0.29	32
SCIM-SS (0–20)[b]															
1–3 months	4.23***	0.54	2.79–5.67	**0.82**	73	2.60***	0.69	0.73–4.47	*0.62*	30	5.34***	0.75	3.31–7.37	**0.97**	43
1–6 months	5.89***	0.58	4.34–7.43	**1.11**	60	3.76***	0.73	1.80–5.73	**1.12**	26	7.44***	0.82	5.24–9.64	**1.26**	34
1–12 months	7.36***	0.58	5.81–8.92	**1.28**	59	5.78***	0.76	3.73–7.84	**1.26**	23	8.40***	0.80	6.24–10.57	**1.33**	36
3–12 months	3.14***	0.59	1.58–4.70	**0.88**	58	3.18***	0.76	1.13–5.24	**0.94**	23	3.06***	0.81	0.89–5.24	**0.83**	35
3–6 months	1.66***	0.58	0.11–3.21	*0.70*	59	1.16	0.73	-0.80–3.13	*0.76*	26	2.10	0.83	-0.12–4.32	*0.72*	33
6–12 months	1.47	0.61	-0.15–3.10	0.42	54	2.02	0.77	-0.07–4.11	*0.55*	23	0.97	0.85	-1.33–3.26	0.31	31

Abbreviations: AIS, American Spinal Cord Injury Association Impairment Scale; SE, standard error; 95% CI, 95% confidence interval; SRM, standardized response mean; n, sample size; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; UEMS, upper extremity motor score; LT, light touch; C6-C8, cervical dermatome 6, 7 and 8; SCIM-SS, Spinal Cord Independence Measure self-care subscale. [a] **Bold** indicates, large responsiveness; *italic* indicates, moderate responsiveness. [b] Range of sum score for both sides; SRM values indicate: 0.2, small; 0.50 medium; > 0.80 large responsiveness.[29]

*** $p < 0.0001$, ** $p < 0.01$, * $p < 0.05$ (Bonferroni adjusted p value).

External responsiveness

The Spearman correlations between GRASSP subtests MMT, SWM and QtG with the reference measures at 1, 3, 6 and 12 months were moderate to high. Detailed results of the correlation analysis are presented in Table 3.5.

ROC analyses showed that the AUC value for MMT, SWM, QtG and SCIM-SS were acceptable to excellent (ranging from 0.68 to 0.87, $p < 0.05$ to $p < 0.001$) at 1, 3, 6 and 12 months post-injury. Detailed results for ROC analysis can be found in Table 3.6 and Figure 3.2 (as visual complement with Table 3.6).

Recovery profile

The overall, annualized motor and prehension recovery rate showed a comparable course in the AIS A-B and AIS C-D subgroups (Figure 3.4) although in the AIS C-D subgroup individuals had higher scores at the beginning of rehabilitation (Figure 3.3 and Figure 3.4). A very high motor and prehension recovery rate between 1–3 months after injury was achieved in both subgroups. After 3 months, this rate rapidly declined (QtG more steeply than MMT) and between 6–12 months the motor and prehension recovery rate was very low, although MMT and QtG continued to show improvement up to 12 months in both subgroups. For detailed results, see Figure 3.4.

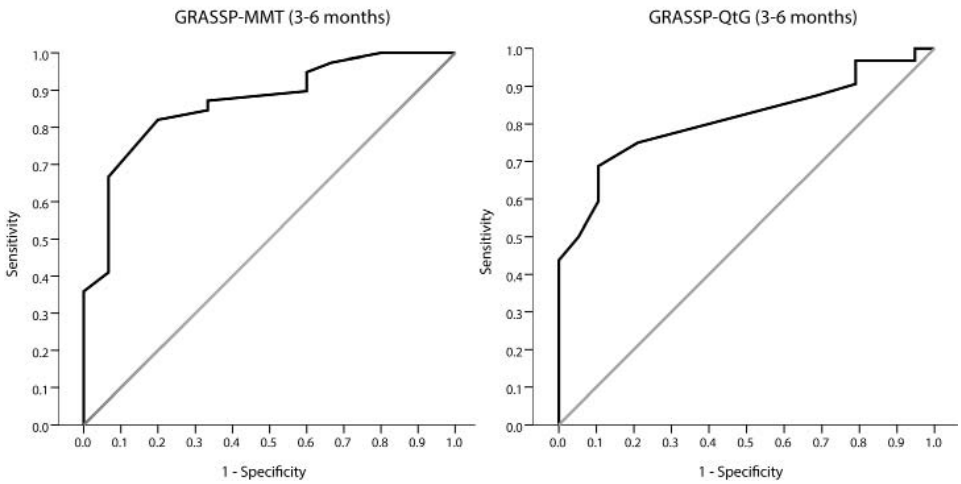

Figure 3.2 Receiver operating characteristics (ROC) curves.
The figures show the GRASSP-MMT and GRASSP-QtG ROC curves between patients with and without improvement as rated by clinicians at 6 months compared to 3 months (as visual complement with Table 3.6). The diagonal represents the line of no discrimination. Points above this line indicate good classification results. The bigger the area under the ROC curve, the better the accuracy between GRASSP changes and clinicians' ratings.
Abbreviations: GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; MMT, manual muscle testing; QtG, quantitative grasping.

Table 3.5 Spearman correlations GRASSP subtests and reference measures

	1 month		3 months		6 months		12 months	
	r_s	n	r_s	n	r_s	n	r_s	n
	ISNCSCI-UEMS		ISNCSCI-UEMS		ISNCSCI-UEMS		ISNCSCI-UEMS	
GRASSP-MMT	0.95***	70	0.94***	64	0.94***	57	0.88***	55
	ISNCSCI-LT (C6-C8)		ISNCSCI-LT (C6-C8)		ISNCSCI-LT (C6-C8)		ISNCSCI-LT (C6-C8)	
GRASSP-SWM (C6-C8)	0.58***	71	0.64***	66	0.65***	58	0.66***	55
GRASSP-SWMP (C6-C8)	0.59***	71	0.62***	66	0.63***	58	0.63***	55
GRASSP-SWMD (C6-C8)	0.55***	71	0.61***	66	0.64***	58	0.62***	55
	SCIM-SS		SCIM-SS		SCIM-SS		SCIM-SS	
GRASSP-MMT	0.78***	73	0.85***	71	0.83***	57	0.82***	56
GRASSP-SWM	0.63***	74	0.68***	71	0.63***	57	0.56***	56
GRASSP-QtG	0.85***	68	0.90***	70	0.86***	55	0.82***	56

Abbreviations: GRASSP, Graded Redefined Assessment of Strength, Sensibility and Prehension; r_s, correlation coefficient; n, sample size; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; UEMS, upper extremity motor score; LT C6-C8, light touch; C6-C8, cervical dermatome 6,7 and 8; SCIM-SS, Spinal Cord Independence Measure self-care subscale; MMT, manual muscle testing; SWM, Semmes and Weinstein Monofilament; SWMP, Semmes and Weinstein Monofilament, palmar; SWMD, Semmes and Weinstein Monofilament, dorsal; QtG, quantitative grasping.

*** $p < 0.0001$ for all variables.

Table 3.6 Output of receiver operating characteristics (ROC) analysis

	External standard[a]								
	1–3 months			3–6 months			6–12 months		
	AUC	95% CI	n	AUC	95% CI	n	AUC	95% CI	n
Delta GRASSP-MMT	0.81***	0.71–0.91	67	0.87***	0.77–0.97	54	0.71**	0.58–0.85	52
Delta GRASSP-SWM	0.77***	0.65–0.89	68	0.68*	0.53–0.82	54	0.86***	0.76–0.96	52
Delta GRASSP-QtG	0.71***	0.57–0.85	64	0.81***	0.70–0.93	51	0.82***	0.70–0.94	50
Delta SCIM-SS	0.80***	0.70–0.90	68	0.75**	0.60–0.90	55	0.72**	0.59–0.86	50

Abbreviations: GRASSP, Graded Redefined Assessment of Strength, Sensibility and Prehension; AUC, area under the curve; 95% CI, 95 % confidence interval; n, sample size; MMT, manual muscle testing; SWM, Semmes and Weinstein Monofilament; QtG, quantitative grasping; SCIM-SS, Spinal Cord Independence Measure self-care subscale.

[a] Clinicians rated patients strength, sensation, fine motor tasks and functional tasks at 3 months compared to 1 month, at 6 months compared to 3 months and at 12 months compared to 6 months.

*** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

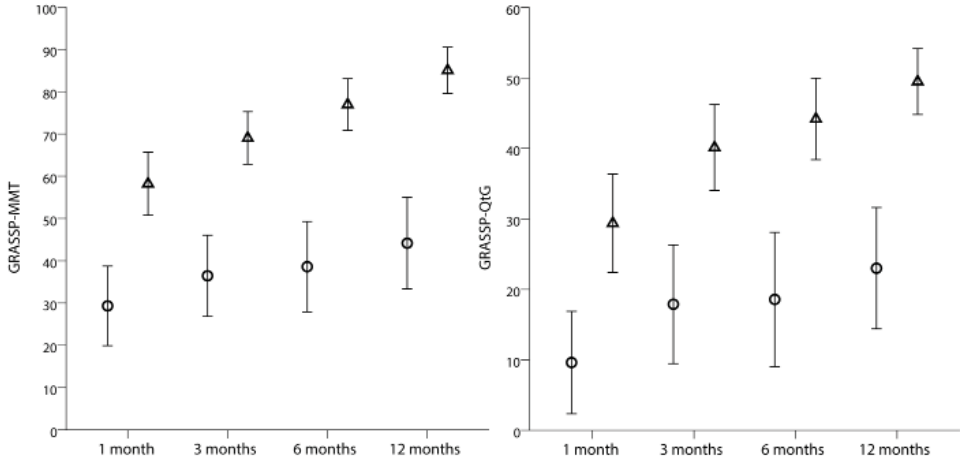

Figure 3.3 GRASSP-MMT and GRASSP-QtG recovery over time.
Indicated are the mean and 95% confidence interval from 1 month to 1 year after cervical spinal cord injury.
Abbreviations: GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; MMT, manual muscle testing; QtG, quantitative grasping; AIS, American Spinal Cord Injury Association Impairment Scale.
o, AIS: A-B, Δ, AIS: C-D.

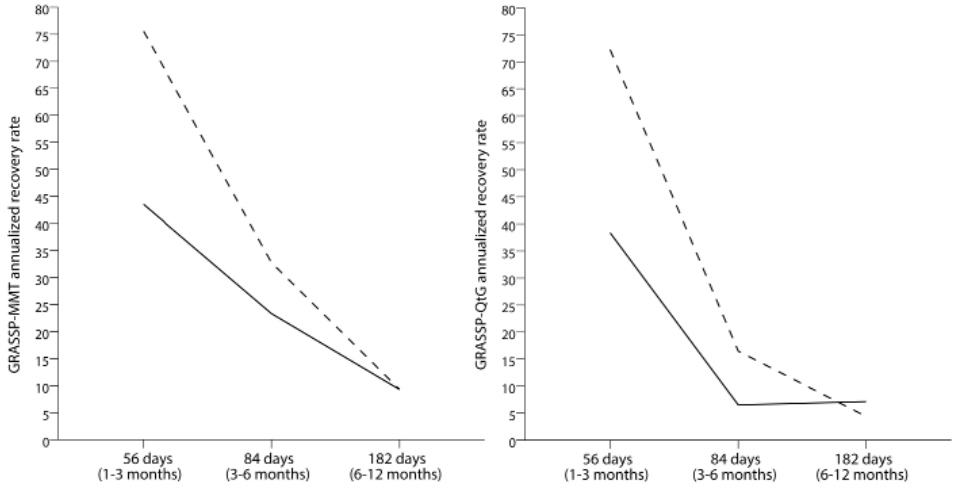

Figure 3.4 GRASSP-MMT and GRASSP-QtG annualized recovery rate.
The figures show the MMT and QtG recovery rate at 56, 84 and 182 days after cervical spinal cord injury. The motor (MMT) and functional (QtG) recovery rate was calculated by dividing the amount of recovery observed between two assessments by the time interval in between the two assessments and by converting this value to change per year. This value indicates the recovery rate, assuming it had remained constant over 1 year.
Abbreviations: GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; MMT, manual muscle testing; QtG, quantitative grasping; ———, AIS: A-B; - - - - -, AIS: C-D.

Discussion

This study showed the excellent internal and external responsiveness of the GRASSP during the first year after cervical SCI and provided distinct motor and prehension recovery profiles. More importantly, the GRASSP is complementary to clinical assessment using ISNCSCI standards due to its higher responsiveness. Furthermore, improvements as indicated by the GRASSP were rated as clinically meaningful changes according the clinicians' impressions of patients' recoveries. These findings suggest that the GRASSP can provide meaningful information for clinical trials beyond the ISNCSCI standards.

Responsiveness

All GRASSP subtests showed good internal responsiveness over time.

MMT was the most responsive GRASSP subtest with even higher, significant changes seen in the AIS A-B group between 6–12 months than in the AIS C-D group.

MMT was more responsive than *UEMS* throughout, likely due to the expanded combination of muscle groups. MMT, as defined in the GRASSP, incorporated additional distal (extensor digitorum, opponens pollicis, flexor pollicis longus and first dorsal interosseus,) and proximal (anterior deltoid) muscle groups in addition to the standard muscles (elbow flexors, wrist extensors, elbow extensors, finger flexors and small finger abductors) assessed by the ISNCSCI protocol. These additional muscles provide important information regarding innervation and contributed to the higher responsiveness in this study in accordance with findings reported in a recent longitudinal study in acute cervical SCI[14] as well as in a cross sectional study in chronic SCI.[13] Therefore, the assessment of additional arm and hand muscles as defined by the GRASSP provides a more sensitive appreciation of upper limb function and supports the application of the GRASSP as a more accurate assessment tool in cervical SCI than those used previously (ISNCSCI).

MMT in the AIS C-D group between 6–12 months post-injury might show a ceiling effect in detecting further small changes at this stage. For future studies, we recommend the additional assessment of strength using hand-held dynamometry in those individuals with less paretic muscles (minimum MMT score of 3) to avoid ceiling effects in individuals with high MMT scores at the beginning of rehabilitation. In general *QtG* was equally sensitive as the *SCIM-SS* to changes in cervical SCI but was more responsive between 6–12 months. SCIM-SS provides a clinically meaningful categorization of functioning in ADLs with a focus on gained independence while the QtG stresses the capacity to

perform standardized movement tasks. Although the QtG score is based on unilateral performance of tasks with no compensatory movements, it reflects similar changes to those detected by the SCIM-SS. The advantage of using GRASSP over other outcome measures such as the Van Lieshout test[31,32] or Capabilities of Upper Extremity Test,[33] that tend to address overall arm and hand usage, is that it provides more detailed information on how functional improvements are achieved. Likewise, a functional measure such as the SCIM III is not designed to establish the neurological state of an individual when performing tasks or whether those tasks are performed bimanually or with compensatory movements. In contrast, the subtest scores of GRASSP are specifically designed to disentangle detailed motor and sensory functions contributing to the outcome of upper limb function. The detailed assessment reveals how changes in function are related to neurological improvements following spinal cord injury, something which cannot be elucidated by the SCIM III. In addition, the GRASSP subtests also include standardized prehension tests that are related to changes in neurological outcomes. These combined assessments permit the determination of whether changes in function are based on improvement through compensatory movements or on improvement of neurological function. Accordingly, QtG provides a detailed scoring of standardized tasks focusing on the form of the grasp and therefore is able to explain how changes up to 1 year post-injury are achieved.

Sensory changes were rather limited as assessed by the *SWM*. However, SWM was significant and more sensitive to small gains between 1–3 months, something not found with *LT (C6-C8)*. The present results suggest that SWM is sensitive to minor impairments, which are less detectable by LT testing; findings also confirmed in cross-sectional studies by Kalsi-Ryan et al. and Velstra et al.[13,34] These authors observed greater sensitivity of the SWM in individuals with acute and chronic SCI compared with the values reported when using LT.

Likely due to the broader scaling of the SWM (by applying different sensory modalities) as well as the additional palmar test locations, more changes in sensation were detected with SWM than with LT.

All GRASSP subtests revealed significant, moderate-to-excellent correlations with the established *reference measures* at each time point (external responsiveness). These findings support previously published data that showed significant and moderate-to-strong correlations of MMT, SWM, QtG or cervical motor levels with self-care in longitudinal as well as cross-sectional studies in acute and chronic cervical SCI.[5,6,13,14,23,35] The large

SRMs, particularly for MMT and QtG, reflect great clinical significance[25,36,37] which was supported by the clinicians' ratings (external standard), used as an indicator for clinically meaningful change. The results showed large AUC, indicating that changes in GRASSP subtests and SCIM-SS were rated as clinically meaningful in accordance with the external standard (external responsiveness).[25,28,38,39]

Recovery profiles

It was expected that strength (MMT) and prehension (QtG) would mostly improve within the first 3 months of injury where improvements in general functional skills and motor recovery are most prominent compared to later stages of rehabilitation.[3-5,40-45] In contrast the present study revealed significant improvements in strength between all timepoints up to 12 months post-injury in the entire group and A-B subgroup and up to 6 months post-injury in the C-D subgroup.

The prehension (QtG) and motor (MMT) recovery rate are comparable with the annualized recovery rate reported elsewhere.[3,4,44,45] This rate decreased with time after cervical SCI. Between 1–3 months post-injury, individuals with AIS C-D showed a motor and prehension recovery rate almost twice as high as that in individuals in the AIS A-B subgroup. From 3 months to 1 year after injury, the motor and prehension recovery rate declined rapidly, although motor changes were larger compared to prehension changes and reached a rate similar in both subgroups at 6–12 months. Strength and prehension still showed improvement up to 12 months in both subgroups, which is a new finding.

Implications for rehabilitation and clinical trials

This study provides data to assist clinicians and researchers on the value of the GRASSP in acute tetraplegia. We found that the responsiveness of GRASSP is excellent and it is applicable as a primary outcome measure in rehabilitation. Specifically MMT and QtG seem to be most valuable for clinical trials as they are strongly responsive to change over the course of recovery and identify clinically meaningful changes complementary to ISNCSCI and SCIM. Measures with greater responsiveness indices provide greater study power, thereby allowing a study to be completed with fewer individuals.[46]

The observed GRASSP subtest changes were also in accordance with the clinicians' impressions of patient changes, which is a novel finding. Therefore, CROM may be useful in clinical trials to incorporate a clinical judgment that references past experiences to benchmark the progress of a patient.[47] Experienced clinicians, such as those involved

in this study, have a good understanding of neurological impairment and functional performance. However, novel questionnaires like the CROM have to be interpreted with caution as they may be influenced by other factors (e.g. clinical judgment, past experience, beliefs regarding treatment effectiveness etc.). Systematic bias in our results cannot be entirely excluded as some assessments of GRASSP and CROM in individual patients were performed by the same therapist. Depending on the study design and research question, it is of course advisable that independent clinicians perform the GRASSP and CROM, thereby minimizing examiner bias.

Limitations

The effect of different baseline levels of lesion was not assessed in this investigation, but consideration of the amount of change for such patients should be investigated with a higher sample size in future studies.

Conclusion

The GRASSP is a responsive and clinically meaningful tool for the evaluation of upper limb outcomes in cervical SCI and can be recommended for follow-up assessments. The combined assessment of neurological (body structure and body function) and functional outcomes, e.g. prehension (activity and participation), focused on segmental cervical spinal cord functions that are closely related to other standard assessment tools (ISNCSCI and SCIM) supports the use of GRASSP in the assessment of rehabilitation as well as in interventional clinical trials that seek to detect both subtle and clinically meaningful changes.

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Chapter 4

Epicritic sensation in cervical spinal cord injury: diagnostic gains beyond testing light touch

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Abstract

Applied as a bedside test of gross dorsal column function, the testing of light touch sensation is of high clinical value in the diagnosis of human spinal cord injury (SCI). However, the assessment of overall dorsal column deficit by testing only light touch may be limited, because the dorsal column pathway conveys several large diameter afferent modalities (e.g., sensation of touch, two-point discrimination and proprioception). Therefore, the objective of this study was to compare the epicritic sensation assessed by light touch (LT), Semmes Weinstein Monofilament (SWM) and electrical perception threshold (EPT) across cervical dermatomes (C3 to C8) in individuals with cervical SCI. A multicenter cross sectional study was performed at 6 months after cervical SCI applying combined measures of LT, SWM and EPT, bilaterally over predefined key sensory points (C3 to C8). A total of 300 left- and right-sided dermatomes were tested for each outcome measure in 25 participants. The percentage agreement between classifications according to LT and SWM/EPT testing for all dermatomes between C3 and C8 ranged from 95.5% to 36.2 %. The degree of agreement showed considerably variable kappa coefficients ($-0.1 \geq k_w \leq 0.7$) for each dermatome between C3 and C8. The additional measurements of epicritic sensation by SWM and EPT increased sensitivity by detecting and quantifying differences in sensory thresholds above, at and below the LT level of injury. This is relevant for early clinical trials (phase I/II), where disclosing any biological activity of an intervention may be revealed by subtle sensory changes that might gain a clinical relevance.

Introduction

Testing of sensory function is essential to sufficiently measure the degree of dysfunction and recovery after acute cervical spinal cord injury (C-SCI), which is paramount for setting reasonable goals in rehabilitation and for accurate stratification in a clinical trial.[1,2] However difficulties arise in selecting outcome measures that can detect small changes to evaluate the success of rehabilitation and to test the efficacy of new interventions, for the different sensory modalities and in the interpretation of those test results.

Light touch (LT) and pinprick (PP) assessment examined according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)[3] is used routinely during neurological examination of sensibility in patients with a SCI. However, the sensory assessment by the ISNCSCI might not be sufficiently sensitive to monitor safety and/or to detect subtle therapeutic benefits.[4] Furthermore, it may not be able to elucidate potential mechanisms of recovery.[5] Therefore, additional quantitative sensory assessments, such as the Electrical Perception Threshold (EPT) and the Semmes and Weinstein Monofilament (SWM), may be used in combination with LT and PP to improve the sensitivity to discrete sensory changes and robustness of sensibility examination in the clinic and research.[6-11] LT, SWM and EPT assess the posterior column pathway for detecting thresholds for tactile cutaneous sensation and electrical cutaneous sensation.[7,12-14]

So far SWM remains the only internationally recognized handheld instrument specifically designed to control application force variables, and to meet sensitivity and repeatability requirements for an objective outcome measure of sensation.[10,15-17] However, to the best of our knowledge, SWM has not been systematically applied in spinal cord disorders,[18] while clinical experience in peripheral nerve damage (i.e. nerve repair surgery in upper extremities) has proven its validity and is well established in clinical use.[17,19]

The pocket version of SWM consists of 5 nylon monofilaments with variable stiffness that apply different amount of grams to quantify cutaneous sensation. The SWM sensory threshold is defined as the force of the lightest filament at which the patient reports sensation. In participants with chronic cervical SCI, the SWM has been reported to have high validity and excellent overall inter- and intra-tester reliability (ICC ranged between 0.84–0.95).[8] However, the ICC between individual cervical dermatomes has not been reported. Recently it has been shown that the ICC is fair for the SWM in C4, T1, T8 and L4 dermatomes in healthy subjects.[20] However ICC values can vary between healthy subjects and patients as a result of inter individual variations of sensory thresholds as well as differences in sensibility between dermatomes. The determination of the SWM sensory threshold has the advantage of being a simple and unobtrusive/discreet method.

EPT testing has been introduced in the assessment of sensory function in spinal cord disorders and holds promise in providing sensitive readouts beyond the clinical scaling.[7,12,21-23] The EPT is defined as the lowest ascending electrical stimulus intensity expressed in mA at which the patient reports sensation.[6,24] The overall inter- and intra-tester reliabilities of EPT appear to be moderate to good in healthy participants[20,21] and participants with incomplete SCI.[24] However, the intraclass correlation coefficient (ICC) varied considerably between individual dermatomes in healthy participants.[23] Thus there are different normative values for each dermatome. The EPT can be applied to all sensory dermatomes and results can be interpreted quickly, but the method is more time-consuming than LT testing.

The LT assessment of sensation roughly grades the ability of detecting a light touch in the affected dermatome by “absent”, “impaired” or “normal”. Thus detection of subtle improvements in sensation or minor sensory impairments is rather impossible. The SWM and EPT contain a greater range of discernable response levels for detecting a tactile cutaneous sensation and electrical stimulation and therefore have the potential of being more sensitive.[22,25] This encompasses a wide range of degrees of impairment and can include hypersensitivity as well as hyposensitivity. However, it is unknown, if EPT or SWM are more sensitive than clinical sensory examination (LT) for an individual cervical dermatome.

While SCI physicians and clinicians have gained great experience of LT testing in the clinical management of patients suffering from SCI the actual sensitivity of LT testing to assess dorsal column function in patients with SCI is less established. To our knowledge there is no study that compares epicritic sensation assessed by LT, SWM and EPT across cervical dermatomes (C3 to C8) in participants at 6 months after cervical SCI. The following study hypothesized that the segmental assessment of epicritic sensation in human SCI can be improved by additional semi-quantitative sensory measures complementary to LT. The latter findings are required for the consideration if LT testing can be assumed sensitive enough in interventional studies.

Methods

Study design

A cross-sectional multi-center study in two specialized SCI rehabilitation centers.

Study population

Participants were recruited between March 2010 and May 2011 from two Swiss SCI centers: the University Hospital Balgrist, Zurich and the Swiss Paraplegic Center, Nottwil. Inclusion criteria consisted of traumatic or non-traumatic cervical SCI with an ASIA Impairment Scale (AIS) grade A, B, C, or D.[3] Exclusion criteria were individuals with any accompanying severe neurological (e.g., traumatic brain injury) or medical disorders and age less than 16 years. The participants were enrolled after having providing written informed consent. The local Ethics Committees of the two participating centers approved the study.

Procedures

The assessors were clinicians (physicians and occupational therapists) who had long lasting experience in working with individuals with SCI. To ensure high-quality and reliable examinations, assessors were trained how to perform all applied outcome measures. A standardized protocol that outlined detailed instructions on performing the assessments was followed for each outcome measure. The recording techniques and materials were standardized across both centers. All participants were tested in a quiet room throughout the exams. For EPT and LT testing, participants were lying in a comfortable supine position, and for SWM testing participants were seated. First the testing procedure was explained to the participants. Before testing of cervical dermatomes, the stimuli of the different outcome measures were applied to a dermatome with normal sensation, i.e. the face, in order for the patient to recognize the sensation. Subsequently, the participants were asked to close both of their eyes, and the testing was started. All outcome measures were assessed in a random order at 6 months after SCI (defined as a time window between 150–186 days).

Assessments

The SWM and EPT outcome measures were applied bilaterally over predefined ASIA sensory key points in the dermatomes C3 to C8.

The clinical neurological examination of touch sensation was assessed by the ASIA LT testing according to the ISNCSCI protocol for the whole body.[3] The PP assessment involves the anterior column pathway (i.e. spino-thalamic fiber tracts) and is therefore not included in the present study. Appreciation of LT sensation at each of the ASIA sensory key points was scored on an ordinal three-point scale as follows: 2 = normal; 1 = impaired and 0 = absent. The LT level of lesion was defined as the last intact sensory level as indicated by normal LT testing.[3]

The tactile cutaneous sensation threshold was assessed by the pocket version of SWM[10] (North Coast Medical, Inc, Campbell, Canada) according to a strict and standardized assessment protocol.[10] The sensory threshold of the SWM was defined as the force of the lightest filament at which the individual reports sensation. An ascending method of threshold testing was used, starting with the smallest diameter monofilament (lightest filament, lowest force, most difficult to detect) and continuing in order of increasing diameter if the patient did not respond to the previous filament. Only ASIA sensory key point locations, which did not respond to the previous filament, were tested with the next filament. The exam was continued until the patient recognized a force/touch in all test locations or until it was established that the patient did not feel even the heaviest filament. Two of three applications of the lightest filament had to be felt, to obtain a positive result. All the other, heavier filaments were applied only once according to the manufacturer's instructions.[10] In the study of Voerman et al.,[13] filament marking 3.61 represents the normal value for sensory thresholds in all cervical dermatomes. In the present study the qualification of normal values was based on the mean threshold and the 95% CI according to Voerman et al.[13] The log of grams of force were represented by numeric values ranging from 0 to 4 as described in the instructions of the SWM mini-kit: 4 = filament 3.61; 3 = filament 4.31; 2 = filament 4.56; 1 = filament 6.65 and 0 = no response.[10,13,16] In our study, a SWM value of 1, 2 or 3 points was defined as impaired, 4 points were defined as normal and 0 points was defined as absent.

The EPT[6,22] was assessed according to previous studies,[6,22] using a modified mobile Compex 2 stimulator (Compex Medical SA, Switzerland), which delivered a square shaped stimulus of 0.5 ms duration at 3 Hz. The perceptual threshold was defined as the lowest ascending stimulus intensity (mA) at which the patient reported sensation. The maximal stimulator-output and the smallest increment were adjusted to 26.9mA and 0.21mA, respectively. The skin was thoroughly cleaned with alcohol wipes, and disposable, self-adhesive ECG-electrodes (cathode) with a diameter of 18mm (3M Red DotTM - type 2248) were applied over the ASIA sensory key points. A large (50 x 90 mm) inactive electrode (anode; Synapse Electrodes, Ambu, Denmark) was attached to the forearm of the testing side. For every dermatome tested, the stimulus intensity was manually increased and decreased with changes applied exactly once per second, until the patient first reported the sensation (ascending) under the cathode. This was repeated three times and the lowest EPT (expressed in mA) of the three measurements was included in the analysis. Van Hedel et al.,[23] have established the normal values for the electrical perception threshold for each

cervical dermatome. In our study the qualification of normal values was based on the mean value of the upper limits of the 95% CI from the two measurements which reflects normality according to van Hedel et al.[23] In the present study, an impaired EPT value was defined as any value greater than the normative EPT value. A normal EPT value was defined as any value equal or smaller than the normative EPT value, and the EPT value was considered absent, if the maximum current intensity (threshold at 8.4 mA) was not perceived. A stimulation above 8.4 mA was avoided as at this level of intensity also additional pathways (i.e. nociceptive A-delta or C-fibers) than dorsal column fibers (i.e. A-beta fibers) might become effectively stimulated and could falsify the perceived sensation by the subjects.[12]

Statistical analysis

Descriptive statistics were used to determine the frequency, median and range of the study participants' characteristics including cause of injury, AIS grade, AIS sensory LT level, sex and age. For comparison with LT scores the study participants' SWM and EPT data were classified as normal, impaired or absent and scored with 2, 1 or 0, respectively. All comparisons were made for the right and left side combined, because there was no statistically significant difference between the right and left side. Dermatomes were classified as having abolished, impaired or normal sensation based on LT, SWM and EPT testing. The frequency and percentage of classification agreement between LT-SWM and LT-EPT for all C3 to C8 dermatomes was determined. Finally the degree of agreement between the three measures, weighted (Fleiss-Cohen) kappa coefficients and confidence intervals were calculated for each dermatome between C3 and C8 as well as for all dermatomes between C3 and C8. Agreement was assessed using the standards as established by Altman: 0.00, poor; 0.01–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect.[26]

All data were analysed using SPSS version 18.0 for Windows and R version 2.15.1 for Windows.

Results

Participants

Table 4.1 presents the characteristics of the 25 cervical SCI participants with a high percentage of incomplete SCI. SCI was scored as complete (AIS A) in five individuals and incomplete in the remaining 20 individuals (AIS B, C and D). In five individuals the

Table 4.1 Demographic and clinical characteristics of participants (n = 25)

Characteristics	All participants
Cause of SCI	
Traumatic	23 (92%)
Non-traumatic	2 (8%)
Site	
Uniklinik Balgrist Zurich (CH)	3 (12%)
Swiss Paraplegic Centre Nottwil (CH)	22 (88%)
Sex	
Females	5 (20%)
Males	20 (80%)
Age (years)	
Median	56
Min–max	20–84
AIS	
A	5 (20%)
B	3 (12%)
C	1 (4%)
D	16 (64%)
Sensory light touch level	
C2	1 (4%)
C3	3 (12%)
C4	7 (28%)
C5	4 (16%)
C6	3 (12%)
C7	1 (4%)
C8	1 (4%)
Below C8	2 (8%)
No detectable light touch level	3 (12%)

Abbreviations: SCI, spinal cord injury; n, sample size;
AIS, American Spinal Injury Association Impairment Scale.

cervical dermatomes did not reveal any touch sensation disturbance. A total of 300 left- and right-sided dermatomes were tested for each outcome measure between C3 and C8 in all 25 participants.

Distribution of findings in LT, SWM and EPT

Classification of dermatomes according to LT, SWM and EPT testing are shown in Figure 4.1. The greatest number of dermatomes was classified as intact when using LT testing (62.7%), while applying SWM (44.3%) and EPT (29.3%) revealed fewer intact dermatomes. Accordingly, the number of dermatomes classified as impaired increased from LT (30%)

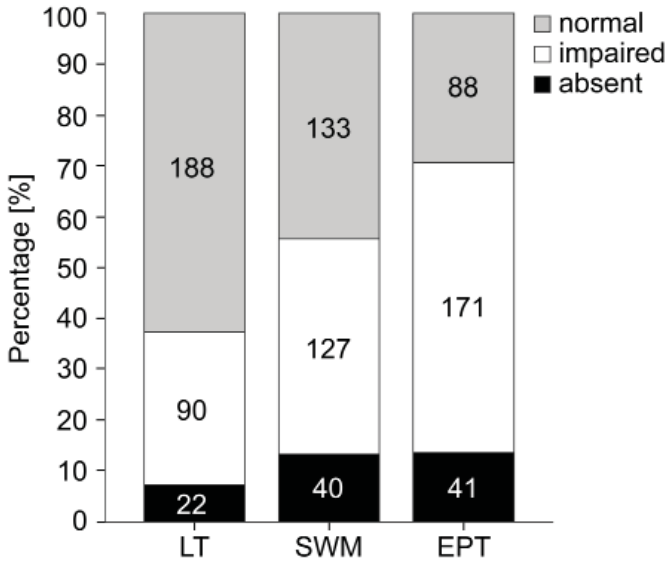

Figure 4.1 Numbers and percentage of dermatomes in absent, impaired and normal sensation for light touch (LT), Semmes and Weinstein Monofilament (SWM), and electrical perception threshold (EPT). A total of 300 dermatomes for each outcome measure between cervical 3 and cervical 8 were tested.

to SWM testing (42.3%) and being greatest for EPT testing (57%) across dermatomes. The number of dermatomes classified as absent were rather similar for SWM and EPT testing (30.3% and 30.7%) and lower for LT (7.3%).

Agreement of LT and SWM classification

The agreement of classification between LT and SWM for all dermatomes between C3 and C8 is reported in Table 4.2. The overall agreement of classifications comparing LT and SWM within same categories was for absent sensation 95.5% (21/22), for impaired sensation 47.8% (43/90) and for normal sensation 54.3% (102/188). In dermatomes with absent light touch sensation (LT 0), 4.5% reported some SWM sensation. However in dermatomes with preserved LT, either impaired (LT 1) or normal LT (LT 2), a high degree of discordance was observed compared to SWM. In dermatomes with normal LT, the SWM testing classified 44.1% (83/188) of dermatomes as being impaired. All 83 dermatomes classified by impaired SWM were at and above the LT level of injury. In dermatomes classified with impaired LT scores, SWM testing revealed normal or absent sensation in 34.4% (31/90) and 17.8% (16/90), respectively. All 31 dermatomes classified by normal SWM were below the LT level of injury.

Table 4.2 Agreement and discordance of frequency of classification in absent, impaired, and normal sensation between LT and SWM (300 dermatomes)

	Agreement absent	Discordance		Agreement impaired	Discordance		Agreement normal	Discordance	
	LT 0 & SWM 0	LT 0 & SWM 1	LT 0 & SWM 2	LT 1 & SWM 1	LT 1 & SWM 0	LT 1 & SWM 2	LT 2 & SWM 2	LT 2 & SWM 0	LT 2 & SWM 1
Dermatome	n	n	n	n	n	n	n	n	n
C3	0	0	0	1	0	0	27	0	22
C4	0	0	0	3	0	3	21	0	23
C5	0	0	0	5	1	11	17	0	16
C6	7	0	0	9	4	3	17	0	10
C7	6	0	0	14	5	9	9	0	7
C8	8	1	0	11	6	5	11	3	5
Overall	21	1	0	43	16	31	102	3	83
Overall percentage	95.5%	4.5%	0%	47.8%	17.8%	34.4%	54.3%	1.6%	44.1%

Abbreviations: LT, light touch; SWM, Semmes and Weinstein Monofilament.
SWM was grouped in three classes: SWM 0 = 0, absent; SWM 1, 2, 3 = 1, impaired; SWM 4 = normal. LT 0, absent (22 dermatomes); LT 1, impaired (90 dermatomes); LT 2, normal (188 dermatomes). n = Frequency of classification.

Agreement of LT and EPT classification

The agreement of classifications between LT and EPT for all dermatomes between C3 and C8 are reported in Table 4.3. Overall the agreement between classifications examined by LT and EPT testing was 90.9% (20/22) for absent of sensation, 52/90 (57.8%) for impaired sensation and 68/188 (36.2%) for normal sensation. A high discordance of classifications for impaired and normal sensation between LT and EPT were recorded in the remaining dermatomes. In dermatomes with normal LT, the EPT testing classified 62.2% (117/188) of dermatomes as being impaired. All 117 classified by impaired EPT were at and above the LT level of injury. Furthermore, in dermatomes classified with impaired LT scores, EPT testing revealed normal sensation in 22.2% (20/90) and an absent sensation in 20% (18/90). All 20 dermatomes classified by normal EPT were below the LT level of injury.

Degree of agreement between LT-SWM and LT-EPT

Table 4.4 shows the level of classification agreement between LT-SWM and LT-EPT for all dermatomes between C3 and C8. The overall weighted kappa coefficient between LT and SWM was moderate (0.5) and fair (0.4) for LT-EPT. However, when evaluated for individual dermatomes the agreement varied considerably. In dermatomes C3, C4 and C5 the weighted kappa coefficients (≤ 0.2) revealed that the level of classification agreement between LT and SWM, as well as between LT and EPT, occurred rather by chance. However in dermatomes C6, C7 and C8 the weighted kappa coefficients was found moderate to substantial (weighted kappa range = 0.5 to 0.7) between the different testing methods.

Discussion

The study reveals for the first time a comprehensive comparison of epicritic sensation as assessed by LT, SWM and EPT across cervical dermatomes (C3 to C8) in individuals with SCI. The sensory testing focused on the assessment of sensory integrity of distinct predefined dermatomes in patients suffering from cervical SCI. Improving the assessment of epicritic sensation will be important in early clinical trials (phase I/II), where segmental and subtle changes in sensory function might provide important readouts about beneficial as well as detrimental (i.e., descending and ascending levels of lesion, respectively) effects of novel interventions. The presented study provides evidence that the segmental assessment of epicritic sensation can be improved by SWM and EPT.

Table 4.3 Agreement and discordance of frequency of classification in absent, impaired and normal sensation between LT and EPT (300 dermatomes)

	Agreement absent	Discordance		Agreement impaired	Discordance		Agreement normal	Discordance	
	LT 0 & EPT 0	LT 0 & EPT 1	LT 0 & EPT 2	LT 1 & EPT 1	LT 1 & EPT 0	LT 1 & EPT 2	LT 2 & EPT 2	LT 2 & EPT 0	LT 2 & EPT 1
Dermatome	n	n	n	n	n	n	n	n	n
C3	0	0	0	1	0	0	22	0	27
C4	0	0	0	4	1	1	12	1	31
C5	0	0	0	11	6	0	4	1	28
C6	7	0	0	9	1	6	14	0	13
C7	6	0	0	15	5	8	8	0	8
C8	7	0	0	12	5	5	8	1	10
Overall	20	2	0	52	18	20	68	3	117
Overall percentage	90.9%	9.1%	0%	57.8%	20%	22.2%	36.2%	1.6%	62.2%

Abbreviations: LT, light touch; EPT, electrical perception threshold.
EPT was grouped in three classes: maximum pain threshold of 8.4 mA not perceived = 0, absent; greater than the normative EPT value = 1, impaired; equal to or less than the normative EPT value = 2, normal. LT 0, absent (22 dermatomes); LT 1, impaired (90 dermatomes); LT 2 normal (188 dermatomes). n = Frequency of classification.

Table 4.4 Agreement of classifications between LT-SWM and LT-EPT for each dermatome between C3-C8 and for all dermatomes between C3-C8

	Dermatome						Overall agreement	Dermatome
Agreement	C3 K_w [95% CI]	C4 K_w [95% CI]	C5 K_w [95% CI]	C6 K_w [95% CI]	C7 K_w [95% CI]	C8 K_w [95% CI]		C3-C8* K_w [95% CI]
LT-SWM	0.0 [-0.2–0.2]	0.0 [-0.2–0.2]	-0.1 [-0.3–0.2]	0.7 [0.4–1.0]	0.6 [0.3–0.9]	0.5 [0.2–0.8]	LT-SWM	0.5 [0.4–0.6]
LT-EPT	0.0 [-0.2–0.2]	0.1 [-0.2–0.3]	0.2 [0.0–0.5]	0.6 [0.3–0.9]	0.6 [0.3–0.8]	0.5 [0.2–0.8]	LT-EPT	0.4 [0.3–0.5]

Abbreviations: LT, light touch; SWM, Semmes and Weinstein Monofilament; EPT, electrical perception threshold. C3, cervical dermatome right and left side combined; Kw, weighted kappa coefficient (Fleiss-Cohen); 95% CI, the lower and upper limit of the 95% confidence interval. C3 - C8*, all dermatomes between C3 to C8, right- and left side combined. Weighted kappa coefficient: 0.00, poor; 0.01–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect.

The challenge of sensory testing

Clinical testing of sensory function is commonly challenged by limitations of test reliability, which is true to some extent for almost all sensory qualities (like epicritic sensation and prothopatic sensation).[7,9,27,28] This becomes even more demanding when assessing different levels of sensory impairment where the subjective rating of patients is not able to define incremental levels of impairment but becomes rather limited to a simplified categorical (ordinal scale, e.g. normal, impaired and abolished sensation) gross scoring. Therefore, the ability to understand minor changes during recovery (improvements or deterioration) is very challenging and clinical testing of one specific sensory quality (like LT) within a complex domain of sensory function (like epicritic sensation conveyed by dorsal column pathways) will be likely of limited sensitivity. One approach to overcome these challenges is to introduce measures with a more defined scaling of sensation (like SWM testing by applying different sensory modalities) or to combine complementary sensory measures that are considered to reflect to some extent the integrity within similar fiber tracts. The latter approach would require modalities that are not redundant, but are able to reveal subtle differences regarding the integrity of function within an entire sensory system. In this context the applied measures should also represent the same anatomical areas (i.e. distinct dermatomes) which can be well achieved by using LT, SWM and EPT testing.

Disparity and sensitivity

The value of combining sensory testing of EPT and SWM complementary LT testing resides in the intention that they provide different insights in the integrity or impairment of epicritic sensation. Accordingly they should not be just redundant but reveal changes that cannot be disclosed by LT testing. Indeed a mismatch of segmental epicritic sensation was observed as SWM was classified in 44.1% dermatomes and EPT classified in 62.2% dermatomes as impaired whereas LT revealed normal response. Interestingly those findings were all at or above the LT level according to ISNCSCI and are for the EPT findings in accordance to other studies.[7,12,22,23] Another discrepancy of segmental epicritic sensation was found below the level of injury according to ISCNSCI. LT revealed impaired response whereas SWM classified 34.4% dermatomes and EPT classified 22.2% dermatomes as normal. These SWM findings are in agreement with the results of Kalsi-Ryan et al.[8] In their study, they used SWM in individuals with chronic cervical SCI and observed greater sensitivity when using SWM, due to increased response levels, compared to the values reported when using ISNCSCI light touch. The EPT findings are in line with the results of Kramer

et al.[21] who observed that individuals with cervical SCI have persisting EPT values below the level of lesion.[22] The present results suggest that SWM and EPT might be sensitive to small sensory impairments and/or preserved innervation in sensory function above, at and below the LT level, which are less detectable by LT testing. This degree of sensitivity could be required to assess differences in sensory recovery, especially when improvements might be limited to one or two dermatomes adjacent to the LT level. Obviously the value of additional sensory testing is most relevant in dermatomes that are clinically considered to be normal or impaired. In dermatomes with abolished sensation SWM and EPT do not provide additional information to LT testing (overall agreement for abolished C3 to C8 dermatomes betweenLT and SWM / EPT testing was about 95.5% and 90.9%, respectively).

Statistical analysis ($k_w \leq 0.5$) confirmed that there is only a limited congruency between the three different assessments addressing epicritic sensation. Interestingly these findings were not uniform across all dermatomes and revealed a higher percentage of congruency (moderate to substantial agreement) specifically in the C6, C7 and C8 dermatomes where a higher percentage of absent sensation was found with all three testing methods. Furthermore, in the C3, C4 and C5 dermatomes a higher percentage of impaired and normal sensation was reported which revealed a poor agreement between the three different assessments. These findings emphasize, as has been shown by the different thresholds for SWM and EPT across these dermatomes, that the clinical assessment using LT is of limited sensitivity to disclose segmental differences in sensory function. Differences in findings across cervical (and thoracic) dermatomes are not specific for epicritic sensation but have been also shown for the assessment of spino-thalamic function (i.e. using laser evoked potentials or contact heat evoked potentials) that reveal marked difference between dermatomes (again these differences between dermatomes are also not adequately reflected by the clinical testing of pin prick sensation).[29,30]

Improving readouts of sensory plasticity

The aims of increasing the sensitivity of testing epicritic sensation after SCI are two-fold: 1) to identify changes within dermatomes, i.e. high resolution of segmental changes, and 2) to provide insight into specific pathways that for the epicritic sensation are characterized by their high level of myelination. Therefore, applying such measures in an interventional study can address if segmental changes occur that are beyond spontaneous or regular findings (both beneficial and detrimental). In addition such measures might be useful if interventions are considered to improve the myelination (i.e. concept of re-myelination)

of damaged spinal fibers, where the recovery of A beta fibers depend on high level of myelination and might reveal superior recovery than less or un-myelinated sensory fibers (like C fibers).[31,32] Therefore, in clinical trials an improved resolution of sensory function by combined LT and SWM/EPT testing could be meaningful in revealing subtle changes that for a proof of mechanism might be critical to enter a next phase where these effects can be amplified by adjusting the intervention.

Conclusion

There is limited agreement of sensory testing specifically in incompletely affected dermatomes between testing of LT, SWM and EPT. This difference is likely attributable to the measurement limitations of each testing and that they individually respond to the differently affected sensory modalities within the epicritic sensation.[28] The results show that SWM and EPT testing can add complementary resolution to LT testing at 6 months after cervical SCI by detecting and quantifying differences in sensory thresholds above, at and below the LT level of injury. The ability of combined sensory testing to gain insights beyond LT warrants consideration in the protocol design of interventional studies where the sensitivity to indicate even subtle differences is of value both in the stratification of patients and the potential (not shown here) to reveal an improved responsiveness in sensory testing.

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Chapter 5

Prediction and stratification of upper limb function and self-care in acute cervical spinal cord injury (SCI) with the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP)

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Abstract

Background: There is inherent heterogeneity within individuals suffering from cervical spinal cord injury (SCI), and early prediction of upper limb function and self-care is challenging. As a result, considerable uncertainty exists regarding the prediction of functional outcome following cervical SCI within 1 year of injury.

Objective: To evaluate the value of Graded Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) in predicting upper limb function and self-care outcomes in individuals with cervical SCI.

Method: A prospective longitudinal multicenter study was performed. Data from the GRASSP, the Spinal Cord Independence Measure (SCIM III), and the American Spinal Injury Association (ASIA) Impairment Scale were recorded at 1, 6, and 12 months after cervical SCI. For prediction of functional outcome at 6 and 12 months, a logistic regression model, receiver operating characteristics (ROC), and unbiased recursive partitioning conditional inference tree (URP-CTREE) were used with 8 different predictor variables.

Results: Logistic regression analysis, ROC analysis, and URP-CTREE all revealed that the strength subtest within GRASSP is the strongest predictor for upper limb function and self-care outcomes. URP-CTREE provides useful information on the distribution of different outcomes in acute cervical SCI and can be used to predict cohorts with homogeneous outcomes.

Conclusion: The GRASSP at 1 month can accurately predict upper limb function and self-care outcomes even in a heterogeneous group of individuals across a wide spectrum of neurological recovery. The application of URP-CTREE can reveal the distribution of outcome categories and, based on this, inform trial protocols with respect to outcomes analysis and patient stratification.

Introduction

Individuals with cervical spinal cord injury (SCI) suffer from a broad spectrum of upper limb impairments. They may experience loss of strength, sensation and movements, as well as limited ability to perform activities of daily living (ADLs). This ultimately leads to decreased independence and restricted participation as well as quality of life. Indeed, individuals with cervical SCI report a strong desire to regain arm and hand function and that such a gain would improve their independence and quality of life.[1,2] Therefore, reliable prediction of future upper limb function and self-care at an early stage after cervical SCI has become increasingly important for several reasons; clinically it would help in treatment planning and goal setting, in a research context it would permit evaluation of novel interventions and patient stratification[3-6] and, from a socioeconomic perspective, would be of benefit in predicting the likely degree of capacity for independent living and required level of caregiver support. After a lesion of the cervical spinal cord, arm and hand function outcomes vary significantly and are not only dependent on the level and completeness of the lesion but also on the degree of recovery, motivation and occupational performance of the individual. This inherent heterogeneity within individuals following cervical SCI[7,8] renders early prediction of upper limb function and self-care challenging.[9]

Although several outcome measures of upper limb function are available,[10] only a few have been specifically developed for SCI and psychometric testing of these measures has revealed deficits.[10,11] The predictive validity of quantitative measures has not yet been established,[12] while the aforementioned cohort heterogeneity in cervical SCI makes identifying appropriate outcome measures difficult.[7,13] To overcome this limitation, the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) was developed as a quantitative outcome measure specific to upper limb function in cervical SCI. Most importantly, GRASSP covers different aspects of upper limb function in order to evaluate changes within the motor and sensory systems and how changes in the level of impairment contribute to complex upper limb functional tasks.[14] In individuals with chronic cervical SCI (i.e. more than 6 months post-injury), the GRASSP has shown high validity and excellent overall inter- and intra-rater reliability,[15] while analysis of responsiveness is still pending.

Little has been published on prediction of functional outcome in general following SCI[16-19] and, in particular, data on prediction and stratification of upper limb function and self-care after incomplete cervical SCI is lacking.[8] The aim of the study, therefore, was to evaluate the predictive value of GRASSP for upper limb function and self-care outcome at 6 and 12 months post-injury in individuals with acute cervical SCI.

Methods

Study design

Prospective longitudinal multicenter study.

Study population

Participants were recruited from five European SCI centers specialized in the rehabilitation of individuals with spinal cord injury (SCI). Participants were recruited between January 2009 and May 2011. Inclusion criteria consisted of traumatic or non-traumatic, acute (16–40 days after injury) tetraplegia with an ASIA Impairment Scale (AIS) grade of A, B, C, or D.[20] Patients were included if their injury was between C3 and T1 in the case of ASIA A patients and C1-T1 in those with incomplete injuries. Excluded were those individuals with any accompanying severe neurological (e.g., traumatic brain injury) or medical disorders or aged less than 16 years. Participants were recruited after providing written informed consent and the study was approved by the relevant local ethics committees.

Procedures

Assessors (physicians and occupational therapists) with at least one year's experience in working with individuals with SCI performed the measurements. To ensure high-quality examinations and to reduce inter-observer variability,[21] assessors received training in how to perform all outcome measure assessments. A unified protocol, outlining in detail how the assessments should be performed, was followed for each outcome measure, with recording techniques and materials standardized across all centers. A quiet room, free of distractions was used for all assessments. For ASIA testing, participants lay in a comfortable supine position while for GRASSP testing they were seated. The SCIM III was scored by trained and experienced physical therapists, nurses and occupational therapists. Assessments were performed at 1 month (range 16–40 days), 6 months (range 150–186 days) and 12 months (range 300–400 days) after cervical SCI.

The AIS classifications were calculated by a computer algorithm,[22] in accordance with definitions in the International Standards for Neurological Classification of Spinal Cord Injury.[20]

Predictor variables

The GRASSP is an upper limb outcome measure for individuals with tetraplegia which includes manual muscle testing (MMT), Semmes and Weinstein monofilament (SWM)

testing, adoption of three prehensile positions (qualitative grasping [QlG]) and performance of six task-oriented prehension skills (quantitative grasping [QtG]). The subtests within GRASSP, assessed between day 16 and 40 after cervical SCI, were selected as baseline predictor variables:

Manual Muscle Testing (MMT). Strength was assessed for both arms using the MMT[23] in 10 muscles of the upper limb (three in the arm, seven in the hand). Each item (muscle) was given a score varying from 0 (response absent) to 5 (normal power). The sum of the MMT subtest score for both sites therefore ranges from 0 to 100 points and the sum of the distal (hand) muscle group of the MMT subtest score for both sites ranges from 0 to 70 points.

Semmes and Weinstein Monofilament (SWM). The tactile cutaneous sensation threshold was assessed with the pocket version of SWM[24] (North Coast Medical, Inc, Campbell, CA) with four probes on three dorsal and palmar sensory test locations in each hand as described in the instructions of the SWM mini-kit[24] and the GRASSP manual. The pressure applied was recorded on an ordinal scale corresponding to numeric values varying from 0 (absent) to 4 (normal). The sum of the dorsal or palmar sensation subtest score for both sites therefore ranges from 0 to 24 points.

Qualitative grasping (QlG). The ability of the participant to perform a cylindrical grasp, lateral key pinch and tip-to-tip pinch was assessed for both hands. Each grasp was given a score varying from 0 (no voluntary control of wrist and digits when grasping) to 4 (normal voluntary control of wrist and digits when generating the grasp). The sum of the grasping quality subtest score for both upper limbs thus ranges from 0 to 24 points.

Quantitative grasping (QtG). The ability of the participant to perform six prehension tasks for each arm separately (like grasping or moving a coin) was assessed in a standardized way. The tasks were scored between 0 and 5 according to the grasp used. One minute and 15 seconds were allowed for the completion of each task and, if the individual was unable to perform the task within this time period, the individual was asked to move on to the next task.[25] The maximum possible sum of the quantitative subtest score was 60 for both sites.

The SCIM III assesses independence in fundamental daily activities and is useful for measuring the status of, or improvement in, everyday functions relevant to individuals with SCI.[26] The SCIM III has been shown to perform well under psychometric testing[27-29] and the self-care subcategory (SCIM-SS) is particularly notable for its high inter-rater reliability and internal consistency.[27] The SCIM III consists of three subcategories: (1) Self-care

(SCIM-SS), (2) respiration and sphincter management, and (3) mobility. In our study, the *SCIM III-SS* was selected as a predictor variable. The sum of the SCIM-SS ranges from 0 to 20 points.

Clinical neurological examination was performed according to the ISNCSCI protocol.[20] Injury characteristics were classified according to the neurological level of injury (NLI) and the overall AIS grade. The Upper Extremity Motor Score (*UEMS*) of ASIA was selected as predictor variable. Strength in five key muscle groups of the upper limb in both arms (two muscles in the arm, three in the hand) were scored between 0 (absent response) and 5 (normal power). The sum value of this score ranges from 0 and 100 for both sides.

Outcome measures

For the purpose of this paper, upper limb function is defined as the capacity to use the upper limb for skilled actions, such as reaching, grasping, and manipulation of objects used in daily life. The GRASSP subtest QtG is therefore taken as reflecting upper limb function. QtG and the SCIM-SS (for details, see above) were used as anchor outcome measures of upper limb function and self-care at 6 and 12 months after cervical SCI.

Statistical analysis

Descriptive statistics were used to determine the frequency, median and range of the study participants' characteristics including AIS grade, lesion level and lateralization, sex and age.

We dichotomized the two outcomes for the logistic regression analysis to assign patients into a *failure* or *success* group. For QtG, individuals were allocated to the failure group (0–36 points) if they met any of the following three conditions: i) not able to perform the task at all, ii) not able to complete the task, and iii) able to complete the task only by using an alternative (i.e. compensatory) grasp (not able to perform standard grasps). All individuals who were able to complete the task using the standard grasp were allocated to the success group (37–60 points), irrespective of any difficulties while performing the task. To distinguish between individuals who were dependent or independent with respect to self-care with or without devices, a cut-off SCIM-SS score of 12 was applied, with scores of 0–12 points defined as dependent (failure), and scores of 13–20 as independent (success), irrespective of supplementary device usage.

Binary logistic regression was performed on the dichotomized outcomes QtG and self-care with the goal to predict upper limb function and self-care at 6 and 12 months using predictors gathered between day 16 and 40 after cervical SCI. The number of

predictors was minimized in line with the goal of producing the simplest possible model suitable for subsequent deployment in clinical practice as a simple bedside test used by rehabilitation staff within six weeks after cervical SCI. We did not use stepwise statistical variable selection procedures, such as forward inclusion or backward elimination, because this may result in biased estimates of regression coefficients and exaggeration of variable p-values.[30-32] Two different single predictors were investigated: MMT subtest strength total score and SWM sensation subtest total score (with the palmar and dorsal components combined). A correlation analysis using Spearman's correlation coefficient was performed between the predictor and outcome variables of the logistic regression (r_s) to determine the relationships between them. The level of significance was set at 0.05. Correlations in the range of 0 to 0.25 were interpreted as none to poor, 0.26 to 0.50 as fair, 0.51 to 0.75 as moderate to good, and 0.76 to 1.0 as very good to excellent.

The performance of each model was assessed by calculating receiver operating characteristics (ROC) curves. The area under the curve (AUC) is a measure for quantifying the discriminative ability of the model.[33] Values between 0.90 and 1.00 indicate excellent predictive discrimination.

Unbiased recursive partitioning is a flexible statistical model used for a variety of regression problems. A regression tool from the family of unbiased recursive partitioning methods called conditional inference tree (URP-CTREE)[34] was used to produce classification trees for the outcomes QtG and self-care at 6 and 12 months, using predictors assessed between day 16 and 40 after cervical SCI. Eight different predictors were investigated: MMT strength subtest total score, MMT distal strength subtest total score, SWM (palmar and dorsal components combined) sensation subtest total score, SWM palmar sensation subtest total score, QlG subtest total score, QtG subtest total score, SCIM-SS and UEMS subtest total score. URP-CTREE creates decision rules, which divide the initial, heterogeneous patient population into increasingly homogeneous subgroups (with respect to outcome). Each rule in the classification tree is based on the singular most significant predictor, and the splits are set as to maximize discrepancy between the subsequently formed groups. The tree stops growing when there is no longer any significant predictor. The decision rules allow prediction of the response variable, and, at the same time, can be used as a stratification tool.

All data were analyzed using SPSS version 18.0 for Windows and R version 2.14.0 for Windows.

Results

Study population

Of the 61 participants included, 56 had a traumatic and five a non-traumatic SCI. Some data was missing for four patients at the 6 month assessment and for five patients at the 12 month assessment. Injury severity and lesion level were variable. Detailed cohort characteristics are presented in Table 5.1.

Table 5.1 Demographic and clinical characteristics of participants (n = 61)

Characteristics	All participants
Cause of SCI	
Traumatic	56 (91.8%)
Non-traumatic	5 (8.2%)
Site	
Klinik Hohe Warte Bayreuth (D)	20 (32.8%)
Unfallklinik Murnau (D)	1 (1.6%)
Orthopädische Universitätsklinik Heidelberg (D)	1 (1.6%)
Balgrist University Hospital Zurich (CH)	14 (23%)
Swiss Paraplegic Center Nottwil (CH)	25 (41%)
Gender	
Female	16 (26.2%)
Male	45 (73.8%)
Age (years)	
Median	48
Mean (SD)	46 (19)
Min/max	17–80
AIS	
1 month (range 16–40 days) (n = 61)	A: 16; B: 9; C: 7; D: 29
6 months (range 150–186 days) (n = 57)	A: 13; B: 7; C: 4; D: 33
12 months (range 300–400 days) (n = 56)	A: 10; B: 6; C: 5; D: 35
Neurological level 1 month (range 16–40 days)	
C1	3 (4.9%)
C2	6 (9.8%)
C3	11 (18%)
C4	22 (36.1%)
C5	11 (18%)
C6	5 (8.2%)
C7	1 (1.6%)
C8	1 (1.6%)
T1	1 (1.6%)

Abbreviations: SCI, spinal cord injury; n, sample size; AIS, American Spinal Injury Association Impairment Scale; C2, cervical dermatome 2; SD, standard deviation; D, Germany; CH, Switzerland.

Spearman correlations

The correlation between MMT total score with the outcome variables QtG and self-care at 6 and 12 months was excellent (QtG, 6 months, $r = 0.885$, $p < 0.001$; 12 months, $r = 0.904$, $p < 0.001$; self-care, 6 months, $r = 0.821$, $p < 0.001$; 12 months, $r = 0.820$, $p < 0.001$). There was a moderate to good correlation between SWM total score and the outcome variables QtG and self-care at 6 and 12 months (QtG, 6 months, $r = 0.651$, $p < 0.001$; 12 months, $r = 0.639$, $p < 0.001$; self-care, 6 months, $r = 0.781$, $p < 0.001$; 12 months, $r = 0.643$, $p < 0.001$).

Logistic regression

For prediction of QtG and self-care outcome at 6 and 12 month based on MMT total score at 1 month, specificity ranged between 72.4% and 92.1%. Sensitivity of MMT total score at 1 month ranged from 81.8% to 90.9% for the two outcomes at 6 and 12 months. In contrast, the SWM total score at 1 month performed less well with predictive specificity ranging from 69.6% to 78.9% and sensitivity from 68.2% to 84.4% at 6 and 12 months for QtG and self-care. Detailed results of the logistic regression analysis are presented in Table 5.2.

ROC

The results of the ROC analysis in predicting QtG and self-care outcome at 6 and 12 months were in line with the results of the logistic regression analysis. The AUC value for MMT was larger (ranged from 0.917 to 0.961, $p < 0.001$) compared to SWM (ranged from 0.802 to 0.842, $p < 0.001$) at 6 as well as 12 months for both outcome measures. Detailed results for ROC analysis are available in Table 5.3.

URP-CTREE

We analyzed eight different predictor variables from our heterogeneous cohort of SCI patients. When these variables were placed into the recursive partitioning-based algorithm, well-defined cohorts for QtG and self-care at 6 and 12 months after cervical SCI could be distinguished. Figure 5.1a, Figure 5.1b, Figure 5.2a and Figure 5.2b show the *URP-CTREE* for QtG and self-care at 6 and 12 months.

Table 5.2 Classification table[a]

	Quantitative grasping at 6 months (n = 56)				Quantitative grasping at 12 months (n = 56)			
	Specificity %	95% CI	Sensitivity %	95% CI	Specificity %	95% CI	Sensitivity %	95% CI
Predictors at 1 month								
MMT	78.6	66.1–78.6	89.3	78.5–95.0	87.0	76.4–93.8	90.9	80.7–96.1
SWM	71.4	58.5–81.6	78.6	66.2–87.3	69.6	56.7–80.1	84.8	72.2–91.3
	Self-care at 6 months (n = 60)				Self-care at 12 months (n = 58)			
	Specificity %	95% CI	Sensitivity %	95% CI	Specificity %	95% CI	Sensitivity %	95% CI
Predictors at 1 month								
MMT	92.1	81.9–96.4	81.8	70.1–89.4	72.4	59.8–82.2	82.8	71.1–90.4
SWM	78.9	66.4–86.9	68.2	55.7–78.7	75.9	63.5–85.0	79.3	67.2–87.8

Abbreviations: MMT, manual muscle testing; SWM, Semmes and Weinstein monofilament; 95%CI, 95% confidence interval; %, percentage; n, sample size.
[a] Binary logistic regression was performed on the dichotomized outcomes *quantitative grasping* and *self-care* at 6 and 12 months using two different predictor variables measured between day 16 and 40 after cervical spinal cord injury.

Table 5.3 Output of receiver operating characteristics (ROC) analysis[a]

	Quantitative grasping at 6 months (n = 56)			Quantitative grasping at 12 months (n = 56)		
	AUC	p value	95% CI	AUC	p value	95% CI
Predictors at 1 month						
MMT	0.950	< 0.001	0.900–1.000	0.961	< 0.001	0.917–1.000
SWM	0.802	< 0.001	0.687–0.917	0.839	< 0.001	0.733–0.944
	Self-care at 6 months (n = 60)			Self-care at 12 months (n = 58)		
	AUC	p value	95% CI	AUC	p value	95% CI
Predictors at 1 month						
MMT	0.917	< 0.001	0.845–0.990	0.917	< 0.001	0.849–0.984
SWM	0.803	< 0.001	0.680–0.926	0.842	< 0.001	0.737–0.947

Abbreviations: MMT, manual muscle testing; SWM, Semmes and Weinstein monofilament; 95% CI, 95% confidence interval; AUC, area under the curve; n, sample size; p value, significance level.

[a] ROC was performed to predict *quantitative grasping* and *self-care* at 6 and 12 months using two different predictor variables measured between day 16 and 40 after cervical spinal cord injury.

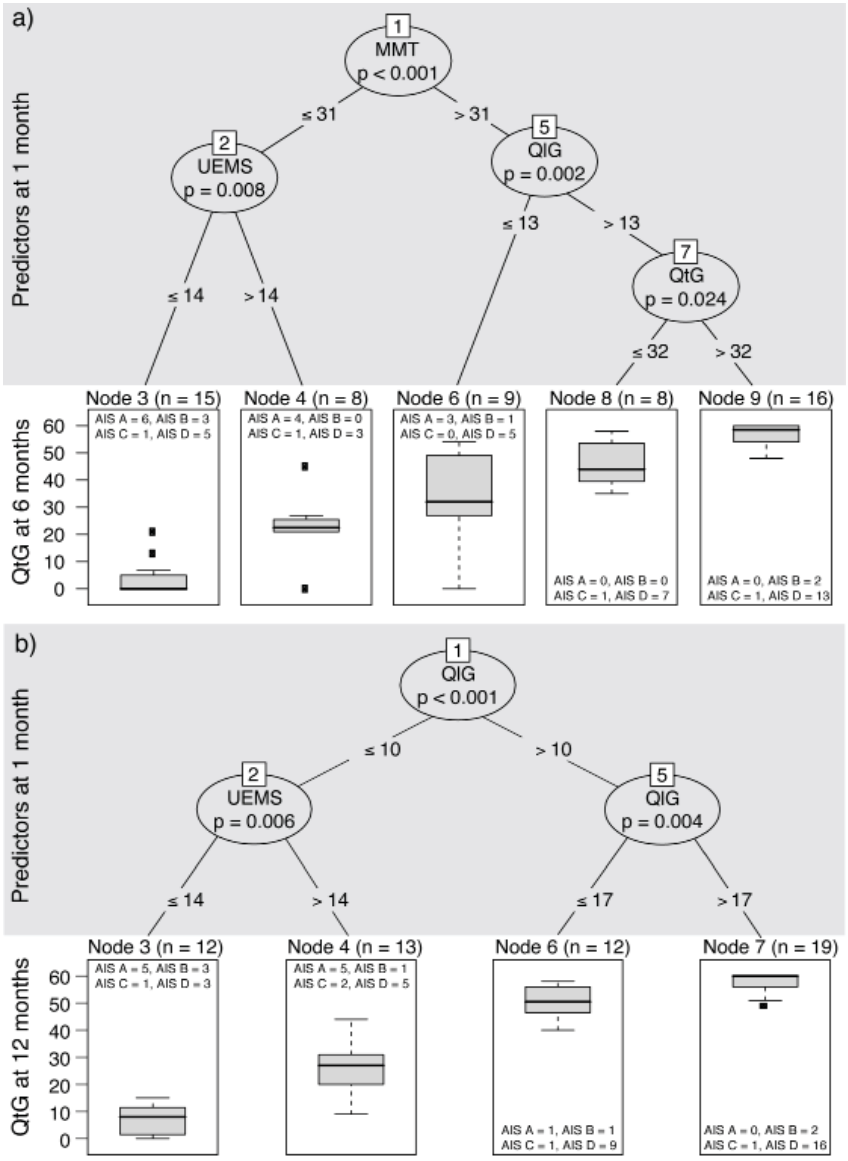

Figure 5.1 Unbiased recursive partitioning conditional inference tree (URP-CTREE) for *quantitative grasping* at 6 and 12 months.

(a) The algorithm led to a partition of the initial patient population into five terminal nodes. Node size is indicated above each terminal node. From left to right, the terminal nodes represent patient subgroups with an increasingly positive quantitativ grasping outcome at 6 months. The first split separates patients with an initial MMT ≤ 31 or > 31 as indicated by the cut-off values on the "branches". Further separation is achieved by UEMS for patients with ≤ 31 MMT and by QIG and QtG for patients with > 31 MMT. For each inner node, a Bonferroni-adjusted p-value describing statistical association between the predictor and the outcome is given. (b) For details on the interpretation of the conditional inference tree for QtG at 12 months, please refer to the explanatory notes for "a." Abbreviations: MMT, manual muscle testing; UEMS, upper extremity motor score; QIG, qualitative grasping; QtG, quantitative grasping; AIS, American Spinal Injury Association Impairment Scale; n, sample size; p, significance level; ≤ less than equal to; > greater than.

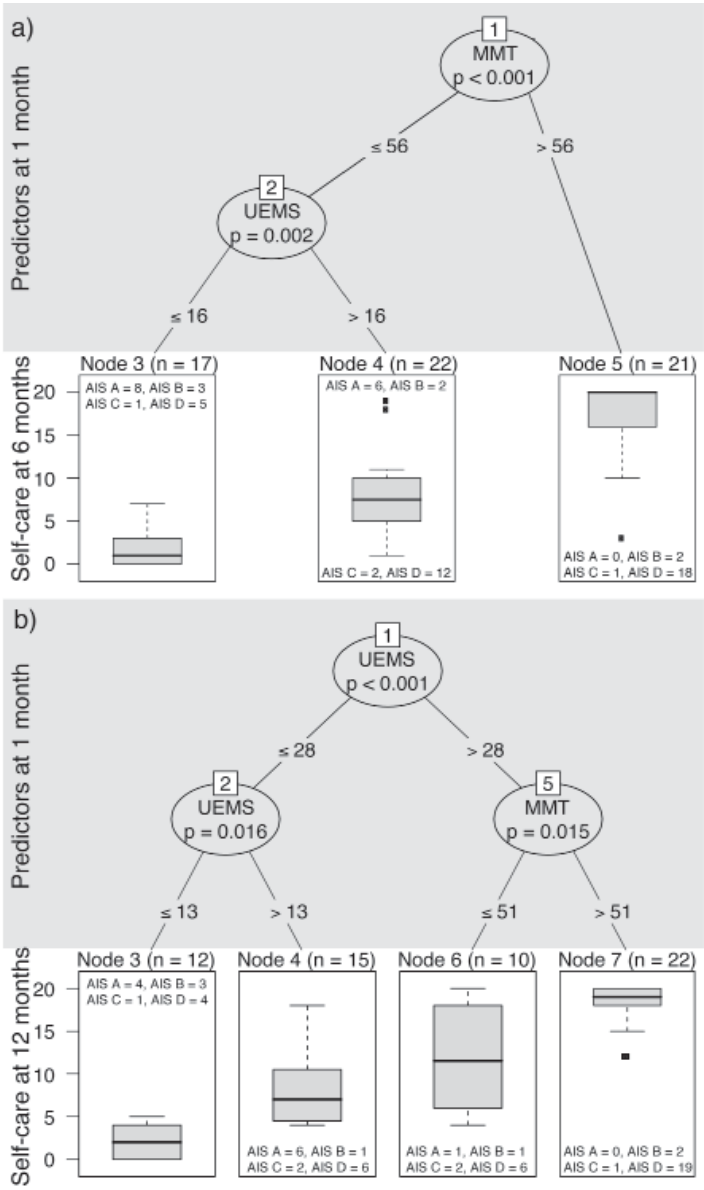

Figure 5.2 Unbiased recursive partitioning conditional inference tree (URP-CTREE) for *self-care* at 6 and 12 months. (a) The algorithm led to a partition of the initial patient population into three terminal nodes. Node size is indicated above each terminal node. From left to right, the terminal nodes represent patient subgroups with an increasingly positive self-care outcome at 6 months. The first split separates patients with an initial MMT ≤ 56 or > 56 as indicated by the cut-off values on the "branches". Further separation is achieved by UEMS for patients with ≤ 56 MMT. For each inner node, a Bonferroni-adjusted p-value describing statistical association between the predictor and the outcome is given. (b) For details on the interpretation of the conditional inference tree for self-care at 12 months, please refer to the explanatory notes for "a".
Abbreviations: MMT, manual muscle testing; UEMS, upper extremity motor score; QIG, qualitative grasping; QtG, quantitative grasping; AIS, American Spinal Injury Association Impairment Scale; n, sample size; p, significance level; ≤ less than equal to; > greater than.

We now present in detail how to read the figure for QtG at 6 months (Figure 5.1a). The algorithm led to a partition of the initial sample (n = 56) into five terminal nodes (cohorts). The terminal nodes represent subgroups with different outcomes ranging from low to high values for QtG at 6 months. Initial MMT was selected as a first predictor variable ($p < 0.001$) and separates the sample into two newly formed subgroups, MMT ≤ 31 or > 31 as indicated by the cut-off value at the "branches". Below this MMT ≤ 31 subgroup (n = 23), further separation was achieved with a UEMS cut-off of 14 points ($p = 0.008$) giving subgroups UEMS ≤ 14 (n = 15; least favorable outcome) and UEMS > 14 subgroup (n = 8; second least favorable outcome). Proceeding from the MMT > 31 subgroup (n = 33), separation was achieved once more through the definition of a QIG cut-off of 13 points ($p = 0.002$), giving two subgroups; QIG ≤ 13 (n = 9; intermediate outcome) and QIG > 13 subgroup (n = 24). This latter grouping (QIG > 13) was further subdivided by QtG score, with a cut-off of 32 showing the largest discrepancy, again with two subgroups QtG ≤ 32 (n = 8; second most favorable outcome) and QtG > 32 (n = 16; most favorable outcome).

Discussion

The aim of this prospective study was to evaluate the value of the GRASSP assessment tool in predicting the outcome of upper limb function and self-care at 6 and 12 months post-injury in individuals with acute cervical SCI. For this purpose, the outcome of upper limb function was assessed based on the performance of hand / upper limb activities (such as the QtG subtest) and ADLs (i.e. self-care items in the SCIM III).

The prediction of upper limb function and self-care in patients with acute cervical SCI can be achieved by using the GRASSP tool, of which the motor scoring in particular is of excellent predictive value for clinical outcomes at 6 and 12 months. The reliable prediction of functional outcome categories is essential for improving the stratification of patients for clinical interventions, in which the enrolment of rather homogenous patient cohorts is required. Improved stratification rules will be of benefit in trials assessing the safety and efficacy of interventions in which the detection of even subtle changes is of crucial importance in the evaluation of therapies.

Clinical outcomes of upper limb function

Given the serious consequences on patients' independence, quality of life, health care service needs and their associated socioeconomic costs, there is strong interest in the development of reliable assessment and categorization of upper limb function in tetraplegia.

While assessments such as the Van Lieshout test (VLT)[35] and the Capability of Upper Extremity Test (CUE)[36] provide important information regarding overall arm and hand usage, they are not designed to provide detailed and reliable information about changes in specific sensory and motor impairments affecting upper limb function. Likewise, the utilization of a global outcome measure such as the SCIM III, although providing clinically meaningful categorization of functioning in ADLs, does not provide insights into the underlying sensorimotor function driving functional recovery. Accordingly, the SCIM III is not well positioned to discern functional improvement arising from actual repair of damaged spinal cord tissue versus rehabilitation training, motivation and mood factors when performing tasks – whether those tasks are performed bimanually or with compensatory movements – given the SCIM's focus on gained independence.[26]

In contrast, measures designed to capture neurological deficits (e.g. the UEMS of the ISNCSCI protocol)[20] that, as opposed to functional readouts, provide detailed scoring of segmental sensorimotor deficits, have been proven to be of value in the diagnosis and prognosis of SCI. Clinical experience, backed up by the literature,[7,8] shows that recovery of upper limb function is highly variable and an assessment matrix combining neurological and functional readouts for application in acute cervical SCI may be desirable.[13] To this end, the GRASSP was developed in an attempt to demonstrate how changes in impairment (i.e. neurological deficit) contribute to complex upper limb function tasks.[15]

Prediction of upper limb function

Analysis of a heterogeneous group of patients with acute and sub-acute cervical SCI revealed that the initial MMT correlated very well both with subsequent upper limb function and self-care at 6 and 12 months and was furthermore superior to the SWM. These findings support previous studies in which significant correlation of MMT and cervical motor levels with self-care in acute and chronic cervical SCI was shown.[7,8,37,38] The strong influence of motor impairment on self-care outcomes has been shown in several studies looking at diverse functional outcome domains, including independence and ambulation.[16,17,39-41] The impact of recovery of sensation, however, although shown to be critical after peripheral nerve damage,[42] is of less obvious relevance in SCI. While recordings of somatosensory evoked potentials (SSEP) correlate with the sensory impairment and have some predictive value for outcome and recovery of hand function, the immediate impact on complex arm / hand function is less marked.[19] In a recent study using the GRASSP, however, it was noted that preserved sensation positively affects upper limb function,[43] although the nature and degree of these relationships during the course of recovery is unknown.

The significant role of MMT as a predictor variable with a high sensitivity and specificity in upper limb function and self-care at 6 and 12 months was also demonstrated using logistic regression and ROC. Both models corroborate the high within-sample validity of using MMT within GRASSP as predictor variable. SWM, although less influential than MMT, was also able to predict outcome of self-care and upper limb function and might be specifically applicable for prediction when motor assessments are limited (for instance when key motor muscles are not defined above C5) or when muscle activation is hindered by other factors, such as limb fractures or bruising. For the logistic regression and ROC analysis, the SCIM-SS and the GRASSP subtest QtG were converted into two dichotomous outcome measures ("dependent" vs "independent" for self-care; "non-functional" vs "functional" for grasping) which represented a wide range of upper limb performance in all subgroups. Logistic regression and ROC analysis do not, however, provide sufficient information about the distribution of outcomes.

URP-CTREE

Few studies to date have examined the stratification of outcomes of upper limb function and self-care in acute tetraplegia.[7,8] For ambulation, recent studies have developed prediction rules in acute SCI,[16,17,44] primarily based on regression analysis with the attendant, aforementioned limitation in terms of providing information about outcomes distribution. For this reason, we applied URP-CTREE to predict upper limb function and self-care as outcome measures at 6 and 12 months based on different predictor variables assessed at 1 month after injury. The results showed that URP-CTREE enables the prediction of the distribution of different outcomes in acute cervical SCI and the definition of more homogenous outcome cohorts. Again, in line with logistic regression and ROC analyses, MMT remained the strongest predictor for outcome of upper limb function and self-care.

MMT, as defined in the GRASSP, includes a greater number of muscles compared to the ISNCSCI protocol (UEMS) by incorporating distal (extensor digitorum, opponens pollicis, flexor pollicis longus, flexor digitorum profundus (tendon to third digit), first dorsal interosseus and abductor digiti minimi) and proximal (anterior deltoid) muscle groups. This expanded combination of distal and proximal muscle groups probably contributes to the high outcome prediction seen in this study, lending further support to the continued development of the GRASSP as a standardized assessment tool of upper limb function. Similar findings were reported in a recent review of upper extremity impairment after stroke in which it was concluded that the whole limb is important for overall function.[45]

Using URP-CTREE, we were able to show that predictors in the model demonstrated significantly differentiated predictive capacity when compared with the logistic and ROC models, including SWM and MMT as single predictors. Studies that assess the significance of combining individual parameters to improve outcome prediction are sparse.[16,17] We provide evidence that the combination of MMT with other predictors, such as QIG and QtG, can improve outcome prediction.

Interestingly, URP-CTREE identified UEMS as a predictor specific to individuals with less favorable functional outcomes. For patients with more favorable functional outcomes, MMT in combination with QIG and QtG demonstrated predictive utility. These data reveal that the combination of MMT strength and dexterity (QIG and QtG) interact to predict improved outcomes of upper limb function, supporting the findings of a previous study.[46] The GRASSP permits the gathering of more comprehensive information (especially in motor incomplete lesions) and is capable of disentangling neurological and functional changes.

In contrast, for self-care outcomes, URP-CTREE demonstrated that the tests of muscle strength (MMT and UEMS) were useful predictor variables while QIG / QtG were not. This finding support those of a previous study which demonstrated that GRASSP subtests QIG and QtG were not superior to the muscle strength tests (UEMS and MMT) in estimating self-care independence.[37]

Limitation

True external validity of the proposed prediction models can only be proven through confirmatory analysis of an independent data set. Many clinical assessments like UEMS, SCIM and GRASSP are analyzed as sum scores of different items and treated as continuous variables, even though they are ordinal scales. We acknowledge that this could produce misleading results where summed scores do not represent a consistent scoring metric.

Conclusion

The GRASSP is a feasible and reliable assessment tool for the prediction of upper limb function and self-care outcomes in individuals with acute cervical SCI. The GRASSP at 1 month can accurately predict functional outcome at 6 and 12 months, even in a heterogeneous group of individuals across a wide spectrum of neurological recovery. Prediction of outcomes can be used to inform rehabilitation goals and regimens and can be applied in improved stratification of patients in evaluation of interventions. The additional

application of URP-CTREE permits insights into the distribution of outcome categories on which clinical trial outcome analysis and stratification may be based.

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Chapter 6

Predictive value of upper limb muscles and grasp patterns on functional outcome in cervical spinal cord injury

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Abstract

Objective: To determine which single or combined upper limb muscles as defined by the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI); upper extremity motor score (UEMS) and the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP), best predict upper limb function and independence in activities of daily living (ADLs) and to assess the predictive value of qualitative grasp movements (QIG) on upper limb function in individuals with acute tetraplegia.

Method: As part of a Europe-wide, prospective, longitudinal, multicenter study ISNCSCI, GRASSP and Spinal Cord Independence Measure (SCIM III) scores were recorded at 1 and 6 months after SCI. For prediction of upper limb function and ADLs, a logistic regression model and unbiased recursive partitioning conditional inference tree (URP-CTREE) were used.

Results: Logistic regression and URP-CTREE revealed that a combination of ISNCSCI and GRASSP muscles (to a maximum of four) demonstrated the best prediction (specificity and sensitivity ranged from 81.8% to 96.0%) of upper limb function and identified homogenous outcome cohorts at 6 months. The URP-CTREE model with the QIG predictors for upper limb function showed similar results.

Conclusion: Prediction of upper limb function can be achieved through a combination of defined, specific upper extremity muscles assessed in the ISNCSCI and GRASSP. A combination of a limited number of proximal and distal muscles along with an assessment of grasping movements can be applied for clinical decision making for rehabilitation interventions and clinical trials.

Introduction

The neurological examination of individuals with spinal cord injury (SCI) is usually performed according to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI),[1] which is considered the gold standard to determine the levels of injury and to classify the severity of injury. The upper extremity motor score (UEMS, Table 6.1), a component of the ISNCSCI, is often used in clinical research to examine the course of spontaneous neurological recovery.[2-5] However, the UEMS is limited to the assessment of only five key muscle groups for each upper limb in SCI. Furthermore, individuals with cervical SCI show a high variability in motor recovery,[4,6-8] following acute injury. Therefore, the sensitivity of the UEMS is limited for both the prediction and measurement of a therapeutic benefit (i.e. suffering from floor and ceiling effects). Accordingly, the ISNCSCI worksheet was recently updated[9] with the description

Table 6.1 Abbreviations

ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
ASIA	American Spinal Injury Association
AIS	American Spinal Injury Association Impairment Scale
MLI	Motor level of injury
UEMS	Upper extremity motor score
ElbowFlex	Elbow flexors
WristExt	Wrist extensors
Triceps	Elbow extensors
FDP	Long finger flexors
AbdDigV	Small finger abductors
SCIM	Spinal Cord Independence Measure
SCIM-SS	Spinal Cord Independence Measure; self-care subscale
SCIM-MobS	Spinal Cord Independence Measure; mobility subscale
GRASSP	Graded Redefined Assessment of Strength, Sensibility and Prehension
MMT	Manual muscle testing
Delto	M. anterior deltoid
EDC	M. extensor digitorum communis
OPP	M. opponens pollicis
FPL	M. flexor pollicis longus
DI1	M. first dorsal interosseus
SWM	Semmes and Weinstein monofilament
QIG	Qualitative grasping
CylGrasp	Cylindrical grasp
LatPinch	Lateral key pinch
TTPinch	Tip-to-tip pinch
QtG	Quantitative grasping

of additional non-key muscle functions for the upper and lower extremities although their sensitivity of prediction and responsiveness has not yet been analysed.

With the intention of providing more sensitive and accurate assessments of upper limb recovery in cervical SCI, the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) was developed by an international research group.[10] The GRASSP has strong potential to improve the current clinical assessments of upper limb function[6,11] since it consists of different comprehensive subtests (i.e. assesses an increased number of upper limb muscles) and has demonstrated excellent psychometric properties.[6,12]

In recent years there have been several investigations into the prediction of functional outcomes after SCI,[13-16] increasing our knowledge of recovery and prediction of upper limb function and self-care after cervical SCI.[6,7,17,18] The GRASSP allows the precise identification of recovery profiles[6] and accurately predicts upper limb function and self-care in acute tetraplegia.[7]

The GRASSP strength subtest assesses ten muscles, of which five are also measured in ISNCSCI-UEMS (please see Table 6.2). The number of muscles to be tested should be kept to a minimum and should only include muscles that are useful in the clinical setting and for research in order to optimise time resources. However, there is insufficient evidence regarding the influence of each individual muscle or muscle group on the prediction of upper limb function and activities of daily living (ADLs). Furthermore, the significance of specific grasp movements presenting early after injury and their potential predictive value for functional outcomes has not been studied so far. These specific grasp movements represent complex outcomes (i.e. combined sensory and motor outputs) that may classify impairment and neurological deficit of the hand more comprehensively than isolated motor and sensory scores. This prospective study on acute cervical SCI up to 6 months thus addressed two aims; firstly, to determine which single or combined upper limb muscles as defined by the ISNCSCI-UEMS and the GRASSP, best predict upper limb function and independence in ADLs, and secondly, to assess the predictive value of qualitative grasp movements (QIG) on upper limb function.

Methods

Study design

This is a European prospective longitudinal multicenter study.

Table 6.2 Key muscle groups or muscles of ISNCSCI and GRASSP

	Predictors at 1 month after cervical spinal cord injury (SCI)	
Root level	Key muscle groups *ISNCSCI-UEMS* 5 items per arm	Muscles *GRASSP-MMT* 10 items per arm
C5		M. anterior deltoid
	Elbow flexors (M. brachialis, M. biceps)	M. biceps
C6	Wrist extensors (M.extensor carpi radialis longus and brevis)	M. ext carpi radialis longus and brevis
C7	Elbow extensors (M. triceps)	M. triceps
		M. extensor digitorum communis
C8	Long finger flexors (M. flexor digitorum profundus) to the middle finger	M. flexor digitorum profundus to the middle finger
		M. opponens pollicis
		M. flexor pollicis longus
T1	Small finger abductors (M. abductor digiti minimi)	M. abductor digiti minimi
		M. first dorsal interosseus

Abbreviations: ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; UEMS, upper extremity motor score; GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; MMT, manual muscle testing; C5, cervical dermatome 5; C, cervical; T1, thoracic dermatome 1; T, thoracic. Dark grey shading indicates the muscle groups common to ISNCSCI and GRASSP.

Study population

Individuals with acute tetraplegia were prospectively enrolled in five European SCI centers from 2009 to 2012. Individuals were included if they had sustained a traumatic or non-traumatic acute (16–40 days after injury) cervical spinal cord injury as defined by the protocol of the American Spinal Injury Association (ASIA)[1] and suffered from any Impairment Scale (AIS) grade of A, B, C or D. Participants with high cervical lesions, continuous complete ventilator dependency and complete loss of upper limb control were excluded. Participants were also excluded if they had any accompanying severe neurological disorder (e.g., traumatic brain injury), any additional cause of upper limb impairment or were younger than 16 years old. The study was approved by relevant authorities at all sites and written informed consent was obtained from all participants.

Clinical assessments and procedures

The main clinical measures included the ISNCSCI, GRASSP and the Spinal Cord Independence Measure (SCIM).

The clinical neurological examination was performed according to the ISNCSCI protocol,[1] which is the gold standard to determine the levels of injury and to classify the severity of the injury. This paper focuses on subcomponents of the ISNCSCI, the UEMS, the motor level of injury (MLI) and AIS.

The GRASSP is a comprehensive measure of upper limb function with motor (manual muscle testing (MMT)), sensory (Semmes and Weinstein monofilament (SWM)), qualitative grasping (QlG) and quantitative grasping (QtG) subtests. The right and left sides are tested separately. The subtests and items within subtests can be evaluated separately or as summed scores. The GRASSP is a relatively new tool, which is being used more and more commonly in clinical research of cervical SCI and has excellent psychometric properties.[6,12] More details about the GRASSP Version 1.0 are described elsewhere.[6,7]

The SCIM III is a global measure of function which assesses independence in fundamental daily activities specific to individuals with SCI.[19] The SCIM III consists of three subcategories: (a) self-care (SCIM-SS), (b) respiration and sphincter management, and (c) mobility (SCIM-MobS). The SCIM III has been shown to perform well under psychometric testing.[20-22]

Rehabilitation physicians trained on the ISNCSCI protocol performed the neurological examination and occupational therapists conducted the GRASSP at 1 month (range = 16–40 days) and 6 months (range = 150–186 days) after cervical SCI. All occupational therapists

involved in data collection had at least one year of experience in working with individuals with SCI and had successfully completed competency training on how to perform the outcome measure assessments. Experienced physical therapists, nurses and occupational therapists obtained SCIM III data at 6 months (range = 150–186 days) after cervical SCI. In addition, a standard protocol, outlining in detail how the assessments should be performed, was provided for each outcome measure with standardised recording techniques and materials across all centers.

Predictor variables

The following baseline variables (assessed between day 16 and 40 after cervical SCI) were selected as predictors: INSCSCI-AIS, INSCSCI-MLI, ISNCSCI-UEMS, GRASSP-MMT and GRASSP-QIG.

ISNCSCI-UEMS. The ISNCSCI upper limb strength measurement consists of five key muscle groups. Each muscle group is scored from 0 (completely paralysed muscle) to 5 (active movement and a full range of movement against maximum resistance) for each arm.

GRASSP-MMT. GRASSP strength measurement consists of ten muscles. Each muscle is scored from 0 (completely paralysed muscle) to 5 (active movement and a full range of movement against maximum resistance) for each arm. For this study, the five muscles which are also assessed in the UEMS were excluded from analysis. The five remaining muscles were selected as predictors. For more details regarding the ISNCSCI and GRASSP predictor variables, please see Table 6.2.

GRASSP-QIG. The ability to perform movements of the hand and fingers as they relate to a cylindrical grasp (CylGrasp), lateral key pinch (LatPinch), and tip-to-tip pinch (TTpinch) is assessed for each hand separately. Each grasp is scored from 0 (no voluntary control of wrist and digits when grasping) to 4 (normal voluntary movement control of wrist and digits when generating the grasp).

INSCSCI-AIS and INSCSCI-MLI. The AIS classifications were calculated using a computer algorithm[23] in accordance with the definitions in the ISNCSCI.[1] As described in the ISNCSCI, the motor level is defined as the most caudal spinal segment, as indexed by the key muscle group for that segment, having a muscle strength score of at least 3/5 (full range contraction against gravity alone) while all the more rostral key muscles are normal (5/5). The MLI was split in three subgroups: 1) C1-C4; 2) C5-C6; 3) C7-T1.

Outcome variables

The appreciation of upper limb function was distinguished into different domains like the quantitative capacity of each single hand to accomplish defined grasping tasks (QtG) and defined measures of independence in activities of daily life (SCIM items). All the outcome variables were assessed at 6 months (range = 150–186 days) after injury.

GRASSP-QtG. The GRASSP subtest QtG reflects upper limb function based on quantitative measures of grasp performance. Six prehension tasks were performed in a standardised way. Each task is graded from 0 (the task cannot be conducted at all) to 5 (the task is conducted without difficulties using the expected grasping pattern and upper limb function is unaffected) for each arm according to the grasp used and completeness of the task within 75 seconds. The scores of the six tasks were added, giving a maximum possible QtG subtest score of 30 points for each side. The scoring was performed according to the GRASSP protocol.

SCIM III. The SCIM-SS and SCIM-MobS were selected as outcome variables because these subcategories have items predominantly related to the use of the upper limb (transfers, wheelchair mobility, grooming etc.) and reflect upper limb performance.[24] The sum of the SCIM-SS ranges from 0 to 20 points. The SCIM-MobS is the sum of the SCIM mobility subcategory minus the score for the “stair” item. The sum of this SCIM-MobS therefore ranges from 0 to 37 points.

Data analysis

Descriptive statistics were used to determine the frequency, mean and range of the study individuals’ characteristics including AIS grade, motor level, gender and age.

Backward multiple binary logistic regression was performed to identify the muscle and muscle group variables that show the greatest effect on the prediction of the dichotomised outcomes QtG, SCIM-SS and SCIM-MobS. The following five ISNCSCI-UEMS muscle group predictors were investigated for each arm: elbow flexors (ElbowFlex), wrist extensors (WristExt), elbow extensors (Triceps), long finger flexors (FDP) and small finger abductors (AbdDigV). The five GRASSP single muscle predictors that are not included in the UEMS muscle groups were investigated in this study: M. anterior deltoid (Delto), M. extensor digitorum communis (EDC), M. opponens pollicis (Opp), M. flexor pollicis longus (FPL) and M. first dorsal intersosseus (DI1) (please see Table 6.1 and Table 6.2 for details). Ten muscles or muscle group predictor variables were therefore included in the model and were subsequently eliminated in a backward stepwise regression method using the Likelihood-Ratio (LR) test.

Sensitivity and specificity were calculated from classification tables with 95% confidence intervals (CIs), to investigate the predictive accuracy of the full and reduced model. Dichotomisation of the QtG and SCIM-SS was based on known cutoff values described elsewhere.[7] Briefly, for the unilateral QtG outcome, individuals were allocated to the success group (19–30 points) if they were able to complete the task using the standard grasp, irrespective of any difficulties while performing the task. All other individuals with scores below 19 points were allocated to the failure group. A cutoff SCIM-SS score of 12 was applied, with scores of 0 to 12 points defined as dependent (failure), and scores from 13 to 20 as independent (success). Dichotomisation of the SCIM-MobS was based on those items that characterised that individuals would need total or partial assistance and/or adaptive devices in mobility activities and are referred to as dependent in mobility (failure) while the other group consisted of individuals that are referred to as independent (success) in mobility. A SCIM-MobS score from 0 to 12 points was therefore defined as failure, and a score from 13 to 37 was defined as success.

We furthermore based our analysis on a flexible tree-structured regression model from the family of unbiased recursive partitioning methods called *conditional inference tree (URP-CTREE)*[25] which is an unbiased technique to directly identify homogenous subgroups without compromising prediction accuracy in SCI.[7,26] We generated classification trees for the outcomes QtG, SCIM-SS and SCIM-MobS at 6 months using the same ten muscle and muscle group predictors as described under the logistic regression section, assessed at 1 month after cervical SCI. In addition to the 10 muscle predictors the two ISNCSCI predictors AIS and MLI were entered in the model. URP-CTREE does not assume linear dependence between predictors and outcomes, and it specifically puts the modelling focus on interactions between predictors. Each decision in the classification tree is based on the singular most significant predictor, and the splits are set as to maximise discrepancy between the groups subsequently formed. The tree stops growing when there is no longer any significant predictor. The same statistics were performed for each hand with the three QIG predictors: CylGrasp, LatPinch and TTpinch. For the unilateral QtG (30 points maximum sum score) outcome variable, the unilateral predictor variable scores (ordinal range from 0 to 5 for strength and 0 to 4 for QIG) were used in the analysis. For the SCIM-SS (20 points maximum summed score) and SCIM-MobS (maximum summed score 37 points) outcome variables, the right and left predictor variables were combined, giving a bilateral predictor variable score (10 points maximum sum score). All data were analysed using SPSS (IBM) version 18.0 for Windows and the computing environment R[27] version 2.14.0 for Windows which based on the package "party: a laboratory for recursive partitioning".[28]

Results

Study population

A total of 61 individuals with cervical SCI were enrolled in the study. For four individuals, no QtG data was available at 6 months and therefore a total of 57 individuals (n = 114 arms) were included for the GRASSP outcome QtG and 61 individuals for the SCIM-SS and SCIM-MobS outcomes. The mean age of the included participants was 47 (±19 SD;

Table 6.3 Demographic and clinical characteristics of participants (n = 61)

Characteristics	n (%)	
Cause of SCI		
Traumatic	58 (95.1%)	
Non-traumatic	3 (4.9%)	
Site		
Klinik Hohe Warte Bayreuth (D)	19 (31.1%)	
Unfallklinik Murnau (D)	1 (1.6%)	
Orthopädische Universitätsklinik Heidelberg (D)	3 (4.9%)	
Balgrist University Hospital Zurich (CH)	13 (31.1%)	
Swiss Paraplegic Center Nottwil (CH)	25 (41.0%)	
Gender		
Female	16 (26.2%)	
Male	45 (73.8%)	
Age (mean years; SD; min/max)	47 (±19; 18–81)	
AIS		
1 month (range 16–40 days) (n = 61)	A 16 (26.2%); B 10 (16.4%); C 7 (11.5%); D 28 (45.9%)	
6 months (range 150–186 days) (n = 61)	A 14 (23.0%); B 7 (11.5%); C 4 (6.6%); D 36 (59.0%)	
Motor level of injury at 1 and 6 months	1 month	6 months
C1	3 (4.9%)	2 (3.3%)
C2	4 (6.6%)	5 (8.2%)
C3	13 (21.3%)	8 (13.1%)
C4	9 (14.8%)	3 (4.9%)
C5	14 (23.0%)	15 (24.6%)
C6	8 (13.1%)	10 (16.4%)
C7	5 (8.2%)	8 (13.1%)
C8	3 (4.9%)	7 (11.5%)
T1	2 (3.3%)	2 (3.3%)
T2		1 (1.6%)

Abbreviations: n, sample size; SCI, spinal cord injury; AIS, American Spinal Injury Association Impairment Scale; C1, cervical dermatome 1; C, cervical; T1, thoracic dermatome 1; T, thoracic; dermatomes are indicated by numbers; SD, standard deviation; D, Germany; CH, Switzerland.

18–81) years and 45 (73.8%) of the individuals were male. Detailed cohort characteristics are presented in Table 6.3.

Logistic regression

Completion of logistic regression analyses based on the previous defined binary outcome variables (see Methods) in general revealed that the best statistical models did not reduce prediction accuracy (represented by the high sensitivity and specificity levels) compared to the full model with ten muscle predictors included. The observed predictions for the full and reduced models are presented in Table 6.4.

Backward logistic regression (LR) identified the combination of ISNCSCI-FDP ($p < 0.0001$) and GRASSP-Delto ($p < 0.014$) as the best statistical model for binary outcome in QtG. For the prediction of the SCIM-SS in categorising individuals as dependent or independent in self-care, the combination of two ISNCSCI muscle predictors (ElbowFlex ($p < 0.0001$) and WristExt ($p < 0.027$)) and two GRASSP muscle predictors (EDC ($p < 0.028$) and FPL ($p < 0.001$) was found as the most accurate prediction model. The combination of two ISNCSCI muscle predictors (WristExt ($p < 0.047$) and FDP ($p < 0.065$)) and two GRASSP muscle predictors (Delto ($p < 0.006$) and FPL ($p < 0.008$)) resulted in the best model for binary outcome in SCIM-MobS.

URP-CTREE

Figures 6.1a and b and Figures 6.2 and 6.3 show the results of the URP-CTREE for the outcomes QtG, SCIM-SS and SCIM-MobS at 6 months after cervical SCI.

The URP-CTREE revealed that a combination of three significant single muscle predictor variables are sufficient to predict a range of different outcomes in QtG, SCIM-SS and SCIM-MobS and identify homogenous subgroups from the cohort of cervical SCI individuals. For the QtG outcome, the URP-CTREE model with the QIG predictors (Figure 6.1b) showed similar results (medians and group formation) compared to the URP-CTREE model with the muscle predictor variables (Figure 6.1a).

As the interpretation of Figures 6.1a and b and Figures 6.2 and 6.3 are analogous, the more detailed interpretation of the URP-CTREE results will be limited to Figure 6.2 with the URP-CTREE for self-care at 6 months. The algorithm resulted in a partition of the initial cervical SCI cohort ($n = 57$) into 4 subgroups, which are represented as final nodes, based on three significant muscle predictor variables (bilateral) at one month. The final nodes represent subgroups with different outcomes ranging from low (least favorable) to high (most favorable) values for SCIM-SS at 6 months.

Table 6.4 Classification table logistic regression

	Quantitative grasping at 6 months				
	Specificity %	95% CI	Sensitivity %	95% CI	Overall %
All 10 unilateral muscle predictors	86.5	74.7–93.3	86.4	75.5–93.0	86.5
2 predictors:	86.5	74.7–93.3	86.4	75.5–93.0	86.5
FDP					
Delto					
	Self-care at 6 months				
	Specificity %	95% CI	Sensitivity %	95% CI	Overall %
All 10 bilateral muscle predictors	89.2	75.3–95.7	86.4	66.7–95.3	88.1
4 predictors:	91.9	78.7–97.2	81.8	61.5–92.7	88.1
ElbowFlex					
WristExt					
EDC					
FPL					
	Mobility at 6 months				
	Specificity %	95% CI	Sensitivity %	95% CI	Overall %
All 10 bilateral strength predictors	91.2	77.0–96.7	92.0	75.0–97.8	91.5
4 predictors:	91.2	77.0–96.7	96.0	80.5–99.3	93.2
WristExt					
FDP					
Delto					
FPL					

Binary backward logistic regression was performed on the dichotomised outcomes QtG, self-care and mobility at 6 months starting with 10 different single ISNCSCI and GRASSP muscle predictors measured between day 16 and 40 after cervical spinal cord injury. The light grey shadow indicates the chosen ISNCSCI predictors and the dark grey shadow are the chosen GRASSP predictors. Abbreviations: QtG, quantitative grasping; FDP, M. flexor digitorum profundus; ElbowFlex, elbow flexors; WristExt, wrist extensors; EDC, M. extensor digitorum communis; FPL, M. flexor pollicis longus; Delto; M. anterior deltoid; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension.

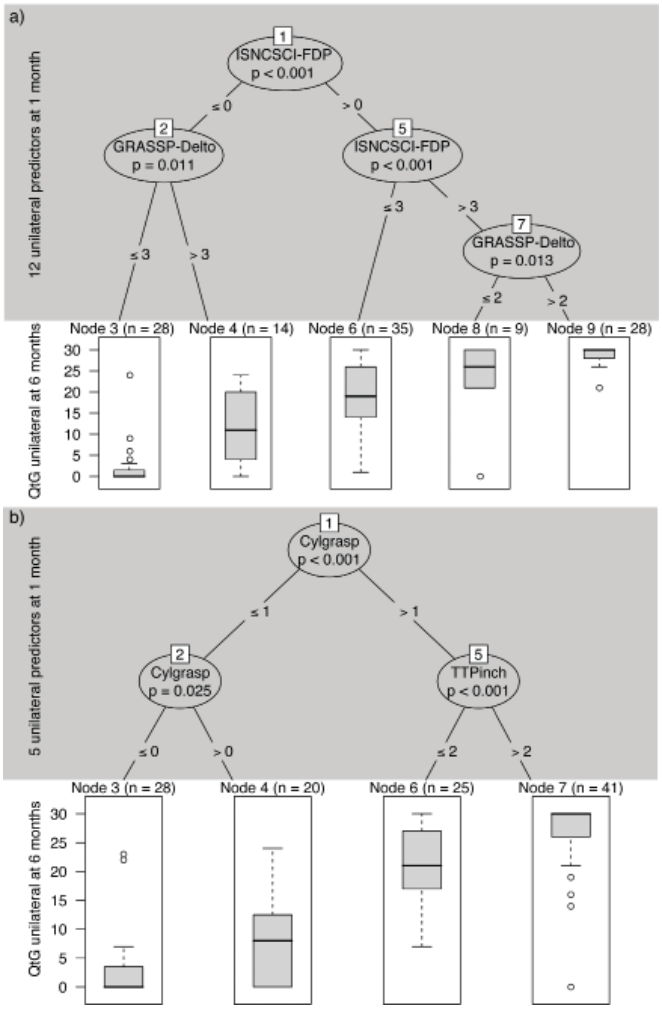

Figure 6.1 Unbiased recursive partitioning conditional inference tree (URP-CTREE) for quantitative grasping at 6 months starting with ten different single unilateral ISNCSCI and GRASSP muscle predictors and two unilateral ISNCSCI predictors AIS and MLI measured between day 16 and 40 after cervical spinal cord injury.
(a) The algorithm led to a partition of the initial cervical SCI cohort into five subgroups, which are represented as terminal nodes. Node size (number of arms) is indicated above each terminal node. From left to right, the terminal nodes represent subgroups from low (least favorable) to high (most favorable) quantitative grasping outcome at 6 months. The ISNCSCI-FDP was selected as the first unilateral predictor variable ($p < 0.001$) and split the cohort into two newly formed subgroups. The initial ISNCSCI-FDP cutoff values ≤ 0 or > 0 are indicated at the "branches". At each branch, a multiple-testing-adjusted p-value is given which describes the strength of the statistical association between predictor and outcome variable. Further separation is achieved by GRASSP-Delto for patients with ≤ 0 ISNCSCI-FDP and by ISNCSCI-FDP and GRASSP-Opp for patients with > 0 ISNCSCI-FDP.
(b) Unbiased recursive partitioning conditional inference tree (URP-CTREE) for quantitative grasping at 6 months starting with three single unilateral GRASSP-QIG predictors and two unilateral ISNCSCI predictors AIS and MLI measured between day 16 and 40 after cervical spinal cord injury. As the interpretation of "a" and "b" are analogous, we refer readers to the explanatory notes for "a" for more details.
Abbreviations: QtG, quantitative grasping; QIG, qualitative grasping; n, arms; p, significance level; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; FDP, M. flexor digitorum profundus; Delto; M. anterior deltoid; Opp, M. opponens pollicis; QualCyl, cylindrical grasp; TTpinch, tip to tip pinch.

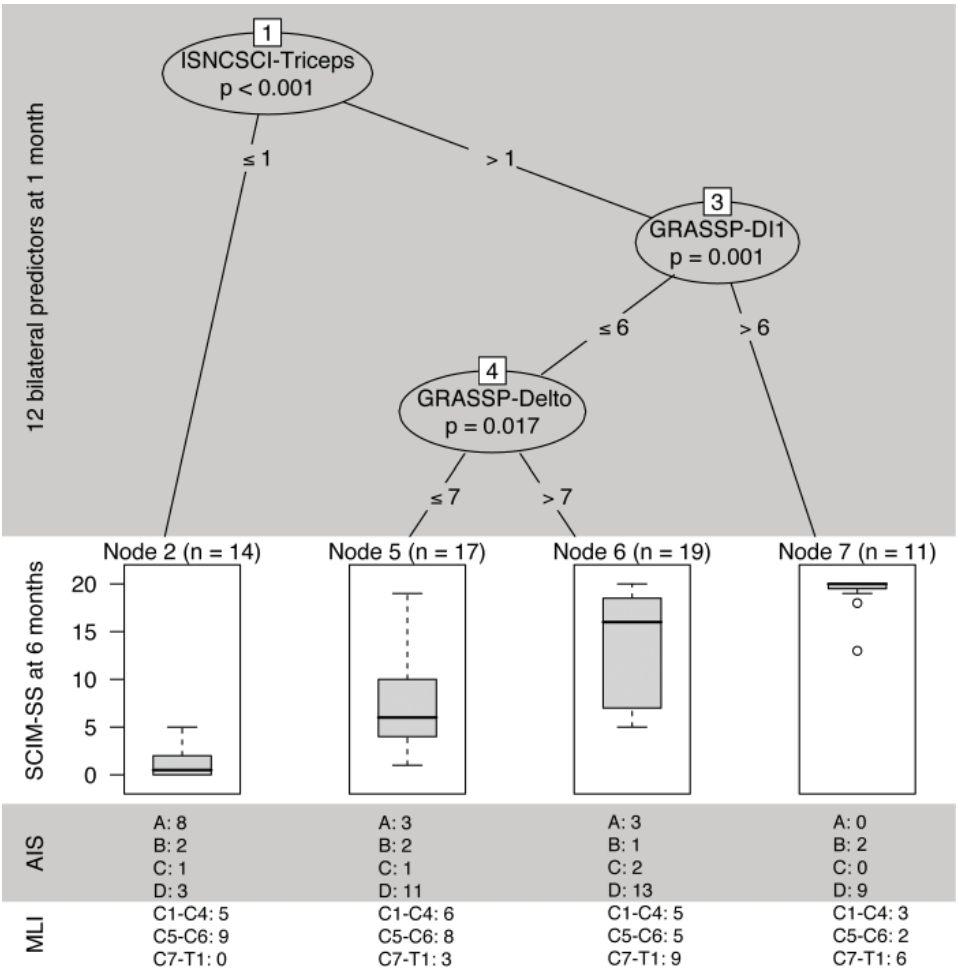

Figure 6.2 Unbiased recursive partitioning conditional inference tree (URP-CTREE) for self-care at 6 months starting with ten different single bilateral ISNCSCI and GRASSP muscle predictors and two bilateral ISNCSCI predictors AIS and MLI measured between day 16 and 40 after cervical spinal cord injury.

The algorithm led to a partition of the initial cervical SCI cohort into four subgroups, which are represented as terminal nodes. Node size (subgroups sample size) is indicated above each terminal node. From left to right, the terminal nodes represent subgroups from low (least favorable) to high (most favorable) self-care outcome at 6 months. The ISNCSCI-Triceps was selected as the first bilateral predictor variable ($p < 0.001$) and split the cohort into one newly formed subgroup. The initial ISNCSCI-Triceps cutoff values ≤ 1 or > 1 are indicated at the "branches". At each branch, a multiple-testing-adjusted P-value is given which describes the strength of the statistical association between predictor and outcome variable. Below the ISNCSCI-Triceps cut-off ≤ 1, no further separation is achieved and the next separation is achieved by GRASSP-DI1 and GRASSP-Delto for patients with > 1 ISNCSCI-Triceps.

Abbreviations: n, sample size; p, significance level; SCIM-SS, spinal cord independence measure: self-care subcategory; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; DI1, first dorsal interosseous; Delto; anterior deltoid; AIS, American Spinal Injury Association Impairment Scale; MLI; motor level of injury; C, cervical dermatome, T, thoracic dermatome.

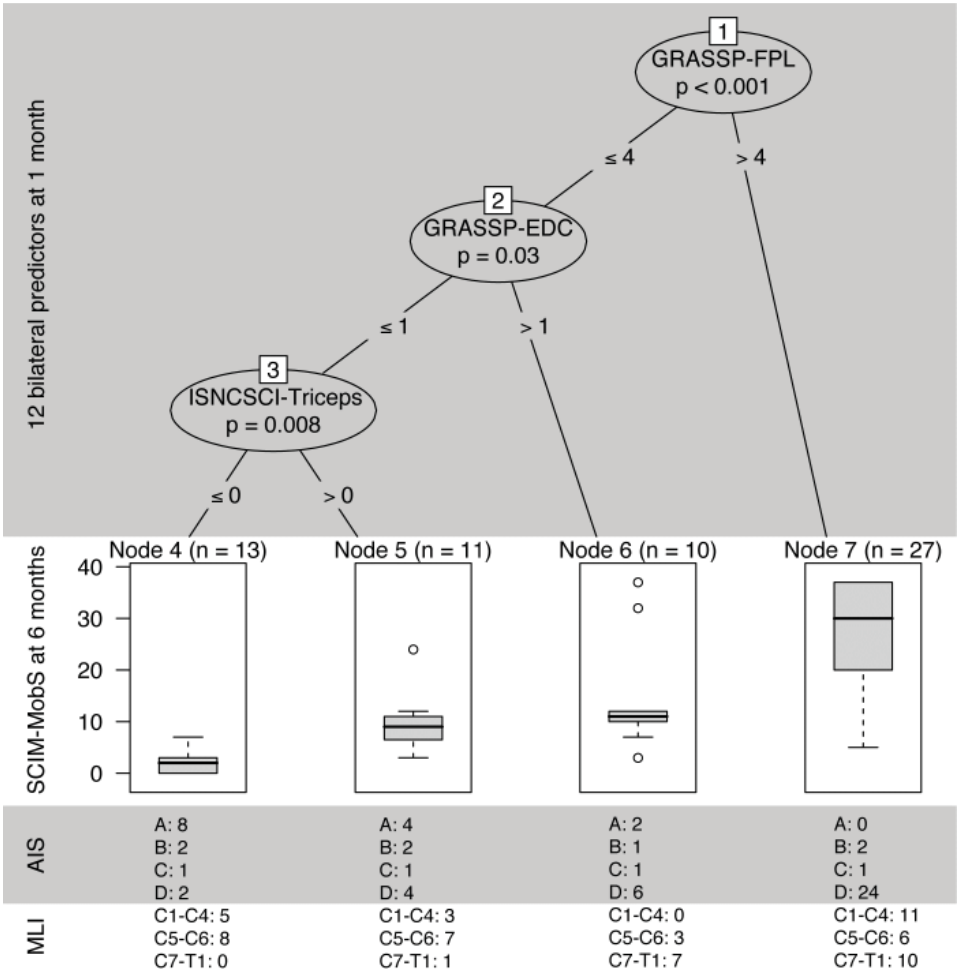

Figure 6.3 Unbiased recursive partitioning conditional inference tree (URP-CTREE) for mobility at 6 months starting with ten different single bilateral ISNCSCI and GRASSP muscle predictors and two bilateral ISNCSCI predictors AIS and MLI measured between day 16 and 40 after cervical spinal cord injury.

As the interpretation of Figure 6.2 and Figure 6.3 are analogous, we refer readers to the explanatory notes for Figure 6.2 for more details.

Abbreviations: n, sample size; p, significance level; SCIM-MobS, spinal cord independence measure: mobility subcategory; ISNCSCI, International Standards for Neurological Classification of Spinal Cord Injury; GRASSP, Graded and Redefined Assessment of Strength, Sensibility and Prehension; FPL, M. flexor pollicis longus; EDC, M. extensor digitorum communis, AIS, American Spinal Injury Association Impairment Scale; MLI; motor level of injury; C, cervical dermatome, T, thoracic dermatome.

The ISNCSCI-Triceps was selected as the first predictor variable ($p < 0.001$) and separates the population into two newly formed subgroups. The ISNCSCI-Triceps cutoff values ≤ 1 or > 1 are indicated at the "branches". At each branch, a multiple-testing-adjusted p-value is given which describes the strength of the statistical association between predictor and outcome variable. Below the ISNCSCI-Triceps cut-off ≤ 1, no further separation was achieved (node 2: n = 14, least favorable outcome). Proceeding from the ISNCSCI-Triceps cut-off > 1 subgroup (n = 47), the next separation was achieved with the DI1 cut-off at 6 points ($p = 0.001$). Proceeding from the GRASSP-DI1 cut-off ≤ 6 subgroup (n = 36), the last separation was performed with the GRASSP-Delto ($p = 0.017$), identifying 2 subgroups with the GRASSP-Delto cut-off ≤ 7 (node 5: n = 17) and GRASSP-Delto cut-off > 7 (node 6: n = 19) subgroups. Below the GRASSP-DI1 cut-off > 6, no further subdividing was achieved (node 7: n = 11, most favorable outcome).

Discussion

The aims of this study were to investigate which single or combined upper limb muscles as defined by ISNCSCI-UEMS and GRASSP best predict upper limb function and independence in ADLs and to assess the predictive value of QlG on upper limb function in individuals with acute tetraplegia. The study reveals that the early assessment of motor strength of specific upper limb muscles is of high predictive value for the recovery of upper limb function and independence in ADLs at 6 months after cervical SCI. The combination of proximal and distal upper limb muscles as well as the early ability to initiate simplified grasp movements (i.e. CylGrasp, LatPinch and TTPinch), predicted upper limb function very well. Statistical methods not only allowed the elucidation of the distribution of outcomes following acute cervical SCI but also the prediction of specific cohorts of outcomes that may be specifically targeted for clinical intervention.

Logistic regression

Correlations between baseline predictors (i.e. upper limb strength) and functional outcomes following acute SCI have been shown in previous studies.[7,12,29] Here, logistic regression was applied to reveal the best constellation of shared predictors on defined upper limb outcomes. Not unexpectly, a combination of standard ISNCSCI muscle groups i.e. FDP, ElbowFlex and WristExt, and additional GRASSP muscles, i.e. FPL, EDC and Delto, showed the best predictive value for the targeted outcomes QtG, SCIM-SS and SCIM-MobS. Specifically, including a proximal shoulder muscle, in this case M. deltoid, improved

prediction as this muscle contributes greatly to daily activities like transferring from bed, toilet or a car to the wheelchair, dressing the upper body or pouring water from a bottle into a cup. If the proximal shoulder and arm cannot be actively positioned and controlled as needed, the ability to use the hand for functional activities will be severely limited. Our refinement in including additional distal key muscles of the hand and fingers also contributed to improved prediction. Activities such as feeding, buttoning a shirt, inserting a key into a lock and turning it depend also on fine hand, finger and thumb movements, i.e. WristExt, FDP, EDC and to a major extend FPL. Our data are comparable to findings in a prior cross-sectional study on upper limb function in cervical SCI,[24] in which a combination of distal muscle groups was proven especially useful in predicting self-care independence.

By performing a LR test, we demonstrated that the reduced model displays a greater predictive capacity than a logistic model containing all ten muscle predictors – an unexpected finding. A combination of a reduced number of proximal and distal muscles provided the same accuracy as the full model. This information is lost when using summed scores because in this case it is still unclear which single muscles contribute to outcome improvement. Moreover, in clinical settings and for research, the muscles to be tested should only include those of which that are useful in predicting functional outcome. The use of a combination of single predictors to enable more reliable prediction of long-term functional outcomes after SCI is in accordance with findings reported in previous longitudinal studies,[7,14,16] although they have, in contrast, focused on total maximum summed scores combined with other predictor variables, making comparisons potentially unreliable.

URP-CTREE

Applying unbiased recursive partitioning resulted in the selection of a combination of proximal and distal muscles (i.e.Triceps and Delto, and FDP, EDC, DI1, FPL and Opp) as the best significant predictor variables for the outcomes QtG, SCIM-SS and SCIM-MobS. The advantage of URP-CTREE lies in the provision of a decision tree with specific threshold values (e.g. muscle strength scored from 0–5) for all outcomes. Our results demonstrated that a combination of a maximum of three significant muscle predictor variables are sufficient to predict a range of different outcomes (least favorable to most favorable) in QtG, SCIM-SS and SCIM-MobS and can reliably identify homogeneous subgroups from the cohort of cervical SCI individuals.

The AIS and MLI predictor variables were not chosen in the URP-CTREE model, indicating that AIS and MLI do not improve prediction accuracy. The combination ISNCSCI-

UEMS and GRASSP muscle predictors with threshold values above the branches (URP-CTREE) are therefore excellent indices for the stratification of patient groups and a good proxy for least and most favorable outcome irrespective of AIS and MLI. The AIS and motor level shown in the terminal nodes of Figure 6.2 and Figure 6.3 demonstrate the high heterogeneity across all nodes at 6 months.

The URP-CTREE finding that GRASSP-QIG items predicted upper limb function accurately is exciting because QIG can be quickly and easily assessed at the bedside in almost all clinical settings and highlights the importance of including this relative simply measure in standard clinical evaluations.

Clinical and research implications

The high variability in neurological recovery requires reliable and sensitive prognostic tools for cervical SCI outcomes if we are to improve the design and conduct of clinical trials. This includes the stratification and enrollment of the most suitable patients (e.g. avoiding the enrollment of patients who will recover well irrespective of treatment) and to provide information regarding meaningful clinical outcome thresholds. Simplified, visually informative yet sensitive prediction models like URP-CTREE are of great value in the clinical trial setting. The magnitude of recovery and expected functional outcome is also of great importance for future rehabilitation interventions and to provide early prognostic information to patients and their families.

Most interestingly, the testing of qualitative grasping (QIG) may be a promising assessment tool as it can be applied easily in individuals with acute tetraplegia. QIG requires little time and can complement the standard assessment of muscle strength.

Limitations

The findings presented here are based on assessments at 1 month (range = 16–40 days) after injury and cannot be easily applied to studies performed within the first days following SCI. The effect of different time intervals on the prediction models following SCI needs to be evaluated in more detail. Validation of an independent data set (i.e. external validation) will also be required to prove to what extent our findings can be generalised.

Conclusion

Our data show that prediction of upper limb function and independence in ADLs at 6 months can be accurately achieved through a combination of a limited number of single

proximal and distal muscle strength tests as provided by the ISNCSCI-UEMS and GRASSP standards in individuals with acute cervical SCI. Furthermore, the combination of ISNCSCI-UEMS and GRASSP muscle predictors are ideal indices for stratifying patient groups and a good proxy for favorable and unfavorable outcomes irrespective of AIS and MLI. Qualitative grasping, a simple test with minimal time demands, predicted upper limb function very well. In summary, the predictive value of standard ISNCSCI-UEMS for upper limb function can be significantly improved with the addition of single GRASSP predictors.

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Chapter 7

General discussion

The aim of this final chapter is to accumulate the findings from the previous chapters and to present clinical implications. In addition, methodological considerations and areas for future research will be formulated.

After cervical spinal cord injury (SCI), motor and sensory impairments cause limitations in upper limb function, which affect the performance of activities of daily living (ADLs), independence and, ultimately, restrict participation and quality of life. Previous studies have shown that individuals with tetraplegia consider improvements in upper limb function to be one of the most significant factors in improving quality of life.[1-3] However, appropriate outcome measures to evaluate the efficacy of rehabilitation and experimental interventions are lacking and research in this field is limited.[4-8] Furthermore, cervical SCI shows large variability,[9,10] which makes interpretation of clinical findings and research difficult. Therefore, the overall objective of this PhD thesis has been to study the assessment, evaluation and prediction of upper limb function up to one year post injury using the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) in individuals with cervical SCI. In order to answer the research questions of this thesis, one systematic review, one multi-center cross-sectional study and one multi-center longitudinal cohort study was performed which is presented in the five chapters of this thesis. Evidence was presented that the GRASSP provides information on multifaceted domains (e.g. strength, sensation and prehension) and allows to detect both subtle and clinical meaningful changes in upper limb function. Furthermore, the GRASSP can accurately predict upper limb function and ADLs, even in a heterogeneous group of individuals across a wide spectrum of neurological recovery. This supports the use of the GRASSP in the assessment of rehabilitation outcome as well as in clinical studies and trials.

Upper limb function and clinical implications

A systematic review of outcome measures for upper extremity function (**chapter 2**) was performed and these were classified on several levels according to the International Classification of Functioning, Disability, and Health (ICF).[11] In the systematic review of the available outcome measures, the five most frequently used outcome measures in the four study populations were determined: (1) peripheral upper extremity conditions, (2) rheumatologic diseases, (3) stroke, and (4) tetraplegia, which resulted in a total of 17 outcome measures. The outcome measures show large variability with regard to the areas of functioning and disability addressed. It appears that there clearly is a gap in the availability of upper extremity-specific outcome measures in studies of individuals with tetraplegia.

Information on psychometric properties of outcome measures is lacking for this specific population. This deficiency is a hindrance for rehabilitation and research in cervical SCI, because relevant outcome measures are not validated and consequently not used. For example, the Disability of the Shoulder, Arm and Hand Questionnaire (DASH)[12] has still not been validated for tetraplegia, even though it could provide great insight into activity limitations and participation restrictions of individuals with tetraplegia. Further research should be performed to study the psychometric properties of the DASH in cervical SCI. The results of the systematic review help clinicians and researchers to select the most appropriate outcome measure for their clinical population or research question according to ICF-based content validity, and psychometric properties of the measures.

The lack of relevant outcome measures to investigate impairment changes over time and how they contribute to complex upper limb tasks, was the rationale and starting point for the development of the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP).[13] It is an outcome measure that quantifies impairment as well as functional outcome, and it will help clinicians to adjust rehabilitation measures and treatment strategies in order to achieve better outcomes. In individuals with chronic SCI (i.e. more than 6 months post-injury), the validity and reliability of GRASSP were found to be good.[14] The responsiveness of the GRASSP (**chapter 3**) was defined as its sensitivity in detecting changes,[15-18] making it possible to evaluate recovery patterns and treatment outcomes in cervical SCI. It was found that the GRASSP has excellent responsiveness for the evaluation of upper limb outcomes up to one year after cervical SCI.[19] The observed GRASSP subtest changes were also in accordance with the clinicians' impressions of patient changes, which is a novel finding. This finding suggests that the GRASSP is a clinically meaningful tool. Therefore, the clinician-rated outcome measure (CROM) may be useful in clinical trials for evaluating the progress of a patient.[20] Experienced clinicians, such as these involved in this study, have a good understanding of neurological impairment and functional performance.

The GRASSP detected clinically significant changes complimentary to the International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI) and Spinal Cord Independence Measure self-care subscale (SCIM-SS). The combined assessment of neurological (body structure and body function) and functional outcomes, for example, prehension (activity and participation), focused on segmental cervical spinal cord functions that are closely related to other standard assessment tools (ISNCSCI and SCIM). This combination supports the use of GRASSP in the assessment of rehabilitation as well as in interventional clinical trials, which seek to detect both subtle and clinical meaningful changes.

Furthermore, in chapter 3 more detailed strength and prehension recovery profiles are presented[19] compared to most other published reports.[9,10,21-27] In the past, the understanding of recovery in cervical SCI was mainly based on ISNCSCI subcategories like the upper extremity motor score (UEMS) and ASIA impairment scale (AIS) grade.[9,23-26,28,29] It was the overall aim of the GRASSP development to provide a measurement tool of upper limb outcome/function on different ICF levels that will be more sensitive and more comprehensive regarding the neurological changes compared to other measures (e.g. ISNCSCI, SCIM). The data suggest that this has been achieved, and comparable studies in this field are yet to be done to confirm this finding.

The ISNCSCI is considered the gold standard in SCI, and is a measure of impairment that generates detailed scoring of segmental sensorimotor deficits. It has been proven to be of value in the diagnosis and prognosis of SCI. It is designed as a classification measure to capture neurological deficits for the whole range of SCI, making it non-specific to the upper limb. Chapter 3 provides evidence that the GRASSP is more responsive than ISNCSCI.[19] The likely reasons for the superior responsiveness of the GRASSP muscle strength and sensation are the expanded combination of muscles and the broader scaling of sensation (by applying different sensory modalities) as well as the additional palmar test locations, respectively.

Furthermore throughout this thesis, the SCIM III was used as a global outcome measure to establish clinically meaningful categorization of functioning in ADLs. In the past[30] as well as in chapter 3, the SCIM-SS has been found to be responsive to change.[19] Likewise it does not provide insights into the underlying sensorimotor function driving functional recovery. Accordingly, the SCIM is not positioned to discern functional improvement arising from actual repair or damaged spinal cord tissue versus rehabilitation training, motivation and mood factors when performing tasks. The SCIM's focus is on gained independence and thus cannot differentiate whether the tasks are performed bimanually or with compensatory movements.[30] Therefore, relying on an activity measure like the SCIM introduces the risk of other unaccounted factors contributing to the outcome and altering the accurate interpretation of a benefit realized by a therapeutic intervention.

Several other assessments such as the Tetraplegie Hand Activity Measure (THAQ),[31] the Van Lieshout Test (VLT),[32,33] the Motor Capacity Scale (MCS),[34,35] Capability of Upper Extremity Test (CUE)[36,37] and Grasp Release Test (GRT)[38] have been developed, however these assessments are not designed to provide detailed and reliable information about the changes in specific sensory and motor impairments affecting upper limb function.

The GRASSP subtest scores were able to disentangle motor and sensory functions contributing to the outcome of upper limb function. The GRASSP assessment reveals, how changes in function are related to neurological improvements following SCI. In addition, the GRASSP subtests also include standardised prehension tests that are related to changes in neurological outcomes. These combined assessments permit to determine whether changes in function are based on improvement through compensatory movements or on improvement of neurological function. Accordingly, quantitative grasping (QtG) provides a detailed scoring of standardised tasks focusing on the grasp form and is therefore able to explain how changes up to 1 year post injury are achieved.

Sensation and clinical implications

Light touch (LT) and pinprick (PP) assessments examined according to the ISNCSCI[39] are used routinely during neurological examination of sensibility in SCI patients. Research is impeded by limited test reliability, which is true for all sensory qualities, such as epicritic sensation and prothopatic sensation, to some extent.[40-44] The assessment of different levels of sensory impairment is furthermore limited, because the subjective rating of patients is not able to define incremental levels of impairment, but represents a rather simplified categorical (ordinal scale, e.g., normal, impaired, and abolished sensation) gross scoring. Therefore, it is very difficult to determine minor changes during recovery (improvements or deterioration), and the clinical testing of one specific sensory quality, such as LT, within a complex domain of sensory function, such as epicritic sensation, conveyed by dorsal column pathways will likely have limited sensitivity. The Semmes and Weinstein monofilaments (SWM) and the electrical perception threshold (EPT) contain a greater range of discernible response levels for detecting a tactile cutaneous sensation and electrical stimulation, respectively. Thus they have the potential of being more sensitive. **Chapter 4** is the first report on the degree of agreement between the two complementary quantitative methods (SWM or EPT) and the ISNCSCI-LT. It has been shown that SWM or EPT reveal deficits that LT alone does not. Therefore, this study provides evidence that the segmental assessment of epicritic sensation is improved by SWM or EPT. This is important in early clinical trials (phase 1, phase 2) where segmental and subtle changes in sensory function provide important information about the beneficial or detrimental (i.e. descending or ascending levels of lesion) effects of a novel intervention. The EPT or SWM should be used in combination with the clinical sensory examination in order to improve the sensitivity to discrete sensory changes and the robustness of sensation examination in

clinical practice and research. Furthermore, comparisons between individual dermatomes can be performed. Therefore the chapters 3 and 4 of this thesis are timely in that they extend the quest for improved assessment techniques that reveal the extent of SCI during the first 6 / 12 months. This time window is relevant for clinical trials of rehabilitative or regenerative treatments for the restoration of function in SCI individuals. As such, these papers will attract the attention of those designing clinical trials for the recovery of SCI and will influence the selection of outcome measures.

Prediction of upper limb function and clinical implications

Reliable prediction of functional outcomes can be used to formulate rehabilitation goals and regimens and is essential for improving the stratification of patients for clinical interventions, for which the enrollment of rather homogenous patient cohorts is required. Improved stratification rules will be of benefit in trials assessing the safety and efficacy of interventions, where the detection of even subtle changes is crucially important in the evaluation of therapies. In **chapter 5**, the focus was on prediction and stratification of upper limb function and self-care after cervical SCI. Results indicate that the GRASSP at 1 month can predict functional outcome at 6 and 12 months accurately, even in a heterogeneous group of individuals across a wide spectrum of neurological recovery. Moreover, evidence has been found that the GRASSP motor scoring (manual muscle testing (MMT) in particular) has an excellent predictive value for clinical outcomes at 6 and 12 months after cervical SCI with a high sensitivity and specificity. Both receiver operating characteristics (ROC) and logistic regression analyses corroborate the high within-sample validity of the MMT within GRASSP as a predictor variable. Semmes and Weinstein monofilament although less influential than muscle strength, is also able to predict outcome of self-care and upper limb function and is specifically useful for prediction when motor assessments are limited (for instance when key motor muscles are not defined above C5) or when muscle activation is hindered by other factors, such as limb fractures or bruising. Logistic regression and ROC analysis do not, however, provide sufficient information about the distribution of outcomes. For this reason, also a regression tool from the family of unbiased recursive partitioning methods called conditional inference tree[45] (URP-CTREE) was used. Due to the relatively low incidence of traumatic SCI,[46] the recruitment of individuals for clinical studies is limited. Cervical SCI comprises a heterogeneous population regarding the diversity of recovery patterns as well as the severity and level of injury,[47] which results in narrow inclusion criteria. The consequences are slow enrollment rates and prolonged study

duration. Conditional inference trees[45] overcome some of these challenges. The results in chapter 4[48] show that simplified, visual informative models like URP-CTREE enable the prediction of the distribution of different outcomes in acute cervical SCI and the definition of more homogenous outcome cohorts for the stratification of study participants, which has also been shown in other recent studies.[28,45] Within the URP-CTREE analysis, in line with logistic regression and ROC analyses, MMT remained the strongest predictor for upper limb function and self-care outcome. The motor scoring, as defined in the GRASSP, includes a greater number of muscles compared to the UEMS within ISNCSCI by incorporating distal and proximal muscle groups. This expanded combination of muscle groups probably contributes to the high outcome prediction seen in this study, lending further support to use the GRASSP as a standardised assessment tool of upper limb function. Studies that assess the significance of combining individual parameters to improve outcome prediction are sparse.[49,50] Based on the results in chapter 5, the combination of MMT with other predictors, such as qualitative grasping (QlG) and quantitative grasping (QtG), can improve outcome prediction.

At the beginning of this thesis, little knowledge was available on the prediction of functional outcome in SCI. In recent years, there have been several investigations into the prediction of functional outcome after SCI,[49-52] increasing our knowledge of recovery and prediction of upper limb function and self-care after cervical SCI.[19,48,53,54] Evidence was presented that the GRASSP allows the precise identification of recovery profiles[19] and accurately predicts upper limb function and self-care in acute tetraplegia.[48] However, there is still limited evidence regarding the influence of each individual muscle or muscle group on the prediction of upper limb function and ADLs. Furthermore, the effect of specific grasp patterns, as described in the GRASSP, on the prediction of upper limb function and functional outcome has not yet been investigated. Therefore, **chapter 6**, describes the predictive value of upper limb muscles and grasp patterns for functional outcome in cervical SCI. The UEMS is often used in clinical research to examine the course of spontaneous neurological recovery.[9,23,24,26,28,29] However, as the UEMS is limited to the assessment of only five key muscle groups for each upper limb in cervical SCI and individuals with cervical SCI can show a high variability in motor recovery following acute injury, the precision of the UEMS regarding motor recovery is not sufficient. The GRASSP-MMT assesses ten muscles, of which five are also measured in ISNCSCI-UEMS. The number of muscles to be tested should be kept to a minimum and should only include muscles that are as useful in the clinical setting and for research. The data in chapter 6 show that prediction of upper

limb function and independence in ADLs at 6 months can be accurately achieved using a combination of some single proximal and distal muscle strength tests, as provided by the ISNCSCI-UEMS, and the GRASSP-MMT in individuals with acute cervical SCI. The AIS and motor level of injury (MLI) predictor variables were not chosen in the URP-CTREE model, indicating that AIS and MLI do not improve prediction accuracy. Therefore, AIS grades and MLI might not be appropriate for stratification in clinical studies or trials. Furthermore, the combination of these limited muscle predictors are ideal indices for stratifying patient groups and a good proxy for favorable and unfavorable outcomes irrespective of AIS and MLI.

In addition, the URP-CTREE finding that GRASSP-QIG items predict upper limb function accurately is exciting, because QIG can be assessed quickly and easily at the bedside in almost all clinical settings. This highlights the importance of including this relative simply measure in standard clinical evaluations. Therefore, the predictive value of standard ISNCSCI-UEMS for upper limb function can be improved significantly with the addition of single GRASSP predictor. From a clinical point of view, it is therefore worthwhile to consider the redundancies and benefits of the different motor testing methods used in the clinic, in order to optimise time resources.

Methodological issues and future directions

- As outlined within this thesis, cervical SCI can affect people in a number of different ways. Relatively narrow inclusion criteria have been used in these investigations. Individuals with high cervical lesions and continuous complete ventilator dependency and complete loss of upper limb control were excluded. Therefore, the results of this thesis are most appropriately generalised to individuals with at least a motor grade of 1 in the M. biceps bilaterally.
- A range of 61 to 74 participants were included in the longitudinal studies. Although this is not a large group, it can be considered to be a good representation of the total population with cervical SCI in Germany and Switzerland. Especially in the field of cervical SCI where the number of patients capable- and willing to participate in clinical research is relatively small and difficult to recruit. Multi-center studies are a solution for the low availability of study participants.
- Further investigations using an independent dataset will be required to prove to what extent the findings in this thesis can be generalised. It is recommended to set up similar longitudinal studies in other countries, in order to compare the results of our German / Swiss longitudinal study with those from other countries.

- Both individuals with traumatic and non-traumatic tetraplegia were included. The overall findings have not been affected by including a few individuals with non-traumatic cervical SCI as the overall percentage of these was around 5 to 8% in the different studies. However, it would be of great interest to investigate the GRASSP in a non-traumatic SCI cohort. There is already an ongoing longitudinal study with individuals suffering from cervical spondylotic myelopathy in North America.
- In the longitudinal studies, the baseline measurement (within 10 days after SCI) was excluded, due to the small sample size (n = 40). The effect of this early time interval is unknown and needs to be evaluated in more detail in longitudinal studies starting early after SCI.
- Novel questionnaires like the CROM have to be interpreted with caution as they may be influenced by other factors (e.g. clinical judgment, past experience, beliefs regarding treatment effectiveness etc.). Systematic bias in the results cannot be entirely excluded as some assessments of GRASSP and CROM in individual patients have been performed by the same therapist. Depending on the study design and research question, it is of course advisable that independent clinicians perform the GRASSP and CROM, thereby minimizing examiner bias.
- The URP-CTREE is applicable to several types of regression problems, including nominal, ordinal and numeric variables.[45] Many clinical assessments like ISNCSCI, SCIM, and GRASSP were analysed as sum scores of different items and treated as continuous variables, even though they are ordinal scales. It is acknowledged that this could produce misleading results[55] when summed scores rely on counts of potentially unequal units and do not represent a consistent metric scoring. The number of statistical methods to analyse this sort of data is limited and using Rasch-analysis,[56,57] e.g., should be considered in future studies.
- In clinical practice, the findings of this thesis will help to improve early management decisions, like discharge and multidisciplinary intervention planning at acute SCI rehabilitation centers. As a consequence, subsequent multidisciplinary rehabilitation services can be optimised in line with the probability for regaining some upper limb function and self-care independence. Knowing the underlying neurological changes of upper limb function, future research should be conducted to further understand the determinants of upper limb function. It would be of great interest to investigate, if and how factors (determinants) like specific injury causes, hand dominance pre- and post-injury, age, length of stay, standard therapies, rehabilitation programs or

intervention frequency, duration of therapy sessions and the start of upper limb rehabilitation program affect upper limb function outcome and the validity of our results. Therefore, future large multi-center studies are needed to study the effect of different determinants, which play a role in outcome effectiveness studies, on upper limb function and thus the prescription of therapeutic interventions. It would also be interesting to determine the optimal time frame and type of intervention as well as to systematic collect and assess costs associated with an intervention (cost analysis).

Furthermore, the change scores up to one year warrant further investigation for their value in determining clinical endpoints for interventional studies, particularly those engaging individuals with acute traumatic cervical SCI.

There is little evidence supporting conventional therapies like splinting or developing a tenodesis grasp.[58,59] In contrast, interventions targeting upper limb recovery and upper limb function are an area which is growing continually. Although efficacy of functional electrical stimulation (FES)[60-62] and somatosensory stimulation[63,64] has been established and despite the functional gains after upper limb surgery,[65-70] as well as recent insights into an upper limb surgery registry,[71] more well designed effectiveness studies are required. The measurement approaches must be standardised across centers and should have consistent baseline and follow up data to enable comparisons between studies and to assess efficacy. The comparison of intervention outcomes requires large homogeneous samples which will require cooperation between multiple centers around the world. GRASSP can serve as an initial step in elucidating upper limb recovery in tetraplegia and will help to establish outcomes that are useful for future clinical studies and trials.

Conclusions

a. This study provides clinicians and researchers with a guide for the selection of the most appropriate outcome measure for their clinical population or research question, taking ICF based content validity (“what do the outcome measures address?”), reliability and responsiveness into consideration.

b. The GRASSP showed excellent responsiveness within the first year after cervical SCI. It detected distinct changes in strength and prehension relating to the severity of cervical SCI. GRASSP detected clinically significant changes complimentary to the ISNCSCI and SCIM-SS assessments.

c. The additional measurements of epicritic sensation by SWM or EPT increased sensitivity by detecting and quantifying differences in sensory thresholds above, at and below the LT level of injury.

d. The GRASSP at 1 month accurately predicted upper limb function and self-care outcomes at 6 and 12 months after cervical SCI. URP-CTREE revealed the distribution of outcome categories and can be used to predict cohorts with homogenous outcomes.

e. The predictive value of standard ISNCSCI-UEMS for upper limb function can be improved significantly with the addition of single GRASSP predictors.

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Summary

The goal of rehabilitation in general is regaining and/or maintaining functionality by decreasing the consequences of health conditions. For this reason, feasible, reliable, valid and responsive outcome measures are needed to provide insight into the underlying causes. For cervical spinal cord injury (SCI) however, research in upper limb function outcome is limited. Moreover, the course of cervical SCI shows large variability regarding recovery, lesion level and density, which makes the interpretation of clinical findings and research challenging.

Chapter 1 of this thesis reports that few outcome measures have been developed for cervical SCI and that they have limited psychometric properties. Thus, there is a clear need for valid, reliable and responsive outcome measures in cervical SCI, in order to assess upper limb function accurately.

The overall aim of this PhD thesis is therefore to study the assessment, evaluation and prediction of upper limb function up to one year post injury using the Graded and Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) in individuals with cervical SCI.

Chapter 2 presents a systematic review of the literature on the availability of current outcome measures for upper extremity function in the four populations: (1) peripheral upper extremity conditions, (2) rheumatologic diseases, (3) stroke and (4) tetraplegia. Seventeen most frequently used outcome measures were identified and classified according the International Classification of Functioning, Disability, and Health (ICF). For each outcome measure a description of the concept, operationalisation into variables and instruments as well as information on the reliability and responsiveness is given. The outcome measures show large variability with regard to the areas of functioning and disability addressed. Reliability and responsiveness data are missing for some outcome measures or for certain populations for which they have been used. Thus, the overview table (table 2) in this chapter can be used to facilitate the selection process of outcome measures for investigations or clinical practice. Furthermore, the table provides an indication of the areas of upper extremity outcome measures in which future research is needed. In addition, the findings in this chapter show that research with a wider focus is needed to encompass the multifaceted problems of upper extremity function. It is therefore important that outcome measures related to upper extremity function capture the entire spectrum of functioning and disability.

This chapter provides clinicians and researchers with a guide for the selection of the most appropriate outcome measure for their clinical population or research question,

taking into consideration ICF based content validity ("what do the outcome measures address?"), reliability, and responsiveness.

Due to the limited research on upper limb function outcome measures in cervical SCI an international research team developed the GRASSP. The GRASSP is an outcome measure that quantifies upper limb impairment changes, and how they contribute to complex upper limb tasks. In **chapter 3**, a prospective study of individuals with acute cervical SCI up to 1 year post injury investigated (1) the responsiveness of the GRASSP subtests, (2) the responsiveness of the GRASSP subtests compared and related to the upper extremity motor score (UEMS) and light touch (LT) scores according to the International Standards of Neurological Classification of Spinal Cord Injury (ISNCSCI) and the spinal cord independence self-care subscale (SCIM-SS), (3) the clinical appreciation of changes in GRASSP and SCIM-SS by using a clinician-rated outcome measure (CROM), and (4) recovery profiles in GRASSP strength and prehension. The outcome measures were assessed at 1, 3, 6 and 12 months after cervical SCI. Seventy-four individuals with acute cervical SCI from 5 European SCI centers were included for this study. The GRASSP subtests proved responsive (standardized response mean [SRM] ranged from 0.79 to 1.48 for strength, 0.50 to 1.03 for prehension, and 0.14 to 0.64 for sensation) between all examination time points. In comparison, UEMS and LT showed lower responsiveness (SRM UEMS ranged from 0.69 to 1.29 and SRM LT ranged from 0.30 to -0.13). All GRASSP subtests revealed significant, moderate-to-excellent correlations with UEMS, LT and SCIM-SS at each time point, and the changes in GRASSP subtests and SCIM-SS were in accordance with the CROM. The large SRMs and the agreement of the GRASSP with the clinicians' ratings (CROM) reflect great clinical relevance. The GRASSP prehension and motor recovery was greatest between 1 and 3 months.

In conclusion, the GRASSP showed excellent responsiveness, detecting distinct changes in strength and prehension relating to the severity of cervical SCI. It detected clinically significant changes complimentary to the ISNCSCI and SCIM-SS assessments.

The study in **chapter 4** compared the epicritic sensation assessed by LT, Semmes-Weinstein monofilament (SWM) and electrical perception threshold (EPT) across cervical dermatomes (C3-C8) in individuals with cervical SCI. A total of 300 left- and right-sided dermatomes were tested for each outcome measure in 25 individuals with tetraplegia 6 months after cervical SCI. The percentage agreement between classifications according to LT and SWM/EPT ranged from 95.5% to 36.2%. The degree of agreement showed considerably variable kappa coefficients ($-0.1 \geq kw \leq 0.7$) for each dermatome between C3 and C8.

In conclusion, the additional measurements of epicritic sensation by SWM or EPT increased sensitivity by detecting and quantifying differences in sensory thresholds above, at and below the LT level of injury.

There is inherent heterogeneity within individuals suffering from cervical SCI, and early prediction of upper limb function and self-care is challenging. As a result, considerable uncertainty exists regarding the prediction of functional outcome following cervical SCI within 1 year of injury. Therefore, the study in **chapter 5** evaluated the value of GRASSP in predicting upper limb function and self-care outcomes in individuals with cervical SCI. A prospective longitudinal multicenter study was performed. Data from the GRASSP, the SCIM III, and the American Spinal Injury Association (ASIA) Impairment Scale (AIS) were recorded at 1, 6, and 12 months after cervical SCI. For prediction of functional outcome at 6 and 12 months, a logistic regression model, receiver operating characteristics (ROC) and unbiased recursive partitioning conditional inference tree (URP-CTREE) were used with 8 different predictor variables. Sixty-one individuals were included for analysis. Logistic regression analysis, ROC analysis, and URP-CTREE all revealed that the motor scoring within GRASSP is the strongest predictor for upper limb function and self-care outcomes. Moreover, the combination of the motor scoring with other predictors, such as qualitative grasping (QlG) and quantitative grasping (QtG), improved outcome prediction. This combination supports the use of GRASSP in the assessment of rehabilitation as well as in interventional clinical trials, which seek to detect both subtle and clinical meaningful changes. In addition, URP-CTREE provided useful information on the distribution of different outcomes even in a heterogeneous group across a wide spectrum of neurological recovery. In conclusion, the GRASSP at 1 month accurately predicted upper limb function and self-care outcomes at 6 and 12 months after cervical SCI. URP-CTREE revealed the distribution of outcome categories and can be used to predict cohorts with homogenous outcomes.

Evidence was presented that the GRASSP allows the precise identification of recovery profiles and accurately predicts upper limb function and self-care in acute tetraplegia. However, there was still limited evidence regarding the influence of each individual muscle or muscle group on the prediction of upper limb function and activities of daily living (ADLs). Furthermore, the effect of specific grasp patterns, as described in the GRASSP, on the prediction of upper limb function and functional outcome had not yet been investigated. In **chapter 6** therefore, it was determined which single or combined upper limb muscles as defined by the ISNCSCI-UEMS and the GRASSP, best predict upper limb function and independence in ADLs. Furthermore, the predictive value of qualitative grasp movements

(QIG) on upper limb function in individuals with acute tetraplegia was assessed. In this study ISNCSCI, GRASSP and SCIM III scores were recorded at 1 and 6 months after SCI. For the prediction of upper limb function and ADLs, a logistic regression model and URP-CTREE were used with 10 different muscle predictor variables and 2 ISNCSCI predictor variables, motor level of injury (MLI) and AIS. Logistic regression and URP-CTREE revealed that a combination of ISNCSCI and GRASSP muscles (to a maximum of four) demonstrated the best prediction (specificity and sensitivity ranged from 81.8% to 96.0%) of upper limb function and identified homogenous outcome cohorts at 6 months. The URP-CTREE model with the QIG predictors for upper limb function showed similar results. The AIS and MLI predictor variables were not chosen in the URP-CTREE model. Therefore, AIS grades and MLI might not be appropriate for stratification in clinical studies or trials. Prediction of upper limb function can be accurately achieved through a combination of defined, specific upper limb muscles assessed in the ISNCSCI and GRASSP. These limited muscle predictors are ideal indices for stratifying patient groups and a good proxy for favourable and unfavourable outcomes irrespective of AIS and MLI. In addition, the combination of a limited number of proximal and distal muscles along with QIG represents a quick and easy assessment tool for clinical decision making during rehabilitation interventions and clinical trials. In conclusion, the predictive value of standard ISNCSCI-UEMS for upper limb function can be improved significantly with the addition of single GRASSP predictors.

Finally, in **chapter 7**, the main findings of this thesis are presented and discussed, and recommendations are made for further research.

Overall conclusion

The work contained in this PhD thesis provides advanced insights and useful data regarding upper limb function outcome in cervical SCI. Evidence was presented that the GRASSP provides information on multifaceted domains (e.g. strength, sensation and prehension) and allows to detect both subtle and clinical meaningful changes in upper limb function. Furthermore, the GRASSP can accurately predict upper limb function and ADLs, even in a heterogeneous group of individuals across a wide spectrum of neurological recovery. This supports the use of the GRASSP in the assessment of rehabilitation outcome as well as in clinical studies and trials.

Samenvatting

Revalidatie heeft als doel om bij mensen met een gezondheidsprobleem het dagelijks functioneren te herstellen of te behouden. Bruikbare, betrouwbare en valide meetinstrumenten, die ook veranderingen in de gezondheidstoestand kunnen vastleggen, zijn nodig om binnen het revalidatieproces inzicht te krijgen in de onderliggende oorzaken van het verminderd functioneren.

Bij mensen met een cervicale dwarslaesie is de arm- en handfunctie aangedaan en daarom is de behandeling van de bovenste extremiteiten van groot belang. Er is echter beperkt onderzoek gedaan naar uitkomstmaten van arm- en handfunctie. Verder kan de uitingsvorm en het verloop van een cervicale dwarslaesie heel verschillend zijn, wat voornamelijk wordt bepaald door variatie in de hoogte, de ernst en het herstel van de laesie. Deze verschillen maken het lastig om de verschijnselen en testresultaten bij individuele patiënten te interpreteren en het bemoeilijkt ook de interpretatie van onderzoeksgegevens.

Hoofdstuk 1 van dit proefschrift laat zien dat er maar weinig meetinstrumenten voor mensen met een cervicale dwarslaesie zijn ontwikkeld en dat de meetinstrumenten die er wel zijn, geen, beperkte of matige klinimetrische meeteigenschappen bezitten. Om arm- en handfunctie nauwkeurig te kunnen weergeven is het daarom nodig om voor deze patiënten betrouwbare, valide en responsieve meetinstrumenten te ontwikkelen of om bij bestaande instrumenten de meeteigenschappen verder te onderzoeken. Het hoofddoel van dit proefschrift is om bij mensen met een cervicale dwarslaesie de arm- en handfunctie te meten, te evalueren en te voorspellen tot een jaar na het ontstaan van de laesie, middels de 'Graded and Redefined Assessment of Strength, Sensibility and Prehension' (GRASSP).

Hoofdstuk 2 beschrijft een systematische literatuurstudie naar de beschikbaarheid van meetinstrumenten voor arm- en handfunctie in vier verschillende patiëntengroepen: 1) aandoeningen van schouder-arm-hand; 2) reumatische ziekten; 3) herseninfarct; 4) tetraplegie. Met tetraplegie wordt een verlamming van zowel beide armen als beide benen bedoeld, zoals die kan ontstaan na een cervicale dwarslaesie. Er bleken 17 veelgebruikte meetinstrumenten te zijn, die volgens de 'International Classification of Functioning, Disability, and Health' (ICF) ingedeeld kunnen worden. Voor ieder meetinstrument is het onderliggend concept, de uit te voeren metingen en informatie over betrouwbaarheid en responsiviteit voor veranderingen gegeven. Samenvattend kan gezegd worden dat deze veelgebruikte meetinstrumenten onderling behoorlijke verschillen vertonen in concept en de metingen. Tevens mist er vaak informatie over de klinimetrische eigenschappen. Het overzicht (tabellen 2.1 en 2.2 in hoofdstuk 2) kan gebruikt worden om de keuze voor een meetinstrument in de klinische praktijk of voor een studie te vergemakkelijken.

Vanwege het gebrek aan goede meetinstrumenten voor de arm- en handfunctie voor mensen met een cervicale dwarslaesie, heeft een internationaal onderzoeksteam de 'Graded and Redefined Assessment of Strength (spierkracht), Sensibility (tastzin) and Prehension (reiken, grijpen, loslaten en manipuleren)' (GRASSP) ontwikkeld. De GRASSP is een meetinstrument dat veranderingen in functie van de arm en hand kan vastleggen, in relatie tot complexe vaardigheden van de arm en hand. In **hoofdstuk 3** wordt een studie beschreven bij 74 patiënten met een acute cervicale dwarslaesie die op 1, 3, 6 en 12 maanden na de dwarslaesie zijn onderzocht. Onderzocht is of de GRASSP responsief is voor veranderingen over die tijd, in vergelijking met andere gestandaardiseerde tests (zoals de 'upper extremity motor score' (UEMS), de gevoeligheid voor lichte aanraking ('light touch', LT) die volgens internationale richtlijnen (ISNCSCI) getest worden en een schaal voor het niveau van zelfstandigheid bij activiteiten van de zelfverzorging (SCIM-SS)). Verder is er gekeken naar het herstelpatroon van de onderdelen 'spierkracht' en 'prehension' in de GRASSP en is er gekeken in hoeverre veranderingen in de GRASSP en SCIM-SS overeenkwamen met veranderingen volgens het oordeel van behandelaars.

De GRASSP is uitstekend in staat is om tot een jaar na de dwarslaesie klinisch relevante veranderingen in arm- en handfunctie te meten. GRASSP spierkracht en prehension herstel waren het grootst tussen 1–3 maanden na het ontstaan van de dwarslaesie en zijn gerelateerd aan de ernst van de dwarslaesie. De metingen van de GRASSP bleken van toevoegende waarde te zijn bij de bestaande standaardmetingen (INSCSCI en SCIM-SS).

Bij mensen met een cervicale dwarslaesie treden niet alleen spierparesen op, maar bestaat er ook uitval van gevoel en tastzin. In **hoofdstuk 4** worden drie verschillende meetmethoden getest, die gebruikt worden om te onderzoeken wat mensen met een tetraplegie nog kunnen waarnemen met de huid van schouder arm en hand (op de dermatomen tussen C3-C8): de gevoeligheid voor lichte aanraking (LT), de Semmes-Weinstein monofilament (SWM) test en de grenswaarde om een elektrische prikkeling nog net waar te nemen (EPT). Bij 25 patiënten met tetraplegie zijn, 6 maanden na de laesie, in totaal 300 huidgebieden getest, zowel links als rechts.

Het percentage van overeenstemming tussen de LT en SWM/EPT testuitslagen varieerde van 95.5% tot 36.2%. De meetinstrumenten SWM en EPT zijn gevoeliger om tastzin te meten dan de LT, doordat er onder, boven en op het LT-niveau van de laesie nog tastzin met EPT en SWM gedetecteerd werd. Dat betekent dat SWM of EPT een goede aanvulling is op LT.

Er bestaat een grote variabiliteit in het verloop na het doormaken van een cervicale dwarslaesie. Voor de patiënt en voor de revalidatie zou het goed zijn als het verloop na de dwarslaesie zou kunnen worden voorspeld om daarmee de patiënten goed te informeren over hun vooruitgang. In **hoofdstuk 5** staat een studie beschreven, waarin onderzocht is of je met de GRASSP-test de arm- en handfunctie en de mate van zelfstandigheid bij zelfverzorging een jaar na de dwarslaesie kan voorspellen. In de studie is bij 61 patiënten 1 maand, 6 en 12 maanden na de dwarslaesie, de GRASSP, SCIM-SS en de American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Gemodificeerde Frankel Classificatie om de mate van stoornis aan te geven) afgenomen. De spierkracht in de GRASSP bleek de beste voorspeller voor het verloop van arm- en handfunctie en zelfverzorging. De voorspelling werd nog beter als de spierkracht met het kwalitatieve grijpen en/of kwantitatieve grijpen werd gecombineerd. Kwalitatief grijpen werd getest met de 'qualitative grasping subtest' (QIG) waarin verschillende grijppatronen zoals de cilindergreep, pincetgreep en lateraalgreep uitgevoerd worden *zonder* dat een voorwerp gepakt wordt. Kwantitatief grijpen werd getest met de 'quantitative grasping subtest' (QtG), waarin zes verschillende taken uitgevoerd worden, bijvoorbeeld water uit een flesje in een glas schenken en moeren op een boutje draaien, waarbij gekeken en beoordeeld wordt met welke greep de patiënt het voorwerp pakt. Bovendien leverde de beslisboomanalyse (decision tree analysis: URP-CTREE) belangrijke informatie op over de verdeling van verschillende homogene uitkomsten, zelfs uit een heterogene groep van patiënten waarvan het neurologische herstel zo verschillend is. In conclusie kan worden gesteld dat de GRASSP afgenomen op 1 maand na de dwarslaesie nauwkeurig het verloop van de arm- en handfunctie en zelfverzorging tot 1 jaar na de dwarslaesie kan voorspellen. Daarnaast laat de URP-CTREE-analyse zien dat de verdeling van uitkomsten uitstekend gebruikt kan worden om cohorten met homogene uitkomsten te voorspellen. Dit was tot nu toe erg moeilijk bij cervicale dwarslaesie en was nooit nader onderzocht. De bovengenoemde factoren ondersteunen het gebruik van de GRASSP in revalidatie en interventiestudies.

Uit de hoofdstukken 3 en 5 is gebleken dat de GRASSP geschikt is om bij mensen met een acute cervicale dwarslaesie nauwkeurig herstelpatronen te beschrijven en om de arm- en handfunctie en zelfverzorging precies te voorspellen. De daaropvolgende vraag is in hoeverre de functie van individuele spieren of spiergroepen, zoals beschreven in de GRASSP en ISNCSCI-UEMS, samenhangt met latere arm- en handfunctie en zelfstandigheid in de zelfverzorging en mobiliteit. Ook was het nog de vraag in hoeverre QIG, zoals beschreven in de GRASSP en het motorische niveau van de laesie (MLI) en de ernst van

de laesie (AIS), samenhangt met latere functionaliteit. In het onderzoek in **hoofdstuk 6** is beschreven dat een combinatie van maximaal vier verschillende spieren of spiergroepen predictoren uit ISNCSCI-UEMS en GRASSP de arm- en handfunctie 6 maanden later nauwkeurig kan voorspellen. Bovendien kan het testen van deze spieren heel bruikbaar zijn om te informeren over de juiste behandeling in de revalidatie. De QIG-predictoren leverden dezelfde resultaten op. Bij alle analyses werden de MLI- en AIS-predictoren niet in het model opgenomen. Dus een beperkt aantal spieren of spiergroepen alsook een eenvoudige en snelle test zoals QIG kunnen uitstekend de arm- en handfunctie voorspellen en patiënten in goede en slechte uitkomsten stratificeren onafhankelijk van MLI en AIS. Er kan geconcludeerd worden dat de voorspellende waarde van ISNCSCI-UEMS voor arm- en handfunctie significant verbeterd kan worden door GRASSP-predictoren toe te voegen.

In **hoofdstuk 7** worden de belangrijkste bevindingen van dit proefschrift gepresenteerd en besproken, en worden aanbevelingen gedaan voor verder onderzoek. Het werk in dit proefschrift geeft nieuw inzicht en waardevolle data over de arm- en handfunctie bij mensen met een cervicale dwarslaesie. De GRASSP is een relatief nieuwe test die informatie geeft over verschillende domeinen van arm- en handfunctie, zoals spierkracht, tastzin en de vaardigheid om naar voorwerpen te reiken, te grijpen, los te laten en te manipuleren. De GRASSP is in staat om de soms kleine maar klinisch belangrijke veranderingen in arm- en handfunctie te meten, die belangrijk zijn voor functieherstel. Met de uitslag van de GRASSP kan ook het verloop van arm- en handfunctie en zelfverzorging nauwkeurig voorspeld worden, zelfs als bij cervicale dwarslaesie de gevolgen voor patiënten zo verschillend kunnen zijn. Dit ondersteunt het gebruik van de GRASSP voor het meten van de uitkomsten in de revalidatie van mensen met een cervicale dwarslaesie en ondersteunt tevens het gebruik van de GRASSP in klinische studies.

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Curriculum vitae

Inge-Marie Velstra was born in 1967 on the 1st of May in Apeldoorn, The Netherlands (NL). She completed her secondary education in 1986 at the Myrtus College in Apeldoorn (NL). In 1990, she obtained her Bachelor's degree as an occupational therapist at the College of Amsterdam, Department of Occupational Therapy, Amsterdam (NL).

In 1992, she moved to Switzerland (CH) and was working as a clinician mainly in the field of spinal cord injury (SCI) care in the Swiss Paraplegic Centre Nottwil (CH) and the Swiss Paraplegic Centre, University Hospital Balgrist, Zurich (CH) until 1997. In 1994, she became the group leader of the occupational therapy department, responsible for the SCI ward at the Uniklinik Balgrist.

In 1997, she started working as a clinician in the sector of peripheral upper limb conditions at the Department of Rheumatology and the Institute of Physical Medicine of the University Hospital Zurich (CH) as the vice head of the occupational therapy department. Additionally, starting in 1998, she was responsible for building up the new hand therapy department and was the head of this department. During those years she has gained experience in management, organisation and teaching and was involved operationally in projects that aimed at improving clinical quality. Due to her professional experience in SCI care, hand therapy and rehabilitation, and the treatment and assessment of patients, she got interested in developing / improving her scientific skills. Inge-Marie received her Master's degree in Health Service Research at the Erasmus University Rotterdam (NL) in 2005. She conducted her master thesis "Applicability of the willingness-to-pay method to evaluate health effects in hand injury rehabilitation" at the Department of Rheumatology and the Institute of Physical Medicine, University Hospital Zurich (CH) in collaboration with the Department of Physical Medicine and Rehabilitation, University Hospital Munich, Ludwig-Maximillian-University, Germany.

At the end of 2006, Inge-Marie began to work as a research assistant at the Swiss Paraplegic Research Institute in Nottwil (CH).

In 2010, she started her PhD studies in the Clinical Trial Unit of the Swiss Paraplegic Centre in Nottwil (CH). Her promotors were Prof.dr. Hans Rietman, Enschede (NL) and Prof.dr. Armin Curt, Zurich (CH), and she was supervised by Dr. Marc Bolliger, Zurich (CH).

Inge-Marie continues her research with the focus on upper limb function and outcome research in SCI. Furthermore, she is looking for opportunities and new challenges to contribute to the improvement of quality, efficiency and effectiveness in SCI research and care. She is still working at the Clinical Trial Unit in Nottwil (CH) and since spring 2015, an important part of her work is monitoring clinical studies at the Swiss Paraplegic Centre, Nottwil (CH).

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